*Haemophilia* (2005), **11**, 261–269 DOI: 10.1111/j.1365-2516.2005.01098.x

# A cost minimization model for the treatment of minor bleeding episodes in patients with haemophilia A and high-titre inhibitors

K. G. PUTNAM, R. L. BOHN, B. M. EWENSTEIN, W. C. WINKELMAYER and J. AVORN
*Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School; and Division of Hematology, Harvard Medical School, Boston, MA, USA*

**Summary.** Treatment of acute bleeding episodes in patients with haemophilia A and inhibitory antibodies to factor VIII (FVIII) most often involves the use of bypassing haemostatic agents, such as activated prothrombin complex concentrates (aPCC) or recombinant factor VIIa (rFVIIa). We constructed a cost minimization model to compare the costs of initial treatment with aPCC vs. rFVIIa in the home treatment of minor bleeding episodes. We developed a clinical scenario describing such a case and presented it to a panel of US haemophilia specialists. For each product class, we asked panellists to provide dosing regimens required to achieve complete resolution of a minor haemarthrosis in a child with high-titre inhibitors, and for the probabilities of success at two time points (8–12 and 24 h). Consensus among the panellists was refined by a second round of the process, and the median values resulting were used as inputs to a decision analysis model. Sensitivity analyses were conducted to determine threshold values for key variables. The base case model found that initial treatment with aPCC would result in a mean cost per episode of $21 000, compared with $33 400 for initial treatment with rFVIIa. Sensitivity analyses over a range of clinically plausible values for cost, dosing, and efficacy did not change the selection of aPCC as the dominant strategy.

**Keywords**: activated prothrombin complex complexes, Costs and cost analysis, decision analysis, factor VIIa, factor VIII, hemophilia, inhibitors

1. **The base case model found that initial treatment with aPCC would result in a mean cost per episode ...**
**Anchor Name: (/p861/col2/para1)** *[NHSM (Neha Sharma)]*

## Introduction

For patients with haemophilia A, the development of inhibitors to factor VIII (FVIII), especially at high titre, is a serious event associated with increased morbidity and mortality. Treatment of minor bleeding episodes in such patients typically requires the use of 'bypassing' agents, including an activated prothrombin complex concentrates (aPCC) or recombinant activated factor VII (rFVIIa). Porcine FVIII, which is currently virtually unobtainable, is often reserved for major bleeding episodes. Several alternative therapeutic strategies are presently in use, but there is a lack of consensus concerning which bypassing agent should be considered first-line therapy [1]. No randomized controlled trial data are available from studies that compared these agents with one another with respect to their relative efficacy, safety and cost.

Minor bleeding episodes in selected patients may be initially treated at home using either rFVIIa or aPCC. In selecting a regimen, the treating physician must consider competing benefits, risks and costs. These include inhibitor titre, inhibitor responsiveness, time to resolution, overall duration of treatment, infectious and thrombotic complications, and, in an environment of limited health care resources, the relative cost of each therapeutic strategy.

With little consensus among clinicians, inadequate comparative literature, and mounting cost considerations, there is a need for further study of the optimal strategy for treating high-titre inhibitor

A preliminary version of this paper was presented orally at the 44th Annual Meeting of the American Society of Hematology, Philadelphia, PA, 10 December 2002.

Correspondence: Jerry Avorn, MD, Division of Pharmacoepidemiology and Pharmacoeconomics, 1620 Tremont St., Boston, MA 02120, USA.
Tel.: (617) 278 0930; fax: (617) 232 8602;
email: javorn@rics.bwh.harvard.edu

Accepted after revision 29 March 2005

haemophilia patients with minor bleeding episodes. We sought to evaluate this issue using decision analytic techniques.

