

Systematic Review of Efficacy of rFVIIa and aPCC Treatment for Hemophilia Patients with Inhibitors

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ABSTRACT

Introduction: The primary treatment for mild-to-moderate bleeding disorders in hemophilia is either recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). The efficacy of both products has been evaluated in individual studies; however, there has not been an overall review to compare the efficacy from these individual studies of rFVIIa and aPCC. Our aim is to establish robust estimates of the efficacy, speed of bleed resolution, and adverse event profile of both rFVIIa and aPCC. **Methods:** A systematic review was conducted of the relevant literature. **Results:** We identified 11 open-label cohort studies, six randomized clinical trials, includ-

ing two head-to-head clinical trials, and a meta-analysis. The definition of efficacy varies between these studies, but is usually a composite measure of definite pain relief, reduction in the size of the hemorrhage, and cessation of bleeding. The individual making the interpretation of efficacy and the time from treatment initiation to recording the efficacy endpoint also varies across the studies. Overall, estimates of efficacy from randomized clinical trials using dosing regimens in line with the guidelines are higher for rFVIIa (81%–91%) than for aPCC (64%–80%). Conclusions from a meta-analysis suggest that treatment with rFVIIa may be associated with a faster time to joint bleed resolution than aPCC due to higher efficacy levels at different time points. The results from a comparative trial support the improved efficacy rates associated with rFVIIa compared with aPCC. **Conclusion:** The wide variations in definitions of efficacy and study methods make comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy.

Keywords: aPCC; efficacy; hemophilia; rFVIIa; systematic review

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INTRODUCTION

The management of mild-to-moderate bleeding episodes for hemophilia A or B patients with inhibitors to factor VIII is primarily undertaken by the administration of either recombinant activated factor VII (rFVIIa [NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark]) or a plasma-derived activated prothrombin complex concentrate (aPCC [FEIBA®; Baxter, Vienna, Austria]). The administration of rFVIIa and aPCC has been shown to be safe, and effectiveness of these agents in resolving a mild-to-moderate bleed has been reported in numerous studies; however, the quality of the available studies has not been evaluated. The level of effectiveness of these treatments is important both from the patient and the health-care payer perspectives. We conducted a systematic review of the literature to identify studies reporting the efficacy of aPCC and/or rFVIIa in resolving mild-to-moderate bleeds in hemophilia patients with inhibitors. The aim of this study was to establish robust estimates of the efficacy

of these two treatments, to address potential gaps in the evidence base, and to inform future study designs. In an attempt to address the issues most of interest to clinicians and patients, the results are presented in five areas or themes: efficacy assessment/cessation of bleeding; time to cessation of bleeding; dosage administered; adverse event (AEs); and reliability/accuracy of response.

MATERIALS AND METHODS

Search Strategy

We conducted a systematic literature review using MEDLINE (from 1990 to April 2008), EMBASE (from 1990 to April 2008), and the Cochrane Library (Issue 1, 2008), including the CENTRAL, CDSR, DARE, and HTA databases. In addition, we carried out both general internet searches (including Medscape, and web sites of medical journals, advocacy groups, and professional societies) and targeted searches of the relevant web sites listed in Table 1.

Table 1. Web sites consulted.

Organization name	URL address
World Federation of Hemophilia	www.wfh.org/index.asp?lang=EN
European Hematology Association	www.ehaweb.org
American Society of Hematology	www.hematology.org
British Society for Haematology	www.b-s-h.org.uk
International Society on Thrombosis and Haemostasis	www.med.unc.edu/isth
National Institute for Health and Clinical Excellence (NICE)	www.nice.org.uk
Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk
Trials Central	www.trialscentral.org
MedWatch	www.fda.gov/medwatch
Current Controlled Trials	www.controlled-trials.com
Medicines and Healthcare Products Regulatory Agency	www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=5
Australian Adverse Drug Reactions Bulletin	www.tga.gov.au/adr/aadrb.htm

All web sites accessed in June–July 2008.

A search was also performed to identify all well-conducted, existing systematic reviews so that the bibliographic references of these studies could be searched to identify any clinical studies that were not retrieved by the searches of the electronic databases. Searches of electronic databases used a combination of terms relating to hemophilia A or B, inhibitors, and interventions of interest (full search strategies are listed in the Appendix).

Selection of Eligible Studies

Two reviewers independently selected the relevant clinical studies by screening the titles

first and then the abstracts. For the selected references, the full-text articles were retrieved for final assessment. The inclusion criteria were based on study type, intervention, patient population, and outcome. The inclusion criteria are defined in Table 2.

RESULTS

Quantity of Available Evidence

The systematic search yielded 349 hits in MEDLINE, 528 in EMBASE, and 33 in the Cochrane Library. Of these 910 references, 264 were identified as duplicates and removed.

Table 2. Inclusion/exclusion criteria.

Criteria	Included	Excluded
Study type	<ul style="list-style-type: none"> • Clinical trials (randomized and nonrandomized) • Observational studies • Retrospective or prospective cohort analyses • Database/registry analyses • Surveys 	<ul style="list-style-type: none"> • Editorials • Commentaries • Case studies • Economic evaluations • Discussion papers • Letters
Patient population/type of bleed	<ul style="list-style-type: none"> • Patients of all ages with hemophilia A or B and inhibitors with acute bleeding 	<ul style="list-style-type: none"> • Patients with acquired hemophilia • Patients with other congenital bleeding disorders • Patients undergoing surgery or other related procedures • Serious bleeds
Interventions	<ul style="list-style-type: none"> • NovoSeven (rFVIIa) and FEIBA or FEIBA-VH (aPCC) 	<ul style="list-style-type: none"> • Any other
Outcomes	<ul style="list-style-type: none"> • Cessation of bleeding • Time to cessation of bleed • Dosage administered • Adverse events (thromboembolic events, immunogenicity) • Reliability of response, percentage of patients that re-bleed 	<ul style="list-style-type: none"> • Outcomes associated with laboratory investigations

Hand searches identified 11 studies. In order to reduce duplication the search for clinical trials was performed together with the search for economic models in hemophilia (studies identified by the latter search are reviewed separately). Among the results retrieved by the search for economic models, six were found relevant for the efficacy and safety review based on titles, and the abstracts of these six studies were included for further examination. A total of 401 studies were excluded at title screening, 206 studies were excluded at abstract screening, and 38 studies were excluded at full-text screening (Figure 1). A total of 18 studies were included in the review. Of these, six were randomized controlled trials, 11 were prospective or retrospective cohort studies, and one was a meta-analysis.

Data Extraction and Quality Assessment

The data from included studies were extracted independently by two reviewers using a predefined data extraction form.

