A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A

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ABSTRACT

Background
Severe hemophilia requires life-long treatment with expensive clotting factor concentrates; studies comparing effects of different therapeutic strategies over decades are very difficult to perform. A simulation model was developed to evaluate the long-term outcome of on demand, prophylactic and mixed treatment strategies for patients with severe hemophilia A.

Design and Methods
A computer model was developed based on individual patients' data from a Dutch cohort study in which intermediate dose prophylaxis was used and a French cohort study in which on demand treatment was used, and multivariate regression analyses. This model simulated individual patients' life expectancy, onset of bleeding, life-time joint bleeds, radiological outcome and concentrate use according to the different treatment strategies.

Results
According to the model, life-time on demand treatment would result in an average of 1,494 joint bleeds during the hemophiliac's life, and consumption of 4.9 million IU of factor VIII concentrate. In contrast, life-time intermediate dose prophylaxis resulted in a mean of 357 joint bleeds and factor consumption of 8.3 million IU. A multiple switch strategy (between prophylactic and on demand treatment based on bleeding pattern) resulted in a mean number of 395 joint bleeds and factor consumption of 6.6 million IU. The estimated proportion of patients with Pettersson scores over 28 points was 32% for both the prophylactic and the multiple switching strategies, compared to 76% for continuous on demand treatment.

Conclusions
The present model allows evaluation of the impact of various treatment strategies on patients' joint bleeds and clotting factor consumption. It may be expanded with additional data to allow more precise estimates and include economic evaluations of treatment strategies.

Key words: hemophilia, prophylaxis, on demand, arthropathy, cost, outcome.

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Introduction

Patients with severe hemophilia A lack clotting factor VIII. As a consequence, they suffer from recurrent spontaneous and trauma-related bleeds. The majority of these bleeds occur in the joints, ultimately resulting in hemophilic arthropathy. Severe arthropathy is associated with chronic pain, joint destruction, and disability. Since the introduction of replacement therapy,[1] treatment has been continuously intensified. Moreover, there has been a shift in treatment towards regular prophylactic infusions to prevent bleeds, especially in children.[2-4] Both in the Netherlands and Sweden, prophylaxis has been standard treatment for over 30 years. In general, more intensive treatment is associated with better outcome. However, the use of clotting factor is very expensive and this may be one of the main factors why prophylaxis is not adopted as standard treatment in all Western countries.[5] For example, the annual consumption for a young adult on prophylaxis in the Netherlands would be 105,000 IU.[6] In Sweden, higher dosages are used, and the average consumption would be 280,000 IU/year.[2] However, on demand treatment may lead to more varied clotting factor consumption and mean consumptions as high as 140,000 IU/year per patient have been reported.[7,8]

Given the high costs of this life-long treatment, it is important to use clotting factor concentrates in the most efficient manner by balancing consumption and effects. This balance may differ per patient and vary in different stages of life. Assessing life-long consumption and effects requires evaluation of all different strategies used. Unfortunately, studies on long-term effects of different treatment strategies for severe hemophilia are scant and usually describe the effects of one strategy only. Randomized controlled clinical trials comparing treatments into adulthood are not feasible and retrospective studies are likely to suffer from confounding by indication as they compare selected groups of patients.[9,10]

In cases in which true experiments are unfeasible or impracticable, modeling techniques can be used to synthesize information from different sources. Moreover, experiments can be simulated to explore alternative strategies both for short- and long-term outcomes. Individualized regimens provided by mixed strategies in which patients switch from one strategy to another depending on bleeding patterns are of particular interest. These individualized regimens are expected to provide the most efficient and thus most cost-effective use of clotting factor concentrates.

Using data from existing cohorts, we aimed to develop a model to allow for the comparison of different treatment strategies, ranging from long-term on demand therapy to different prophylactic strategies.

