ORIGINAL RESEARCH

Modeling Costs and Outcomes Associated with a Treatment Algorithm for Problem Bleeding Episodes in Patients with Severe Hemophilia A and High-Titer Inhibitors

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Background: No evidence-based treatment guidelines are currently available for the treatment of problem bleedings in patients with hemophilia who develop clotting factor inhibitors. A treatment algorithm was developed previously to help providers optimize the approach to the treatment of this patient population. The algorithm provides the specific intervals between treatments; however, it does not specify dosing recommendations and does not offer insights into the likelihood of outcome improvements at each time interval.

Objective: To develop a model to analyze the impact on patient outcomes and costs of adhering to a current treatment algorithm for the 2 available clotting therapies to treat bleeding episodes in patients with hemophilia who develop clotting factor inhibitors.

Methods: A simulation model was developed using a modified Delphi method approach based on a consensus opinion of an expert panel. The model was used to analyze the impact of following the available treatment algorithm on patient outcomes and costs. Treatment patterns and the likelihood of a resolved bleeding episode associated with following the treatment algorithm (ie, adherence) were compared with not following the algorithm (ie, nonadherence). This model assumed 2 scenarios in which treatment was initiated with each of the 2 bypassing agents currently available, and clinical and economic outcomes were mapped for adhering to and not adhering to the consensus treatment algorithm.

Results: The simulation model shows that adhering to the treatment algorithm would result in 74.4% of patients improving at 72 hours compared with only 56.7% of patients when not adhering to the algorithm. According to this model, regardless of the bypassing agent used at initiation, adherence to the treatment algorithm would result in fewer patients requiring combined sequential therapy with the 2 bypassing agents for 3 days. In addition, using this analytic model, reducing the percentage of patients with hemophilia who required combined sequential therapy by 17.6% resulted in an average cost-savings of $16,305 per patient.

Conclusion: Adherence to an algorithm in which treatment is altered at regular intervals based on a patient's clinical response has the potential to improve patient outcomes and reduce the number of nonresponsive patients requiring sequential therapy in patients with hemophilia who have clotting factor inhibitors and are experiencing problem bleeding episodes. Adherence to the algorithm would also result in reduced costs to patients and payers.

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KEY POINTS

- Factor replacement therapy is the standard treatment for hemophilia, but many patients develop clotting factor inhibitors, which can lead to increased mortality.
- No evidence-based treatment guidelines are available for this patient population; a treatment algorithm has previously been developed, but it does not specify dosing recommendations or provide insights into the likelihood of improvements at each time interval.
- In this study, a simulation model was developed based on a consensus opinion of an expert panel to assess the clinical and economic impact of adhering to the treatment algorithm.
- Adhering to this algorithm would result in 74.4% of patients improving at 72 hours compared with only 56.7% of patients when not adhering to the algorithm; in addition, fewer patients would require combined sequential therapy.
- Reducing the percentage of patients who required combined sequential therapy by 17.6% resulted in an average cost-savings of $16,305 per patient.
- This model shows that adherence to the treatment algorithm, regardless of the bypassing agent used, improves clinical outcomes and reduces costs.
- In the absence of studies assessing the impact of guideline adherence on clinical and economic outcomes in this patient population, these data provide the best available estimate for those outcomes.

Factor replacement therapy is the standard treatment for hemophilia. However, some patients with hemophilia develop inhibitors (alloantibodies) against the clotting factor administered. The development of these clotting inhibitors may render replacement therapy ineffective and, consequently, increase morbidity because of the inability to control or prevent hemorrhages. Inhibitor development has been reported to occur in as many as 33% of patients with hemophilia A, and as many as 7.5% of patients with hemophilia B.[1-3]

Currently, 2 bypassing agents are available for use in patients who develop clotting factor inhibitors:

1. Factor VIII inhibitor bypassing activity, an activated prothrombin complex concentrate (aPCC), also known as anti-inhibitor coagulant complex[4]
2. A recombinant activated factor VII (rFVIIa).[5]

The ability of these agents to control bleeding episodes has been documented, with success rates ranging from 80% to 93%.[6-9] However, responses can vary between patients,[10-12] as well as within the same patient during the course of a single bleeding episode.[13] Therefore, making appropriate adjustments to therapeutic regimens is critical for controlling problem bleedings in this patient population.[14,15]

Treatment Algorithm, Definitions

Systematic approaches to treating hemorrhagic episodes can potentially guide the most appropriate pharmacologic decisions for patients with hemophilia who develop clotting inhibitors. To date, there are no approved treatment guidelines for such patients who are experiencing problem bleeding episodes.

In the present study, problem bleeding is based on the definition by Teitel and colleagues, who have published a consensus algorithm addressing the treatment of problem bleedings (specifically iliopsoas muscle hematoma as the archetypal limb-threatening bleeding and intracerebral hemorrhage as the archetypal life-threatening bleeding) in this population (**Figure 1**).[14]

Teitel and colleagues have defined problem bleeding as bleeding unresponsive to initial therapy with a single agent within a reasonable time (8-12 hours for non–life-threatening bleedings and 2-4 hours for life-threatening bleedings).[14]

The goal of the treatment algorithm was to aid physicians in determining the appropriate timing for treatment approaches to optimize patient outcomes. This algorithm includes the designation of time intervals between assessments, to allow for more effective treatment changes or dosage adjustments based on individual responses, in an effort to facilitate faster responses and improved outcomes.[14]

Although the algorithm specifies intervals and general recommendations for the treatment of problem bleedings (eg, increasing a dose or increasing the frequency of doses), it does not give specific dose recommendations or provide insight into the likelihood of improvement for patients at each interval. The lack of readily available clinical data precludes a direct comparison of outcomes and costs associated with adherence versus nonadherence to the consensus treatment algorithm.

Methods: Developing a Simulation Model

To circumvent the absence of data for this patient population, a simulation model was developed, informed by expert opinion, to estimate the likely outcomes and costs in relation to the treatment algorithm. Outcomes and costs were modeled for following the treatment algorithm (ie, adherence) and for not following it (ie, nonadherence) for each of these scenarios and for each of the 2 bypassing agents (ie, aPCC and rFVIIa). The present article describes the development of this simulation model and its benefits in evaluating outcomes and costs in this patient population.

