

Defining the role of recombinant activated factor VII in pediatric cardiac surgery: Where should we go from here?*

Oliver J. Warren, BSc (Hons), MRCS; Paula L. B. Rogers, MBBS; Amy L. Watret, MBBS; Katie L. de Wit, MA (Hons); Ara W. Darzi, FMedSci, KBE; Ravi Gill, FRCA; Thanos Athanasiou, PhD, FETCS

Objectives: Postoperative hemorrhage is a recognized complication of pediatric cardiac surgery. Both the immature coagulation system and increased susceptibility to hemodilution increase the likelihood of pediatric patients developing coagulopathy when compared with adult counterparts. Treatment options remain limited. Recombinant factor VII (rFVIIa) is a hemostatic agent increasingly used to reduce hemorrhage in other surgical settings, the role of which is unclear in this population. This article systematically reviews the published literature on the use of rFVIIa in pediatric cardiac surgery.

Data Sources and Study Selection: A systematic literature search identified reports of rFVIIa administration in pediatric patients undergoing cardiac surgery. Where possible, individual patient-specific data were extracted and pooled statistical analysis was performed.

Data Extraction and Synthesis: Twenty-nine articles reporting on the administration of rFVIIa to 169 patients were identified. rFVIIa has been administered to patients with predefined congenital abnormalities of hemostasis to arrest hemorrhage refractory

to other interventions and prophylactically in the hope of reducing blood loss. Treatment regimens vary widely, in terms of both first and cumulative dose. Data on chest tube blood loss and two markers of coagulation were pooled and analyzed, and significant improvements were demonstrated. Mortality was 4.4% for the entire cohort but 20% of patients on extracorporeal membrane oxygenation suffered significant thromboembolic complications.

Conclusions: rFVIIa has an increasingly accepted role in the management of patients with congenital coagulopathies undergoing major surgery. However, randomized trials are required to define the role of rFVIIa as an adjunct to control major hemorrhage in the pediatric cardiac surgical population. Any future work must focus not only on benefits but also on patient safety, particularly, risk of morbid thromboembolic complication. (*Pediatr Crit Care Med* 2009; 10:572–582)

KEY WORDS: cardiac surgical procedures; pediatrics; cardiopulmonary bypass; hemorrhage; treatment outcome; recombinant factor VIIa

Postoperative hemorrhage is a recognized complication of pediatric open-heart surgery and remains a major source of postoperative morbidity and mortality (1, 2). Its causation is multifactorial. The procedure itself creates significant tissue injury, leading to consumption of platelets and clotting factors and initiating a systemic inflammatory response, thus, increasing the possibility of developing a coagulopathy. This is compounded by cardiopulmonary by-

pass (CPB), an essential component of pediatric open-heart surgery, in two ways. First, despite administration of heparin, simultaneous activation of the hemostatic and fibrinolytic systems occurs (3). Second, the CPB circuit requires priming with a mixture of allogenic blood and/or crystalloid solutions, e.g., normal saline, which causes a significant hemodilution of clotting factors and platelets. A resulting variable dysfunction of hemostasis is seen in all pediatric patients (4, 5).

The Pediatric Coagulation System

Bleeding in pediatric cardiac surgery patients is exacerbated by an underdeveloped coagulation system, particularly, in neonates and young infants. Vitamin K-dependent clotting factor levels are all <70% of mean adult values, not increasing to 80% to 90% until 6 mos of age (4, 6). Although platelet levels are similar, platelets are less reactive until 2 wks of age (7, 8). Levels of certain natural coagulation inhibitors are elevated, e.g., heparin cofactor II, but others are significantly lower, e.g., antithrombin III, which does not reach adult levels until 3–6 mos (6, 9, 10), impairing the ability of heparin to provide adequate anticoagulation (11). Because both clotting factor and natural inhibitor levels are altered, standard tests of coagulation, such as prothrombin time and activated partial thromboplastin time, are not as reliable as in adults, and the ability of infant plasma to generate fibrin as measured by fibrin/fibrinogen degradation products

*See also p. 604.

From the Department of BioSurgery and Surgical Technology (OJW, PLBR, ALW, KLdW, AWD, TA), Imperial College London, St. Mary's Hospital, London, United Kingdom; and Shackleton Department of Anaesthesia (RG), Southampton University Hospitals NHS Trust, Southampton, United Kingdom.

This work was performed as part of ongoing work into recombinant factor VIIa being performed within, and funded by, the Department of BioSurgery and Surgical Technology, Imperial College London and the Shackleton Department of Anaesthesia, Southampton University Hospitals NHS Trust, Southampton, United Kingdom. This work has been partly, but not solely,

subsidized by an unrestricted educational grant from NovoNordisk, the manufacturers of NovoSeven.

Drs. Warren, Gill, and Athanasiou have received grant support from NovoNordisk. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: o.warren@imperial.ac.uk

Copyright © 2009 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies

DOI: 10.1097/PCC.0b013e3181a642d5

and D-dimers may be a better measure of the coagulant potential of infant blood (12–15). Taken as a whole, the inherent ability of the neonate or young infant patient to clot is reduced when compared with their older counterparts (16).

Hemodilution

CPB-associated hemodilution is more pronounced in pediatric patients because of the significant discrepancy between the volume required to prime the CPB circuit and a child's circulating volume. Unsurprisingly, this is more pronounced in smaller, younger children. Some studies have suggested that age is the most important risk factor for subsequent bleeding (17, 18), whereas others have suggested low weight to be a predictor of coagulopathy, independent of the effect of age (19). Keeping aside the relative importance of these two interdependent variables, it is clear that neonates bleed more and are exposed to more transfusion than any other group undergoing cardiac surgery (20).

Other Factors

Cyanosis is a common problem in children undergoing surgery to correct congenital heart disease and further impairs their hemostatic performance. Polycythaemia and the ensuing hyperviscosity are major causative factors (21), but patients with cyanotic congenital heart disease also produce less coagulation factors, particularly, fibrinogen, and natural thrombin inhibitors (e.g., heparin cofactor II) because of impaired intestinal absorption of Vitamin K and delayed hepatic maturation secondary to impaired oxygen perfusion (22). Several other patient-specific factors, such as reoperation, duration of CPB, and complexity of the procedure, will increase the chance of postoperative hemorrhage.

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) (NovoSeven; NovoNordisk, Bagsvaerd, Denmark) was first licensed for the treatment of hemorrhage in patients with hemophilia A or B with neutralizing autoantibodies (coagulation inhibitors) to factor VIII or IX (23–26). In 2005, the U.S. Food and Drug Administration increased the license of rFVIIa to include surgical procedures in the same patient group and patients with congenital factor

VII deficiency (27). There are an increasing number of reports, within both pediatric and surgical practice, of the off-license administration of rFVIIa to treat hemorrhage refractory to standard allogenic transfusion therapy (28–31). The mechanism of action of rFVIIa has been described extensively previously (32–34), and we will not repeat a description here.

Aims of Review

We have previously investigated the role of rFVIIa in cardiac surgery (33). However, this review focused predominantly on adults. The literature pertaining to rFVIIa in pediatric cardiac surgery are relatively small and heterogeneous, predominantly based on case reports, but has increased considerably in the past 2 yrs, allowing more in-depth pooled data analysis to be performed. In this article, we describe a systematic review of the available evidence on the efficacy, dosage, safety, and cost implications of rFVIIa use in pediatric cardiac surgery and formulate proposals for future research.