Design and Methods

A model was developed in Matlab™ scripting language to simulate the life-time clinical evolution of a patient with severe hemophilia A. Knowledge on clotting factor consumption and effects of treatment for severe hemophilia from different sources was used to simulate the long-term effects of different therapeutic strategies. In order to explore all possible combinations of patients' characteristics 20,000 patients were simulated, and four treatment strategies were applied to each patient: a pure prophylactic strategy, a pure on demand strategy, and two strategies in which patients start off with prophylaxis but may switch to on demand treatment according to their bleeding pattern and age. The project was approved by the Institutional Review Board of the University Medical Center Utrecht, Utrecht, the Netherlands.

Treatment strategies

Based on the original data, the mean dose of factor VIII used for a joint bleed was 50 IU/kg for on demand treatment. A detailed description of prophylaxis according to the Dutch regimen was published elsewhere.[11] In brief, prophylaxis is started after the first joint bleed. The dosage and frequency of the clotting factor are adjusted according to the bleeding pattern: the minimum frequency of prophylaxis is 2x/week for hemophilia A. In this intermediate dose regimen, the weekly dosage is 24 – 45 IU/kg.

In the model, four strategies were applied to each simulated patient (Table 1). In the *pure prophylaxis* strategy, intermediate dose prophylaxis was started at an early age and administered at least twice a week. *On demand treatment* is defined as treatment if a bleeding episode occurs, sometimes combined with short courses of prophylaxis. In addition, two switching strategies were modeled, both assuming that patients started with prophylaxis after the first joint bleed and would continue with prophylactic treatment until the age of 18 years. In the *single switch strategy (SSW)* all patients changed to on demand therapy at the age of 18 years. This strategy investigates the long-term effects of minimizing the number of joint bleeds during early age. The *multiple switch strategy* allows for repeated switching between prophylaxis and on demand treatment based on bleeding pattern in adulthood, tolerating less intensive treatment of patients with milder bleeding patterns.

Table 1. Simulated treatment strategies. Prophylaxis is started after the first joint bleed. Dosage and frequency according to bleeding pattern: minimum frequency 2x/week, weekly dosage 24-45 IU/kg.

Strategy	Treatment
1. Pure on demand (OD)	Treatment in case of bleeding only
2. Pure prophylaxis, Dutch regimen (PR)	Start prophylaxis after first joint bleed Switch: none, lifetime prophylaxis
3. Single switch strategy (SSW)	Start prophylaxis after first joint bleed Switch to OD: at 18 years
4. Multiple switch strategy (MSW)	Start prophylaxis after first joint bleed Switch to OD: at ≥ 18 years, if: ≤ 1 joint bleed/year for 2 consecutive years. Switch back to PR: if either ≥ 9 joint bleeds in any year, or ≥ 7 joint bleeds/year for 2 consecutive years, or ≥ 6 joint bleeds/year for 3 consecutive years. Maximum 8 switches of PR to OD.

Data

Various characteristics of the original datasets are shown in Table 2. The model for simulation of the pure prophylactic strategy was based on data concerning treatment and outcome in the period of 1988 – 1997 in 111 patients receiving prophylactic therapy at the Van Creveldkliniek in the Netherlands. All had severe hemophilia (factor VIII activity <0.01 IU/dL), were born between 1965 and 1993, had no history of inhibitors, and were primarily treated with prophylaxis.[4]

The model for simulation of the on demand strategy was based on the original dataset of a French multicenter study by Molho *et al.*[7] This study provided data on 69 patients with severe hemophilia A, born between 1970 and 1982, without a history of inhibitors, who were primarily treated on demand and received no prophylaxis at evaluation. Data on joint bleed frequencies and factor VIII consumption were collected cross-sectionally in 1997.

Modelling process

The model simulates three main characteristics of a patient with severe hemophilia: (i) the average of the patient's annual number of joint bleeds, (ii) the age at first joint bleed and (3) the patient's life expectancy. The first step in the model is to draw these three main characteristics of a patient. All data were drawn from actual distributions obtained from the Dutch data (Appendix) and, therefore, properly reflect the heterogeneity among patients with hemophilia A. The median age at first joint bleed was 2.2 years (95% CI: 0.29 – 5.24 years). The median life expectancy for men was derived from the Dutch National Bureau of Statistics and was estimated to be 77 years (95% CI: 51 – 95 years). The age at first joint bleed and life expectancy are independent of treatment strategy.