## Methods

### *Decision analytic model*

We developed a cost minimization model to determine the most economical strategy for treating patients who present with high-titre inhibitors to FVIII. The comparators of interest were two strategies using aPCC vs. rFVIIa as first-line therapy for home treatment of minor bleeding episodes. The model assumed that the eventual efficacy of each approach was comparable in that all patients eventually achieved haemostasis. Figure 1 is a representation of the decision tree. We then convened an expert panel of haemophilia specialists who participated in a consensus exercise to generate estimated values for all components of the model, as described below. We calculated the cost of each treatment by modelling the type and amount of product required to manage a given acute bleeding episode. The primary outcome was the cost of each treatment. A secondary outcome was the number of hours of treatment required to resolve the bleeding episode. The analysis was performed in accordance with recommendations set forth by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine [2] and employed a societal perspective. We used the average wholesale price per unit of factor product [3], and performed sensitivity analyses around that price. TreeAge software was used for model development and sensitivity analyses [4].

### *Literature review*

As background to development of the model, we first conducted an extensive review of published studies and case series ($n > 3$) of minor bleeding episodes treated with either rFVIIa or aPCC. Papers in which bolus dosing was used were included. If several reports appeared to refer to the same patient population, we included either the one with the largest sample size or with the largest sample size that provided adequate dosing and efficacy information. For the aPCC agents, data were included from studies of anti-inhibitor coagulant complex (Autoplex), factor eight inhibitor bypassing activity (FEIBA), and FEIBA-VH. From each report, we extracted relevant information about the design, the nature of treatment (first or second line, dose limited or not), the number of bleeding episodes, the proportion of episodes that resulted in haemarthroses, the time at which efficacy was assessed, the average dose required to resolve the bleed and the overall efficacy of the product. However, because of the heterogeneity of the literature (randomized trials vs. observational data, variability of patient populations, etc.), we used the output of the consensus process (see below) to define the values for all variables in the model.

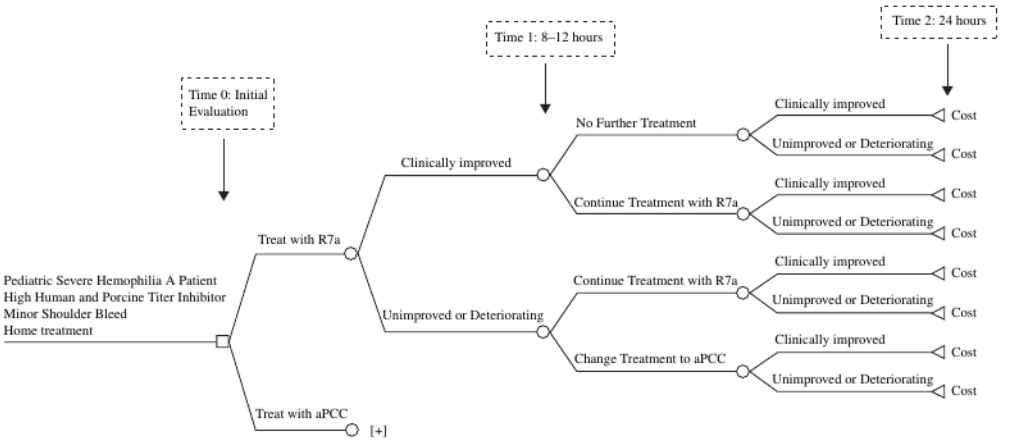


**Fig. 1.** Schematic diagram of the model.




[no notes on this page]

*Clinical scenario*

We then presented the following scenario to 11 US-based haemophilia experts:

> A 10-year-old patient with severe haemophilia A develops a shoulder haemarthrosis with symptoms that began approximately 1 h prior. He has a history of frequent minor bleeds that have been treated with either rFVIIa or aPCC. Additionally, 2 months prior he experienced a major illiopsoas bleed for which a protracted course of porcine FVIII was administered. His last inhibitor titres were 120 BU (human) and 16 BU (porcine), measured 1 week ago. You and the patient have elected to begin treatment at home. The two choices for first-line therapy are rFVIIa and aPCC.

