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Modeling to Predict Factor VIII Levels Associated with Zero Bleeds in Patients with Severe Hemophilia A Initiated on Tertiary Prophylaxis

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Abstract

Background Factor VIII (FVIII) trough levels > 1 IU/dL in patients with severe hemophilia A receiving regular prophylaxis may optimize bleed protection.

Objectives In this post hoc analysis of patients receiving tertiary prophylaxis for approximately 1 year, the relationship between estimated FVIII levels and reported bleeds was investigated to predict the potential for zero bleeds.

Methods Sixty-three patients (median [range] age, 28 [7–59] years) with severe hemophilia A (229 bleeds) were included. FVIII levels at time of each bleed were estimated from single-dose individual pharmacokinetics. The highest estimated FVIII level at which patients experienced a bleed was considered the "potentially effective trough level" for that bleed type. Kaplan–Meier estimates of proportions of patients with no bleeds above certain estimated FVIII levels were determined. Those not experiencing a bleed in the trial were assumed to have a bleed at 0 IU/dL (pragmatic approach) or at their median trough level (conservative approach).

Results Kaplan–Meier estimates based on pragmatic approach predicted zero all bleeds, joint bleeds, and spontaneous joint bleeds in 1 year in 40, 43, and 63% of patients, respectively, when the potentially effective trough FVIII level was set at

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- coagulation factors
- hemophilia A/B
- factor VIII
- pharmacodynamics

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1 IU/dL. Between 1 and 10 IU/dL, every 1 IU/dL rise in estimated FVIII level was associated with an additional 2% of patients having zero all bleeds.

Conclusion This post hoc analysis confirms benefits with trough levels of approximately 1 to 3 IU/dL in most patients starting tertiary prophylaxis; prophylaxis with higher trough levels may help patients to achieve zero bleeds.

Introduction

Patients with severe hemophilia A have a deficiency of coagulation factor VIII (FVIII) characterized by recurrent spontaneous and trauma-induced joint and soft-tissue bleeds. Hemarthroses cause progressive arthropathy, chronic pain, and musculoskeletal disability.[1,2] Standard treatment is to reduce or prevent bleeds with regular infusions of FVIII, a practice called prophylaxis. Prophylactic infusions of FVIII should be started in young children before, or at the time of, their first hemarthrosis.[3,4] In young children, this treatment strategy has been shown to reduce or prevent joint bleeds and arthropathy.[5,6]

The original concept for prophylaxis was to infuse FVIII on a regular basis to convert the bleeding phenotype from that of severe hemophilia to one of moderate hemophilia. The hypothesis was that maintaining the FVIII trough level $>$ 1 IU/dL would limit the number of spontaneous joint bleeds and thus decrease joint damage.[7] Although this practice is associated with a marked reduction in the number of bleeds, it does not completely eradicate spontaneous joint bleeds in all patients, and joint disease has still been observed in young adults over a 25- to 30-year period.[8,9] Although the role of the FVIII trough level in reducing the risk of breakthrough bleeding is undoubtedly important, other parameters that play a role are now known, including the amount of time spent at low FVIII levels[10] and peak FVIII levels.[11] The annualized number of joint bleeds experienced by a patient with hemophilia is related to their baseline FVIII level; the number of bleeds decreases rapidly as the FVIII level increases from $<$ 1 to approximately 3 IU/dL, and continues to fall until the FVIII level has reached approximately 12 IU/dL.[12]

Prophylaxis is used routinely in children, and is now becoming standard care for adults with severe hemophilia A.[13] If prophylaxis is started later in life, it is inevitable that arthropathy will have developed and target joints may be present. This may affect the efficacy of prophylaxis and influence the level of FVIII required to prevent bleeds.

The level of FVIII required to prevent all bleeds in patients with severe hemophilia A is not well described and will vary between individuals (pharmacokinetic [PK] profile, level of activity). It is likely that patients starting tertiary prophylaxis will have active target joints with established arthropathy, and in this situation, higher FVIII levels may be needed to prevent spontaneous joint bleeds, at least initially. To investigate the relationship between FVIII levels and bleeds, we performed a post hoc analysis of data derived from a study of patients initiated on tertiary prophylaxis[14] (i.e., regular continuous treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints[15]). The data set was used to predict FVIII trough levels that could be potentially effective in the prevention of all bleeds and spontaneous joint bleeds in patients receiving regular prophylaxis. Prevention of all bleeds is a measure of the overall protection provided and prevention of spontaneous bleeds is arguably the minimum outcome expected of a prophylactic treatment regimen.