The annual number of joint bleeds on prophylaxis drawn from the Dutch data is an average, and comes with its own distribution. Using this average number of annual joint bleeds for a particular patient, the model derives the actual annual number of joint bleeds for each year on prophylaxis for this patient (Appendix). For on demand treatment, only cross-sectional data were available, which contain no information on time-dependent variation in a given patient. In order to compensate for this we assumed the time-effect to be proportional to that observed among patients on prophylaxis. In the datasets, the average annual number of joint bleeds in patients treated on demand (20.9/year) was 4.39 times higher than that for patients on prophylaxis (4.76/year). The distribution of bleeds in patients receiving on demand treatment was modeled using bleeding frequencies in patients on prophylaxis multiplied by 4.39 (Appendix).

Finally, two additional outcomes were deduced: the Pettersson score and the annual clotting factor consumption. The radiological Pettersson score reflects the degree of arthropathy (minimum score 0 for joints without signs of arthropathy, to a maximum score of 78 points).[12] The relationship between bleeds and the Pettersson score has been reported previously and is one point increase in the Pettersson score per 12.6 joint bleeds, on average (95% CI: 11.1 – 14.7).[13]

The relationship between bleeds, treatment, and clotting factor consumption on prophylaxis was determined using the Dutch dataset. For on demand treatment, the French dataset was used (Appendix).

For the two switching strategies, the model used either the pure prophylactic strategy or the on demand strategy for different treatment intervals.

All four strategies were applied for each simulated patient. Differences in outcomes are a direct result of differences in therapeutic approaches as all the patients' characteristics were equal for all treatment strategies. A simulation was performed for 20,000 patients and their bleeding histories, Pettersson scores, and cumulative clotting factor consumption were recorded and compared. An internal validity check showed good concordance of results, confirmed by a Kolmogorov-Smirnov goodness of fit test comparing simulated number of joint bleeds and the historical number of joint bleeds in the patients' datasets (Kolmogorov-Smirnov = 0.32).

Results

The estimated average cumulative number of joint bleeds, Pettersson score, and clotting factor consumption per patient according to age and therapeutic strategy are shown in Table 3. The comparison of pure intermediate dose prophylaxis and pure on demand strategies using this model showed that pure prophylaxis greatly reduces the life-time number of bleeds: from 1494 if treated on demand, to 357 if given prophylaxis. However, clotting factor consumption on prophylaxis was much higher at 8.3 million IU, compared to 4.9 million IU for those treated on demand. At the end of life, the average Pettersson score in patients treated with life-time prophylaxis was only about 23 points (95% CI: 0-78), which is generally associated with little functional impairment,[6] whereas the mean score for those treated on demand only was very high at 55 points (95% CI: 0-78).

The single switch strategy, when applied to all patients

Table 2. Characteristics of the datasets. The simulation model is based on both the original prophylaxis and on demand datasets as reported by Fischer[4] and Molho.[7]

		Prophylaxis[4]	On Demand[7]
Study Design			
	Number of patients	111	69
	Dataset	Longitudinal 1988-1997	Cross-sectional 1997
	Total years of follow up	610	69
Data			
	Mean age	16.4 (1.3-33.4)	22.47 (16.7-28.0)
	Mean age at first joint bleed	2.43 (0.17-13.18)	Not Available
	Mean annual number of joint bleeds per patient	4.91 (0-37.7)	20.91 (0-104)
	Mean clotting factor use (IU/kg/year)	2100 (251-6277)	1369 (0-6352)

Data are means (range).

Table 3. Results of the simulation according to age and treatment strategy.