Model Structure

The structure of the model was constructed from a consensus algorithm previously developed for controlling limb-threatening muscle bleedings in patients who have severe hemophilia A and high-titer inhibitors.[14] Using the algorithm as a foundation, the new model allowed the investigators to assess the impact of guideline adherence on outcomes and costs, assuming therapy would be initiated with either an aPCC or an rFVIIa.

Treatment patterns (ie, dosing and frequency) and the likelihood of a successful clinical outcome (defined as improvement in bleeding status at specific time points) associated with guideline adherence versus nonadherence were analyzed in this study based on the consensus opinion of an expert panel.

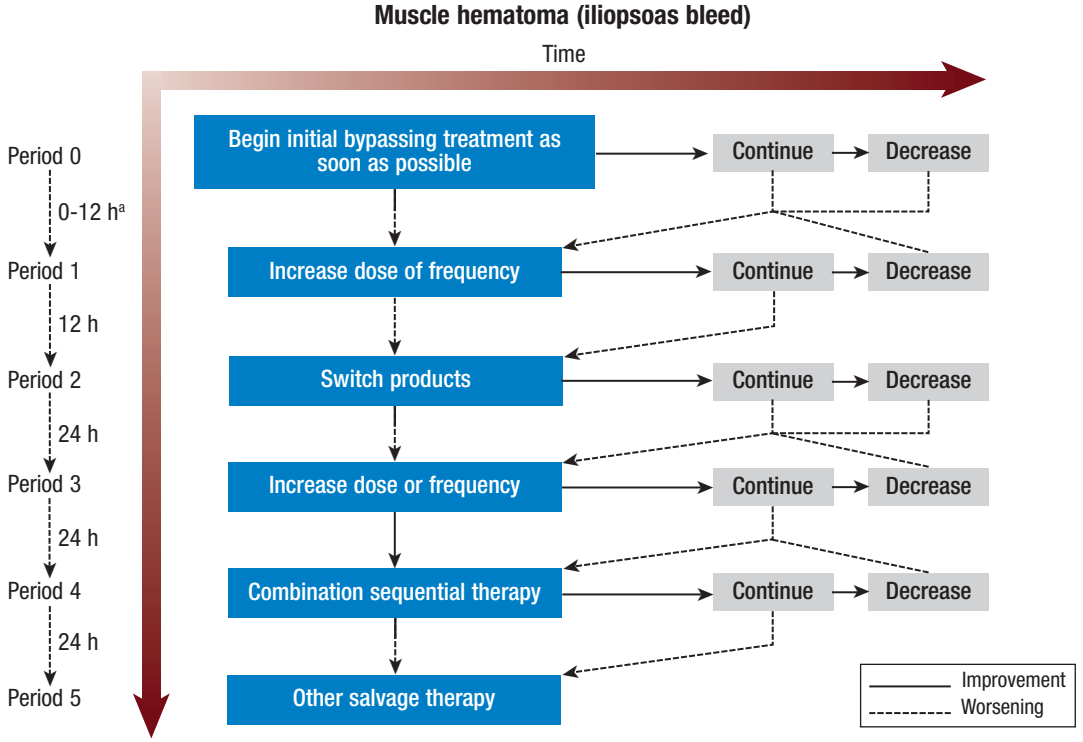
A decision-analytic model was used to evaluate the clinical and economic impact of adherence to the algorithm. Panel members developed the model to assess improvement at 12, 24, 48, and 72 hours after bleeding onset.

According to the treatment algorithm, after initial treatment, the dose or frequency of administration of both bypassing agents should be increased in patients who do not improve after 12 hours. If no improvement is observed after the specified adjustment at 24 hours, the algorithm suggests switching to the other bypassing agent. If no improvement has occurred at 48 hours, the dose or frequency of administration of the new agent should be increased.

Finally, the algorithm specifies that patients not improving after 72 hours should receive combined sequential therapy with aPCC and rFVIIa for 3 days. Combined sequential therapy consists of aPCC 50 units/kg administered every 12 hours (for a total of 7 doses in 3 days), with rFVIIa 90 mcg/kg (12 doses in 3 days) given between the aPCC doses. It is further assumed that after 3 days of sequential therapy, all bleeding episodes would be resolved and treatment stopped.

A corresponding scenario assuming nonadherence to the treatment algorithm has also been constructed in the present model. In that scenario, patients who did not improve at 12 hours would continue at the same dose and frequency for another 12 hours, thereby delaying the increase in dose or frequency of administration to 24 hours and the switch in agents to 48 hours.

Figure 1 Managing Limb-Threatening Bleeding Episodes in Patients with High-Titer Inhibitors



[a]Hemostatic evaluation periods may be shortened, depending on patient status.

Reprinted with permission from Teitel J, et al. A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors. *Haemophilia*. 2007;13:256-263.