MATERIALS AND METHODS

Literature Search. A literature search was performed using PubMed, Ovid, Embase, Google Scholar, and Cochrane databases. The following MeSH headings were used when searching PubMed: “Cardiac Surgical Procedures,” “Pediatrics,” “Cardiopulmonary Bypass,” “Hemorrhage,” and “Treatment Outcome,” along with the substance heading “recombinant FVIIa.” The “related articles” function was used to broaden the search, and all abstracts, studies, and citations were scanned and reviewed. Studies in all languages were sought. No date restrictions were placed on articles. The last date for this search was January 1, 2008.

Peer-reviewed cardiac surgery, pediatric, and anesthetic journals' databases were searched, including published conference proceedings. Searches were also made of previous reviews, including cross-references. Ongoing trials were searched for *via* the Website (www.controlled-trials.com). References of the acquired articles were all searched manually to identify any further studies for inclusion.

Inclusion and Exclusion Criteria. To be considered for inclusion in this systematic review, articles had to report on the administration of rFVIIa to patients undergoing pediatric open-heart surgery. After deliberation, we defined “pediatric” as ≤ 18 yrs of age for the purpose of this review. This was to allow the inclusion of two articles reporting on a significant number of pediatric cases, ranging from neonate to adolescent, that had defined the pediatric cohort (35, 36). Thus, articles that

studied the effect of rFVIIa on a mixed cohort of patients, e.g., those in pediatric intensive care units or reported results obtained from databases were studied, and data pertaining to pediatric open-heart surgery patients were extracted. Patients were excluded if they were placed on extracorporeal circulatory support for noncardiac surgery conditions. Animal studies were excluded. Articles were classified as case reports, case series, retrospective database (or chart) reviews, and comparative studies.

Selection of Trials for Inclusion. On the basis of the inclusion and exclusion criteria outlined earlier, two reviewers (O.W. and P.R.) independently selected studies for further examination by reading titles and abstracts of all identified citations. All potentially eligible studies were retrieved in full for further assessment. Any disagreement was resolved by discussion with the senior author (T.A.).

Data Extraction. Two reviewers (O.W. and P.R.) independently extracted the following data from each article: first author, year of publication, study type, number of subjects, study population demographics, pathology, and procedure type (including the use of artificial circulatory support). Data were retrieved wherever possible on the following outcomes of interest: dosage (initial and cumulative), preintervention and postintervention transfusion requirements and blood loss, adverse events (thromboembolic and nonthromboembolic), and mortality. Data extraction was performed independently by the same reviewers, using a standardized excel spreadsheet.

Data Analysis. The presence of only one single prospective randomized controlled trial in the literature prevented a formal meta-analysis being performed. However, where articles reported individual patient-specific data regarding outcomes, such as clotting parameters, blood product transfusion requirements, blood loss, and pre-rFVIIa and post-rFVIIa administration, this was extracted and a pooled analysis performed where possible. Data are expressed either as raw count and percentages, ranges, mean value \pm SD or as median and interquartile range. Kolmogorov-Smirnov test was performed to test the normality of distributions on all extracted data sets. Where data were non-normally distributed, Wilcoxon's signed-rank test was performed; and where normally distributed, a paired samples *t* test was performed. All statistical analysis was performed using SPSS 14.0 (SPSS, Chicago, IL).

RESULTS

Study Identification. The results of the systematic search strategy are shown in Figure 1. Thirty-one studies fulfilled our inclusion criteria. However, one patient was replicated in two articles by the same group (37, 38), therefore, the older article was excluded because it contained

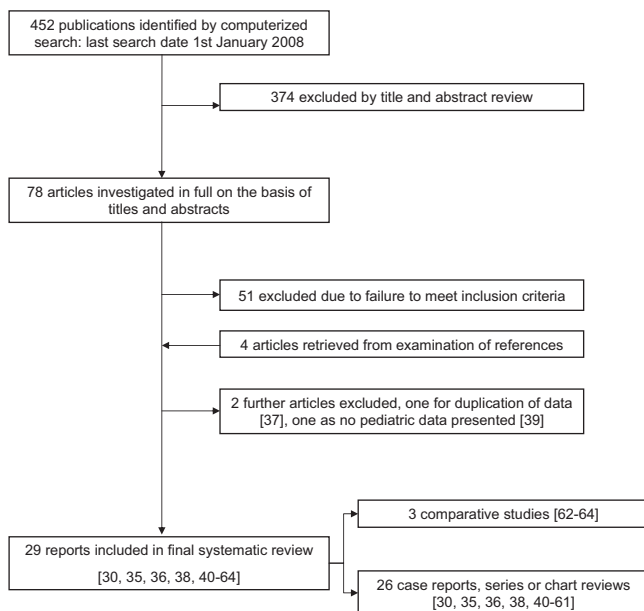


Figure 1. The results of the systematic search strategy.

less data (37), and one article reporting a mixed case registry was excluded because no specific pediatric data were presented (39). Therefore, 29 publications were included in our final analysis (30, 35, 36, 38, 40–64), four on mixed pediatric populations containing some cardiac surgery patients (35, 36, 41, 61).

Study Type and Literature Heterogeneity. The included articles report on 235 patients, of whom 66 are controls and are excluded from further analysis. To facilitate data synthesis, reporting of key outcomes, and statistical analysis, we divided the remaining 169 patients treated with rFVIIa into two groups. The first group is made up of six articles (35, 36, 61–64) reporting on the administration of rFVIIa to 122 patients, where all data were reported as average values pertaining to the group being investigated, thus, preventing the extraction of individual patient-specific data. This group includes three comparative studies that focus solely on pediatric cardiac surgery (62–64); the first is a small case series of nine patients, compared with a historical matched control group of eight patients (62); the second is a retrospective matched case-control study published recently by Agarwal et al (63), which includes 24 treated patients; the third, by Ekert et al (64), is the only randomized controlled trial identified, which, unlike the other two, investigates the *prophylactic* role of rFVIIa and is the only article in the literature to do so in a general pediatric study

(i.e., in patients without hemophilia A, factor VII deficiency, etc.).

The second group comprised the other 23 articles (30, 38, 40–60), a mixture of case reports or series, where extraction of individual and patient-specific data was possible. This effectively allowed us to create a new “cohort” of 47 patients and allowed, on occasions, pooled statistical analysis to be performed. Three case series each reported on more than five patients, thus, contributing 21 (45%) of the patients in this group (30, 49, 56).

Patient Demographics and Case Mix. The patient demographics, surgical procedures (including the use of extracorporeal membrane oxygenation [ECMO]), and dosing regimens used in articles reporting pooled data are described in Table 1, and where extraction of individual patient-specific data was possible, the same information is presented for *each individual patient* in Table 2. A broad range of pediatric patients, in terms of age, weight, and pathology, is described in both Tables 1 and 2. The cohort described in Table 2 has a mean age of 37.2 ± 55.9 mos and mean weight of 15.0 ± 6.8 kg. The smallest patient in the review weighs only 2.4 kg (63). Unsurprisingly, the predominant procedures are surgical corrections of major congenital abnormalities. However, the literature also includes the use of rFVIIa in three patients following cardiac transplant (44, 47, 51) and in one patient who underwent resection of a left ventricular tumor (49).

