Impact of Adopting Population Pharmacokinetics for Tailoring Prophylaxis in Haemophilia A Patients: A Historically Controlled Observational Study

Michaela Stemberger[1,2] Felix Kallenbach[2] Elisabeth Schmit[2] Alanna McEneny-King[3] Federico Germini[4,5] Cindy H. T. Yeung[4] Andrea N. Edginton[3] Sylvia von Mackensen[6] Karin Kurnik[7] Alfonso Iorio[4,8]

[1] Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany
[2] Abteilung für Transfusionsmedizin, Zelltherapeutika und Hämostaseologie, Klinikum der Universität München, Munich, Germany
[3] School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada
[4] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[5] Department of Health Sciences, Università degli Studi di Milano, Milan, Italy
[6] Institut und Poliklinik für Medizinische Psychologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
[7] Zentrum für Pädiatrische Hämostaseologie, Dr. von Haunersches Kinderspital, Klinikum der Universität München, Munich, Germany
[8] McMaster-Bayer Chair for Clinical Epidemiology Research in Bleeding Disorders, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Address for correspondence Michaela Stemberger, DrMed, Medizinische Klinik IV, Klinikum der Universität München, Campus Innenstadt, Pettenkoferstr. 8a, 80336 Munich, Germany (e-mail: michaela.stemberger@med.uni-muenchen.de).

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Abstract

Background Performing individual pharmacokinetics (PK) studies in clinical practice can be simplified by adopting population PK-based profiling on limited post-infusion samples. The objective of this study was to assess the impact of population PK in tailoring prophylaxis in patients with haemophilia A.

Patients and Methods Individual weekly treatment plans were developed considering predicted plasma factor activity levels and patients' lifestyle. Patients were trained using a visual traffic-light scheme to help modulate their level of physical activity with respect to factor infusions timing. Annualized joint bleeding rate (ABJR), haemophilia-specific quality of life questionnaire for adults (Haemo-QoL-A) and factor utilization were measured for 12 months before and after tailoring, compared within patients and analysed separately for those previously on prophylaxis (P), situational prophylaxis (SP) or on-demand (OD).

Results Sixteen patients previously on P, 10 on SP and 10 on OD were enrolled in the study. The median (lower, upper quartile) ABJR changed from 2.0 (0, 4.0) to 0 (0, 1.6) for P ($p = 0.003$), from 2.0 (2.0, 13.6) to 3.0 (1.4, 7.2) for SP ($p = 0.183$) and from 16.0 (13.0, 25.0) to 2.3 (0, 5.0) for OD ($p = 0.003$). The Haemo-QoL-A total score improved for 58% of P, 50% of SP and 29% of OD patients. Factor utilization (IU/kg/patient/year) increased by 2,400 (121; 2,586) for P, 1,052 (308; 1,578) for SP and 2,086 (1,498;

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- haemophilia
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- personalized

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2,576) for OD. One of 138 measurements demonstrated a factor activity level below the critical threshold of 0.03 IU/mL while the predicted level was above the threshold.
Conclusion Implementing tailored prophylaxis using a Bayesian forecasting approach in a routine clinical practice setting may improve haemophilia clinical outcomes.

Introduction

Long-term factor replacement, known as prophylaxis, has improved care for patients suffering from severe haemophilia A, and is now considered the gold standard in haemophilia care.[1,2] Prophylactic treatment is usually prescribed in routine clinical practice assuming the same average pharmacokinetics (PK) for all patients, and selecting a body weight-based dose targeting a trough level of $>$ 0.01 IU/mL.[3] The observed variability in the PK of factor concentrates is large enough across and narrow enough within patients[4] to support the hypothesis that a PK-tailored individualized dosing approach would allow more appropriate dosing.[3] Many empirical dose adjustments are required to get the same desired trough level in different patients, with final doses spanning from 15 to 50 IU/kg.[4,5] With more patients reaching their target factor levels earlier and more consistently, waste of resources for both excessive and ineffective treatments would be reduced.[6,7] Assessment of individual PK using the traditional approach[8] is very time-consuming for both the patient and the clinic and rarely performed in routine clinical practice. Population PK (PopPK) and Bayesian forecasting methods, enabling limited blood sampling at two to three flexible time points, have been recommended for individual PK assessment.[9] This approach does not require the potentially dangerous washout phase as the traditional approach and it facilitates simulation of doses and frequencies needed to achieve the target.[3]