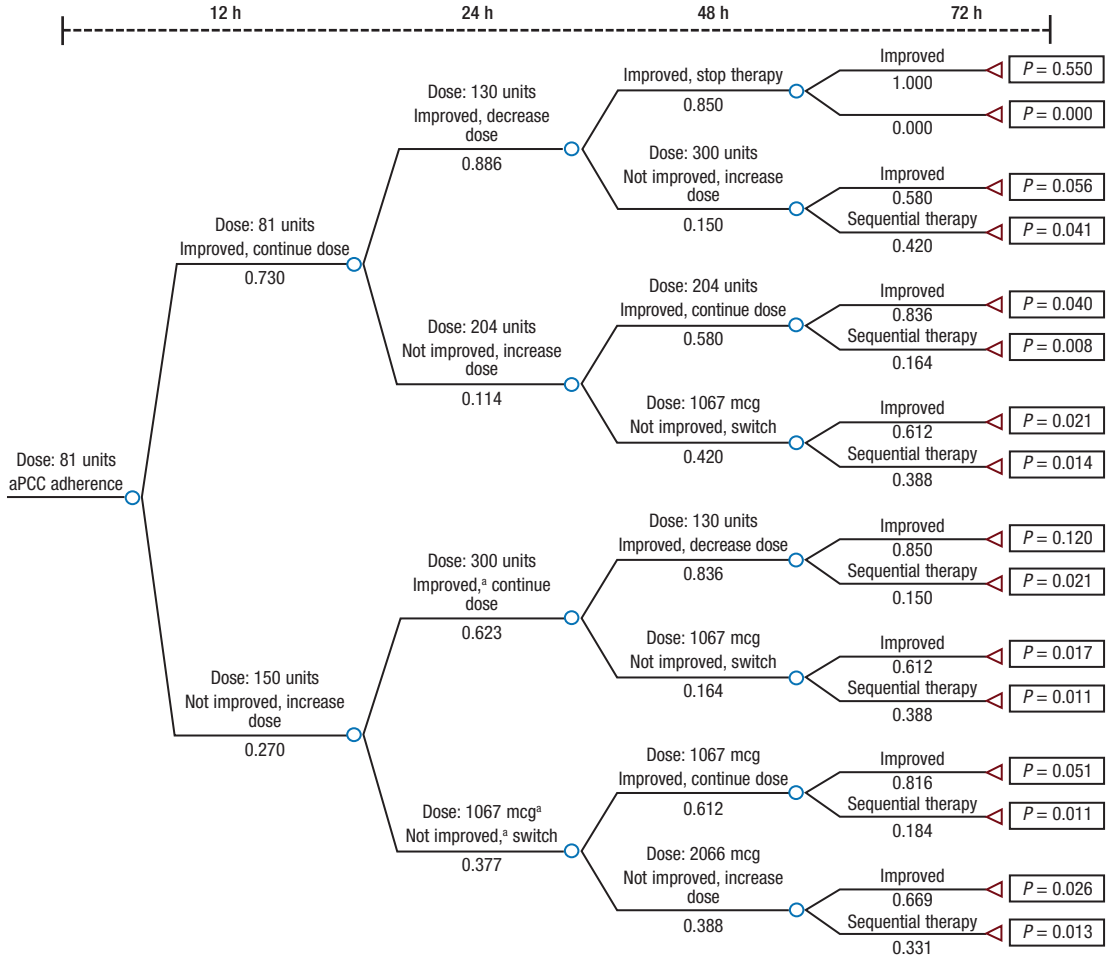
The model assumed 2 possibilities: one in which treatment was initiated with aPCC and one in which treatment was initiated with rFVIIa. Within each treatment possibility, clinical outcomes and costs were mapped for following (ie, adherence) and not following (ie, nonadherence) the algorithm. Outcomes evaluated included resolution of bleedings at 72 hours, the need for combined sequential therapy, and treatment cost, which were compared for adherence and nonadherence to the algorithm.

Total drug costs were calculated according to the 2008 Medicare Part B allowance payment limits for aPCC and rFVIIa, considered to be $1.48/U for aPCC and $1.23/mcg for rFVIIa. One-way sensitivity analyses were performed to determine if the results were affected by changes in dosing or in drug pricing.

Expert Panel and Delphi Methodology

No evidence-based guidelines have been validated for the treatment of problem bleedings, and clinical studies have not been conducted to establish guidelines. Therefore, we used a modified Delphi approach[16] in conjunction with the consensus algorithm to populate the parameters in the decision-analytic model. The Delphi method is a systematic interactive process led by a facilitator who relies on a panel of experts to anonymously answer questions during 2 or more rounds of discussion.[16]

Figure 2 Treatment Algorithm with aPCC as Initial Agent



NOTE: The first 2 nodes represent 12-hour intervals. The subsequent nodes represent 24-hour intervals. The probability of improving/not improving is provided for each chance node, and overall probabilities for each path are provided at the terminal nodes.

[a]Indicates that consensus was not reached on probability of improving or on dosage amount, as indicated by placement.

aPCC indicates activated prothrombin complex concentrate.

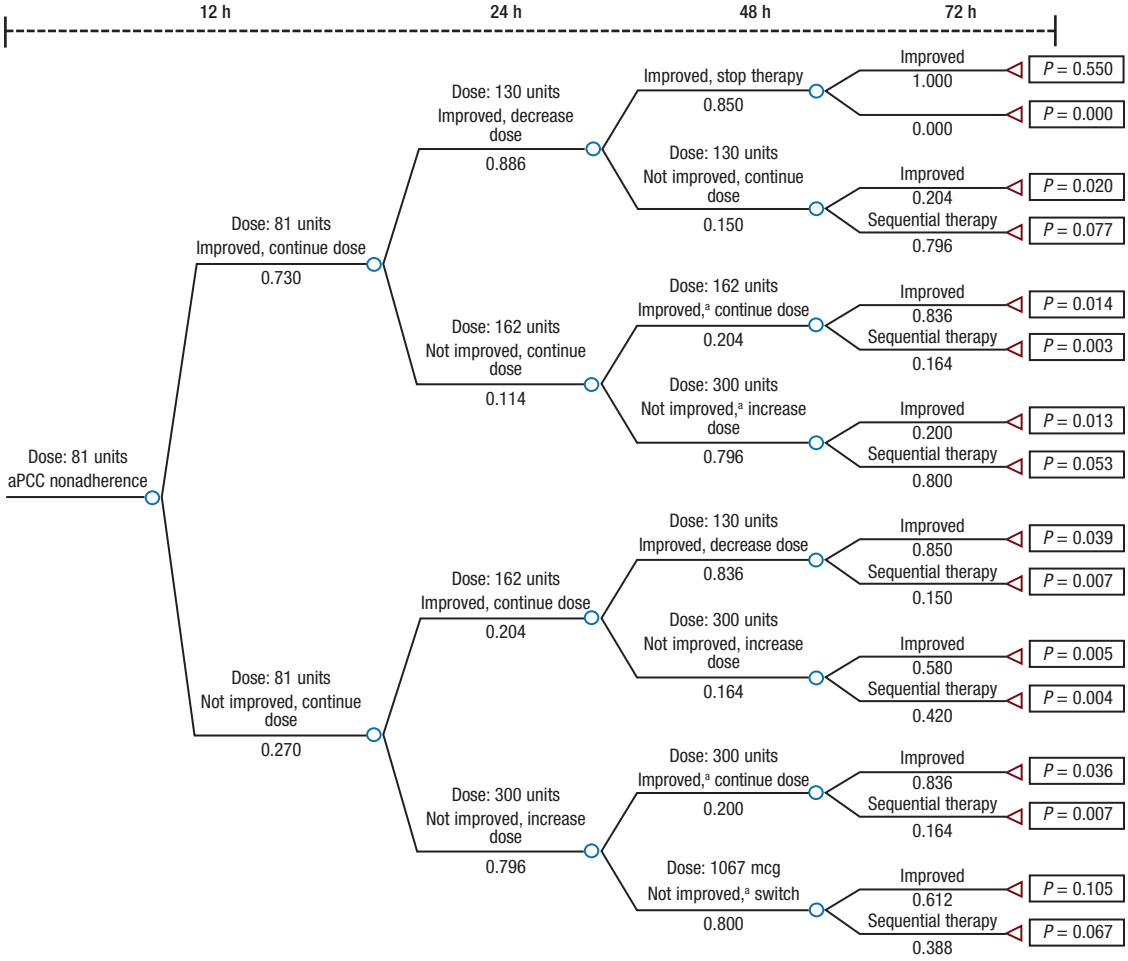
After each round, a summary of responses or forecasts is presented, and panelists reevaluate their answers in light of the replies. During this process, the range of answers becomes smaller as the group converges on consensus. The process is repeated until a predefined stop criterion is reached. The average scores of the final round determine the end result.[16,17]