There were six randomized controlled trials identified in the review: two direct head-to-head comparisons of aPCC and rFVIIa,^{1,2} three trials comparing different doses of rFVIIa,³⁻⁵ and one trial comparing aPCC with a non-activated prothrombin complex concentrate (PCC).⁶ The main trial details are outlined in Table 3. The number of patients who were treated within each study varied from 15 to 62 hemophilia patients with inhibitors; this provided between 48 and 150 bleeds within each study. In these trials, blinding was not always undertaken or possible due to different modes of administration. The main trial details for the 11 uncontrolled cohort studies, which tended to have a greater sample size, are shown in Table 4.⁷⁻¹⁷

Each study was reviewed with the intention of establishing estimates for both aPCC and

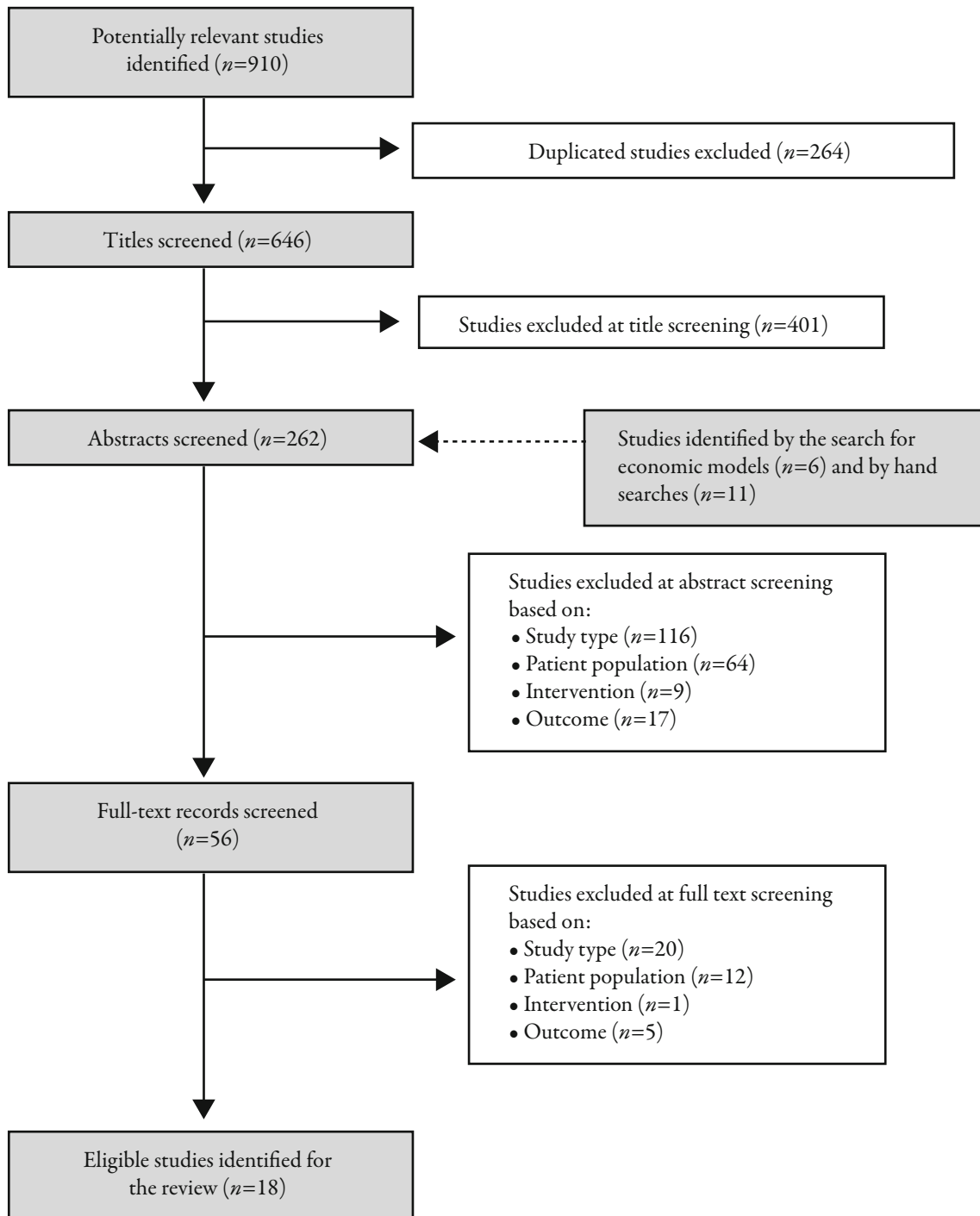
rFVIIa for each of the five areas:

- Efficacy assessment/cessation of bleeding
- Time to cessation of bleeding
- Dosage administered
- AEs
- Reliability/accuracy of response.

Efficacy Assessment/Cessation of Bleeding

The primary goal of hemostatic agents is to stop the current bleeding episode and alleviate the pain.¹⁸ While the definition of efficacy varies between the studies identified, efficacy was usually defined as a combination of definite relief of pain, reduction in the size of the hemorrhage, and cessation of bleeding.

Among the six randomized trials identified, three trials categorized efficacy as effective, partially effective, or not effective.^{1,3,6} In these trials, the difference between effective and partially effective was either related to the time taken to achieve the improvements or a measure of the degree of improvement. Evaluation of efficacy was undertaken by the patient/caregiver, the physician, or both. In the randomized trial by Lusher et al., efficacy was categorized as excellent, effective, partially effective, or not effective.³ Response was rated as excellent if at least one of the following clinical responses occurred within 8 hours following treatment initiation: a definite relief of pain, a measurable decrease in the size of the hemorrhage, or an arrest of bleeding. Again the difference between excellent, effective, and partially effective was related to the time taken to achieve the improvements. In the randomized trial by Kavakli et al., efficacy was reported using a unique global response tool based on reported pain and mobility scores.⁵ The Young et al.² trial employed two methods of evaluating efficacy: the first approach defined efficacy as percentage of patients achieving hemosta-

Figure 1. Inclusion/exclusion flow diagram.

sis without requiring use of rescue medication within 9 hours of first administration of product; the second used the unique global response tool reported by Kavakli et al.⁵

The FEIBA NovoSeven Comparative (FENOC) study comparing rFVIIa with aPCC reported similar effective or partially effective rates for the two treatments (78.7% and 84.4%

Table 3. Outcome of identified randomized clinical trials.