Panellists were asked to report doses used and expected outcomes for two possible strategies, rFVIIa first, as well as aPCC first. For each treatment option, panellists were asked to provide their initial dosing recommendations (units $kg^{-1}$) for the first 8–12 h of treatment, and then to reassess therapy at Time 1 (8–12 h). If the patient was improving, the options were either to stop or to continue treatment with the same agent. If the patient's clinical status was unchanged or deteriorating, the options were either to continue treatment with the same agent or to change product. Panel members were next asked to provide their estimates of efficacy at Time 2 (24 h) as well as the product and dosage (if any) they would use to achieve complete resolution of the bleed if the patient was experiencing continued improvement, or had begun to improve as the adjustment made at Time 1, or was unchanged or deteriorating despite these adjustments. One change of product was allowed, but once changed, the physician was required to continue with that product. The respondents were instructed to be very explicit in their dosing recommendations and to specify the exact number of doses they would use in the scenario, based on their clinical experience. Open-ended responses (e.g. 90 mcg $kg^{-1}$ q 2–3 h 'until resolved') were not included (considered unanswered). Lastly, panellists were asked to provide an estimate of the probability of success at each time point given the product used, the dosage administered and the history of success through the previous time point.

*Expert panel consensus*

Responses to the initial clinical scenario survey were recorded and averages (mean, median and mode) tabulated. Using a Delphi panel framework [5], we then sought to improve the consensus among the panellists by sending each a second questionnaire showing his or her initial responses as well as the panel averages and the range of responses. They were then asked to provide a new response if they wished to change their initial answer based on this feedback. We used the median results from this consensus round of questioning as inputs to the model. This included the consensus-round responses for the eight of 11 panellists who responded to the consensus questionnaire and the initial-round responses for the three of 11 panellists who did not respond further.

*Sensitivity analyses*

Selected variables were subjected to sensitivity analysis. We used a range of plausible values consistent with the literature to identify threshold values that would cause the model to change the preferred strategy. For initial dosing, the sensitivity range used was 50–150% of the median doses provided, which reflected the range of dosing possibilities provided by the panellists. For the initial probabilities of success, a range of 50–95% for both rFVIIa and aPCCs likewise reflected the range of responses provided by the panel. The sensitivity range for product cost was chosen as 20% higher and lower than the baseline estimate for each product.

## Results

*Cost minimization model*

Initial dosing and efficacy values submitted by the panellists were consistent with the published literature. When the panellists' responses were inserted into the decision analysis model, the base case model indicated that home treatment for minor bleeding episodes would be less expensive for the aPCCs treatment strategy ($21 000) than the rFVIIa treatment strategy ($33 400). This difference was attributable primarily to the acquisition cost of rFVIIa.

*Sensitivity analyses*

The base case model was insensitive to clinically plausible changes in efficacy, price and dosage for all products studied (Table 1). Efficacy at the earliest time point (8–12 h) was unlikely to have influenced the selection of preferred strategy, because the baseline values were high for both arms (rFVIIa, 90%; aPCC, 75%), leaving little room to vary the




[no notes on this page]

**Table 1.** One-way sensitivity analyses.

| Parameter varied | Baseline value | Plausible range |
|---|---|---|
| Cost of rFVIIa | \$1.40 mcg$^{-1}$ | 80–120% of baseline (\$1.12–1.68) |
| Cost of aPCC | \$1.30 unit$^{-1}$ | 80–120% of baseline (\$1.04–1.56) |
| Initial probability of success with rFVIIa (8–12 h) | 0.90 | 0.60–0.95 |
| Initial probability of success with aPCCs (8–12 h) | 0.75 | 0.50–0.90 |
| Initial dosing of rFVIIa | 270 mcg kg$^{-1}$ | 50–150% of baseline (135–405 mcg kg$^{-1}$) |
| Initial dosing of aPCC | 75 units kg$^{-1}$ | 50–150% of baseline (37–113 units kg$^{-1}$) |
| Subsequent treatment after initial improvement with rFVIIa | 27% Discontinue, 73% continue treatment (270 mcg kg$^{-1}$ in next 12–16 h) | 100% Discontinue |
| Subsequent treatment after initial improvement with aPCC | 9% Discontinue, 91% continue treatment (120 units kg$^{-1}$ in next 12–16 h) | 100% Discontinue |

rFVIIa, recombinant factor VIIa; aPCCs, activated prothrombin complex concentrates; aPCCs was the preferred strategy for all sensitivity analyses listed.