Methods

Clinical Study Summary

Details of the prophylaxis study of antihemophilic factor (recombinant; ADVATE; Baxalta US Inc., a member of the Takeda group of companies, Lexington, Massachusetts, United States; NCT00243386) have been described previously.[14] This multicenter, randomized, two-arm study compared annualized bleeding rates (ABRs) between two prophylactic treatment regimens (standard prophylaxis or PK-guided prophylaxis).

To meet key inclusion criteria for initiation of tertiary prophylaxis, patients needed to be aged $\geq$ 7 and $<$ 65 years, have moderately severe or severe hemophilia A (baseline FVIII level $\leq$ 2 IU/dL), have received on-demand treatment for $\geq$ 12 months with a minimum of 150 exposure days to FVIII concentrates, and have had a minimum of eight joint hemorrhages before enrollment. Joint disease was inferred by the presence of target joints. After a washout period of $\geq$ 72 hours, all enrolled patients underwent a PK study consisting of an intravenous bolus infusion with 50 $\pm$ 5 IU/kg of antihemophilic factor (recombinant) followed by 10 postinfusion venous blood samples up to 48 hours after infusion. Of the 82 enrolled patients, 66 were randomized to one of the two prophylactic regimens following 6 months of on-demand treatment in the trial. The randomization at 6 months was stratified according to the presence of target joints, defined as joints in which at least four hemorrhages had occurred within a period of 6 months, or in which $>$ 20 lifetime hemarthroses had occurred. Patients assigned to standard prophylaxis received 20 to 40 IU/kg of antihemophilic factor (recombinant) every other day—the precise dosage determined by the investigator on the basis of the individual patient's FVIII half-life, incremental recovery, and clinical status. This resulted in a median measured FVIII trough level of 3 IU/dL.[14] Patients assigned to PK-guided prophylaxis received 20 to 80 IU/kg of antihemophilic factor (recombinant) every 72 hours, with the aim of achieving a FVIII trough level of 1 IU/dL.

Post Hoc Analysis of the Relationship between Bleeds and Estimated FVIII Levels at the Time of Each Bleed

This post hoc analysis only included patients with severe hemophilia A (defined as having at least one observed FVIII level of $<$ 1 IU/dL during the study) who were treated with

prophylaxis for $\geq$ 180 days. Bleeds were self-reported by patients, and descriptions of bleeding episodes (including etiology [spontaneous and traumatic/injury-related], severity, and anatomical site[s]) were recorded in patient diaries and verified by the investigator. The severity of the bleeding episode was determined by the following scale: (1) minor: little or no pain; little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity; (2) moderate: mild to moderate pain; some decrease in range of motion of affected joint (if joint bleeding event); moderate decrease in mobility and activity; and (3) major/life-threatening: significant pain; substantial decrease in range of motion of affected joint (if joint bleeding event); incapacity; life threatening.

A total of 63 patients and 229 bleeds were eligible for analysis. Of the 63 patients included in the analysis, 41 recorded at least one bleed during the prophylactic treatment period.

Estimation of FVIII Level at the Time of Each Bleed

Patient-specific PK profiles were obtained from the patients' FVIII activity level measurements collected during the PK study. Each patient had between 7 and 10 postinfusion FVIII activity level measurements. A two-compartmental model, parameterized in terms of macro constants with a Poisson error, was fitted independently to the postinfusion PK data from each patient using iteratively reweighted least squares with SAS (Base SAS 9.3 Procedures Guide, Second Edition, and SAS/STAT 12.1 User's Guide; 2012; SAS Institute Inc., Cary, North Carolina, United States) and R (R: a language and environment for statistical computing; 2019; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). If this model did not converge, or the resulting estimates (such as those of FVIII half-life) were unrealistic, then a one-compartmental model, also parameterized in terms of macro constants with a Poisson error, was fitted using iteratively reweighted least squares. The goodness-of-fit plots were examined to deem the suitability of this model. There were 12 missing date-time values for bleeds and 9 missing date-time values for infusions; these values were imputed using an algorithm based on median values for the analysis. A sensitivity analysis was undertaken to understand the impact of imputed date-time values, which was found to be minimal when the analysis was rerun, with entries with missing date-time values deleted.