Study	Comparators	Population	Definition of effectiveness	Effective bleed resolution	Conclusions
Astermark et al. 2007 (FENOC) ¹	1×75-100 IU/kg rFVIIa every 3 h for 9 h vs. 1×270 µg/kg rFVIIa vs. 75 IU/kg aPCC	48 hemophilia A patients with inhibitors from 27 centers in Europe and N. America. Total of 96 bleeds assessed (48 pairs). Median total dose 85 IU/kg aPCC and 212.5 µg/kg rFVIIa.	Patient self-evaluates effectiveness as effective, partially effective, poorly effective, or not effective. Primary outcome was evaluation at 6 h. Time to bleed stopped defined as first time point at which participant thought bleed had stopped.	Effective or partially effective at 2 h, 6 h, and 12 h: aPCC: 75.0%, 80.9%, 80.0% rFVIIa: 60.4%, 78.7%, 84.4% Effective only (based on graphical results): aPCC: 33.3%, 53.2%, 58.7% rFVIIa: 33.3%, 48.9%, 52.2% Bleed stopped at 2 h, 6 h, and 12 h: aPCC: 53.2%, 76.1%, 77.8% rFVIIa: 38.3%, 65.2%, 75.6%	Results of 1×85 IU/kg aPCC and 2×105 µg/kg rFVIIa failed to show equivalence. Significantly more knee bleeds in the rFVIIa group. Efficacy includes bleeds rated both effective and partially effective. Effective-only rates were ascertained from graphical representation of the data.
Young et al. 2008 ²	90 µg/kg rFVIIa every 3 h for 9 h vs. 1×270 µg/kg rFVIIa vs. 75 IU/kg aPCC	27 hemophilia A or B patients with inhibitors randomized to receive 270 µg/kg rFVIIa at time 0 followed by placebo at hours 3 and 6; 90 µg/kg rFVIIa at time 0, 3 and 6; or 75 IU/kg aPCC at time 0.	Independent, external, blinded physicians evaluated efficacy. Primary efficacy measured as percentage of patients achieving hemostasis without use of rescue medication within 9 h of administration. Secondary, a subjective global treatment response algorithm (same as Kavakli et al. 2006 ⁵).	Percentage of bleeds not needing rescue medication at 9 h: 3×90 µg/kg rFVIIa: 90.9% 1×270 µg/kg rFVIIa: 91.7% 1×75 IU/kg aPCC: 63.6% Secondary at 9 h: 3×90 µg/kg rFVIIa: 54.5% 1×270 µg/kg rFVIIa: 37.5% 1×75 IU/kg aPCC: 27.3%	For the primary measure of efficacy, percentage of bleeds requiring additional hemostatic medication was significantly higher for the aPCC group than the 1×270 µg/kg rFVIIa group ($P=0.03$). Comparing the 3×90 µg/kg rFVIIa group and the aPCC group, the efficacy difference approached significance ($P=0.069$). In conclusion, a single 270 µg/kg dose of rFVIIa is safe and as effective as 3×90 µg/kg rFVIIa, and significantly reduces the need for rescue medication compared with aPCC.

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Table 3. (continued)

Study	Comparators	Population	Definition of effectiveness	Effective bleed resolution	Conclusions
Lusher et al. 1998 ³	35 µg/kg rFVIIa vs. 70 µg/kg rFVIIa	From a total of 78 patients from 20 sites with hemophilia A or B, 66 patients had inhibitors. Results presented for inhibitors only. Bleeds treated at treatment center. 37 bleeding episodes with inhibitors treated with 35 µg/kg and 62 with inhibitors treated with 70 µg/kg rFVIIa. Mean doses 3.1×70 µg/kg, 2.7×35 µg/kg.	Excellent response: One or more within 8 h of: (a) definite relief of pain/tenderness; (b) measurable decrease in size of hemorrhage; (c) arrest of bleeding. Effective: as above but between 8 h and 14 h. Partial: as above after 14 h or bleed slowed, else ineffective.	Excellent or effective at 14 h: 35 µg/kg: 78% 70 µg/kg: 68% Partially effective: 35 µg/kg: 19% 70 µg/kg: 19%	The two dose groups were clinically and statistically equivalent although for muscle bleeds the 70 µg/kg group achieved higher responses. Delay in receiving treatment (median >8 h) as patients had to travel to treatment center thus would affect response rates.
Santagostino et al. 2006 ⁴	90 µg/kg rFVIIa every 3 h vs. high-dose 270 µg/kg rFVIIa	Hemophilia A or B with inhibitors. 20 patients with 68 hemarthroses randomly assigned to either 90 µg/kg rFVIIa every 3 h for 9 h, or 270 µg/kg.	Response assessed by patients/caregivers for up to 48 h grading improvement of symptoms on a VAS scale. Rating response as effective, partially effective, or ineffective.	At 9 h: 3×90 µg/kg: 31% effective. 59% partially effective. 1×270 µg/kg: 25% effective. 56% partially effective	The two dose groups were clinically and statistically equivalent. However, bleed resolution results were lower than expected, which was probably due to 71% of bleeds being in target joints.
Kavakli et al. 2006 ⁵	90 µg/kg rFVIIa every 3 h for 9 h vs. high-dose 1×270 µg/kg rFVIIa	20 hemophilia A or B patients with inhibitors from 6 countries aged 6-60 (mean 28) y. 21 bleeds in each treatment arm.	Unique global response tool (combination of mobility and pain). Same as Young et al. 2008. ² Secondary measure: bleed controlled without additional hemostatic agents.	At 9 h: Primary: 3×90 µg/kg: 65%, 1×270 µg/kg: 70% Secondary: 3×90 µg/kg: 85.7%, 1×270 µg/kg: 90.5%	1×270 µg/kg as effective as 3×90 µg/kg. Small study (20 patients). No information on patients who may have responded to only one or two doses of 90 µg/kg.
Sjamsodin et al. 1981 ⁶	PCC vs. aPCC	15 hemophilia A and inhibitors with 150 bleeds. Dosage 88 IU/kg.	At 24 h, patient and physician rated bleed as effective, partially effective, ineffective, or not sure	Effective or partially effective at 24 h: aPCC: 66% patient, 64% physician PCC: 46% patient, 52% physician	aPCC as efficacious as PCC. Pairwise comparison shows aPCC significantly more effective than PCC.

(a) PCC=(activated) prothrombin complex concentrate; rFVIIa=recombinant activated factor VII; VAS=visual analog scale.

Table 4. Outcome of open-label studies.