The impact of PK-tailored prophylaxis on patient-relevant outcomes and societal-relevant outcomes remains to be quantified.[10]

The rationale for this study was to assess the impact of adopting PopPK-tailored prophylaxis into routine clinical practice. The primary objective was to assess the effect of PopPK-tailored prophylaxis on patient-relevant outcomes (e.g. health-related quality of life and bleeding rate) and societal important outcomes (e.g. factor VIII utilization). The secondary objective was to assess the performance of the Bayesian approach in predicting plasma factor activity levels.

Patients and Methods

Patients and Setting

Consecutive severe haemophilia A patients attending the Munich University Hospital were screened for eligibility. The inclusion criteria were age $\geq$ 16 years, diagnosis of severe haemophilia A (baseline factor VIII plasma activity of $<$ 0.01 IU/mL) and being treated on prophylaxis, or willing to start prophylaxis if currently treated on-demand (OD). Patients with detectable factor VIII inhibitors at screening (titer $>$ 0.6 BU/mL) were excluded.

Study Design

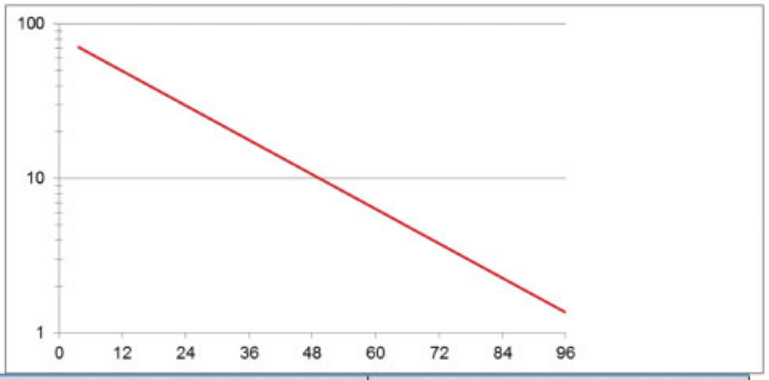
This is an open-label cohort study with 1 year prospective follow-up and 1 year retrospective control period.

Study Procedure

Baseline assessments: At baseline, a detailed medical history, including the patient's previous treatment regimen and the Hemophilia Joint Health Score (Version 2.1)[11] were extracted from patient records, and infusion and bleeding logs for the previous 12 months were extracted from patient paper diaries. Anti-factor VIII antibodies were measured with the Nijmegen modification of the Bethesda assay to confirm the absence of inhibitors.

Population-based individual PK profiling, tailored treatment recommendation and clinical follow up: All patients underwent population model-based PK profiling at study inclusion. The PK study protocol was based on the sampling scheme proposed by Björkman and Collins.[12] One pre-dose and 3 post-infusion blood samples were collected approximately 6, 24 and 32 to 48 hours after infusion of factor VIII, with a mandatory minimum of 2 post-infusion samples. Individual PK parameters of each patient and individualized prophylaxis regimens targeting a trough level of between 0.01 and 0.03 IU/mL were estimated using concentrate-specific models mounted on a pre-release installation of the Web Accessible Population Pharmacokinetics Service – Hemophilia platform.[13,14] A textual and graphical individualized treatment recommendation sheet was provided to each patient (►**Fig. 1**), defining the risk of bleeding for each day of the week according to the predicted factor concentrate plasma activity levels; specifically, days with plasma factor activity levels above 0.15 IU/mL were defined as low risk of bleeding (green colour coding); days between 0.15 and 0.03 IU/mL as intermediate risk (yellow colour coding); and below 0.03 IU/mL as high risk (red colour coding). Days where the patient was expected to transition between different levels of risk were coded accordingly to the higher risk level. All patients were encouraged to adopt the proposed individualized prophylaxis regimen for the entire study duration. Patients were instructed to modulate their activity level accordingly to their treatment regimens with the goal of minimizing extra infusions and to log infusions and bleeds as usual. Follow-up visits were performed every 6 months as per standard of care in Munich. Additional visits were organized as needed. Blood was drawn for factor VIII plasma activity measurement at follow-up visits. The clinician responsible for the patients' care had complete autonomy in deciding the treatment regimen of enrolled patients; any change to the treatment regimen was documented.