The individually fitted PK model, along with the dose and time of prophylactic infusions, was used to model the FVIII activity levels through the duration of the study for each patient. This model was used to estimate the FVIII level at the time of each bleed as reported by the patient.

Estimation of the FVIII level at the time of each bleed was based on the following assumptions:

1. The FVIII activity level–time profile could be suitably characterized by a compartmental model.
2. PK were linear, implying dose-proportionality.
3. There was no interoccasion variability: this is negligible on the basis of Björkman et al.[16]
4. Residual FVIII activity level was suitably accounted for under the principle of superposition.
5. The constant underlying risk of bleed for each patient (i.e., physical activity or sports) was not taken into account.

Modeling Bleed Prevention in Relation to Estimated FVIII Levels Associated with Bleeds

Three bleed types were considered in the analyses: all bleeds, joint bleeds, and spontaneous joint bleeds. For each patient, the highest FVIII activity level at which they experienced each type of bleed during prophylactic treatment was considered their "potentially effective trough level" for that bleed type, above which the patient would likely be bleed free.

During prophylactic treatment, some patients did not experience any bleeds at all, whereas others did not experience bleeds of certain types. To avoid biasing the results by removing patients from the analysis who did not experience a bleed (type), an assumption was made regarding the level at which these patients may be expected to bleed (if FVIII trough levels dropped below a certain threshold). Analyses were performed using pragmatic and conservative approaches for these patients:

Pragmatic ("Best-Case") Approach

The pragmatic approach assumed that patients who did not experience a bleed (type) would have had a bleed (of that type) only if their FVIII level was 0 IU/dL. Doses were selected to achieve a trough level of 1 IU/dL (known to be associated with decreased bleeding tendency); therefore, not all patients would be expected to experience levels of $<$ 1 IU/dL during the period of prophylaxis.[10,12,17]

Conservative ("Worst-Case") Approach

The conservative approach assumed that patients who did not experience a bleed (type) would have had a bleed (of that type) if their FVIII level fell below their median estimated trough level. This approach errs on the side of caution because patients did not actually experience a bleed at their median trough level; it assumes that FVIII levels maintained throughout the period of prophylaxis were at least equal to or greater than the median trough level.

Results

Patient Characteristics

Of the 66 patients with severe ($n = 58$) or moderately severe ($n = 8$) hemophilia A randomized to one of the prophylactic regimens, 63 were considered in this analysis because they received $>$ 180 days of prophylaxis. Of these 63 patients, 59 received prophylaxis for 365 days $\pm$ 10%. The characteristics of the cohort included are detailed in ►**Table 1**.

During the prophylaxis period of the study, 22 patients (34.9%) did not report any bleeds, whereas the remaining 41 patients experienced at least one bleed. A total of 26 patients (41.3%) experienced at least one spontaneous joint bleed, whereas 37 patients (58.7%) did not record any spontaneous joint bleeds during the study period on prophylaxis. At study entry, only 3 patients had no target joints and 60 patients had between 1 and 10 target joints (median, 3).

Table 1 Patient characteristics

Parameter	Mean ± SD	Median (range)
Age (y)	30.32 ± 12.61	28 (7–59)
Weight (kg)	70.98 ± 15.47	71 (18.7–120)
Number of target joints[a]	3.49 ± 2.12	3 (0–10)
FVIII $t_{½}$ for the group	12.18 ± 3.21	12.25 (7.28–21.89)
On-demand period		
ABR of all bleeds	50.04 ± 21.56	45.89 (13.04–121.13)
ABR of joint bleeds	43.53 ± 21.00	39.13 (6.52–115.54)
ABR of spontaneous joint bleeds	31.90 ± 18.52	29.94 (0–91.31)
Prophylaxis period		
ABR of all bleeds	2.10 ± 4.22	0 (0–17.11)
ABR of joint bleeds	1.94 ± 3.99	0 (0–17.11)
ABR of spontaneous joint bleeds	0.97 ± 2.21	0 (0–10.23)

Abbreviations: ABR, annualized bleeding rate; FVIII, factor VIII; SD, standard deviation; $t_{½}$, half-life.
[a]Target joints were defined as joints in which ≥ 4 hemorrhages had occurred within a period of 6 months, or in which > 20 lifetime hemarthroses had occurred.