Study	Population	Dosage	Result
aPCC (FEIBA)			
Hilgartner & Knatterud 1983 ⁷	49 hemophilia A or B patients, 165 bleeds.	50 IU/kg repeated twice at 12 h intervals.	At 12 h (1 infusion): 36% controlled At 36 h (>1 infusion): 78% controlled At 72 h (>1 infusion): 93% controlled
Hilgartner et al. 1990 ⁸	41 hemophilia A or B patients, 106 bleeds.	75 IU/kg repeated twice at 12 h intervals.	At 12 h (1 infusion): 52% controlled At 36 h (>1 infusion): 78% controlled Total controlled: 88% (72 h)
DiMichele & Negrier 2006 ⁹	49 hemophilia A or B patients, 163 bleeds. 119 home treated, 105 joint bleeds.	Median 72 IU/kg per dose. Median total dose for responders 155 IU/kg.	Efficacy rate good or excellent in 82% of episodes. 1 infusion: 21% controlled 2 infusions: 37% controlled 3 infusions: 48% controlled 65% total acute bleeds controlled, 27% slowed, 8% not controlled
Negrier et al. 1997 ¹⁰	60 hemophilia patients, 433 bleeds of which 30 surgical.	Intermittent boluses of 65 to 100 U/kg at intervals of 6 to 12 h. 65-510 U/kg/day.	Efficacy rate excellent or effective in 81.3% of episodes. Joint bleeds controlled: 1 infusion: 50.7% controlled 2 infusions: 81.9% controlled 3 infusions: 89.3% controlled
Negrier 1998 (abstract) ¹¹	10 hemophilia A patients, 134 bleeds over 3 y.	Mean 74 IU/kg per dose.	Efficacy rate good or excellent in 96% of episodes.
rFVIIa			
Key et al. 1998 ¹²	52 severe hemophilia A or B patients, 614 bleeds treated at home.	90 µg/kg every 3 h + 1 maintenance dose: mean number of doses = 2.2 + maintenance.	Hemostasis achieved in 92% of evaluated bleeds. 1×90 µg/kg: 29% 2×90 µg/kg: 53% 3×90 µg/kg: 92%
Shirahata et al. 2001 ¹³	10 hemophilia A or B patients, 157 evaluated bleeds.	Initial dose 90 µg/kg (individually adjusted to 60-120 µg/kg, mean 96.5 µg/kg). Mean 5.3 doses per bleed. Mean total dose 510 µg/kg.	All bleeds: Excellent: 31.2% Effective: 26.8% Partially effective: 38.9% Ineffective: 3.2%

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for rFVIIa, and 80.9% and 80.0% for aPCC at 6 and 12 hours, respectively).¹ However, the Young et al. head-to-head trial reported differences between treatment with the two rFVIIa

regimens and treatment with aPCC.² The percentage of patients not requiring additional hemostatic medication in the aPCC group was 63.6%, which was significantly less than

Table 4. (continued)

Study	Population	Dosage	Result
rFVIIa			
Parameswaran et al. 2005 ¹⁴	38 patients generated 555 bleeds from registry data. 45% spontaneous, 38% traumatic, 27% surgery. 80% at home. Effect and efficacy reported for dose ranges (<100, 100-150, 150-200, and >200 µg/kg). Efficacy defined as complete hemostatic control.	Median dose over 72 h: 360 µg/kg (mean 537 µg/kg). Mean number of doses administered in each groups was 4.3, 5.2, 3.4, and 2.3.	At 72 h: efficacy, bleed stopped: <100 µg/kg: 82%, 84.9% 100-150 µg/kg: 88%, 84.4% 150-200 µg/kg: 87%, 83.8% >200 µg/kg: 98%, 96.6%
Bech 1996 ¹⁵	111 hemophilia A or B patients (89 with inhibitors), 494 bleeds (423 inhibitors).	60-120 µg/kg initially then 90 µg/kg every 2 h. Average number of doses was 11.2, 13.6, and 64.8 for joint, muscle, and compartment syndrome, respectively.	End of treatment: Joint: effective 79%, partially effective 20% Muscle: effective 62%, partially effective 29% Compartment syndrome: effective 79%, partially effective 20%
Laurian et al. 1998 ¹⁶	202 bleeds from 21 hemophilia A or B patients. 11% severe.	90 µg/kg every 2 h until clinical improvement; subsequent doses every 3-12 h.	Excellent or effective in 90% of hemarthrosis, 80% of hematomas, and 79% of other bleeds. Hemostasis achieved in 74% of bleeds within 8 h of first injection.
Santagostino et al. 1999 ¹⁷	10 hemophilia patients with inhibitors (1 acquired). 45 hemarthroses and 8 hematomas.	90 µg/kg up to 4 doses every 3±1 h. For effective treatments average 1.5 doses vs. 3.0 for partially and ineffective.	Effective 79%, partially effective 11%. Effective treatments initiated earlier (median: 0.6 h vs. 2.7 h) compared to partially effective and ineffective.

aPCC=activated prothrombin complex concentrate; rFVIIa=recombinant activated factor VII.

the 270 µg/kg rFVIIa group (91.7%, $P=0.032$), and also less than the 3×90 µg/kg rFVIIa group (90.9%), which approached but did not reach significance ($P=0.069$). In the remaining studies reporting efficacy of rFVIIa, rates of efficacy reported as effective or partially effective ranged between 65% and 91%.³⁻⁵ In the trial comparing efficacy of aPCC and PCC,⁶ the efficacy rate of aPCC at 24 hours was 64%, much lower than the 80.9% at 6 hours reported in the FENOC study.¹

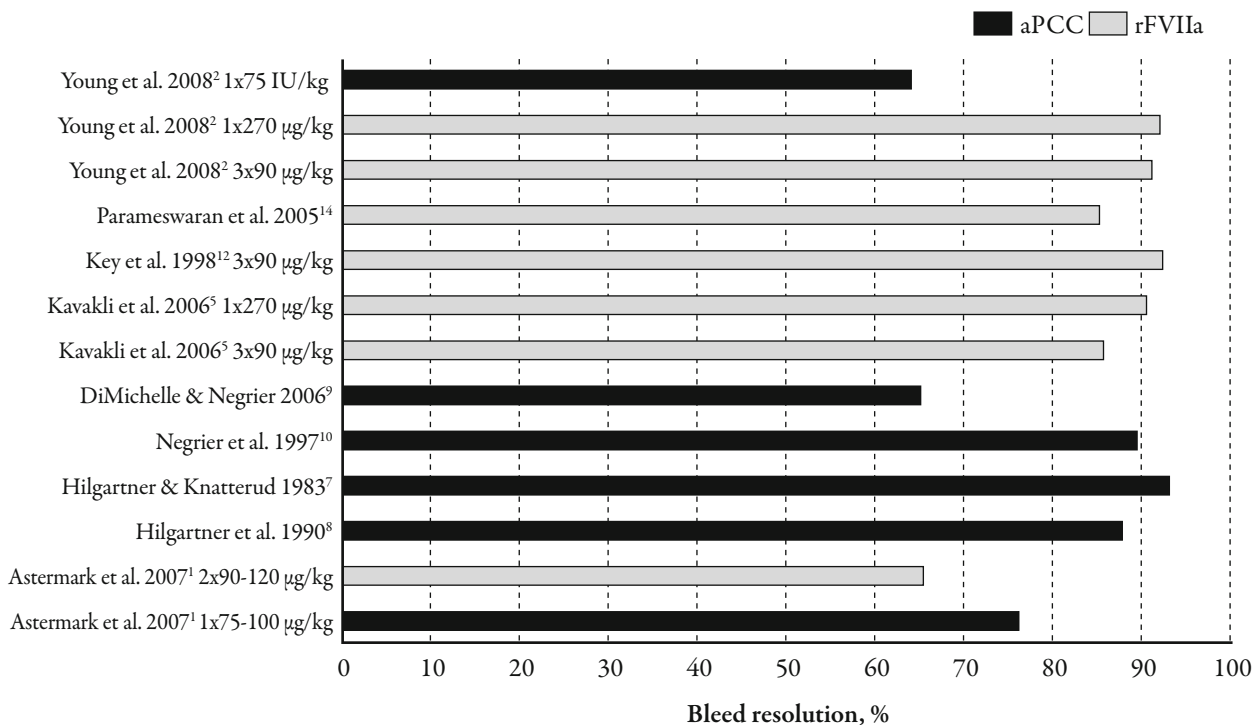
Among the 11 observational studies identified, seven studies categorized efficacy as excellent, effective/good, or partially effective. Three of these studies examined efficacy of aPCC and reported rates as excellent or effective/good in 81%-96% of patients.⁹⁻¹¹ Four of these studies examined efficacy of rFVIIa and reported rates as excellent or effective/good in 58%-90% of patients.^{13,15-17} The study by Shirahata et al. reported rFVIIa treatment being excellent or effective in 58% of patients and partially effective