range. Allowing the cost of the two agents to vary by 20% from their baseline values did not influence the strategy selection. A threshold value for rFVIIa was identified at which it would have been the preferred strategy. This was \$0.64 mcg$^{-1}$, about half its baseline per-unit cost. A greater proportion of simulated patients initially treated with aPCC who were expected to be unimproved or deteriorating at Time 1 were switched to rFVIIa (45%) by the panel than *vice versa* (9%). The degree to which the cost affected the result varied by strategy; the cost of rFVIIa weighed more heavily in the aPCC strategy than did the cost of aPCC in the rFVIIa strategy. Panellists were more likely to state that the specified dosing for rFVIIa during the initial 8–12 h would be adequate to achieve complete resolution of the bleed compared with aPCC. For rFVIIa, 27% opted to discontinue treatment at Time 1, compared with only 9% for aPCC. It should be noted that in 8–12 h three to four doses of rFVIIa would be administered, compared with just one dose of aPCC.

We conducted several two-way sensitivity analyses in which we varied two model parameters at once to determine the effect of such changes on the model's output. Varying the cost per unit of both agents (from 80% to 120% of their baseline values) had no influence on the result of the model (Fig. 2). Similarly, varying the dosage administered at the time of initial treatment (from 50% to 150% of baseline values) still left aPCC as the preferred strategy (Fig. 3). The model did indicate a change in the preferred strategy when we varied the initial dosing and cost of agents. However, the combinations needed to make rFVIIa preferred were clinically unlikely (i.e. a roughly threefold higher initial dose of aPCC, and half the initial dose of rFVIIa); these values were beyond the range deemed plausible *a priori*, greatly exceed the labelled dosing range for aPCC, and run counter to the trend toward higher initial dosing with rFVIIa [6].

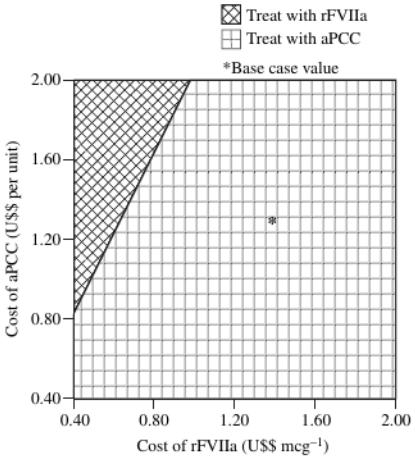


**Fig. 2.** Two-way sensitivity analysis of cost of recombinant factor VIIa and activated prothrombin complex concentrates.

### *Estimates of total use*

Panellists were also asked to separately estimate the overall average dosage needed and expected time to resolution for the bleed described, for each treatment strategy. Although all costs were lower using this approach, the total regimen cost was still lower for aPCC (300 U kg$^{-1}$) than for rVIIIa (360 mcg kg$^{-1}$).




[no notes on this page]

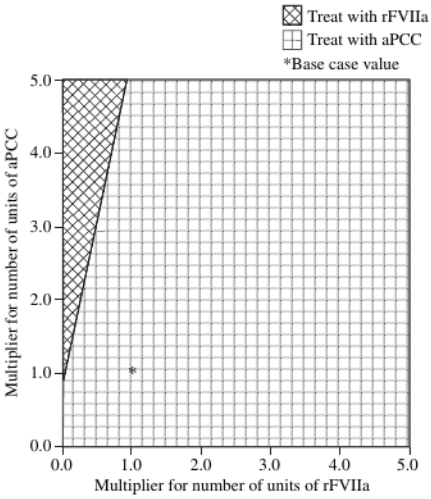


**Fig. 3.** Sensitivity analysis on the number of units of activated prothrombin complex concentrates and recombinant factor VIIa at initial treatment. Both *x* and *y*-axis use a multiplier (where 1.0 = base case number of units) of units rather than the actual number of units.