Consensus groups have been utilized previously to address the treatment of hemophilia.[12,14] In addition, the Delphi method has been used in other complex disease states, such as asthma and epilepsy.[18,19]

To obtain model parameters for input, a modified Delphi methodology was used. Given the specialized nature of hemophilia, 7 international physician experts with experience in treating hemophilia in patients with clotting inhibitors convened in person to form the panel. An audience response system allowed panelists to respond anonymously to questions using a numeric keypad and displayed the results immediately. A moderator facilitated the questions and subsequent discussion for each question addressed to the panel.

A consensus was considered to be reached when the standard deviation of the responses divided by the mean response was less than 0.25. If a consensus was not achieved, a panel discussion would ensue, followed by a revote. Because this was a modified approach, as many as 3 revotes were allowed per question. Input was provided on the number of doses, average dose in U/kg

Figure 3 Nonadherence to Algorithm with aPCC as Initial Agent



NOTE: The first 2 nodes represent 12-hour intervals. The subsequent nodes represent 24-hour intervals. The probability of improving/not improving is provided for each chance node, and overall probabilities for each path are provided at the terminal nodes.

[a]Indicates that consensus was not reached on probability of improving or on dosage amount, as indicated by placement.

aPCC indicates activated prothrombin complex concentrate.

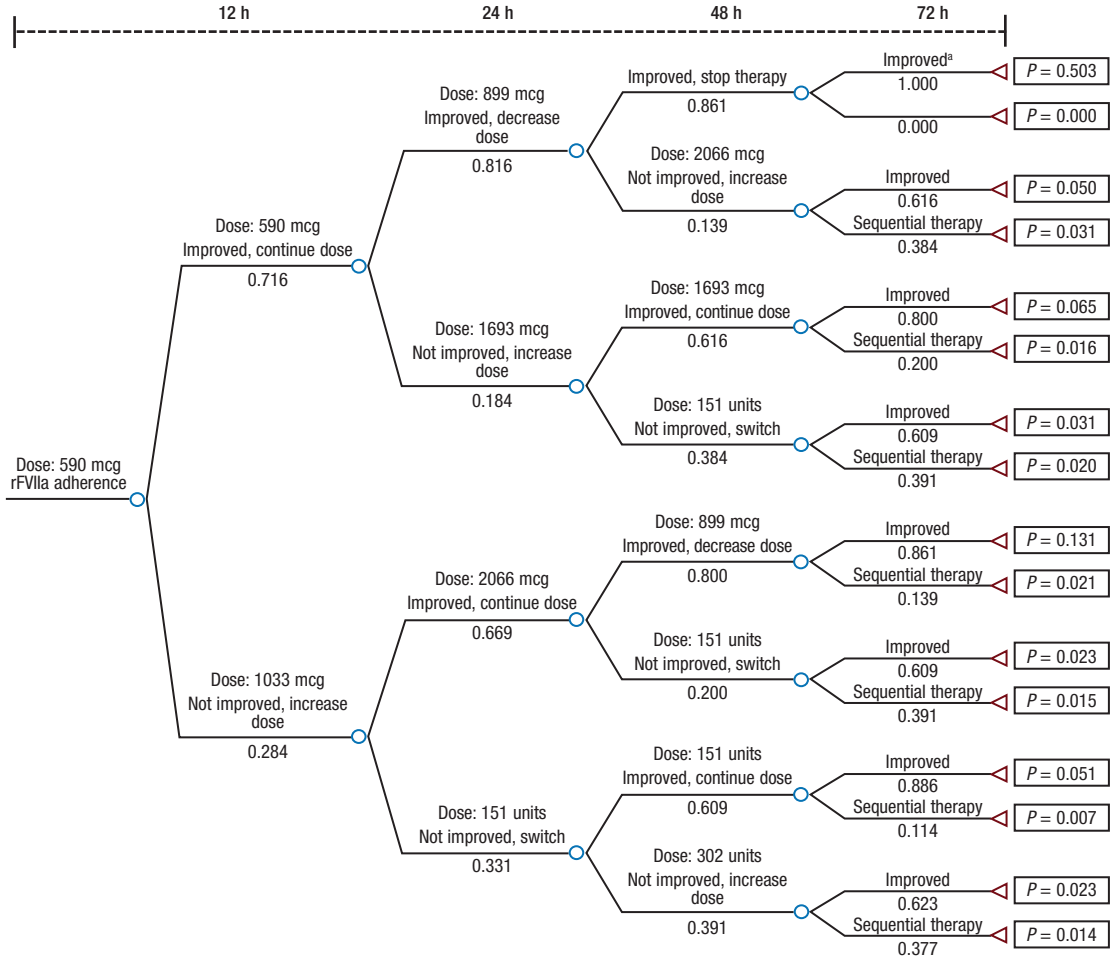
or mcg/kg, and probability of improvement for each agent at specified intervals (12, 24, and 48 hours) separately for aPCC and for rFVIIa.

For example, panelists were initially asked how many doses they would administer during the interval from 0 hours to 12 hours. After panelists responded to the question the first time, discussion ensued, and after the question was asked again, a consensus was reached on the number of doses initially administered. Questioning continued to further delineate the dosing strength until all dosing parameters were established.

Because clinical data are not readily available, an approach similar to what was used to get dosing information from the physicians was used to determine the likelihood of improvement in bleedings based on the panelists' own experience. No specific parameters were established for determining clinical improvement, because there is currently no standardized routine laboratory assay available,[14] and improvement status would ultimately be up to each physician's evaluation of a patient's response.