tive in 38.9% of patients.¹³ However, they found that the interval between rFVIIa administrations varied depending on the clinical response, and the efficacy rate was 90% for bleeds that administered rFVIIa within every 3 hours.

Some studies also report the bleed stopped/controlled rates as a secondary outcome. Figure 2 shows the bleed controlled rates for the nine identified studies where it was reported. The FENOC study reported 76.1% of bleeds treated with aPCC and 65.2% of bleeds treated with rFVIIa were controlled/stopped within 6 hours after treatment initiation.¹ The other four studies examining bleed controlled/stopped rates with rFVIIa reported rates of 85% and above.^{2,5,12,14} Three of the other four studies examining bleed controlled/stopped rates with aPCC reported rates in excess of 88%.^{7,8,10} The exceptions to this were the study by Young et

al., which reported a low bleed-controlled rate of around 64%,² and the study by DiMichele and Negrier, which reported a bleed controlled/stopped rate of 65%.⁹ This is in contrast to the overall efficacy rates reported in this study: 82% of bleeds were rated as excellent or effectively treated.⁹ Due to the different definitions of efficacy between trials, it is difficult to compare rates. The FENOC trial, designed to test equivalence of the two products (ie, the degree to which they provide equivalent clinical efficacy), is currently one of two published trials that directly compares aPCC and rFVIIa.¹ The overall results from this study showed that at no time point was the criterion for declaring the two products equivalent met. The other trial that directly compares aPCC and rFVIIa is the Young et al. study.² These two trials cannot be directly compared due to the differences in

Figure 2. Bleed controlled/stopped rates from all studies. Note: Parameswaran et al.¹⁴ rates shown are from bleeds treated with <100 µg/kg doses of rFVIIa. aPCC=activated prothrombin complex concentrate; rFVIIa=recombinant activated factor VII.



the study design and efficacy endpoints. The Young study was designed to compare the efficacy of a single high dose of rFVIIa versus three lower doses of rFVIIa and versus aPCC, and was not designed to show equivalence across the three treatment regimens.²

The work by Kavakli et al. echoes the importance of eliminating the differences between studies regarding how hemostasis effectiveness is measured.⁵ They developed a global response scoring system, devised based on patient self-assessment (Table 5). The global treatment response score was based on patient self-assessment of pain and mobility at each of the four time periods, giving eight total scores (one for pain, and one for mobility, at each of four time points tested). The global response to treatment was defined as effective if the patient gave six or more positive scores for each bleed. Using the global treatment response tool, 65% (13/20) of patients scored the 1×270 µg/kg rFVIIa dose regimen as effective compared to 70% (14/20) of patients who scored the 3×90 µg/kg rFVIIa dosage

regimen as effective. Although these efficacy rates for rFVIIa could be viewed as low when compared with other rFVIIa studies,^{4,12,14} a subanalysis of the data from this trial showed that around 90% of bleeds were controlled with a single dose of 270 µg/kg rFVIIa and 86% of bleeds were controlled with the 3×90 µg/kg rFVIIa regimen.⁵ The Young et al. trial—which also employed the same global response tool—reported low successful response rates of 37.5%, 54.5%, and 27.3% for treatment with 1×270 µg/kg rFVIIa, 3×90 µg/kg rFVIIa, and 1×75 IU/kg aPCC, respectively, compared with its primary efficacy measure.² It could be argued that this unique global response measure has a more strict definition of a clinical response than the other trials and thus has resulted in the lower efficacy rates reported relative to the high bleed-controlled rates. The global response tool has not been formally validated and, with some bleeds being defined as unsuccessful despite not requiring additional hemostatic medication, it could be argued that this algorithm is not as robust as initially thought.

Table 5. Global response scoring system.

Time after first injection	Pain			Mobility		
	More	No difference	Less	More	No difference	Less
1 hour	N	P	P	P	P	N
3 hours	N	P	P	P	P	N
6 hours	N	N	P	P	N	N
9 hours	N	N	P	P	N	N

For the primary analysis pain was defined as negative if pain had increased (“more”) at any of the time points or not changed (“no difference”) after 6 or 9 hours. Pain received a positive score when assessed as “less” at any of the time points, or when assessed as “no difference” after 1 or 3 hours. Mobility was defined as positive when “more” mobility was observed at any of the time points, or when it was characterized as no difference after 1 or 3 hours. Mobility received a negative score when assessed as “less” at any time point, or when as “no difference” after 6 or 9 hours. The global response to treatment was defined as effective if the patient gave six or more positive scores for each bleed, and ineffective if the patient gave less than six positive scores for each bleed.

N=negative; P=positive; <6P=global treatment ineffective.

Taken from: Kavakli K, et al. Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors. *Thromb Haemost.* 2006;95:600–605.

The meta-analysis by Treur et al., which is currently only a conference abstract, reports the results from a Bayesian meta-regression following a systematic review of the efficacy of rFVIIa and aPCC.¹⁹ Almost 2000 joint bleeds were included in the Bayesian model, the results of which estimated the efficacy of rFVIIa as 75%, 94%, and 98% at 12, 24, and 36 hours, respectively. In contrast, the model estimated for aPCC that only 36%, 63%, and 78% of bleeds would have been treated effectively after 12, 24, and 36 hours, respectively.