PK graph after infusion of 2000 IU of coagulation factor based on a baseline elimination half-life of coagulation factor of 16.3 hours.



Recommended prophylactic dosing schedule
Favored administration interval:
☐ Fixed intervals
■ Fixed weekdays: 2000 IU every Tuesday and Friday

	Prophylactic dose (IU)	Recommended activity	Extra Infusion (IU)
Monday		Office day	≥ 1000
Tuesday	2000	Top-rope climbing	
Wednesday			
Thursday			≥ 500
Friday	2000	Squash	
Saturday			
Sunday		Swimming	≥ 500

Color codes

	Safe
	Safe for low-impact activities
	Not safe

- Trough levels should never fall below 1% and ideally not below 3% to avoid subclinical bleeds.
- For high-impact activities, factor levels above 15% are required.
  For low-impact activities, factor levels above 3% are required.
- Please plan any sports activities to coincide with green time windows; otherwise, extra infusions may be required as indicated in the table above.

Fig. 1 Excerpt of the patient-specific hand-out. The figure reproduces the form used to communicate to study patients their individualized treatment recommendation.

Outcome Measurements

Study outcomes were assessed at the beginning and at the end of the observation period. *Primary outcomes*: Annualized joint bleeding rate (AJBR). Joint bleeds and effective duration in months of the observation period were extracted from the patient logs for the pre- and on-study observation period. Haemophilia-specific quality of life questionnaire for adults (Haemo-QoL-A) questionnaire,[15] covering physical functioning, role functioning, worry, consequences of bleeding, emotional impact and treatment concern. Domain scores range from 0 to 5 and the total score is derived by summing the domain scores (range, 0–30). Domain and total scores are transformed to a 0 to 100 scale with higher scores indicating a better haemophilia-related quality of life (HRQoL). Since average changes on any scale may be difficult to interpret, we adopted a responder analysis approach measuring the proportion of patients experiencing a change of $\geq$ 2 points on the Haemo-

QoL-A scale, assumed to represent a clinically relevant change. As a sensitivity analysis for the responder analysis, we adopted the conservative estimation of a clinically relevant difference proposed by Valluri et al[16] who estimated the minimal important differences for the Haemo-QoL-A total score at approximately 6.4 points and for the physical functioning domain at approximately 8.9 points. Amount of infused factor concentrate was extracted from patient diaries and reported as

$$IU/kg/year = \frac{total\ amount\ infused\ (IU)}{weight\ (kg)} \times \frac{12}{months\ of\ observation}.$$

Secondary outcome: Factor VIII plasma activity levels were analysed in a single laboratory with a one-stage clotting test (Hemosil, ACL Top, Instrumentation Laboratories, Werfen, Germany).

Statistical Analysis

Baseline data: Baseline characteristics of the population were tabulated using standard descriptors of central tendency and variability (mean and standard deviation, median and percentiles or ranges as appropriate). Patients were divided in three sub-groups based on their regimen at study entry: regular prophylaxis (P), situational prophylaxis (SP) and OD. SP was used to define infusing factor concentrates before the occurrence of specific situations, for example, intense physical activity, to prevent bleeding. Treatment characteristics before and after treatment tailoring, including doses, number of infusions, AJBR, proportion of patients without joints bleeding and the proportion of time spent with factor activity levels above 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL, were described. All analyses were separately performed for each sub-group.

Primary outcomes: AJBR before and after starting the individualized regimen were compared using negative binomial univariate regression.[17] Number of patients presenting a positive or negative change of $\geq$ 2/100 on the Haemo-QoL-A score were reported. HRQoL (for each domain and for the total score) and factor utilization before and after starting the individualized regimen were compared with the Wilcoxon signed rank test.