The general assumption provided to the panelists regarding improvement was based on the criteria established for the timing algorithm by Teitel and colleagues: treatment should continue until the bleeding resolves, as indicated by the functional recovery of the muscle.[14] Questioning ensued for both aPCC and rFVIIa for the adherence and nonadherence algorithm

Figure 4 Algorithm with rFVIIa as Initial Agent



NOTE: The first 2 nodes represent 12-hour intervals. The subsequent nodes represent 24-hour intervals. The probability of improving/not improving is provided for each chance node, and overall probabilities for each path are provided at the terminal nodes.

[a]Indicates that consensus was not reached on probability of improving or on dosage amount, as indicated by placement.

rFVIIa indicates recombinant activated factor VII.

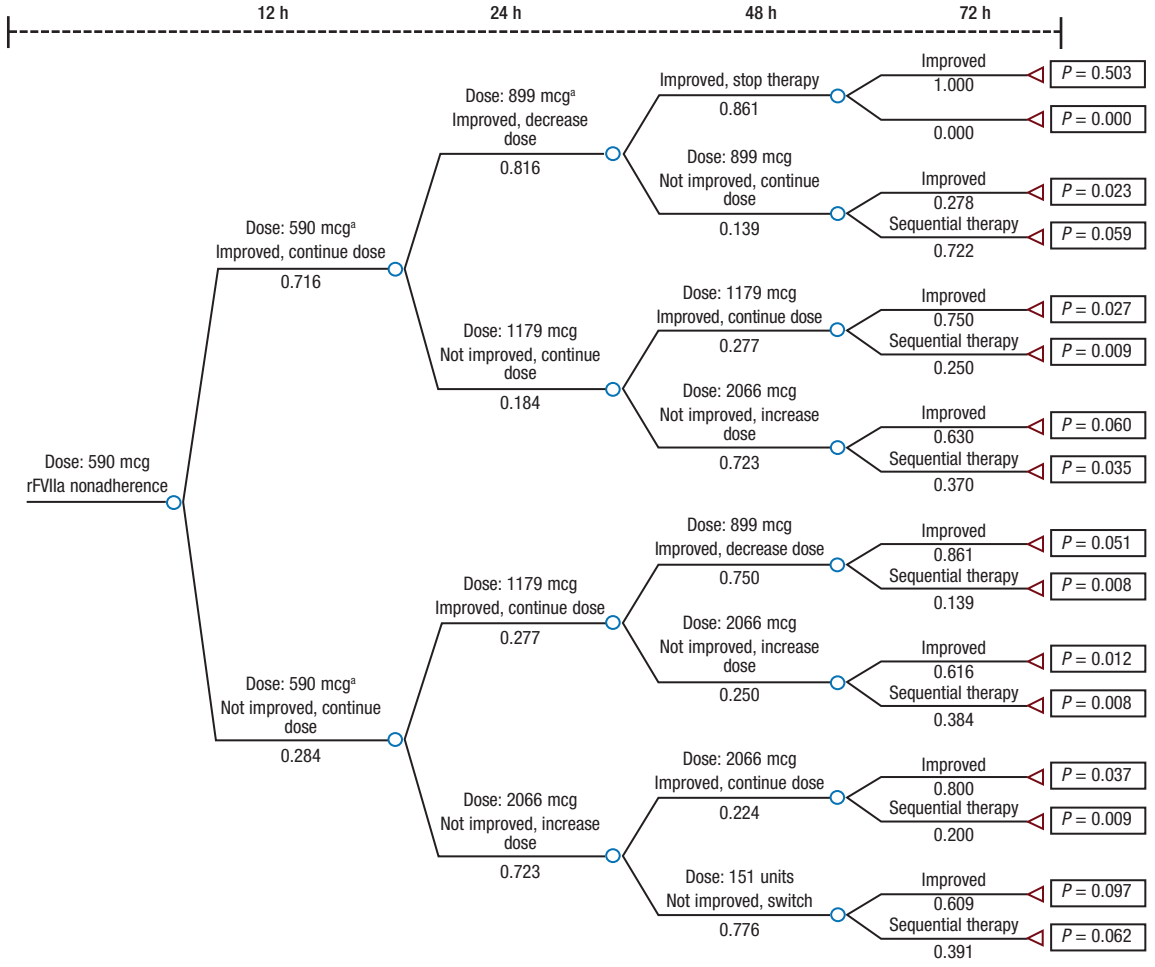
situations. Specific questions posed to the panelists are listed in **Appendices A** and **B** (available at www.AHDBonline.com).

Results

Figures 2, **3**, **4**, and **5** (pages 222-225) show the treatment algorithm chosen by the panel. Results of the modified Delphi process regarding the dosing, switching patterns, and likelihood of bleeding improvement are provided in Appendices A and B. Consensus was achieved for approximately 70% of the questions. Data obtained from questions for which consensus was not reached were still used in the model; however, these are indicated in Figures 2, 3, 4, and 5 by a superscript "a." None of the 4 pathways modeled had 100% consensus for dosing/frequency or likelihood of improvement.

The total dosing for each interval, as well as the likelihood for improvement, are provided for each time interval. Of note, the dosing displayed in the figures is reflective of the total dose for each time interval. For example, in the algorithm with aPCC as the initial agent, a patient who improves at 12 hours and at 24 hours should receive a decreased dose. Initially, this patient would have received 81 units in the first 12 hours and 81 units in the next 12 hours but would receive 130 units total during the next 24 hours (assuming 2 doses of 65 units).

Figure 5 Nonadherence to Algorithm with rFVIIa as Initial Agent



NOTE: The first 2 nodes represent 12-hour intervals. The subsequent nodes represent 24-hour intervals. The probability of improving/not improving is provided for each chance node, and overall probabilities for each path are provided at the terminal nodes.

[a]Indicates that consensus was not reached on probability of improving or on dosage amount, as indicated by placement.

rFVIIa indicates recombinant activated factor VII.

Table Outcomes and Costs, by Adherence to Treatment Algorithm

Impact of the algorithm[a]	Adherence	Nonadherence
Patients improving at 72 hr	74.4%	56.7%
Patients requiring sequential therapy	25.6%	43.3%
Overall average cost	$87,436	$92,604

NOTE: Sequential therapy was estimated at $92,604 for 3 days, based on the regimen described in this article and the cost of aPCC and rFVIIa used in the model. If adherence to the model could help reduce sequential therapy by 17%, the savings would be $92,604 × 0.176 = $16,305 per patient.

[a]Excludes patients who demonstrate consistent improvement from the initiation of bypassing agent therapy.