## Discussion

This decision analysis indicated that for patients with haemophilia A and high-titre inhibitors, a strategy using aPCC first would minimize expenditures compared with a strategy using rFVIIa first. This finding remained robust across a wide variety of assumptions. However, this analysis has several important limitations that must be considered. First, as a cost minimization study in which all minor bleeds ultimately resolve, it does not take into account the time to resolution, which the expert panel judged would be more rapid with rFVIIa than with aPCC. Secondly, we relied on the clinical judgment of experienced haemophilia physicians for estimates of the expected performance of the products studied, and this process may not have captured all the nuances of a real clinical situation. If the panellists' judgments were incorrect or would differ today in light of subsequent experience, this could be another source of imprecision. However, in the absence of adequate comparative trials of one agent vs. another, such a model remains the most unbiased way of placing all agents on the same 'level playing field.' Changes in product prices as the initial analysis can be taken into account in the sensitivity analyses on cost presented in the figures.

An additional potential limitation concerns our choice of the shoulder as the site of the bleed in the clinical scenario. Because this site is often more difficult to assess clinically than bleeds in other joints, there is a possibility that it may have led the panel to make somewhat more conservative dosing decisions, which should be considered in assessing the generalizability of these findings.

Most available literature for the dosing and efficacy of aPCC in minor bleeding is observational; Table 2 includes several case series and few controlled trials. By contrast, the bulk of the literature on the dosing and efficacy of rFVIIa in minor bleeding comes from clinical trials (Table 3). We identified a total of 831 bleeds treated with aPCC as either first or second line therapy for minor bleeding episodes, described in eight published reports. Four papers describing the use of rFVIIa as first-line therapy for 861 minor bleeding episodes were likewise identified. The overall average efficacy from these reports (mean, weighted by the number in each study) for aPCC was 79% assessed between 6 and 36 h (median = 30). Respective values for rFVIIa were 84% efficacy assessed between 16 and 24 h (median = 20). Several important factors preclude comparing the available literature for each agent; it therefore served only as a guide for the model. Trial data is generally dose or time limited and may therefore reflect lower doses and lower efficacy than would be used in an observational setting. In addition, observational studies include both primary and secondary (salvage) treatment, whereas trial data often include only primary treatment of inclusion criteria selected bleeding episodes. Trial standards can also bias dosing and efficacy estimates unfavourably in comparison with observational studies (i.e. low efficacy reported because protocol called for a single dose). Additionally, many literature-based estimates of efficacy use time until first response as an endpoint, which is not the same as time until complete resolution of the bleed. This may account for some of the apparently long terminal dosing specified by the expert panel based on their clinical experience in comparison with literature-based estimates. In spite of this, there was great consistency between the literature and the expert panel for initial dosing and efficacy values for both agents.

Eight of 11 panellists responded to the follow-up questionnaire with estimates very close to their original values. Analyses using only the initial round of values produced the same outcome (aPCC strategy preferred). The dosing questions we used were open-ended, allowing panellists to choose any dose




[no notes on this page]