Secondary outcome: Predicted and (prospectively) observed plasma factor VIII activity levels were compared with four different approaches. First, predicted and observed plasma factor VIII activity levels were plotted against each other, and a regression line fitted to visually inspect their correlation. Second, the difference of observed and predicted plasma factor VIII activity levels was plotted against their average according to the Bland–Altman approach.[18] Third, each plasma factor VIII activity measurement was coded as concordant/discordant with the predicted risk window (e.g. a measured plasma factor activity level of 0.05 IU/mL was considered concordant if occurring at a post-infusion time falling in the predicted window of 0.03–0.15 IU/mL, and discordant if falling in either the window of $<$ 0.03 or $>$ 0.15 IU/mL). The agreement between predictions and observations was measured using the kappa statistic. Fourth, the number of cases for which a measured plasma factor activity level below the safety threshold of 0.03 IU/mL was incorrectly predicted was reported. We selected this threshold, as this was the one chosen for our tailoring exercise.

Factor usage modelling: Since we were expecting to enrol a sizeable number of patients not on P at study entry, the direct comparison of factor usage before and after the adoption of the tailored regimen could only show an increase in utilization, as any other study comparing prophylaxis with OD treatment.[3,19–23] Therefore, we planned to compare the amount of factor concentrate utilization on tailored prophylaxis with the theoretical amount which would have been used by applying local and international guidelines for weight-based dosing across a range of doses. Specifically, we have chosen the lower dose according to the Utrecht protocol[24] (15 IU/kg three times per week), the Austrian guideline[25] (25 IU/kg every other day), and the higher dose according to most guidelines (40 IU/kg three times per week).[2,26]

Our hypothesis was that tailored prophylaxis would have produced across the population a higher proportion of time above target. Indeed, assuming a comparable usage, PK-tailored prophylaxis would theoretically ensure a more appropriate and equitable distribution of factor concentrates in the population, yet obtaining a very low AJBR as observed in similar populations on tertiary prophylaxis.[19,20,27]

Ethical Approval

This study was conducted in compliance with international guidelines on Good Clinical Practice and local regulatory requirements and approved by the Ethics Committee of the University of Munich. Written consent was obtained before enrolment.

Results

Patients were enrolled between December 2012 and January 2015. The study was closed early on September 2015 due to increasing enrolment of patients in competing studies. At study closure, 15 patients had less than the planned 12 months' follow-up. The median (first quartile [Q1], third quartile [Q3]) follow-up length after PK-tailoring was 12 months (9, 14). Ninety-seven patients were screened and 75 deemed eligible for the study. Thirty-nine patients were enrolled, 2 did not complete the PK study, 1 did not obtain a valid PK estimate and 36 were started on the tailored regimen. Of the 36, 16 were previously on P, 10 on SP and 10 OD. Of the 22 patients considered ineligible, 16 declined to consent and 6 were judged by the treating physician at high risk of non-compliance (►**Supplementary Fig. S1**, available in the online version). ►**Table 1** shows the characteristics of the patients at enrolment, and ►**Supplementary Table S1** (available in the online version) details their treatment characteristics. The median proportion of time spent, after the PopPK tailoring, with factor activity levels above 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL, is reported in ►**Fig. 2**. The median proportion of time spent with factor activity levels above 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL, according to the treatment regimen used before the introduction of the PK-tailored prophylaxis, is presented in ►**Table 2**.

Table 1 Baseline patients' characteristics

Characteristic	Value
Age in years (median [range]) ($n = 36$)	38 [16–61]
Prophylaxis ($n = 16$)	33 [16–60]
Situational prophylaxis ($n = 10$)	32 [21–54]
On-demand ($n = 10$)	54 [23–61]
Hemophilia Joint Health Score (median [range]) ($n = 32$)	24 [2–49]
Prophylaxis ($n = 14$)	15 [2–49]
Situational prophylaxis ($n = 10$)	24 [8–37]
On-demand ($n = 8$)	36 [9–45]
Products used (n [%]) ($n = 36$)	
Beriate	11 (31)
Advate	10 (28)
Kogenate	8 (22)
Haemoctin	3 (8)
Fanhdi	2 (5)
Immunate	1 (3)
Refacto AF	1 (3)
FUP duration in months (median [Q1, Q3]) ($n = 25$)	12 [9–14]
Prophylaxis ($n = 11$)	9 [8–14]
Situational prophylaxis ($n = 7$)	16 [10–17]
On-demand ($n = 7$)	12 [11–12]

Abbreviations: FUP, follow-up; Q1, first quartile; Q3, third quartile.