Clinical Impact

In the evaluation of clinical outcomes, patients who demonstrated consistent improvement from initiation of therapy were excluded from the model, because they would not be expected to require changes deviating from the treatment algorithm. The model showed that regardless of the initial bypassing agent administered, when the treatment algorithm was followed, an average of 74.4% of patients would improve during 72 hours (73.7% for aPCC; 75.1% for rFVIIa) compared with an average of 56.7% (51.7% for aPCC; 61.7% for rFVIIa) when the algorithm was not followed—a 31.2% relative increase in clinical improvement after 72 hours, which was attributed to algorithm adherence (**Table**).

Similarly, the proportion of patients not improving after 72 hours and requiring combined sequential therapy was lower when the algorithm was followed. If the subset of patients who consistently improved from initiation of therapy is removed, an average of 25.6% (26.3% for aPCC; 24.9% for rFVIIa) of patients would require combined sequential therapy when the algorithm is followed; if it is not followed, an average of 43.3% (48.3% for aPCC; 38.3% for rFVIIa) would require this regimen (Table).

Algorithm nonadherence increased the requirement for combined sequential therapy by 69.1%.

Economic Implications

Based on a decision-analysis approach, costs associated with bypassing agent therapy are lower for adhering to the algorithm, regardless of the agent initiated. If 50% of patients used aPCC initially and 50% used rFVIIa, adhering to the treatment algorithm would reduce the overall costs by 5.6%.

Additional cost-savings are noted from algorithm adherence as a result of a reduction in the percentage of patients requiring combined sequential therapy (Table). Using combined sequential therapy for 3 days is estimated to be $92,604 per patient in drug costs alone. Avoidance of combined sequential therapy in 17.6% of patients, based on an absolute reduction from 43.3% to 25.6% of patients requiring sequential therapy, would generate savings as high as $16,305 per patient.

Sensitivity Analysis

Sensitivity analyses indicated that the model is robust to changes in drug prices and clinical efficacy. When modeled prices were increased or decreased by 20% around base-case pricing, treatment algorithm application still resulted in cost-savings from 3.3% to 7.7% for aPCC use and from 2.3% to 9.7% for rFVIIa use.

Cost-savings were also demonstrated when initial efficacy (improving or worsening after the first dose) varied by as much as 20%. The range of savings for patients requiring combined sequential therapy was between 17.4% and 17.6% among those receiving aPCC initially and between 16.6% and 18.4% among those receiving rFVIIa initially.

Discussion

The model's purpose was to quantify the clinical impact of adherence to a treatment algorithm in addressing problem bleedings and to assign a monetary value associated with adjusting therapy in a timely manner, based on a systematic approach to therapy. The efficacy of bypassing agents in controlling bleeding episodes in patients with hemophilia who develop inhibitors has been documented, and the reported success rates range from 80% to 93%.[6-9] Variability in response to therapy does occur[11] and is attributed by some investigators to the different mechanisms of action of aPCC and rFVIIa.[10,20,21]

Responsiveness to treatment has also been documented to change during the course of a single bleeding episode.[13] A clinical trial comparing aPCC and rFVIIa determined that both agents exhibit a similar effect on joint bleedings, but that the efficacy of the 2 agents is rated differently by a substantial proportion of patients with clotting inhibitors.[10]

Further complicating matters is the lack of agreement on dosing.[22] Some protocols suggest the use of high daily doses, whereas others propose lower doses, and the success rates with both approaches are similar.[23] These factors underscore the need to assess the adequacy of the response at regular intervals and make appropriate therapy adjustments in suboptimal situations.[14,15]

If patients who are not improving received treatment according to the algorithm, the dose or frequency of administration would be increased at 12 hours; therapy

would be switched to the alternate bypassing agent at 24 hours for those still not improving; followed by an increase in dose or in frequency of administration at 48 hours for those whose bleeding remains refractory. As a final step, patients would be given combined sequential therapy if they demonstrated no improvement at 72 hours.

If the treatment algorithm was not followed, the model assumed that no treatment evaluation would be made at 12 hours, and all subsequent decisions would be delayed. Based on the model simulation, adhering to the algorithm could result in a relative improvement of more than 30% at 72 hours. This increase in improvement demonstrates the effect of timely therapy adjustments in this population.

Regardless of the bypassing agent used at the initiation of therapy, algorithm adherence also results in fewer patients requiring combined sequential therapy. Based on the present model results, reducing the percentage of patients requiring sequential therapy by 17.5% has the potential for average cost-savings of $16,035 per patient.

Combined sequential therapy has been used for severe refractory bleedings,[24] but its use is controversial.[12] Although there may be situations when this approach is justifiable, minimizing the number of patients who require this regimen clearly has economic advantages and averts theoretical patient safety concerns. However, the agents examined in this analysis are not approved for sequential therapy, and adverse events, such as an increased risk of thrombosis, are a concern for some physicians.[12]

The costs of managing problem bleedings in patients with inhibitors can vary tremendously, depending on the bleeding episode itself and on the medication used.[12] As a result, payers, providers, and patients face a significant challenge in trying to contain costs while achieving the best possible patient care. In view of the complexity of the condition, and the lack of consensus on optimal treatment, models such as the one described in this article can help providers with the decision-making process. Because this model is based on expert opinion, the information and recommendations set forth may assist with the construction of clinical guidelines to guide future therapies. Utilizing the assumption that the inputs derived from the consensus panel reflect real-world costs and outcomes, the information contained in this model may provide insight to clinicians when assessing patients with problem bleeding. In addition, guideline implementation may assist with payment and reimbursement strategies for the use of these agents.

Limitations

No evidence-based treatment guidelines are currently available for this patient population, and the results of this study are based on a simulated model and must be interpreted as such. As with any model, there are limitations associated with interpreting the results. The model considers only limited direct costs associated with bypassing agent therapy (ie, drug costs). Additional direct costs, including those for hospitalization, physician visits, and rehabilitation care, as well as indirect costs associated with decreased productivity, were not considered.

In addition, costs were assessed according to Medicare Part B limits, which may not be reflecting an individual institution's costs. The model aimed to apply the consensus algorithm to a real-world setting by using a panel of experts to characterize treatment patterns and effectiveness in an assessment of the clinical and economic benefits and consequences of algorithm adherence.

For several of the questions posed to the panel, no consensus was reached. In both of the consensus algorithm adherence and nonadherence scenarios presented here, the panel did not reach a consensus on multiple occasions regarding the dosing of rFVIIa. The panel was mostly in agreement with the likelihood of clinical improvement, with the noted exception regarding bleeding worsening at 12 hours and again at 24 hours.