The Impact of ECMO. Of the 169 included patients, 35 were on ECMO at the time of rFVIIa administration, 19 of those are reported as individual cases in Table 2. Veldman et al (56) and Wittenstein et al (59) have both reported case series in which all treated patients were on ECMO following surgery for congenital heart disease. In the series by Veldman et al, three of the seven patients died, but only one of these could be considered secondary to thrombotic pathology (a myocardial infarction). In another two cases, thrombus was seen inside the circuitry after successful weaning from ECMO, and one patient required an oxygenator change because of occlusion. Velik-Salchner et al (57) reported thrombotic occlusion of the truncus brachiocephalicus and both subclavian arteries in a neonate supported by ECMO. In both these articles, rFVIIa was given in combination with other procoagulant factor concentrates, including factor XIII, antithrombin III concentrates, and fibrinogen. Both groups conclude that administration of rFVIIa simultaneously with other procoagulants must be avoided because of risk of life-threatening ECMO occlusion. Fifty percent of the study group in Agarwal et al was placed on ECMO, and when analyzed as a subgroup they experienced more chest tube bleeding and required more blood products than those without. Of the 24 patients receiving rFVIIa, two patients suffered major thrombosis, both from the ECMO subgroup, one with a resulting major morbidity. All the four patients on ECMO in the study by Wittenstein et al (59) survived with no thromboembolic events. Other complication-free reports of rFVIIa use in patients on ECMO can be found elsewhere in the literature (42, 44, 58). Of the entire cohort, 7 (20%) are reported to have suffered symptomatic thrombotic phenomena following rFVIIa.

Dosing. Where possible, we extracted the initial dose, the number of doses given, and the interval between them. Patient-specific data were extracted for all 47 patients detailed in Table 2. The first dose administered in this population ranges from 17 to 200 $\mu\text{g}/\text{kg}$, with a mean dose of 93.2 ± 50.3 $\mu\text{g}/\text{kg}$. The total dose ranged from 17 to 4650 $\mu\text{g}/\text{kg}$, with a median total dose of 210 (256) $\mu\text{g}/\text{kg}$ (the data were not normally distributed due to the effect of one case where rFVIIa was given for every 2 hrs, at a dose of 90 $\mu\text{g}/\text{kg}$, over 7 days to treat a factor VII–deficient patient undergoing

Table 1. Patient demographics, surgical procedures, and dosing regimens from articles reporting pooled data

Reference	Type of Article	No. Patients			Lesion and Procedure	ECMO	Age ^a	Weight (kg)	Dose (μg/kg)	No. Doses	Interval Between Successive Doses (hr)
		Total	Cardiac rFVIIa	Controls							
61	1	46	11	—	Cardiac surgery	—	4.6 ± 5.7 yrs ^b	21.7 ± 26 ^b	160 ± 225 ^b	1.6 ^b	16.8 (1–48) ^c
35	1	10	1	—	Bleeding post-CPB	—	3–18 ^c	3.7–49 ^c	50–100 ^c	2.2 ^b	—
36	1	111	37	—	Bleeding post-CPB +/-or ECMO	4	<1 mo to 18 yrs ^c	—	2,789 μg/ patient	—	—
62	2	17	9	8	CHD, including ToF, VSD, ASD, and mitral valve repair	—	9 ± 4 yrs ^b 9.5 d	29 ± 12 ^b 3.5	90 46.9 ± 29.3 ^b	1 1 (n = 15)	— 3.9 ± 1.7 ^b
63	3	46	24	22	CHD, including HLHS, TGA, aortic stenosis, and bidirectional Glenn Shunt	12	(4–3285) ^d	(2.4–51) ^c	46.8 ± 16.3 ^b 31.6 ^b 24.3 ± 6.9 ^b	2 (n = 7) 3 (n = 1) 4 (n = 1)	3.3 ± 2.9 ^b 2 2
64	4	76	40	36	CHD, including TGA, ToF, and AVSD	—	4 mos ^b	5.2 ^b	40 63 ^b	1 (n = 40) 2 (n = 22)	Prophylactic dose given during CPB to all patients Second dose given after 20 mins if “excessive bleeding”

ASD, atrial septal defect; CHD, congenital heart disease; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; rFVIIa, recombinant factor VIIa; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

^aYears unless otherwise stated; ^bmean, or mean ± SD; ^crange, or median + range; ^ddays. Type of article: 1, Centre Registry based on chart reviews; 2, case series with case-matched control group; 3, case control study; 4, randomised controlled trial.

heart transplantation [51]). The mode interval that different groups have waited before administering further doses is 2 hrs. The smallest dose reported is 17 μg/kg and had no reported impact on bleeding. It is not explained why such a small dose was given (56). Where patient-specific data were not reported (Table 1), a significant range of dosing is still present, on occasions even within the same study. Agarwal et al (63), for example, gave patients anything from one to four doses, starting with a first dose of 46.9 ± 29.3 μg/kg, based on clinician discretion and subjective response to first dose.

Preoperative Coagulopathy. Table 3 shows the frequency of preoperative coagulopathy in all 169 patients. Only one of the six articles described in Table 1 did not state whether or not patients with preoperative hemostatic disturbance were included in their article (36), but in all others, patients with coagulopathy were excluded. Of the patients detailed in Table 2, 11 had a preexisting coagulopathy, of which four were congenital defects in hemostasis and seven were acquired preoperatively (due to conditions, such as multiorgan failure, thrombocytopenia, and hypoxic-ischemic liver injury). The congenital clotting disorders in which rFVIIa has been used to facilitate cardiac

surgery include factor XI deficiency (40) and hemophilia A with high titers of inhibitors to factor VIII (51), both with successful outcomes. Tokunaga et al (55) reported the only case of rFVIIa being used to allow surgery in a neonate with factor VII deficiency. They used four 30 μg/kg doses preoperatively, intraoperatively, and postoperatively with good effect, the patient maintaining 15% to 20% levels of normal FVII activity for the first 3 days postoperatively and surviving to discharge.

Effect on Blood Loss and Transfusion Requirements. Most articles report some reduction in blood loss, as witnessed by the surgeon during operation (64), a reduction in chest tube drainage (38, 42), or a decrease in subsequent requirement for blood products (44, 50).

Although most articles present some data regarding chest tube blood loss, this is measured in different ways and at different points. We extracted patient-specific data pertaining to blood loss, pre-rFVIIa and post-rFVIIa administration from 11 articles and were able to analyze data on 14 patients from eight of these (Table 4). A statistically and clinically significant reduction in chest tube drainage following rFVIIa administration was demonstrated ($p = .001$). To ensure that the findings were not related to the articles

studied, regression analysis was performed, taking into account the article from which the data were extracted. A group effect (using rFVIIa = yes as an independent group variable and blood loss as dependent variable) was detected.