Time to Cessation of Bleeding

The time taken to stop a bleeding episode is very important to the patient as it reduces the time a patient is in pain, the amount of hemostatic agent required, the potential long-term damage to the joint, and the subsequent cost of undergoing a joint arthroplasty.²⁰

Comparing the response times in achieving hemostasis reported in various trials reveals a comprehensive story except for the FENOC study.^{1,2,7,8,12} Excluding the FENOC trial data,¹ the rFVIIa and aPCC data from the cohort studies suggest that bleeds would be more quickly resolved if treated with rFVIIa rather than with aPCC: in excess of 90% for rFVIIa at 9 hours and between 36% and 52% for aPCC. This is also the finding of the Treur et al. meta-analysis, which calculates that 75% of bleeds treated with rFVIIa would be resolved by 12 hours as opposed to only 36% of bleeds treated with aPCC.¹⁹ However, in the FENOC trial the percentages reporting that bleeding had stopped were similar for both aPCC and rFVIIa over time. For aPCC the bleed resolved rate was significantly shorter than seen in other studies measuring the response times for aPCC. The bleed resolved rate for aPCC was 53.2% within the ≤ 3 -hour time point, 76.1%

by the ≤ 6 -hour time point, and by the 12-hour time point was almost twice as high as the rates reported by both Hilgartner papers.^{7,8} The Young et al. study reports hemostasis achieved in 63.6% of bleeds treated with aPCC within 9 hours.² Although this is again high compared to both Hilgartner papers it is lower than that reported in the FENOC trial.^{7,8} The rFVIIa bleed resolved rate from the FENOC study is also high in comparison with the study by Key et al. at the 6-hour mark although not to the same degree.¹² The rFVIIa bleed resolved rate from the FENOC study is lower by the 12-hour time point, which would be due in part to only having two doses of 90 $\mu\text{g}/\text{kg}$ rFVIIa administered as opposed to the three doses as per Food and Drug Administration (FDA)-approved label.²¹ There is no efficacy rate reported for the 270 $\mu\text{g}/\text{kg}$ rFVIIa dose before 9 hours due to the nature of the studies. However, a proportion of the 90.5% and 91.7% bleed controlled rates reported by Kavakli et al.⁵ and Young et al.² may have been resolved before the 9-hour time period was reached. If the speed to bleed resolution of the 270 $\mu\text{g}/\text{kg}$ dose of rFVIIa was indeed considerably greater than that reported by the lower dosage regimen of rFVIIa and by aPCC, then this could have considerable effect on alleviating pain quicker and reducing the potential long-term joint damage.

Dosage Administered

The amount of rFVIIa and aPCC administered may have an effect on the efficacy rates. Parameswaran et al. conducted a study using the Hemophilia and Thrombosis Research Society Registry and looking at the effect the amount of rFVIIa dose had on efficacy in hemophilia patients with inhibitors.¹⁴ Bleeding episodes were grouped by bolus dos-

age range: <100, 100-150, 150-200, and >200 µg/kg. Efficacy reported after 72 hours from treatment initiation showed that the bleeding cessation rate was around 84% for each of the three lower dose groups and 97% for the highest dose group.

Although an optimal dosing schedule remains to be determined, labeling suggests that the dosing schedule for rFVIIa should be either 90 µg/kg every 2 hours or 1×270 µg/kg.²¹ For aPCC, guidelines recommend 50-100 IU/kg every 6-12 hours, depending on bleed type and severity.¹⁸ The dosing schedule for aPCC, where reported, varied between 50 and 100 IU/kg, with the average dose per infusion around 75 IU/kg for up to three infusions—in line with the recommended dosing regimens (Table 3 and 4).

Most of the clinical trials of rFVIIa reported dosing regimens in line with guidelines. The only exceptions were the dose-finding trial (pre-FDA approval) by Lusher et al.,³ which used rFVIIa regimens of 35 µg/kg and 70 µg/kg every 2.5 hours (lower doses than those suggested by the rFVIIa labeling information) and the FENOC study. The FENOC study only allowed 2×90-120 µg/kg rFVIIa to be administered and thus the efficacy rates reported at 9 and 12 hours for rFVIIa would be expected to be lower than if the third 90 µg/kg dose had been given.¹

Since the dosing regimens reported in the randomized trials for aPCC and rFVIIa and in many of the cohort studies are based on the dosing schedules reported in the guidelines, we can assume that the efficacy rates reported from these studies are a fair reflection of the efficacy rates for the recognized dosing schedules. Therefore, comparisons of these efficacy rates can be assumed to be fair comparisons that would reflect clinical practice.

Adverse Events

Not all studies reported AEs. Among the studies that did report AEs, the only significant AE reported was anamnestic responses, which were identified in aPCC studies.^{7,10} This was expected, as patients with factor VIII inhibitors who are exposed to a product containing a small amount of factor VIII can experience an anamnestic response in terms of an increase in the inhibitor level. Negrier et al. reported that 31.5% of patients experienced an anamnestic response defined as the inhibitor level increasing by more than 50%.¹⁰ However, following further administrations of aPCC, the titer level gradually fell in 65% of patients. Hilgartner and Knatterud reported that 10 patients (22%) had a significant rise in titer level (>10 Bethesda units) without an effect on the efficacy.⁷ The rise in the inhibitor titer level does not appear to affect the ability to resolve the bleed for patients treated with aPCC, but could have a significant impact on patients undergoing immune tolerance induction (ITI) to eradicate the inhibitors. Titer level is related to an increase in the duration of ITI and to a decrease in the probability of success for ITI therapy.^{22,23}

In the studies that reported AEs other than anamnestic response, rates of these AEs were very small (<5%).^{1,2,7-10,12-14} Serious AEs such as thromboembolic events were reported in <0.5% of patients. Most AEs were mild in severity, and included headaches, slight increase in blood pressure, and rashes at the injection/infusion site. There were no significant differences in the AE rates between products.

Reliability/Accuracy of Response

The difference in how efficacy is measured and how it could affect the accuracy of response

has already been addressed. The reliability or robustness of each study is another important aspect in determining the credibility of the efficacy response rates.

The FENOC and the Young et al. studies are currently the only direct comparisons of rFVIIa and aPCC in hemophilia patients with inhibitors.^{1,2} The Young et al. study was a randomized, multicenter, crossover, double-blind study to evaluate the efficacy and safety of rFVIIa, using two different blinded dosing schedules, and an open-label aPCC, in deriving hemostasis in joint bleeds within a home setting.² Twenty-seven patients out of 42 randomized were treated; 24 patients were exposed to a single 270 µg/kg rFVIIa dose at hour 0 and received placebo at hours 3 and 6; 22 patients were exposed to the standard 90 µg/kg dose of rFVIIa given at hours 0, 3, and 6; 22 patients were exposed to a single 75 IU/kg dose of aPCC at hour 0. Twenty-one patients completed all three arms of the study.

The primary outcome was the percentage of patients who required additional hemostatic medication 9 hours after initiation of treatment. A significantly lower percentage of patients in the 270 µg/kg rFVIIa treatment group required rescue medication compared with the aPCC treatment group. It was a similar story for the 3×90 µg/kg rFVIIa group although the difference was nonsignificant. The authors highlight that both rFVIIa treatment groups had similar use of rescue medication but theorize that patients who have undergone three infusions in 6 hours may be reluctant to receive further medication. However, they counter this by suggesting that patients in either of the rFVIIa treatment arms may suspect that they have been administered a placebo so would desire further medication. Other potential bias is suggested from three patients who endured three bleeds into the

same target joint in a period of 2 months. For each patient treatment for the third bleed was with aPCC when joint responsiveness may be considered to be at its lowest. However, the data suggest that treating a third target joint bleed with aPCC did not bias the primary outcome measure in favor of rFVIIa as none of these three patients received rescue medication. The limitations of the study relate to the small sample size, which reduced the statistical power and the global response tool, that although was intended to reduce subjectivity, had not been formally validated.