Conclusion

The data presented in this article are based solely on expert opinions, recommendations, and assumptions; therefore, generalizing this information to real-world settings should be done cautiously. However, in the absence of studies directly assessing the impact of guideline adherence on clinical and economic outcomes associated with the use of bypassing agents to control spontaneous bleeding episodes in patients with hemophilia who develop inhibitors, these data provide the best available estimate for those outcomes.

Future studies that assess treatment algorithms such as this one may be warranted to obtain further evidence for the outcomes of bypassing agent therapy in patients with hemophilia. Being able to incorporate real-world data may further help to clarify areas of hemophilia treatment where currently no consensus exists.

Adherence to an algorithm in which treatment is altered at regular intervals based on clinical response has the potential to result in an increase in clinical improvement and reduction in the number of nonresponsive patients requiring sequential therapy. Moreover, algorithm adherence would result in a modest cost-savings in patients with hemophilia who develop clotting factor inhibitors and are experiencing problem bleedings. ■

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Continued

Author Disclosure Statement

Dr Gringeri has received research grants from Baxter Healthcare, Biotest, CSL Behring, and Grifols; he is a Consultant to Baxter Healthcare and Wyeth and is on the Speakers' Bureau of Baxter Healthcare, Biotest, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, and Wyeth. Dr Gomperts is a Consultant to Baxter Healthcare. Dr Leissinger has received research support from and is on the Speakers' Bureau of Baxter Healthcare and Novo Nordisk. Dr d'Oiron is a Consultant to and on the Speakers' Bureau of Baxter Healthcare, and Novo Nordisk. Dr Teitel is a Consultant to Baxter Healthcare and Pfizer and has received grant support from CSL Behring. Dr Young is a Consultant to Baxter Healthcare and Novo Nordisk. Dr Berntorp has received honoraria and research support from Baxter Healthcare. Dr Bonnet, Dr Ewenstein, and Dr Franklin have nothing to disclose.

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STAKEHOLDER PERSPECTIVE

Potential Cost-Savings Using a Treatment Algorithm for Problem Bleeding Episodes in Patients with Hemophilia and Inhibitors

MEDICAL/PHARMACY DIRECTORS: Approximately 30% of people with hemophilia will develop a neutralizing alloantibody, called an inhibitor, to the clotting factor used to treat or prevent their bleeding episodes.[1,2] The mechanism and reason for developing inhibitors are unknown; however, the following risk factors for developing an inhibitor have been identified[1]:

- Age
- Race/ethnicity
- Type of hemophilia gene defect
- Frequency and amount of treatment (inhibitors typically occur within the first 50 exposures to clotting factor)
- Family history of inhibitors
- Type of factor treatment product
- Presence of other immune disorders.

Developing an inhibitor is one of the most serious and costly complications of hemophilia, and direct medical costs are significantly higher for hemophilia patients with inhibitors than those without. The presence of inhibitors has significant clinical implications

STAKEHOLDER PERSPECTIVE *(Continued)*

and an increased morbidity for those with hemophilia. In addition, the healthcare costs associated with inhibitors are significant, because of the cost and amount of product required to stop bleeding.[1] Moreover, patients with hemophilia with inhibitors are twice as likely to be hospitalized for a bleeding complication.[1]

Having been involved with the specialty pharmacy provision of clotting factor to individuals with hemophilia and von Willebrand disease for more than 20 years, hemophilia patients with inhibitors represent the greatest clinical challenge to medical staff and to specialty pharmacies that provide clotting factor to them.

Patients with inhibitors consume a disproportionate amount of the specialty "drugs spending" for payers and for managed care organizations. In fact, patients with inhibitors use the most costly clotting factors commercially available, such as activated prothrombin complex concentrate (aPCC; factor VIII inhibitor bypassing activity [FEIBA]) and recombinant activated factor VII (rFVIIa; NovoSeven RT).

PATIENTS: As a parent of 2 sons with bleeding disorders, when your child experiences a major bleed or a life- or limb-threatening bleed, it does not matter what a treatment algorithm suggests you do as a first step. Your immediate priority is to stop the bleeding, even if it means using doses that are higher or have more frequent dosing intervals than what is listed in the product's package insert or in published treatment algorithms.

PROVIDERS: The information presented in the study is useful and does demonstrate a theoretical cost-savings for treating patients with inhibitors. The algorithm serves as a useful road map in treating individuals with inhibitors. For patients with hemophilia, particularly those with inhibitors, bleeding episodes can be severe if not immediately treated.

Patients with hemophilia, particularly those with inhibitors, vary in their responses to treatment. Recommended doses for one patient may not work or may be unsuitable for another patient. For that reason, treatment guidelines for hemophilia are only that, guidelines, and physicians must still have the flexibility to manage the patient based on their knowledge and the clinical background of the patient, as well as the type of hemorrhagic episode.

Additional Clinical Considerations

Viral safety. An important consideration in using the aPCC bypassing agent is viral safety. To date, there have been no confirmed reports of transmission of viruses definitely associated with the use of aPCC. However, because this product is derived from human plasma, as is the case with all plasma-derived products, the risk of transmission of infective agents (eg, viruses and the Creutzfeldt-Jakob disease agent) cannot be totally eliminated.[3] By contrast, rFVIIa is a recombinant product, entirely free of human plasma.

Thromboembolic events. Serious thrombotic side effects are associated with the use of rFVIIa outside of approved US Food and Drug Administration indications. It should also be noted that people taking aPCCs/PCCs concomitantly with rFVIIa may be at increased risk for thrombotic side effects. When used according to package insert guidelines, rFVIIa has a 1% risk of adverse thrombotic events in patients with inhibitors.[4] Thrombotic adverse events with aPCC therapy are <0.009%.[3]

Payers must not assume that following these published guidelines closely will automatically result in significant cost-savings. An interesting follow-up study would involve patients with inhibitors and the resolution of their bleeding episode as a result of using these treatment algorithms compared with any differences between inhibitor patients who did not follow the algorithm and associated cost differentials between the 2 groups.