Despite being a better indicator of the impact of rFVIIa on hemorrhage, fewer studies report blood product transfusion rates, and this, along with significant heterogeneity, meant it was not possible to synthesize these data to allow any meaningful statistical analysis. Agarwal et al (63) reported a reduction in packed red cells, fresh frozen plasma, platelet, and cryoprecipitate transfusions ($p < .001$) in patients treated with rFVIIa when compared with matched controls. Razon et al (50) reported a significant difference in transfusion requirements pre-rFVIIa and post-rFVIIa in three patients, two of whom required no further blood products once they had received rFVIIa, and Dominguez et al (44) reported two cases of children on ECMO after surgery, whose requirements for blood products reduced dramatically following rFVIIa administration.

Finally, Ekert et al (64) investigated a possible prophylactic role for relatively low-dose rFVIIa in neonates undergoing surgery for congenital heart disease, but

Table 2. Patient demographics, surgical procedures, and dosing regimens from articles reporting individual patient-specific data

Patient	Reference	Type of Article	Lesion and Procedure	ECMO	Age	Weight (kg)	Gender	Coagulation Disorder	Dose ($\mu\text{g}/\text{kg}$)		Interval Between Successive Doses
									Per Administration	Total	
1	38	1	TGA arterial switch + closure ASD + pulmonary artery construction	No	2.5 yrs	10	M	—	30	30	—
2	40	1	Mitral valvuloplasty	No	4.5 yrs	9	M	FXI deficiency 5% of normal	90	810	2–4 hrs
3	41	2	VSD repair	No	4 mos	3.7	F	—	90	90	—
4	41	2	TGA repair	No	4 wks	4.8	M	—	90	90	—
5	42	1	Intra-aortic balloon pump + ECMO for cardiac failure	Yes	17 yrs	—	M	—	120 (dose 1), 103 (dose 2)	223	1 hrs
6	43	1	Supravalvular aortic stenosis requiring resection + aortic reconstruction	Yes	3.5 yrs	16	M	—	200 (dose 1), 500 (dose 2)	700	15 mins
7	44	1	Heart transplant	Yes	11 yrs	29	M	Previous DIC following LVAD	90	270	4 hrs
8	30	2	Repair of VSD + pulmonary atresia	No	5 yrs	17	—	—	180	360	2 hrs
9	30	2	Ebstein's anomaly, redo systemic-pulmonary shunt	No	8 yrs	19	—	—	180	360	2 hrs
10	30	2	Repair of VSD + pulmonary atresia	No	4 yrs	16	—	—	180	360	2 hrs
11	30	2	TGA arterial switch	No	2 wks	3	—	—	180	360	2 hrs
12	30	2	TGA arterial switch	No	2 wks	3	—	—	180	360	2 hrs
13	30	2	VSD repair and TGA arterial switch	No	15 mos	10	—	—	180	180	—
14	45	2	Hypoplastic left heart syndrome	No	40 wks	3.8	—	Hypoxic-ischemic liver failure post low cardiac output	130	520	—
15	46	1	Repair AVD	No	10 wks	3	F	—	100	400	2, 5, 9 hrs
16	47	1	Cardiac transplant	Yes	4 yrs	—	F	—	180	360	5 hrs
17	48	1	Repair of pulmonary atresia and VSD	Yes	10 yrs	—	F	—	35	70	2 hrs
18	49	2	Norwood procedure for left heart hypoplasia	No	5 d	—	M	—	32	32	—
19	49	2	Norwood procedure for left heart hypoplasia	No	15 d	—	F	—	34	102	0.5, 1.5 hrs
20	49	2	Norwood procedure for left heart hypoplasia	No	4 wks	—	F	—	33	66	0.5 hrs
21	49	2	Norwood procedure for left heart hypoplasia	No	11 d	—	F	Nonspecific preoperation coagulopathy \pm MOF	60	240	10 mins, 110 mins, 10 mins
22	49	2	Resection LV tumor	No	2 mos	—	M	Nonspecific preoperation coagulopathy \pm MOF	60	120	10 mins
23	49	2	Closure ASD + VSD + LV outflow enlargement	No	3 wks	—	M	Nonspecific preoperation coagulopathy \pm MOF	57	114	1 hrs
24	49	2	Rastelli procedure for TGA, pulmonary trunk stenosis + ASD	Yes	8 yrs	—	M	—	30	60	30 mins
25	49	2	Rastelli procedure for TGA, pulmonary trunk stenosis + VSD	No	4 yrs	—	M	Nonspecific preoperation coagulopathy \pm MOF	60	60	—

Table 2.—Continued

Patient	Reference	Type of Article	Lesion and Procedure	ECMO	Age	Weight (kg)	Gender	Coagulation Disorder	Dose ($\mu\text{g}/\text{kg}$)		Interval Between Successive Doses
									Per Administration	Total	
26	50	2	B-T shunt for TGA + DILV + mitral + pulmonary atresia	No	3 d	2.8	M	—	78	78	—
27	50	2	Pulmonary homograft for Noonan syndrome + pulmonary stenosis	No	14 yrs	25	F	Thrombocytopathy and extended bleeding time	96	96	—
28	50	2	Tetralogy of Fallot repair	No	3.5 mos	10.7	F	—	84	84	—
29	51	1	Cardiac transplant (initiated day 6 postoperation)	No	14 yrs	—	M	Haemophilia A with high FVIII inhibitor titer	90 $\mu\text{g}/\text{kg}$ (for 7 d) 95 $\mu\text{g}/\text{kg}$ (for 1 d)	4650	2–4 hrs
30	52	1	“Complex congenital heart surgery”	No	15 yrs	—	M	—	30	60	2 hrs
31	53	1	Repair ASD (second dose for pulmonary artery catheter removal)	No	4 mos	3.7	F	—	70	140	7 d
32	54	1	ASD repair in patient with Noonan syndrome	No	10 mos	6	M	—	90	270	7, 4 hrs
33	55	1	Repair of right ventricular outflow tract and right modified B-T shunt	No	60 d	3.64	M	FVII deficiency	30	120	2 hrs preoperation, induction, end of operation, 1 hr postoperation
34	56	2	HLHS, combined Norwood I + II procedure	Yes	4 mos	5.1	F	—	90, 62, 78	230	—
35	56	2	TGA arterial switch and closure of VSD	Yes	10 d	3.61	M	—	83	332	—
36	56	2	HLHS, combined Norwood I + II procedure	Yes	6 mos	4.6	F	—	130	260	—
37	56	2	HLHS-total cavopulmonary connection	Yes	31 mos	11.6	F	—	17	17	—
38	56	2	HLHS, Norwood I procedure	Yes	2 wks	2.75	F	—	110	330	—
39	56	2	TGA arterial switch	Yes	10 d	2.9	M	—	103	206	—
40	56	2	HLHS, heart transplant	Yes	23 mos	10	M	—	48, 48, 48, 60	204	—
41	57	1	Replacement of partially occluded pulmonalis graft day 7 post-Ross procedure	Yes	15 d	3	F	—	90	90	—
42	58	1	TGA arterial switch	Yes	12 d	3.2	M	—	30	30	—
43	59	2	TGA arterial switch + VSD closure	Yes	27 d	3.7	—	—	90–120	180–240	4 hrs
44	59	2	TGA arterial switch + VSD closure + patch repair of coarctation of the aorta	Yes	6 d	3.2	—	—	90–120	180–240	4 hrs
45	59	2	DORV arterial switch + patch repair of coarctation of the aorta	Yes	7 d	2.7	—	—	90–120	180–240	4 hrs
46	59	2	Aortic arch patch and enlargement for supraaortic stenosis + coronary sinus augmentation	Yes	33 mos	12.5	—	—	90–120	180–240	4 hrs
47	60	1	VSD and valvular pulmonary stenosis	No	8 yrs	—	M	Glanzmann's thromboasthenia	90	360	2 hrs

ASD, atrial septal defect; B-T shunt, Blalock-Taussig shunt; CHD, congenital heart disease; CPB, cardiopulmonary bypass; DIC, disseminated intravascular coagulopathy; DILV, double inlet left ventricle; DORV, double outlet right ventricle; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; LVAD, left ventricular assist device; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Type of article: 1, case report; 2, case series.