Table 2 Bleed details by location and severity

	Bleed location, *n* (%)		
	Total	Joint	Nonjoint
Type			
Total	229	200	29
Spontaneous	116	105	11
Traumatic	113	95	18
Severity assessment for total bleeds (*n* = 229)			
Mild	78 (34.1)	59 (29.5)	19 (65.5)
Moderate	127 (55.5)	121 (60.5)	6 (21.0)
Severe	15 (6.6)	14 (7.0)	1 (3.5)
Missing	9 (3.9)	6 (3.0)	3 (10.0)
Severity assessment for spontaneous bleeds (*n* = 116)			
Mild	36 (31.0)	NA	NA
Moderate	71 (61.2)	NA	NA
Severe	7 (6.0)	NA	NA
Missing	2 (1.7)	NA	NA
Severity assessment for traumatic bleeds (*n* = 113)			
Mild	42 (37.2)	NA	NA
Moderate	56 (49.6)	NA	NA
Severe	8 (7.1)	NA	NA
Missing	7 (6.2)	NA	NA

Abbreviation: NA, not available.

Bleed Details

A total of 229 bleeds were considered in this analysis, of which 200 were joint bleeds and 105 were spontaneous joint bleeds. The location, severity, and etiology of the bleeds are described in ►**Table 2**.

Estimated FVIII Levels in Relation to Reported Bleeds

The estimated FVIII levels at which bleeds occurred against the time at which bleeds occurred after infusion of anti-hemophilic factor (recombinant) are shown in ►**Fig. 1**, for all bleeds observed during prophylaxis. Bleeds were reported at FVIII levels up to 60 IU/dL, with spontaneous joint bleeds only occurring below a FVIII level of 35 IU/dL.

Relationship between Estimated FVIII Levels and Bleeds

The proportion of patients who would experience zero bleeds in a year if their trough FVIII levels were maintained above the potentially effective trough level was estimated for each bleed type, using the pragmatic and conservative approaches described earlier. This information is presented by bleed type in ►**Tables 3** and **4**. It is also presented graphically using Kaplan–Meier curves for all bleeds and spontaneous joint bleeds in ►**Figs. 2** and **3**, respectively. For each bleed type, results are presented under the pragmatic and conservative approach on the same plot, for comparison.

The analysis that utilized the pragmatic approach indicated that 40, 43, and 63% of the patients were expected to have zero all bleeds, joint bleeds, or spontaneous joint bleeds while maintaining a trough level of 1 IU/dL. With the conservative approach, similar outcomes were derived at around 3 IU/dL for all bleeds and joint bleeds, and at 5 IU/dL for spontaneous joint bleeds. A measurable level of 1 IU/dL provided substantial benefit in the prevention of bleeds, and higher levels were associated with smaller incremental benefits.

When a modeled FVIII level was set as a trough level between 1 and 10 IU/dL, under the pragmatic approach, a 1 IU/dL increase in FVIII level was associated with a 2% increase in the number of patients who might achieve zero bleeds in a year. No bleeds occurred between estimated FVIII trough levels of 10 and 12 IU/dL.

Further, there was no obvious difference in the estimates between the two approaches when the modeled FVIII level exceeded 10 IU/dL, the level at which near maximal efficacy was seen. Continuing with the pragmatic approach, beyond a modeled FVIII level of 10 IU/dL, for every 10 IU/dL increase, we might expect on average a 10 to 15% change in the proportion of patients achieving zero bleeds in a year, depending on the bleed type; after 30% there was minimal gain. The proportion predictions at the higher FVIII levels had wide confidence intervals, and indeed, the potential for misreporting pain as bleeds increased with increasing FVIII levels.

Discussion

In this post hoc analysis of patients with severe hemophilia A with multiple target joints initiated on tertiary prophylaxis,