Age		On demand	Prophylaxis	Single-switch strategy	Multiple-switch strategy
20					
	Cumulative joint bleeds	352 (8-1322)	84 (6-280)	116 (8-400)	85 (8-280)
	Pettersson score	23 (0-72)	4 (0-19)	6 (0-28)	4 (0-19)
	Cumulative clotting factor use (IU×10^6)	0.7 (0.2-2.6)	1.4 (1-1.8)	1.3 (0.9-1.8)	1.3 (1-1.8)
40					
	Cumulative joint bleeds	768 (17-2868)	184 (10-652)	533 (22-1962)	198 (22-652)
	Pettersson score	41 (0-78)	11 (0-48)	33 (0-78)	12 (0-48)
	Cumulative clotting factor use (IU×10^6)	2.2 (0.5-8.3)	4 (3-5.3)	2.8 (1.1-7.4)	3.3 (1.1-5.2)
60					
	Cumulative joint bleeds	1183 (27-4432)	283 (13-1023)	948 (34-3519)	310 (34-1020)
	Pettersson score	51 (0-78)	18 (0-77)	46 (0-78)	20 (0-77)
	Cumulative clotting factor use (IU×10^6)	3.8 (0.8-13.9)	6.5 (4.7-8.8)	4.3 (1.1-12.9)	5.2 (1.1-8.5)
Lifetime					
	Cumulative joint bleeds	1494 (32-5754)	357 (14-1333)	1258 (40-4826)	395 (40-1333)
	Pettersson score	55 (0-78)	23 (0-78)	52 (0-78)	26 (0-78)
	Cumulative clotting factor use (IU×10^6)	4.9 (1-18.7)	8.3 (4.8-12.5)	5.4 (1.2-17.8)	6.6 (1.2-12.9)

Data are mean values (95% CI) excluding patients who died before reaching the presented age.

without consideration of bleeding pattern, resulted in a rapid increase of the cumulative number of joint bleeds and subsequent arthropathy from 18 years onwards. At the end of life patients still suffered considerable arthropathy, with an average Pettersson score only three points lower than that of patients receiving life-time on demand treatment. The additional clotting factor use of this strategy was 0.55 million IU of concentrate. Compared to life-time on demand treatment, the multiple switch strategy reduced, on average, the cumulative number of joint bleeds by 1,099, for an additional clotting factor use of 1.7 million IU of concentrate.

The long-term effects for each of the treatment strategies may best be described by arthropathy, reflected by Pettersson scores. Considering a Pettersson score of 28 as the threshold for clinically relevant damage,[14] the effects of the different treatment strategies are illustrated in Figure 1. This figure shows the proportion of patients with a Pettersson score higher than 28 points, according to age and treatment strategy. The effects of preventing joint bleeds with prophylactic treatment are clear: at the age of 20, 32% of the patients treated on demand and 2% of those treated with a single switch strategy had a Pettersson score higher than 28 while none of the patients treated with the other two strategies had reached a Pettersson score of 28 points. At the age of 40 years, this proportion had increased to 59% for patients treated on demand, 47% for those treated with the single switch strategy and 11% for those treated with the multiple switch or the prophylactic strategy. Proportions eventually rose to 76% (on demand treatment), 72% (single switch strategy), and 32% (prophylaxis and multiple switch strategy) at the end of life. At the age of 50, which is still a productive phase of life, the probability of having crippling joint damage (Pettersson score > 70) was 38% in patients treated on demand, 28% among those treated with the single switch strategy and 1.7% for patients treated with prophylaxis or the multiple switch strategy. The fluctuation in outcomes for patients aged over 90 are caused by the limited number of surviving patients.

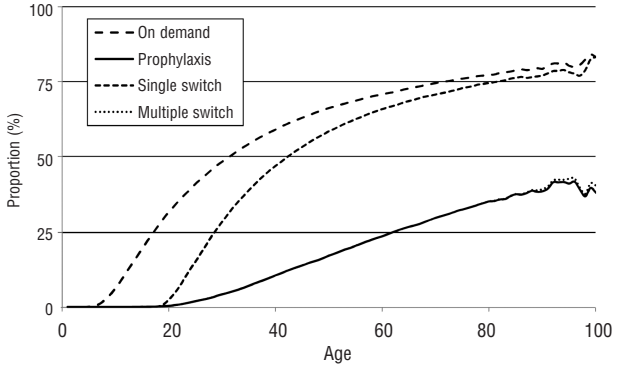

Figure 1. Proportion of patients with a Pettersson score > 28 according to age and therapeutic strategy. The single switch strategy and the on demand (years) strategy curves stay close together, while the multiple switch strategy and the pure prophylaxis strategy results are almost identical. These results suggest that the multiple switch strategy is very effective at preventing arthropathy.