Table 3. Frequency of preoperative coagulopathy in patients

Data Source	Total No. Patients	Data Not Available	Data Available	No	Yes		
					Total	Congenital	Acquired
Articles with combined data sets	122	37	85	85	0	0	0
Articles with individual patient-specific data	47	0	47	36	11	4	7
Total	169	37	132	121	11	4	7

Table 4. Outcome measures pre-rFVIIa and post-rFVIIa administration in selected patients

Outcome Measure	No. Patients	References From Which Data Was Derived	Pre-rFVIIa	Post-rFVIIa
Blood loss (mL·kg ⁻¹ ·hr ⁻¹), median (IQR)	14	30, 38, 43, 44, 48, 50, 53, and 58	21 (17.1)	3 (2.4)
INR, mean ± SD	16	30, 45, 47, 48, 52, 53, 55, and 58	2.42 ± 1.67	1.16 ± 0.29
APTT, mean ± SD	16	30, 40, 43, 46, 48, 50, 52, 53, and 58	88.04 ± 43.46	52.15 ± 23

rFVIIa, recombinant factor VIIa; APTT, activated partial thromboplastin time; INR, international normalized ratio; IQR, interquartile range.

Table 5. Morbidity and mortality data for all patients

	Total Patients	Data Not Available	Data Available	Mortality (Where Data Available)	Major Morbidity But Survived	Survived Limited or No Morbidity
Table 1—articles with combined data sets	122	11	111	0	7	104
Table 2—articles with individual patient-specific data	47	0	47	7	4	36
Total	169	11	158	7	11	140

found no impact on blood loss or transfusions when compared with controls.

Effect on Coagulation Studies. Where possible, results of hematology laboratory studies were extracted for all patients in Table 2. Only a small number of studies reported prothrombin time, preventing us from using this as an outcome measure. Twenty-one patients had an international normalized ratio (used as a surrogate measure for prothrombin time) reported just before rFVIIa administration, results ranging from 0.42 to 15 (median = 2.69), but only 16 had post-rFVIIa measurements also available. Sixteen patients had activated partial thromboplastin time results reported pre-rFVIIa and post-rFVIIa administration. Results are displayed in Table 4, and for both, there was a statistically significant improvement following rFVIIa administration ($p = .002$ and $p = .001$, respectively).

Morbidity and Mortality. Morbidity and mortality data for the 169 patients identified in the literature are presented in Table 5. Mortality data were available for all but 11 patients, who were reported as part of a larger series in which mortality rates were reported for the entire cohort (61). Seven patients are reported as having died following rFVIIa administration; four from cardiac failure and/or

an inability to wean from extracorporeal circulatory support (50, 56, 58); one from brain death after severe hemodynamic compromise during surgery (47); and two from potential thrombosis, both of whom were on ECMO and have been discussed previously in this report. The mortality rate for the entire cohort, therefore, is 4.4%. Eleven other patients suffered major morbidity, including cardiac arrest and re-exploration for tamponade, atrial thrombi, and clot evacuation. One patient in the study by Agarwal et al (63) suffered a below-knee amputation because of a femoral artery thrombus, which occurred after multiple unsuccessful attempts to place a percutaneous femoral arterial line after surgery.

DISCUSSION

We have used a systematic approach to synthesize the available literature on the administration of rFVIIa to pediatric cardiac surgery patients. rFVIIa has been used in this population in three distinct ways (1): to allow patients with congenital coagulopathies to undergo major surgery that otherwise would be fatal; (2) to arrest hemorrhage that has otherwise proven refractory to all other interventions; and (3) prophylactically, in an at-

tempt to reduce bleeding and transfusion requirements.

There seems little contention about the first of these indications; as mentioned previously, the license of rFVIIa has been extended to cover these patients during surgery (27), and we have highlighted a number of cases where rFVIIa has been used successfully to this end. The third of these indications has only been investigated by one group, and with no benefit to patients (64). Although a prophylactic role has been investigated in other settings (65–67), including adult cardiac surgery (68), the lack of evidence to support this role in pediatric cardiac surgery, plus the significant and valid concerns expressed by many commentators regarding safety, lead us to recommend that rFVIIa is not to be used prophylactically in patients without congenital coagulation disorders. Furthermore, research into any potential prophylactic role should only occur once a stronger evidence base is in existence regarding the second indication, that of arresting hemorrhage refractory to other interventions, and it is this role that we shall focus on for the rest of this discussion.

Efficacy. The published literature suggests that rFVIIa is an effective hemo-

static agent, particularly, when other interventions seem to have failed. By combining individual patient-specific data, previously reported in isolation, we have demonstrated a statistically significant reduction in blood loss following rFVIIa administration, a result that supports the findings of the two comparative studies assessing this role for rFVIIa (62, 63). One reason why assessing the ability of rFVIIa to control hemorrhage is so difficult is the absence of a validated laboratory test to monitor its biological effect. Some authors have advocated a potential role for thromboelastography and this deserves more investigation (43, 69). We have demonstrated statistically significant changes in both the activated partial thromboplastin time and the international normalized ratio on rFVIIa administration, a finding replicated elsewhere (70). However, the relevance of these findings is disputable; almost invariably rFVIIa is administered alongside or just after many other blood products, clotting factors, and antifibrinolytics. Finally, whether rFVIIa is more efficacious than other procoagulant interventions, such as activated prothrombin complexes, is yet to be established.

The optimal dosing regimen for pediatric patients is unclear. We have demonstrated that a large range of doses have been used, with positive results at lower doses (38, 49). When rFVIIa was originally licensed for hemophilia patients, the standard recommended dose was 90–120 $\mu\text{g}/\text{kg}$ every 2–3 hrs until bleeding stopped (71), and indeed, most of the studies in our review reporting on patients with congenital coagulopathies have used that regimen (40, 44, 51, 60). However, it does not automatically extrapolate that this is the correct treatment for nonhemophilic children who are post-surgery and “in extremis” with the resulting physiologic disturbance this brings. Furthermore, the 2–3-hr interval, which again we have demonstrated in our review, is the most frequent chosen in this setting, is based on the half-life of rFVIIa in adults, but there is evidence that the half-life in children is about 50% that of adults (1.32 vs. 2.72 hrs), and that children have a much more rapid rate of clearance of rFVIIa, indicating that children may need relatively higher doses than adults to achieve the same plasma concentration (72, 73). Finally, it is likely that the required dose is affected by the adequacy of clotting factor replacement (in the form of

blood product transfusion) that has occurred pre-dose.