**Table 2.** Literature on activated prothrombin complex concentrates efficacy and minor bleeding episodes.

| Reference | Study design | Therapy | *n* Episodes (% haemarthrosis) | Efficacy assessed (h) | Average dosage administered | Efficacy (%) |
|---|---|---|---|---|---|---|
| Abildgaard *et al.* [13] (Autoplex) | Case series | P, S | 10 (70) | 24 | 53.2 (U kg$^{-1}$) × 1.4 doses (S)<br>33.3 (U kg$^{-1}$) × 1.5 doses (F) | 80* |
| Buchanan and Kevy [14] (Autoplex)† | Case series | P, S | 31 (87) | – | 75 (U kg$^{-1}$) × 1.4 doses (range 1–5 doses) | 65 |
| Hilgartner *et al.* [15] (FEIBA) | Uncontrolled open-label study | P | 155 (66) | 36 | 50–70+ (U kg$^{-1}$ q12 h) (closed bleeding) | 81‡ |
| Hilgartner *et al.* [16] (FEIBA) | Case series w/historical control | P | 98 (74) | 36 | 75 (U kg$^{-1}$) × 1.4 doses (S – haemarthrosis) | 80§ |
| Lusher *et al.* [17] (Autoplex) | Trial PCC vs. aPCCs | P, S | 82 (100) | 6 | 62.9 (U kg$^{-1}$) × 1 dose | 54 |
| Negrier *et al.* [18] (FEIBA) | Retrospective survey | P, S | 298 (100) | <36‖ | 65–100 (U kg$^{-1}$ q6–12 h) × 1.52 doses (S)<br>65–100 (U kg$^{-1}$ q6–12 h) × >3 doses (F) | 89 |
| Sjamsoedin *et al.* [19] (FEIBA) | Trial PCC vs. aPCCs | P | 74 (–) | 24 | 88 (U kg$^{-1}$) up to two doses | 64 |
| Kantrowitz *et al.* [20] (Autoplex) | Uncontrolled trial, observational series | P | 83¶ (64) | –†† | Mean 3.8 infusions per bleed | 84 |
| Total | | | 831 | <30 (median) | | 79 |

Autoplex, anti-inhibitor coagulant complex; FEIBA, factor eight inhibitor by-passing activity; aPPC, activated prothrombin complex concentrates; P, primary treatment; S, secondary treatment (in the column 'therapy'); S, successful treatment; F, failed treatment (in the column 'average dose administered').

To reflect the clinical scenario used, data for haemarthrosis only are footnoted wherever separately reported. All bleeds are minor bleeds in the presence of high human and porcine titres (to the best of our ability to sort them out in the literature).

*71% for haemarthroses.

†This was called Auto-Factor IX (investigational product) at the time.

‡82% for haemarthroses.

§79% for haemarthroses.

‖Inferred from dosing interval.

¶Only closed bleeding episodes are reported here.

††The only indication of time frame is that 'excellent' or 'good' response was defined as 'abrupt, dramatic haemostasis with accompanying pain relief, or by a slight delay in response' respectively.

**Table 3.** Literature on recombinant factor VIIa efficacy.

| Reference | Study design | Therapy | *n* Episodes (% haemarthroses) | Efficacy assessed (h) | Dosage administered | Efficacy (%) |
|---|---|---|---|---|---|---|
| Key *et al.* [21] | Trial (up to four doses) | P (home) | 614 (80) | 24 | 90 ($\mu$g kg$^{-1}$) × 3.2 injections | 88* |
| Lusher *et al.* [22] | Trial (high vs. low dose – up to six doses) | P | 179 (81) | 12 ± 2 | 57 ($\mu$g kg$^{-1}$) × 2.5 (S)<br>57 ($\mu$g kg$^{-1}$) × 4.5 (F) | 72† |
| Santagostino *et al.* [23] | Trial (up to four doses) | P (home) | 53 (85) | 16 | 90 ($\mu$g kg$^{-1}$) × 1.5 doses (S)<br>90 ($\mu$g kg$^{-1}$) × three doses (F) | 79 |
| Shapiro [24] | Uncontrolled trial (up to three doses) | P (home) | 15 (67) | 24 | 90 ($\mu$g kg$^{-1}$) × three injections | 53‡ |
| Total | | | 861 | 20 (median) | | 84 |