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Appendix A Panel Discussion on Dosing and Frequency Questions and Consensus Results

Questions	Number of rounds for discussion	Consensus reached (adherence)	Consensus reached (nonadherence)
aPCC as initiating agent			
Based on your experience, if therapy was initiated with aPCC, how many doses would you give a patient between 0 h and 12 h?	3	Yes	Yes
How many units/kg would you give per dose?	3	Yes	Yes
According to the algorithm, if bleeding improved at 12 h and 24 h, the dose or frequency of administration should be decreased. Given this, how many doses of aPCC would you give between 24 h and 48 h?	3	Yes	Yes
How many units/kg would you give per dose?	1	Yes	Yes
According to the algorithm, if bleeding improved at 12 h but worsened at 24 h, the dose or frequency of administration should be increased. Given this, how many doses of aPCC would you give between 24 h and 48 h?	2	Yes	Yes
How many units/kg would you give per dose?	1	Yes	Yes
According to the algorithm, if bleeding worsened at 12 h, the dose or frequency of administration should be increased. Given this, how many doses of aPCC would you give between 12 h and 24 h?	2	Yes	Yes
How many units/kg would you give per dose?	1	No	Yes
According to the algorithm, if bleeding worsened at 12 h and at 24 h despite increasing the dose or the frequency of administration, treatment should be switched to rFVIIa. Given this, how many doses of rFVIIa would you give between 24 h and 48 h?	1	No	NA
How many units/kg would you give per dose?	1	No	NA
What is the total amount of rFVIIa from 24 h to 48 h?	1	No	NA
rFVIIa as initiating agent			
Based on your experience, if therapy was initiated with rFVIIa, how many doses would you give a patient between 0 h and 12 h?	1	Yes	Yes
How many mcg/kg would you give per dose?	1	Yes	Yes
How many mcg/kg would you give total?	1	Yes	Yes
According to the algorithm, if bleeding improved at 12 h and 24 h, the dose or frequency of administration should be decreased. Given this, how many doses of rFVIIa would you give between 24 h and 48 h?	1	Yes	No
How many mcg/kg would you give per dose?	2	Yes	No
How many mcg/kg would you give total?	2	Yes	No
According to the algorithm, if bleeding improved at 12 h but worsened at 24 h, the dose or frequency of administration should be increased. Given this, how many doses of rFVIIa would you give between 24 h and 48 h?	1	Yes	Yes
How many mcg/kg would you give per dose?	1	Yes	Yes
How many mcg/kg would you give total?	1	Yes	Yes
According to the algorithm, if bleeding worsened at 12 h, the dose or frequency of administration should be increased. Given this, how many doses of rFVIIa would you give between 12 h and 24 h?	1	Yes	No
How many mcg/kg would you give per dose?	2	Yes	No
How many mcg/kg would you give total?	1	Yes	No
According to the algorithm, if bleeding worsened at 12 h and at 24 h despite increasing the dose or the frequency, treatment should be switched to aPCC. Given this, how many doses of aPCC would you give between 24 h and 48 h?	1	Yes	NA
How many units/kg would you give per dose?	1	Yes	NA

aPCC indicates activated prothrombin complex concentrate; h, hours; NA, not applicable, because this is where the algorithm differs for nonadherence; rFVIIa, recombinant activated factor VII.

Appendix B Panel Discussion on Likelihood of Improvement Questions and Consensus Results

Questions	Number of rounds for discussion	Consensus reached (adherence)	Consensus reached (nonadherence)
aPCC as initiating agent			
Based on your experience with aPCC, what % of patients would improve at 12 h if treatment was initiated with aPCC?	3	Yes	Yes
If bleeding improved at 12 h and aPCC treatment was continued at the same dose, what % of patients would still be improving at 24 h?	2	Yes	Yes
If bleeding improved at 12 h and 24 h and the dose of aPCC was decreased at this time point, what % of patients would still be improving at 48 h?	1	Yes	Yes
If bleeding improved at 12 h but worsened at 24 h and the dose of aPCC was increased at this time point, what % of patients would now be improving at 48 h?	2	Yes	NA
If bleeding worsened at 12 h and the dose of aPCC was increased at this time point, what percentage of patients would now be improving at 24 h?	3	No	Yes
If bleeding worsened at 12 h and aPCC was continued at the same dose, what % of patients would now be improving at 24 h?	3	NA	Yes
If bleeding worsened at 12 h but improved at 24 h, what % of patients would still be improving at 48 h if aPCC was continued at the same dose?	1	Yes	Yes
If bleeding worsened at 12 h and 24 h, and patients were switched from aPCC to rFVIIa, what % of patients would now be improving at 48 h?	2	No	NA
If bleeding worsened at 12 h and 24 h and the dose of aPCC was increased at this time point, what % of patients would now be improving at 48 h?	2	Yes	No
If bleeding worsened at 12 h and 24 h and the dose of aPCC was continued at this time point, what % of patients would now be improving at 48 h?	2	Yes	No
rFVIIa as initiating agent			
Based on your experience with rFVIIa, what % of patients would improve at 12 h if treatment was initiated with aPCC?	2	Yes	Yes
If bleeding improved at 12 h and rFVIIa treatment was continued at the same dose, what % of patients would still be improving at 24 h?	2	Yes	Yes
If bleeding improved at 12 h and 24 h and the dose of rFVIIa was decreased at this time point, what % of patients would still be improving at 48 h?	2	Yes	Yes
If bleeding improved at 12 h but worsened at 24 h and the dose of rFVIIa was increased at this time point, what % of patients would now be improving at 48 h?	3	Yes	NA
If bleeding worsened at 12 h and the dose of rFVIIa was increased at this time point, what percentage of patients would now be improving at 24 h?	1	Yes	Yes
If bleeding worsened at 12 h and rFVIIa was continued at the same dose, what % of patients would now be improving at 24 h?	2	NA	Yes
If bleeding worsened at 12 h but improved at 24 h, what % of patients would still be improving at 48 h if rFVIIa was continued at the same dose?	3	Yes	Yes
If bleeding worsened at 12 h and 24 h and patients were switched from rFVIIa to aPCC, what % of patients would now be improving at 48 h?	2	Yes	NA
If bleeding worsened at 12 h and 24 h and the dose of rFVIIa was increased at this time point, what % of patients would now be improving at 48 h?	2	Yes	Yes
If bleeding worsened at 12 h and 24 h and the dose of rFVIIa was continued at this time point, what % of patients would now be improving at 48 h?	2	Yes	Yes

aPCC indicates activated prothrombin complex concentrate; h, hours; NA, not applicable, because algorithm differs; rFVIIa, recombinant activated factor VII.