Overall it is a well-designed study that compares appropriate treatment regimens of rFVIIa with an appropriate aPCC treatment. The authors acknowledge potential biases and limitations, yet the conclusions suggesting that efficacy of 270 µg/kg rFVIIa and 3×90 µg/kg rFVIIa are equivalent, and that rFVIIa treatment is potentially more effective than 75 IU/kg aPCC, appear valid.²

The FENOC study was designed to demonstrate equivalence between one dose of aPCC (75-100 IU/kg) and a regimen of rFVIIa 2×90-120 µg/kg.¹ The patients self-evaluated the treatment effectiveness by deciding whether each treatment was effective, partially effective, poorly effective, or not effective. There was no blinding in the study due to the differences in administration of the products. Lack of blinded treatment could be considered a source of bias, particularly due to the subjective rating structure. The criteria for equivalence, defined as ≤15% difference in the confidence intervals of the proportion of patients who reported that bleed as being treated effectively or partially effective within 6 hours of treatment initiation, was not met. Additionally, with only 48 patients and 96 bleeds, this trial may have been underpowered to show equivalence.

The primary outcome of the FENOC study was the hemostatic effect at 6 hours following treatment. The results at 6 hours showed that 80.9% and 78.7% of bleeds were rated as effective or partially effective for aPCC and rFVIIa, respectively. The study reported results at 2 hours before the second administration of rFVIIa, which clearly puts rFVIIa at a disadvantage with the objective being to compare 2×90-120 µg/kg rFVIIa with 75-100 IU/kg aPCC. The efficacy results reported at 2 hours were higher for aPCC than for rFVIIa, counting partially effective and effective but identical (33%) if only considering effectively treated bleeds. By 6 and 12 hours, the reported efficacy rates were numerically similar between groups, but failed to demonstrate equivalence between agents (Table 3). This pattern is repeated for the proportion of patients reporting the bleed had stopped at 2, 6, and 12 hours.

A second concern with the FENOC trial is the distribution of study joints between the treatments. For rFVIIa, 58.4% of bleeds occurred in the knee compared to only 31.3% for aPCC. The authors acknowledge this, but state that patient rating of efficacy of knee treatments were similar in both groups and that knee bleeding was not related to efficacy at any of the time points. It is generally accepted that bleeds in the knee are more difficult to treat due to the weight-bearing nature of the knee joint. Additionally, immobilizing an elbow is much easier than immobilizing a knee.

The bleed cessation rate reported in the FENOC trial for aPCC of 53.2% at 2 hours and 77.8% at 12 hours for one infusion is higher than reported by any other aPCC trial or cohort study for one infusion in these time periods (Table 3 and 4). The next highest value is reported by Hilgartner et al.,⁸ who reported

52% of bleeds controlled at 12 hours. The lowest value reported was 21%.⁹ Given these variations in results, the reliability of efficacy of aPCC would need to be explored in further randomized controlled trials.

The current dosing schedule of rFVIIa is either a single dose of 270 µg/kg or 3×90 µg/kg (total 270 µg/kg) and aPCC is 75-100 IU/kg every 12 hours. It could be argued that the rFVIIa treatment in the FENOC head-to-head trial should have considered three doses and not just two to more closely reflect clinical practice. While the authors of the FENOC study conclude that both aPCC and rFVIIa exhibit similar effects on joint bleeds, the efficacy between products is rated differently, especially in the first 12 hours. The authors suggest that efficacy results in the first 12 hours suggest that aPCC may be the preferred product. However, since the FENOC study was designed to test equivalence of the products, and the criteria were not met at any time point, any statement regarding differences favoring one product over the other is inappropriate.

Despite these non-neglectable study design limitations, the FENOC study is still an important study and due to the difference in results from the other head-to-head trial further highlights the need for more head-to-head trials between aPCC and rFVIIa in treating bleeding episodes for patients with hemophilia with inhibitors.

The double-blind trial reported by Sjamsoedin et al. investigated the effect of aPCC on joint and muscle bleeding compared with PCC in hospitalized patients.⁶ The results show that aPCC was judged to be more effective than PCC by both the physician and patient and by pairwise comparison of bleeds into the same joint or muscle (Table 3). The study had effective blinding, and both patient and clini-

cian-reported outcomes; however, this study reported considerably lower efficacy rates than the FENOC study.

The three randomized clinical trials comparing different doses of rFVIIa employed different methods in defining efficacy.³⁻⁵ Lusher et al. compared 35 µg/kg and 70 µg/kg rFVIIa, and efficacy was determined by clinical opinion and incorporated pain relief, arrest of bleeding, and decreases in hemorrhage size.³ The Santagostino et al. non-inferiority trial comparing a 3×90 µg/kg dosing regimen with a 1×270 µg/kg dose of rFVIIa used a visual analog scale completed by patients and caregivers to assess whether treatment for the bleed had been effective, partially effective, or ineffective.⁴ The Kavakli et al. double-blind trial developed a unique global response tool to evaluate efficacy for bleeds treated with either 3×90 µg/kg or 1×270 µg/kg rFVIIa.⁵ The blinding undertaken in this study adds robustness to the results despite the small number of patients in the trial. There is no obvious lack of quality nor any reliability issues to raise regarding these three trials.

The quality of the open-label cohort studies identified in Table 4 is difficult to assess. Like all cohort retrospective studies, they are open to the charge of bias due to there being no control. With both the patients and investigators knowing the treatment they are receiving the patients may psychologically react in favor of the treatment.²⁴

The meta-analysis undertaken by Treur et al. suggests that treatment with 90 µg/kg rFVIIa every 3 hours may be associated with a faster time to joint bleed resolution than 1×75 IU/kg aPCC every 12 hours.¹⁹ It is difficult to evaluate due to the fact these data are currently only available as a poster. This is the first indirect comparison of rFVIIa and aPCC efficacy rates that has been undertaken. If

the results of this analysis can be substantiated then it would suggest that the efficacy of rFVIIa may be significantly greater than aPCC, which could have a major impact on future role of each product in the treatment of hemophilia patients with inhibitors.