To reflect the clinical scenario used data for haemarthrosis only are footnoted wherever separately reported.
P, primary treatment; S, secondary treatment (in the column 'therapy'); S, successful treatment; F, failed treatment (in the column 'average dose administered').
*As treated analysis: 566/614 = 92% bleeds initially effective, 538/614 = 88% effective at 24 h.
†Efficacy for haemarthrosis = 71%. In this trial, no difference was seen between high and low doses, so efficacy is combined.
‡Four target joint bleeds, all failures – removing these from analysis, efficacy = 73%.

they deemed appropriate. This accommodated a variety of practice patterns and dosing approaches. Despite this variability, the average dosing specified by panel members was remarkably consistent for the first 24 h of treatment. During this time, 90% or more of the panellists' prescribed doses were within two standard deviations of the mean dose. Once beyond the initial 24-h time period, dosing was more erratic. To reduce the influence of disparate dosing regimens, we used the median values from the consensus round of the expert panel for all model inputs.

Doses exceeding 120 units kg$^{-1}$ of aPCC are associated with thrombogenic complications, although they can occur with rFVIIa as well [7,8]. This may explain the nearly threefold higher probability of panellists recommending switching therapy after starting with aPCC compared with rFVIIa. The cumulative probability of switching treatments was 11% for the rFVIIa strategy, compared with 30% for the aPCC strategy.

Our cost minimization model included neither quality of life measures nor utilities that are designed to encompass a broader measure of effectiveness. Such measures would have to take several additional factors into consideration. For example, complete resolution of the bleed required on average 39 h for rFVIIa and 53 h for aPCC; this time advantage is not valued in our model. Additionally, patients and payers may have a greater willingness to pay for recombinant products because of perceived safety advantages over plasma derived products (the so-called 'recombinant premium') and a potentially greater willingness to pay for possible differences in thrombogenicity or for ease or frequency of drug administration. Adding such considerations probably would have improved the performance of the rFVIIa arm of the model. We did not include the cost of hospitalization, because the literature demonstrates that factor concentrates account for over 80% of the total cost of managing inpatient or outpatient bleeding episodes [9,10].

To assess the possibility that the model was overly influenced by dosing decisions made after the initial 24 h, we performed a sensitivity analysis that ignored all dosing beyond 24 h. It produced qualitatively similar results, with a cost for the aPCC regimen of $10 400 and $22 200 for the rFVIIa regimen. When the number of units used beyond 24 h was varied across a wide range for both agents, aPCC remained the economically preferred strategy.

These results differ substantially from those of Odeyemi and Guest [11], who used a different approach to compare aPCC and rFVIIa for minor

bleeding episodes treated at home. Initial treatment is defined differently; Odeyemi and Guest [11] compared the effects of specified doses of each product whereas our model asked panellists for product dosing over set-time periods (8–12 and 16–24 h). Despite divergent cost estimates, the estimated time to bleed resolution in both models was similar. The panellists' responses were consistent with the available literature for treatment through the first 24 h and with the probabilities of successful treatment at 24 h.

Our results were insensitive to changes in model parameters for which the literature is weak (i.e. terminal dosing) as well as to variables for which the literature is more robust (i.e. initial dosing and efficacy). Further modelling that includes haemophilia-specific quality of life measures, or the willingness to pay for a potential recombinant premium or other product safety perceptions, could alter these findings. Controlled trials comparing the two strategies are underway [12], the results of which are likely to provide important new data to confirm or refute the estimates of this analysis.

## Acknowledgements

The authors thank the members of the expert panel for their valuable input. Additionally, we thank Josh Benner, PharmD, ScD for constructive comments about the modelling process and Kristen M. Michallyszyn for technical assistance provided.

Supported by an unrestricted research grant from Novo Nordisk.

One of the authors (BME) is currently employed by a company or a competitor of a company (Baxter Healthcare Corp.) whose product was studied in the present work.