The individualization of treatment achieved by the multiple switch strategy is illustrated in Figure 2, showing the estimated distributions of clotting factor consumption according to treatment strategy. While lifetime clotting factor consumption in 95% of patients on pure prophylaxis was between 4.8 and 12.5 million IU, patients treated on demand showed wide variation of clotting factor consumption, including 36% of patients with a life-time consumption of over 4.8 million IU. Thus, these patients had consumed as much as patients on prophylaxis, while their eventual number of joint bleeds, with resulting damage, was considerably higher. At the other end of the distribution, 19% of patients treated on demand bled only infrequently and used less than one million IU.

The distribution of the multiple switch strategy shows a two-peak pattern, the left peak representing patients treat-

ed mostly on demand and the right peak patients treated with prophylaxis only. Simulations showed that 53% of patients received life time prophylaxis and 25% of the patients switched to on demand therapy, remaining with this strategy for the rest of their life. The remaining 22% switched several times between on demand and prophylaxis until the maximum number of eight switches was reached and eventually received prophylactic therapy.

Discussion

This study presents a micro-simulation model based on real data which may be used to simulate the life-time consumption and effects of different treatment strategies for patients with severe hemophilia A. The outcome of the present model suggests that life-time prophylactic therapy is associated with the highest clotting factor consumption and the lowest degree of arthropathy. Switching strategies that are guided by an individual patient's bleeding pattern may significantly reduce clotting factor consumption with an only limited increase in arthropathy, by treating low bleeders with on demand therapy.

For a correct interpretation of the results, some aspects of the design of the model need to be discussed.

The validity of the model depends heavily on the data it is built upon. In this case, the estimated baseline characteristics are corroborated by published data: the estimated age at first joint bleed was in accordance with previous reports[15] and the current life expectancy of patients with severe hemophilia but negative for human immunodeficiency and hepatitis viruses has almost reached that of the normal population.[16] Estimates of bleeding frequencies and clotting factor consumption on intermediate dose prophylaxis were based on data from hemophilia A patients in a cohort from the Van Creveldkliniek.[17] As expected, Pettersson scores at the age of 20 were lower in the simulated patients than in the actual cohort studied in 1997. This may be attributed to an earlier start of prophylaxis in the simulated cohort. For the interpretation of the results of prophylactic treatment, it must be emphasized that these data concern an intermediate dose prophylactic regimen used in the Netherlands. The estimated effects of the pure prophylactic strategy cannot, therefore, be directly compared with results of prophylactic regimens using higher doses. However, higher dosed strategies could easily be incorporated into the present model.

Model parameters for the simulation of bleeds during on demand treatment could not be determined as accurately as for the prophylactic strategy. Due to the limited data on the number of joint bleeds and clotting factor consumption, it was assumed that the bleeding frequency for on demand treatment was independent of age, previous treatment and/or the presence of arthropathy. For young children around 6 years old, the mean number of joint bleeds during on-demand treatment has been reported to be 0.6/month, which is lower than in our model.[18] For adult patients, however, simulated bleeding frequencies for patients treated on demand (mean 20.9 joint bleeds per year) were in accordance with the frequencies of 16.5 per year and 11.1 per 6 months reported in large studies by Aledort[19] and Schramm,[8] respectively. The mean Pettersson score at 23 years old was 26 in the model, and 19 in the group studied by Molho.[7] The mean simulated clotting factor consumption for on demand treatment was