DISCUSSION

This review has identified 18 studies evaluating the efficacy of rFVIIa and/or aPCC. The efficacy rates reported from the randomized trials are around 64%-80% for aPCC (50-85 IU/kg) and 81%-91% for rFVIIa (90 µg/kg every 2-3 hours or 1×270 µg/kg) 12 hours after treatment initiation. This level of efficacy is also reported in the nonrandomized literature with around 65%-88% of bleeds controlled for aPCC (50-100 IU/kg at 12-hour intervals) and around 90% for rFVIIa treatment. The efficacy, defined as treatment reported as effective or partially effective, appears higher for rFVIIa than for aPCC. However, without a universally accepted definition of hemostatic response or efficacy measure, comparison between studies is difficult. There are currently two direct comparative studies between rFVIIa and aPCC. The FENOC study, which has quality issues and did not include a standard treatment regimen for rFVIIa, failed to show that 75-100 IU/kg aPCC was equivalent to 2×90-120 µg/kg rFVIIa.¹ While the Young et al. study, which seems more robust as it evaluates approved treatment regimens, suggests that treatment of bleeding episodes with rFVIIa has a higher efficacy than treatment with aPCC.² The results of these two studies highlight the need for more direct comparative trials.

One of the big issues for patients and health service payers is the speed to bleed resolution due to the reduced time patients are in pain and potential savings in cost. The single dose of

270 µg/kg of rFVIIa, which has been shown to be as effective as the 3×90 µg/kg rFVIIa regimen, may reduce the time to bleed cessation.²⁻⁵

With only two direct comparative studies, patient preference of the hemostatic agents was not addressed and neither regimen showed any obvious preference between the single dose of 270 µg/kg rFVIIa or the 3×90 µg/kg rFVIIa regimen in terms of efficacy rates.^{3,5,6}

As hemophilia has been shown to have a negative impact on quality of life, a health-related quality of life assessment, which is also lacking in any of the studies, would be a good instrument in possibly differentiating between the two treatments and providing insight into how the different mechanisms of action employed by the treatments affect patient wellbeing.²⁵

Since the introduction of a vapor-heated formulation of aPCC in 1985 there have been no reports of viruses such as HIV or hepatitis being transmitted due to aPCC administration.²⁶ However, factor concentrates can transmit a small non-enveloped parvovirus B19, which is associated with joint damage and can potentially carry risk of future transmission of previously unknown pathogens.^{27,28} This may be an important factor to patients and clinicians in choosing between aPCC and rFVIIa.

CONCLUSIONS

To our knowledge, this is the first systematic review analyzing the efficacy of rFVIIa and aPCC in the treatment of hemophilia patients with inhibitors. The key findings from this analysis are:

- Although randomized trials examining the efficacy of rFVIIa and/or aPCC exist, there is a paucity of comparative studies with currently only two direct head-to-head trials.

- Overall, the studies do report higher efficacy and bleed cessation rates for rFVIIa than for aPCC; however, the measurement of effectiveness of the agents is open to interpretation due to a wide variety of methods being used to evaluate effectiveness.
- Conclusions from the meta-analysis undertaken by Treur et al. suggest that treatment with rFVIIa may be associated with a faster time to joint bleed resolution than aPCC due to higher efficacy levels at 12-, 24-, and 36-hour time points.¹⁹ The results from the Young et al. comparative trial support the improved efficacy rates associated with rFVIIa compared with aPCC.²
- There appears to be a need for a standardized validated efficacy assessment tool to be employed in all future studies in an attempt to enable results from different studies to be compared.
- A health-related quality of life scoring system should be considered in future studies to help measure the wellbeing of hemophilia patients with inhibitors, and to possibly elicit differences in efficacy and speed of bleed resolution between rFVIIa and aPCC.

While this review did not incorporate any indirect comparison analysis such as meta-analysis, such analyses may have provided further insight. However, the variation in definition of efficacy between the studies may have made any indirect comparison difficult. In conclusion, further head-to-head, randomized, controlled trials should incorporate a validated standard method of efficacy assessment.

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APPENDIX

Search Strategies

Within the searches presented below are the searches for cost-effectiveness studies that were carried out as part of a separate review.

MEDLINE (via PubMed)

Search undertaken in April 2008.

#14	Search #13 NOT #12 Limits: Publication Date from 1990 to 2008, Humans 326
#13	Search #1 AND #11 Limits: Publication Date from 1990 to 2008, Humans 398
#12	Search ((hemophilia OR "hemophilia A" OR "hemophilia B" OR hemophil*) AND (inhibitors OR inhibit* OR anti-inhibit* OR antibod*) NOT (acquired[Title])) AND ((apcc*) OR (aPCC) OR ("activated prothrombin complex concentrate") OR (FEIBA) OR (Autoplex) OR ("recombinant factor VIIa") OR (rFVIIa) OR (NovoSeven) OR (bypass*)) AND ((cost) OR (cost*) OR (cost-analysis) OR (cost analysis) OR (cost-effectiveness) OR (cost effectiveness) OR (*economic*) OR (pharmacoeconomic) OR (pharmaco-economic) OR (cost-utility) OR (cost utility) OR (cost-benefit) OR (cost benefit) OR (economic-model) OR (QALY[Title/Abstract]) OR (modelling) OR ("decision model")) Limits: Publication Date from 1990 to 2007 73
#11	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 90119
#10	Search bypass* 88914
#9	Search NovoSeven 645
#8	Search rFVIIa 848
#7	Search "recombinant factor VIIa" 630
#6	Search Autoplex 30
#5	Search FEIBA 160
#4	Search "activated prothrombin complex concentrate" 68
#3	Search aPCC 65
#2	Search apcc* 92
#1	Search (hemophilia OR "hemophilia A" OR "hemophilia B" OR hemophil*) AND (inhibitors OR inhibit* OR anti-inhibit* OR antibod*) NOT (acquired[Title]) 4520

EMBASE (via Dialog)

Search undertaken in April 2008.

Set	Items	Description
S1	4413	(HEMOPHIL? OR HEMOPHILIA!) AND (INHIBIT? OR ANTI()INHIBIT? OR ANTIBOD?)
S2	4091	S1 NOT ACQUIRED/TI
S3	760	S2 AND (APCC? OR ACTIVATED()PROTHROMBIN()COMPLEX OR FEIBA OR AUTOPLEX OR RECOMBINANT()FACTOR()VIIA OR RFVIIA OR NOVOSEVEN OR RECOMBINANT()BLOOD()CLOTTING()FACTOR()7A OR BYPASS?)
S4	190	S3 AND (COST OR COSTS OR COSTED OR COSTING OR COST! OR ECONOMIC? OR ECONOMICS! OR PHARMACOECONOMIC? OR PHARMACOECONOMICS! OR QALY/TI,AB OR MODELLING OR MODELING OR DECISION()MODEL? OR MODEL!)
S5	185	S4/1990:2007
S6	730	S3/HUMAN
S7	647	S6/1990:2007
S8	470	S7 NOT S5

The Cochrane Library (including CENTRAL [Cochrane Central Register of Controlled Trials], CDSR [Cochrane Database of Systematic Reviews], DARE [Database of Abstracts of Reviews of Effects], and Technology Assessment Database)

Search undertaken in April 2008.

#1 Hemophilia AND inhibitors