## References

1 Teitel J. Recombinant factor VIIa versus aPCCs in haemophiliacs with inhibitors: treatment and cost considerations. *Haemophilia* 1999; **5**(Suppl. 3): 43–49.
2 Gold M, Gold S, Weinstein ME. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press, 1996.
3 Shord S, Lindley C. Coagulation products and their uses. *Am J Health System Pharm* 2000; **57**: 1403–20.
4 TreeAge Software Inc. *Data [program]*, 3.5.8 version. Williamstown, MA: TreeAge Software Inc., 1988–2000.
5 Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; **311**: 376–80.
6 Abshire T. Dose optimization of recombinant factor VIIa for control of mild to moderate bleeds in inhibitor patients: improved efficacy with higher dosing. *Semin Hematol* 2004; **41**(Suppl. 1): 3–7.
7 Kulkarni R, Aledort L, Berntorp E, Brackman H, Brown D, Cohen A. Therapeutic choices for patients with hemophilia and high-titer inhibitors. *Am J Hematol* 2001; **67**: 240–6.
8 Hedner U. Factor VIIa in the treatment of haemophilia. *Blood Coagul Fibrinolysis* 1990; **1**: 307–17.
9 Lusher J, Giangrande P, Ewenstein B *et al.* Workshop 2: efficacy, safety and treatment cost considerations. *Haemophilia* 1997; **3**(Suppl. 3): 12–23.
10 Bohn R, Avorn J, Glynn R, Choodnovskiy I, Haschemeyer R, Aledort L. Prophylactic use of factor VIII: an economic evaluation. *Thromb Haemost* 1998; **79**: 932–7.
11 Odeyemi IAO, Guest JF. Modeling the economic impact of recombinant activated factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting factors VIII and IV in the UK. 5:119. *J Med Econ* 2002; **5**: 119–33.
12 Hind D, Llyod-Jones M, Makris M, Paisley S. Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia A and inhibitors (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004, Chichester, UK: John Wiley & Sons, Ltd.
13 Abildgaard C, Penner J, Watson-Williams E. Anti-inhibitor coagulant complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. *Blood* 1980; **56**: 978–84.
14 Buchanan G, Kevy S. Use of prothrombin complex concentrates in hemophiliacs with inhibitors: clinical and laboratory studies. *Pediatrics* 1978; **62**: 767–74.
15 Hilgartner M, Knatterud G, and the FEIBA study group. The use of factor eight inhibitor by-passing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. *Blood* 1983; **61**: 36–40.
16 Hilgartner M, Aledort L, Andes A, Gill J. Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in haemophilia patients. *Transfusion* 1990; **30**: 626–30.
17 Lusher J, Blatt P, Penner J *et al.* Autoplex versus Proplex: a controlled, double-blind study of effectiveness in acute hemarthroses in hemophiliacs with inhibitors to factor VIII. *Blood* 1983; **62**: 1135–8.
18 Negrier C, Goudemand J, Sultan Y *et al.* Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. *Thromb Haemost* 1997; **77**: 1113–9.
19 Sjamsoedin L, Heijnen L, Mauser-Bunschoten E *et al.* The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. *New Engl J Med* 1981; **305**: 717–21.

 

[no notes on this page]

20 Kantrowitz J, Lee M, McClure D, Kingdon H, Thomas W. Early experience with the use of anti-inhibitor coagulant complex to treat bleeding in hemophiliacs with inhibitors to factor VIII. *Clin Ther* 1987; **9**: 405–19.
21 Key N, Aledort L, Beardsley D *et al.* Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 1998; **80**: 912–8.
22 Lusher J, Roberts H, Davignon G *et al.* A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. *Haemophilia* 1998; **4**: 790–8.
23 Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. *Br J Haematol* 1999; **104**: 22–6.
24 Shapiro A. American experience with home use of NovoSeven: recombinant factor VIIa in hemophiliacs with inhibitors. *Haemostasis* 1996; **26**(Suppl. 1): 143–9.




[no notes on this page]