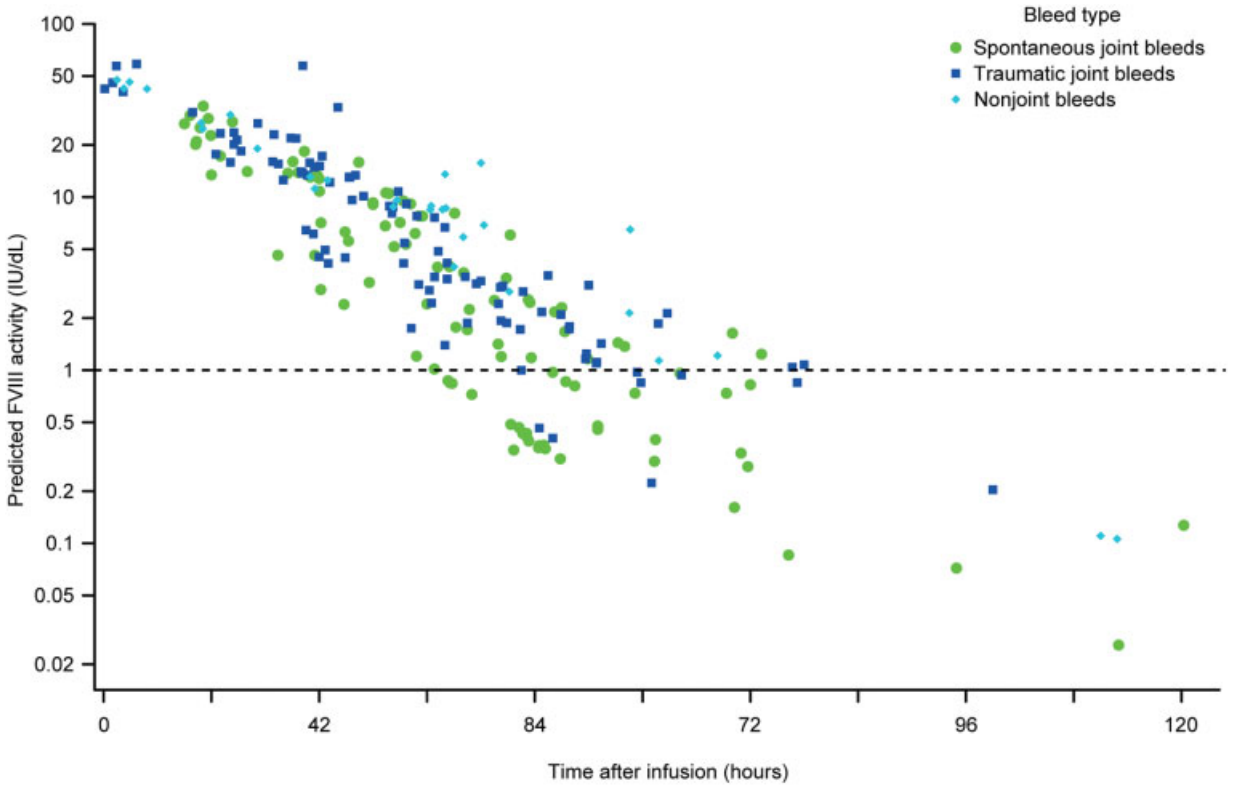

Fig. 1 Predicted factor VIII (FVIII) activity levels at the time of each bleed.

Table 3 Pragmatic approach for the prediction of zero all bleeds, joint bleeds, and spontaneous joint bleeds in a year, according to estimated FVIII levels

Estimated FVIII activity level (IU/dL)	Patients with zero bleeds (%)								
	All bleeds			Joint bleeds			Spontaneous joint bleeds		
	Proportion	95% CI for proportion		Proportion	95% CI for proportion		Proportion	95% CI for proportion	
1	39.7	28.5	52.0	42.9	31.4	55.1	63.5	51.2	74.3
3	44.4	32.9	56.7	47.6	35.8	59.7	68.3	56.0	78.4
5	50.8	38.8	62.7	54.0	41.8	65.7	71.4	59.3	81.1
10	60.3	48.0	71.5	63.5	51.2	74.3	79.4	67.8	87.5
12	60.3	48.0	71.5	63.5	51.2	74.3	79.4	67.8	87.5
15	66.7	54.4	77.1	69.8	57.6	79.8	85.7	75.0	92.3
20	74.6	62.7	83.7	76.2	64.4	85.0	88.9	78.8	94.5
30	88.9	78.8	94.5	88.9	78.8	94.5	98.4	91.5	99.7
40	90.5	80.7	95.6	90.5	80.7	95.6	100.0	94.3	100.0
50	95.2	86.9	98.4	95.2	86.9	98.4	100.0	94.3	100.0
60	100.0	94.3	100.0	100.0	94.3	100.0	100.0	94.3	100.0

Abbreviations: CI, confidence interval; FVIII, factor VIII.
Note: The estimated FVIII level is the assumed effective FVIII level specific to the individual and type of bleed.

the proportions of the cohort that would have been bleed free if the estimated FVIII level of 1 IU/dL was set as the lowest FVIII level of clinical interest (i.e., trough level) were 40% for all bleeds, 43% for joint bleeds, and 63% for spontaneous joint bleeds.