Safety. The patients we identified within the literature have an estimated mortality rate of 4.4%, in keeping with other aggregated mortality data reported elsewhere (33, 74). A review of thromboembolic complications in patients treated with rFVIIa reported to the Food and Drug Administration database from 1999 to 2004 suggested an increased rate in those treated for unlabeled conditions, and we have previously emphasized that the potential side effects of rFVIIa must not be overlooked (75). rFVIIa can have impressive results, but can also lead to significant morbidity and possibly mortality (57, 63). There are certain scenarios in which most clinicians would not prescribe rFVIIa, such as disseminated intravascular coagulopathy, in which activated monocytes and platelets express tissue factor, increasing the risk of spontaneous thrombosis away from the site of tissue injury. There is evidence that extracorporeal circulatory support increases the levels of tissue factor, and two recent case reports have reported fatal thrombosis in patients (one adult, one infant) receiving rFVIIa during ECMO (76, 77). Twenty percent of the patients we identified in the literature as receiving rFVIIa while on ECMO suffered some form of thrombosis, either *in vivo* or within the circuit. This is not an insignificant figure, but is the same figure found in a cohort of 30 neonates and young children not treated with rFVIIa, who underwent Doppler surveillance for venous thrombosis during and after ECMO (78). Although this suggests that rFVIIa is unlikely to be the sole causative factor of thrombosis in the ECMO subgroup, we would still recommend extreme caution when considering rFVIIa in this setting.

Cost. rFVIIa costs US \$972 per 1.2-mg vial, with many non-neonatal patients requiring more than one vial (30). Using the median total dose reported earlier in the results section, this translates to a total cost per patient of \$170/kg. Although this cost may be offset against the costs of multiple transfusions, length of hospital stay, or even death, it is clear that rFVIIa is an expensive option, and the one that currently many units may be unable to afford, particularly, in the non-developed world.

Limitations of this Study. There are a number of limitations to this study. The cases are highly heterogeneous and are likely to be affected by publication bias,

i.e., reports including failures of treatment or serious adverse events are less likely to be published. Although the literature is rapidly expanding (>50% of the included articles have been published in the past 3 yrs), it remains small and almost entirely based on retrospective and noncomparative reports, preventing any meta-analysis and resulting in there being almost no control patients available with whom new results can be compared. Although significant maturation of the coagulation system occurs within the first 6 mos of life, significant differences remain throughout childhood and into early teens (6, 9). Our cohort includes neonates to teenagers, but analyzing patients as subgroups, so as to assess any age-related difference in response to rFVIIa was not possible because of the small number of patients in the literature. However, the primary value of our article is to formulate recommendations for future research and to guide clinicians caring for pediatric cardiac surgery patients.

Recommendations for Future Research. We believe our findings justify further research being performed and to this end we have formulated recommendations using the “EPICOT” guidelines (79). There is only one randomized controlled trial within the literature, and its focus is on the prophylactic role of rFVIIa in patients without congenital coagulopathies, a role that is not currently supported by the available evidence. We feel that well-designed, randomized controlled trials would be the best way to definitively answer questions regarding the appropriate dosing regimen, the relative indications for administering rFVIIa, and how best to monitor any effect. Patient safety must be central to any such investigation, although risk-free administration of rFVIIa to these patients is an impossible goal, we must focus on bringing clarity when rFVIIa administration may be considered to be in patients’ interest based on known risks and benefits, and when it should be considered relatively contraindicated. Outcomes must focus on morbidity (particularly, thromboembolic adverse events) and mortality (particularly, in the first 30 days) rather than on surrogate markers of hemorrhage, such as chest tube drainage.

Which patients should be studied? Many of the articles we have identified report on the administration of rFVIIa to widely differing age groups within the same series or study (50, 61). Although this is likely a reflection of clinical prac-

tice, the pathophysiology of neonates differs considerably compared with older children, and, thus, so may the response to rFVIIa. As such, future work should focus more closely on specific age groups or weight ranges. We have highlighted concerns regarding spontaneous thrombosis, either intra-arterial or within ECMO circuits, and, thus, trials must initially focus on patients “in extremis,” in whom all other efforts to staunch hemorrhage have been exhausted. Interesting ethical dilemmas arise from these recommendations that may prohibit such work being undertaken. Could any clinician judge with equipoise the use of a placebo in the face of life-threatening hemorrhage if it meant withholding a potentially effective but unregulated therapy? One such answer may lie in the paradox that patients with active bleeding are more at risk of thrombotic complications after rFVIIa (27), suggesting that rescue therapy may be too late and too risky (80). If true, perhaps, a placebo-controlled trial becomes justified? And if not, perhaps, a crossover trial, allowing delivery of the other treatment (placebo or rFVIIa) if the first fails to have an impact? This would allow for a prospective randomized study to be conducted, as might a “head-to-head” trial of rFVIIa against other licensed treatments used in this setting, such as activated prothrombin complex concentrates or factor VIII inhibitor bypassing activity.

Recommendations for Clinical Practice. Recommendations regarding the use of rFVIIa in cardiac surgery have been made previously; however, in every case, pediatric patients were either excluded from the recommendations at the outset (81) or no special consideration was given to their differing circumstances (32, 33, 82). Currently, there is no good evidence for a specific dosing regimen for pediatric patients, which leaves those who make decisions about these patients relatively short of guidance. We would currently recommend that clinicians consider a relatively low starting dose of around 40–60 µg/kg, because positive effects have been seen at this level. In light of the possibly shorter half-life, and lower starting dose, clinicians could then consider giving a second dose within 2 hrs if no clinical improvement is seen. It is not clear what the indications are for rFVIIa administration, but we wish to emphasize that a detailed risk-benefit analysis must be made, in particular, for patients on ECMO. When clinicians are faced with a

situation in which bleeding is so severe as to be imminently life threatening, despite adequate blood product replacement or surgical cause, then we believe rFVIIa should be considered.

CONCLUSIONS

In conclusion, rFVIIa has an increasingly accepted role in pediatric patients with congenital coagulopathies undergoing major cardiac surgery. The literature suggests that there is a role for rFVIIa in the setting of life-threatening hemorrhage refractory to other interventions, but that dosing should be relatively low, and only repeated based on clinical need. Any decision to treat must be made on the basis of a full risk-benefit analysis and particular care should be taken in patients on ECMO. There is currently no evidence to suggest a general prophylactic role. Any future work should focus not only on clarifying treatment protocols but also on patient safety, particularly, risk of morbid thromboembolic complications.

ACKNOWLEDGMENTS

O.W., A.D., R.G. and T.A. were responsible for the study design, data interpretation, manuscript drafting, and important intellectual content. P.R., O.W., and A.W. were responsible for the collection, extraction, and synthesis of data. T.A. and O.W. were responsible for statistical analysis. A.D., O.W., and R.G. were responsible for providing important intellectual content throughout the manuscript's production and for approval of the final version. K.L.d.W. and O.W. performed extensive revisions following peer review. T.A. is the guarantor. His involvement was critical to every phase of this work and he had access to the data and controlled the decision to publish. All authors read and approved the final manuscript.