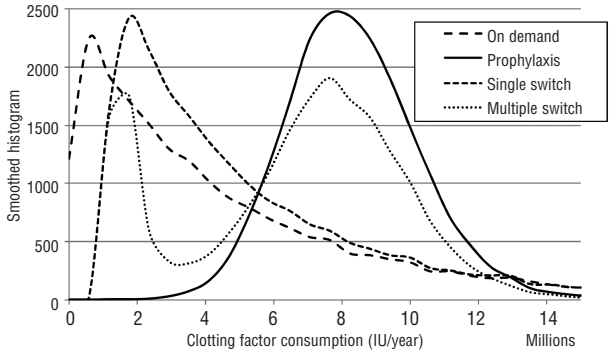

Figure 2. Distribution of the lifetime clotting factor consumption according to treatment strategy. Note the double peak pattern for the multiple switch strategy as a result of mixing the prophylaxis and on-demand treatment strategies.

1330 IU/kg/year. Reported means were 1038 IU/kg/year[19] and 1224 IU/kg/year.[8] All estimates of bleeding rates and clotting factor consumption were, however, based on data from patients with hemophilia A under the age of 30. As bleeding frequencies appeared constant across ages, the model-based estimate is expected to be accurate. For clotting factor consumption, however, we assumed stabilization from the age of 30 onwards. This is in contrast with previous studies, suggesting an increase of clotting factor consumption with increasing joint damage.[20] If this is correct, clotting factor consumption after the age of 30 would be underestimated by the current model.

The estimated effect of joint bleeds on arthropathy was only studied for patients on prophylaxis. Modification of the effect of bleeds by age was not considered. Some authors suggest that immature cartilage is more susceptible to damage by blood;[21] if this is the case, it would lead to an overestimation of arthropathy in the single-switch strategy by our model. In this model the effects of different treatment strategies are expressed in terms of the number of joint bleeds and the Pettersson scores only. However, the relationship between the Pettersson score and a measurement of the quality of life (e.g. degree of invalidity) are not yet fully clear.[14]

Due to the lack of data for patients with hemophilia B, the present model was built only for patients with hemophilia A. Its results may not be directly applied to hemophilia B patients, as the dosing of factor IX is different and there is growing evidence that patients with hemophilia B have a milder bleeding phenotype.[22-24]

In this study, clotting factor consumption was used to reflect treatment intensity, which is strongly associated with direct medical costs.[7,25] By adding information on other medical costs (e.g. costs of orthopedic surgery), and benefits, the model can evolve to become an instrument for economic evaluations. Until now, only Smith *et al.*,[25] Miners[26,27] and Risebrough[28] have used modeling techniques to study the cost-effectiveness of prophylactic and on demand treatment. None of these models was based on modeling individual patients' data and, therefore, none can be used to explore the clinical consequences of alternating different treatment strategies.

In order to enhance the validity of the micro-simulation model, additional data are needed. In particular, longitudi-

nal data on the natural history of bleeding episodes in patients subject to on demand treatment are lacking in the current version. Moreover, additional relevant outcome parameters could be incorporated, including health-related quality of life, quality-adjusted life-years and labor force participation, to produce more enhanced estimates of long-term effects. By introducing additional data on costs and benefits, the model could be used to perform economic evaluations.

How could the results from the current micro-simulation model be used? The model can be used to evaluate expected effects of hypothetical treatment strategies for hemophilia A. The results of the strategies modeled here clearly show that different treatment strategies yield very different results, and suggest that individualization according to bleeding phenotype should be considered. In the case of hemophilia, a disease for which long-term clinical trials are unfeasible, models help to consider the outcome of different potential treatment strategies with a life-long perspective. However, their predictive power relies entirely on their ability to predict bleeding patterns accurately.

In conclusion, the present model enables the simulation and evaluation of different treatment strategies in individual patients. It is a first step towards an instrument that allows evaluation of the consequences of different treatment strategies for patients with severe hemophilia A with a life-time perspective, and may eventually evolve into a full economic evaluation model.

Authorship and Disclosures

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