For all bleeds, a 1% rise in the modeled FVIII level between 1 and 10 IU/dL increased the proportion of the cohort achieving zero all bleeds by approximately 2%. At a modeled FVIII level of 10 IU/dL using the pragmatic approach, 60.3% of patients recently initiated on tertiary prophylaxis were

Table 4 Conservative approach for the prediction of zero all bleeds, joint bleeds, and spontaneous joint bleeds in a year, according to estimated FVIII levels

Estimated FVIII activity level (IU/dL)	Patients with zero bleeds (%)								
	All bleeds			Joint bleeds			Spontaneous joint bleeds		
	Proportion	95% CI for proportion		Proportion	95% CI for proportion		Proportion	95% CI for proportion	
1	19.1	11.3	30.4	19.1	11.3	30.4	27.0	17.6	39.0
3	36.5	25.7	48.9	36.5	25.7	48.9	50.8	38.8	62.7
5	47.6	35.8	59.7	49.2	37.3	61.2	63.5	51.2	74.3
10	60.3	48.0	71.5	61.9	49.6	72.9	77.8	66.1	86.3
12	60.3	48.0	71.5	61.9	49.6	72.9	77.8	66.1	86.3
15	66.7	54.4	77.1	69.8	57.6	79.8	85.7	75.0	92.3
20	74.6	62.7	83.7	76.2	64.4	85.0	88.9	78.8	94.5
30	88.9	78.8	94.5	88.9	78.8	94.5	98.4	91.5	99.7
40	90.5	80.7	95.6	90.5	80.7	95.6	100.0	94.3	100.0
50	95.2	86.9	98.4	95.2	86.9	98.4	100.0	94.3	100.0
60	100.0	94.3	100.0	100.0	94.3	100.0	100.0	94.3	100.0

Abbreviations: CI, confidence interval; FVIII, factor VIII.
Note: The estimated FVIII level is the assumed effective FVIII level specific to the individual and type of bleed.

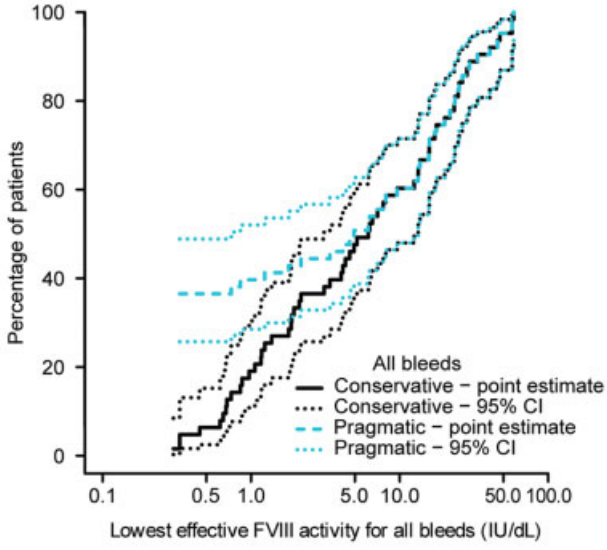

Fig. 2 Comparison of the pragmatic and conservative approaches, showing the proportion of the cohort predicted to have zero all bleeds according to factor VIII (FVIII) levels of clinical interest (the minimum effective estimated FVIII level specific to the individual and the type of bleed).

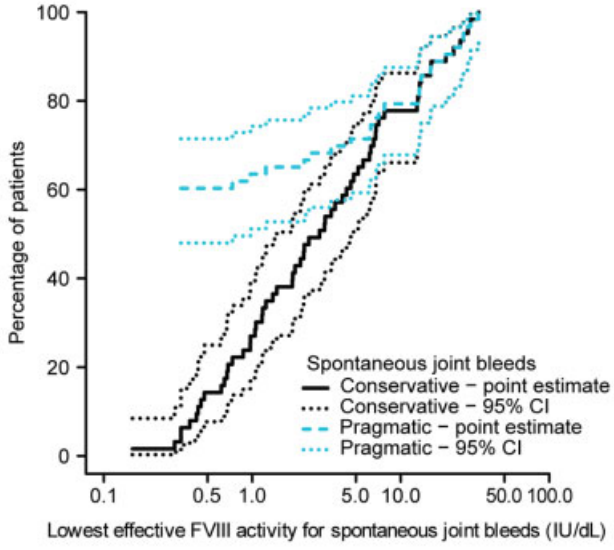

Fig. 3 Comparison of the pragmatic and conservative approaches, showing the proportion of the cohort predicted to have zero spontaneous joint bleeds according to factor VIII (FVIII) levels of clinical interest (the minimum effective estimated FVIII level specific to the individual and the type of bleed).