REFERENCES

- Chambers LA, Cohen DM, Davis JT: Transfusion patterns in pediatric open heart surgery. *Transfusion* 1996; 36:150–154
- Petaja J, Lundstrom U, Leijala M, et al: Bleeding and use of blood products after heart operations in infants. *J Thorac Cardiovasc Surg* 1995; 109:524–529
- Paparella D, Brister SJ, Buchanan MR: Coagulation disorders of cardiopulmonary bypass: A review. *Intensive Care Med* 2004; 30: 1873–1881

- McEwan A: Aspects of bleeding after cardiac surgery in children. *Paediatr Anaesth* 2007; 17:1126–1133
- Kern FH, Morana NJ, Sears JJ, et al: Coagulation defects in neonates during cardiopulmonary bypass. *Ann Thorac Surg* 1992; 54: 541–546
- Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood. *Blood* 1992; 80:1998–2005
- Michelson AD: Platelet function in the newborn. *Semin Thromb Hemost* 1998; 24: 507–512
- Rajasekhar D, Barnard MR, Bednarek FJ, et al: Platelet hyporeactivity in very low birth weight neonates. *Thromb Haemost* 1997; 77: 1002–1007
- Lippi G, Franchini M, Montagnana M, et al: Coagulation testing in pediatric patients: The young are not just miniature adults. *Semin Thromb Hemost* 2007; 33:816–820
- Monagle P, Michelson AD, Bovill E, et al: Antithrombotic therapy in children. *Chest* 2001; 119:344S–370S
- Guzzetta NA, Miller BE, Todd K, et al: An evaluation of the effects of a standard heparin dose on thrombin inhibition during cardiopulmonary bypass in neonates. *Anesth Analg* 2005; 100:1276–1282, table of contents
- Odegard KC, Zurakowski D, Hornykewycz S, et al: Evaluation of the coagulation system in children with two-ventricle congenital heart disease. *Ann Thorac Surg* 2007; 83: 1797–1803
- Stanworth SJ, Bennett C: How to tackle bleeding and thrombosis in the newborn. *Early Hum Dev* 2008; 84:507–513
- Guay J: Invited commentary. *Ann Thorac Surg* 2007; 83:1803–1804
- Lippi G, Salvagno GL, Rugolotto S, et al: Routine coagulation tests in newborn and young infants. *J Thromb Thrombolysis* 2007; 24:153–155
- Richardson MW, Allen GA, Monahan PE: Thrombosis in children: Current perspective and distinct challenges. *Thromb Haemost* 2002; 88:900–911
- Williams GD, Bratton SL, Ramamoorthy C: Factors associated with blood loss and blood product transfusions: A multivariate analysis in children after open-heart surgery. *Anesth Analg* 1999; 89:57–64
- Williams GD, Bratton SL, Riley EC, et al: Association between age and blood loss in children undergoing open heart operations. *Ann Thorac Surg* 1998; 66:870–875; discussion 875–876
- Miller BE, Mochizuki T, Levy JH, et al: Predicting and treating coagulopathies after cardiopulmonary bypass in children. *Anesth Analg* 1997; 85:1196–1202
- Chan AK, Leaker M, Burrows FA, et al: Coagulation and fibrinolytic profile of paediatric patients undergoing cardiopulmonary bypass. *Thromb Haemost* 1997; 77:270–277
- Henriksson P, Varendh G, Lundstrom NR: Haemostatic defects in cyanotic congenital heart disease. *Br Heart J* 1979; 41:23–27