expected to have zero all bleeds, 63.5% were estimated to have zero joint bleeds, and 79.4% were estimated to have zero spontaneous joint bleeds. Above a modeled FVIII level of 10 IU/dL, the reductions in bleeds were less substantial. However, bleeds were also reported at much higher modeled FVIII levels in some patients, even outside the range of FVIII levels associated with hemophilia (0–40 IU/dL).

These data are similar to those published in another post hoc analysis of 143 previously treated patients in three pivotal clinical studies of antihemophilic factor (recombinant).[10] In the pivotal antihemophilic factor (recombinant) cohort, the median ABR in children was 3.1 (patients aged 1–6 years, $n = 44$, arthropathy 2%, adherence 89%, zero ABR 25%) and in adolescents and adults it was similar at a median of 3.3 (patients aged 10–65 years, $n = 99$, arthropathy 67%, adherence 78%, zero ABR 16%). A multivariate analysis predicted the probability of having zero bleeds when patients spent no time with FVIII levels < 1 IU/dL during prophylaxis to be 55% for adults (vs. 40% in this analysis, where the regimen was optimized to achieve a trough level of 1%) and 90% for children.

The increasing bleed rate in adolescents and adults in addition to its association with increasing time spent at a FVIII level < 1 IU/dL was also inversely related to the average frequency of infusions, which is logical if one considers that frequency and adherence to frequency have the greatest impact on trough levels. The higher ABRs in adolescents and adults may potentially be related to their physical activity and arthropathy, implying a potential role for other nonhematological factors in bleed prevention, particularly in adolescents and adults.[18]

One nonhematological factor that has been studied in children with hemophilia receiving regular prophylaxis is the transient increase in the risk of bleeding associated with vigorous physical activity.[19] The authors noted that most bleeds associated with physical activity were manifest within 1 hour of activity and the National Hemophilia Foundation risk categorization was used to categorize physical activity.[20] Category 2 and 3 physical activities were associated with a transient increase in the risk of bleeding, with odds ratios of 2.7 and 3.7, respectively. The data demonstrate a moderate increase in relative risk, however, the absolute increase was low. Further, the bleeding incidence was lower by 2% for every 1 IU/dL increase in clotting factor level. These results are similar to those demonstrated in this cohort with the pragmatic approach, where every 1 IU/dL increase in the modeled FVIII level > 1 IU/dL was associated with a lower bleed rate and a 2% increase in the proportion of the cohort predicted to have zero joint bleeds, both spontaneous and traumatic; however, the nature of activity responsible for the traumatic bleeds was not categorized in the study.

A major limitation of this analysis is the assumption that bleed risk is independent of time and activity. Other confounding factors in the analysis include the different trough levels and bleeding risk per patient, the varying observation period per patient, and the need for imputation to provide bleed-rate estimates in relation to set FVIII levels. Other limitations include the presence of active target joints at enrollment, because the Kaplan–Meier estimates in this analysis are for the first year of tertiary prophylaxis and estimates for subsequent years may change, as it is well known that the cohort's median ABR decreased with increasing length of time spent on prophylaxis.[21] In addition, all bleeds were self-reported and, in patients with chronic arthropathy, it is not uncommon for arthritic pain to be misinterpreted as early bleeds: previous studies have shown that this may be the case in as many as one-third of all bleeds.[22,23] Further, patients have been educated to treat when in doubt and it is likely that the reported bleeds at high FVIII levels were probably not true bleeds. Similarly, there may be underreporting of bleeding events toward the tail end of the prophylaxis period when the next infusion was due. This limitation applies to almost all studies in the field.

The analysis confirms that the greatest benefit is seen at FVIII levels of approximately 1 IU/dL, which is the first target in the prophylactic management of hemophilia A.[1,10] The analysis also confirms the results from the post hoc analysis of the antihemophilic factor (recombinant) pivotal cohort[10] and is congruent with the findings published on the natural history of joint bleeding in patients with mild, moderate, and severe hemophilia receiving prophylaxis.[12] It also supports the role of other factors in the development of bleeds, potentially including activity and trauma.[9,18] This multifactorial pathogenesis of bleeds underlies the philosophy of personalized prophylaxis that considers other determinants in designing the optimal prophylaxis regimen, including personalized trough levels for patients.[9,24,25]

Higher peak and trough levels can be achieved either empirically and through the calculation of half-life with formal PK analysis, or through Bayesian analysis.[16,26–30] The benefit of higher trough levels has been observed in post hoc analyses of various cohort studies. In addition, this hypothesis was tested in a randomized controlled trial comparing trough levels of 1 to 3 IU/dL versus 8 to 12 IU/dL (NCT02585960).[31]

In conclusion, this post hoc analysis confirms previous observations with regard to the FVIII level of 1 IU/dL where maximum benefit is seen. However, to prevent all spontaneous joint bleeds, some patients may require higher FVIII levels, which can be determined on the basis of clinical outcomes and PK evaluation.

What is known about this topic?

- Prophylaxis in severe hemophilia A increasingly targets factor VIII (FVIII) troughs ≥ 1 IU/dL.
- Data on tertiary prophylaxis can be used to model FVIII trough levels and zero bleeding.

What does this paper add?

- Modeling showed greatest benefit with FVIII trough levels of 1–3 IU/dL.
- FVIII > 3 IU/dL was associated with an extra 2% of patients with no bleeds per 1 IU/dL rise.

Authors' Contributions

P.C., K.F., P.W.C., and G.S. jointly designed the analysis, interpreted the results, and wrote the first draft of the manuscript. A.C. performed the statistical analysis and discussed and interpreted the results. B.A.K., V.B., and S.W.P. discussed and interpreted the results. E.B. participated in designing the study and discussed and interpreted the results. M.W. performed the PK analysis and discussed and interpreted the results. W.E. revised the graphical representation of results and discussed and interpreted the results. All authors reviewed the manuscript drafts and approved the final version.

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Conflict of Interest
All authors report nonfinancial (medical writing) support from Baxalta US Inc., a Takeda company, during the conduct of the study. P.C. has received consulting fees from Bayer, Baxalta*, Biogen, Biovertiv, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Shire*, Spark and Sobi; and research funding from CSL Behring, Novo Nordisk, and Pfizer. K.F. has received consulting fees from Bayer, Baxter*, Biogen, Freeline, Novo Nordisk, and Pfizer; research funding from Bayer, Baxter*, Novo Nordisk, and Wyeth/Pfizer; and has been a member of speaker bureaus for Bayer, Baxter*, Biotest Octapharma, CSL Behring, Novo Nordisk, and Pfizer. P.W.C. has received consulting fees from CSL Behring, Novo Nordisk, Shire*, and Sobi; research funding from CSL Behring; and has been a member of a speaker bureau for Shire*. At the time of the current study, A.C. was an employee of Baxalta Innovations GmbH, a member of the Takeda group of companies. B.A.K. has received consulting fees from BioMarin, Genentech, Sigilon, and Spark; and research funding from Bioverativ, Pfizer, Sangamo, Shire*, and Spark. V.B. has served as Chair of the International Prophylaxis Study Group (supported by grants to the Hospital for Sick Children Foundation, Toronto, Canada, from Bayer HealthCare, Bioverativ, Novo Nordisk, Pfizer, Shire*, and Spark); has served on data safety monitoring boards for Octapharma and Shire*; has served on speaker bureaus/advisory boards for Amgen, Bayer HealthCare, Novo Nordisk, Pfizer, and Shire*; and has received research support from Bayer HealthCare, Bioverativ, and Shire*. S.W.P. has received consulting fees from Apcintex, Bayer, BioMarin, Bioverativ, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sanofi, Shire*, Spark, and uniQure. E.B. has received research funding from Bayer, CSL Behring, Shire*, and Sobi; has been a member of speaker bureaus from Bayer, Octapharma, and Shire*; and has served on an advisory board for LFB. M.W. and W. E. are employees of Baxalta Innovations GmbH, a member of the Takeda group of companies, and are Takeda stock owners. At the time of the current study, G.S. was an employee of Baxalta US Inc, a member of the Takeda group of companies.
*A member of the Takeda group of companies.

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