22. Tempe DK, Virmani S: Coagulation abnormalities in patients with cyanotic congenital heart disease. *J Cardiothorac Vasc Anesth* 2002; 16:752–765
23. <http://www.fda.gov/cber/products/novoseven.htm>. Accessed May 1, 2008
24. <http://www.emea.europa.eu/humandocs/Humans/EPAR/novoseven/novoseven.htm>. Accessed May 1, 2008
25. Hedner U, Glazer S, Pingel K, et al: Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988; 2:1193
26. Hedner U: Recombinant coagulation factor VIIa: From the concept to clinical application in hemophilia treatment in 2000. *Semin Thromb Hemost* 2000; 26:363–366
27. O'Connell KA, Wood JJ, Wise RP, et al: Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295:293–298
28. Mathew P: The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics. A systematic review. *Thromb Haemost* 2004; 92:738–746
29. Millar CG, Stringer MD, Sugarman I, et al: The use of recombinant factor VIIa for bleeding in paediatric practice. *Haemophilia* 2005; 11:171–174
30. Egan JR, Lammi A, Schell DN, et al: Recombinant activated factor VII in paediatric cardiac surgery. *Intensive Care Med* 2004; 30: 682–685
31. Uhrig L, Blanot S, Baugnon T, et al: Use of recombinant activated factor VII in intractable bleeding during pediatric neurosurgical procedures. *Pediatr Crit Care Med* 2007; 8:576–579
32. Roberts HR, Monroe DM, White GC: The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004; 104: 3858–3864
33. Warren O, Mandal K, Hadjianastassiou V, et al: Recombinant activated factor VII in cardiac surgery: A systematic review. *Ann Thorac Surg* 2007; 83:707–714
34. Lisman T, De Groot PG: Mechanism of action of recombinant factor VIIa. *J Thromb Haemost* 2003; 1:1138–1139
35. Tobias JD, Groeper K, Berkenbosch JW: Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. *South Med J* 2003; 96:12–16
36. Heller M, Lau W, Pazmino-Canizares J, et al: A comprehensive review of rFVIIa use in a tertiary care pediatric center. *Pediatr Blood Cancer* 2007; 50:1013–1017
37. Al Douri M, Shafi T, Al Khudairi D, et al: Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis* 2000; 11(Suppl 1):S121–S127
38. Aldouri M: The use of recombinant factor VIIa in controlling surgical bleeding in non-haemophilic patients. *Pathophysiol Haemost Thromb* 2002; 32(Suppl 1): 41–46
39. Isbister J, Phillips L, Dunkley S, et al: Recombinant activated factor VII in critical bleeding: Experience from the Australian and New Zealand Haemostasis Register. *Intern Med J* 2008; 38:156–165
40. Avci Z, Malbora B, Gokdemir M, et al: Successful use of recombinant factor VIIa (NovoSeven((R))) during cardiac surgery in a pediatric patient with congenital factor XI deficiency. *Pediatr Cardiol* 2008; 29:220–222
41. Brady KM, Easley RB, Tobias JD: Recombinant activated factor VII (rFVIIa) treatment in infants with hemorrhage. *Paediatr Anaesth* 2006; 16:1042–1046
42. Brose S, Sirbu H, Engel M, et al: Successful use of recombinant factor VIIa in a patient with intractable bleeding during extracorporeal membrane oxygenation. *Thorac Cardiovasc Surg* 2005; 53:389–390
43. Davis MC, Andersen NE, Johansson P, et al: Use of thromboelastograph and factor VII for the treatment of postoperative bleeding in a pediatric patient on ECMO after cardiac surgery. *J Extra Corpor Technol* 2006; 38: 165–167
44. Dominguez TE, Mitchell M, Friess SH, et al: Use of recombinant factor VIIa for refractory hemorrhage during extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2005; 6:348–351
45. Grizelj R, Vukovic J, Filipovic-Grcic B, et al: Successful use of recombinant activated FVII and aminocaproic acid in four neonates with life-threatening hemorrhage. *Blood Coagul Fibrinolysis* 2006; 17:413–415
46. Leibovitch L, Kenet G, Mazor K, et al: Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. *Pediatr Crit Care Med* 2003; 4:444–446
47. López-Herce Cid J, Arriola Pereda G, Zunzunegui Martínez JL, et al: [Effectiveness of activated factor VII in postoperative bleeding after cardiac surgery with extracorporeal membrane oxygenation]. *An Pediatr (Barc)* 2005; 62:471–474
48. Milano Manso G, Rodriguez Amuedo F, Aragones Manzanero R, et al: [Use of activated factor VII in severe acute hemorrhage]. *An Pediatr (Barc)* 2005; 62:467–470
49. Pychynska-Pokorska M, Moll JJ, Krajewski W, et al: The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. *Pediatr Crit Care Med* 2004; 5:246–250
50. Razon Y, Erez E, Vidne B, et al: Recombinant factor VIIa (NovoSeven) as a hemostatic agent after surgery for congenital heart disease. *Paediatr Anaesth* 2005; 15:235–240
51. Sheth S, Dimichele D, Lee M, et al: Heart transplant in a factor VIII-deficient patient with a high-titre inhibitor: Perioperative management using high-dose continuous infusion factor VIII and recombinant factor VIIa. *Haemophilia* 2001; 7:227–232
52. Skalski JH, Czaplak J, Nadziakiewicz P, et al: [New possibilities in the postoperative measures to prevent bleeding in cardiac surgery. Will the recombinant activated factor VII improve surgical results?] *Przegl Lek* 2002; 59: 941–945
53. Tobias JD, Berkenbosch JW, Russo P: Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Pediatr Crit Care Med* 2003; 4:49–51
54. Tofil NM, Winkler MK, Watts RG, et al: The use of recombinant factor VIIa in a patient with Noonan syndrome and life-threatening bleeding. *Pediatr Crit Care Med* 2005; 6:352–354
55. Tokunaga C, Hiramatsu Y, Horigome H, et al: Palliative open heart surgery in an infant with factor VII deficiency. *Ann Thorac Surg* 2003; 76:2093–2094
56. Veldman A, Hoffman M, Ehrenforth S: New insights into the coagulation system and implications for new therapeutic options with recombinant factor VIIa. *Curr Med Chem* 2003; 10:797–811
57. Velik-Salchner C, Sergi C, Fries D, et al: Use of recombinant factor VIIa (Novoseven) in combination with other coagulation products led to a thrombotic occlusion of the truncus brachiocephalicus in a neonate supported by extracorporeal membrane oxygenation. *Anesth Analg* 2005; 101:924
58. Verrijckt A, Proulx F, Morneau S, et al: Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2004; 127:1812–1813
59. Wittenstein B, Ng C, Ravn H, et al: Recombinant factor VII for severe bleeding during extracorporeal membrane oxygenation following open heart surgery. *Pediatr Crit Care Med* 2005; 6:473–476
60. Yilmaz BT, Alioglu B, Ozyurek E, et al: Successful use of recombinant factor VIIa (NovoSeven) during cardiac surgery in a pediatric patient with Glanzmann thrombasthenia. *Pediatr Cardiol* 2005; 26:843–845
61. Reiter PD, Valuck RJ, Taylor RS: Evaluation of off-label recombinant activated factor VII for multiple indications in children. *Clin Appl Thromb Hemost* 2007; 13:233–240
62. Tobias JD, Simsic JM, Weinstein S, et al: Recombinant factor VIIa to control excessive bleeding following surgery for congenital heart disease in pediatric patients. *J Intensive Care Med* 2004; 19:270–273
63. Agarwal HS, Bennett JE, Churchwell KB, et al: Recombinant factor seven therapy for postoperative bleeding in neonatal and pediatric cardiac surgery. *Ann Thorac Surg* 2007; 84:161–168
64. Ekert H, Brizard C, Eyers R, et al: Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: A randomized, double-blind, parallel group, placebo-controlled study of

- rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. *Blood Coagul Fibrinolysis* 2006; 17:389–395
65. Pugliese F, Ruberto F, Summonti D, et al: Activated recombinant factor VII in orthotopic liver transplantation. *Transplant Proc* 2007; 39:1883–1885
 66. 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; 71:402–405
 67. 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; 361:201–205
 68. Diprose P, Herbertson MJ, O'Shaughnessy D, et al: Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: Randomized double-blind placebo-controlled pilot study. *Br J Anaesth* 2005; 95:596–602
 69. Trowbridge CC, Stammers AH, Ciccarelli N, et al: Dose titration of recombinant factor VIIa using thromboelastograph monitoring in a child with hemophilia and high titer inhibitors to factor VIII: A case report and brief review. *J Extra Corpor Technol* 2006; 38:254–259
 70. Martinowitz U, Michaelson M: Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: A report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 2005; 3:640–648
 71. Seremetis S: Dose optimization of recombinant factor VIIa in the treatment of acute bleeding in haemophilia-associated inhibitors. *Blood Coagul Fibrinolysis* 2003; 14(Suppl 1):S29–S30
 72. Shapiro AD: Recombinant factor VIIa in the treatment of bleeding in hemophilic children with inhibitors. *Semin Thromb Hemost* 2000; 26:413–419
 73. Villar A, Aronis S, Morfini M, et al: Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. *Haemophilia* 2004; 10:352–359
 74. Levy JH, Fingerhut A, Brott T, et al: Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: Review of safety profile. *Transfusion* 2006; 46:919–933
 75. Warren OJ, Darzi AW, Athanasiou T: Recombinant activated factor VII in cardiac surgery—first, do no harm. *J Cardiothorac Surg* 2007; 2:50
 76. Swaminathan M, Shaw AD, Greenfield RA, et al: Fatal thrombosis after factor VII administration during extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth* 2008; 22:259–260
 77. Chalwin RP, Tiruvoipati R, Peek GJ: Fatal thrombosis with activated factor VII in a paediatric patient on extracorporeal membrane oxygenation. *Eur J Cardiothorac Surg* 2008; 34:685–686
 78. Riccabona M, Kuttinig-Haim M, Dacar D, et al: Venous thrombosis in and after extracorporeal membrane oxygenation: Detection and follow-up by color Doppler sonography. *Eur Radiol* 1997; 7:1383–1386
 79. Brown P, Brunnhuber K, Chalkidou K, et al: How to formulate research recommendations. *BMJ* 2006; 333:804–806
 80. Welsby IJ, Ortel TL: Invited commentary. *Ann Thorac Surg* 2007; 84:168–169
 81. Shander A, Goodnough LT, Ratko T, et al: Consensus recommendations for the off-label use of recombinant human factor VIIa (NovoSeven) therapy. *Pharmacy Therapeutics* 2005; 30:644–658
 82. Goodnough LT, Lublin DM, Zhang L, et al: Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; 44:1325–1331