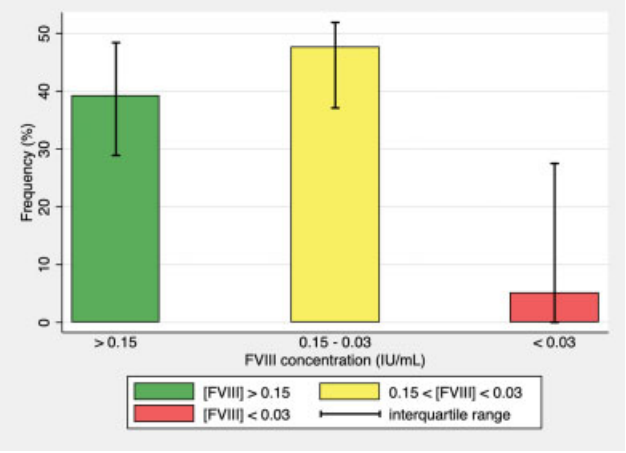


Fig. 2 Average proportion of time spent with factor levels > 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL, according to population pharmacokinetics (PopPK) predictions. Q1: first quartile, Q3: third quartile. Median (Q1, Q3) time spent above 0.15 IU/mL: 39% (29, 48); between 0.15 and 0.03 IU/mL: 48% (95% confidence interval [CI], 37, 52) and below 0.03 IU/mL: 5% (95% CI, 0, 28).

Median observed AJBR and Haemo-QoL-A score with their reduction and changes in the 25 patients with available data are reported in ►**Table 3**. The number of patients with improvement (≥ 2 points) in the QoL score was 7 (58%) (P), 3 (50%) (SP) and 2 (29%) (OD). Only one patient (P) showed a deterioration (≥ 2 points) in the score. Using the conservative threshold of > 6.4 points, the number of patients with improvement was 2 (17%) (P), 2 (33%) (SP) and 2 (29%) (OD). No patient showed a deterioration of > 6.4 points. The score for each domain of the Haemo-QoL-A at baseline and end of study is reported in ►**Supplementary Table S2** (available in the online version).

For the 23 evaluable patients, the median change (Q1; Q3) in factor VIII usage on study versus the previous regimen was 2,400 (121; 2,586) IU/kg/year (P, $p = 0.0033$), 1,052 (308; 1,578) IU/kg/year (SP, $p = 0.0277$) and 2,086 (1,498; 2,576) IU/kg/year (OD, $p = 0.0277$). An additional 520 (59; 2,385) IU/kg/year were used for the treatment of bleedings, trauma or invasive procedures.

Precision of the PK estimates: One hundred thirty-eight factor activity levels were measured from the 25 patients and used for regression and Bland–Altman analysis (►**Fig. 3** and ►**Supplementary Fig. S2** [available in the online version]). The mean difference between predicted and observed plasma factor level activity was –0.005 IU/mL (95% confidence interval, –0.130, 0.119). ►**Table 4** presents the predicted factor VIII activities and their concordance to measured factor levels according to the three risk bands (> 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL). The overall agreement between predictions and observations was found to be 92.8% (kappa, 0.79, $p < 0.0001$). In nine cases (6.5%), the predicted level was > 0.15 IU/mL while the observed level was between 0.03 and 0.15 IU/mL. In one case (0.7%), the predicted level was above 0.03 IU/mL while the actual measurement was found to be below that threshold. The results of the modelling analysis are presented in ►**Table 5**.

Discussion

Our trial demonstrates that the adoption of PopPK-tailored prophylactic treatment in routine clinical practice may improve patient-relevant outcomes like bleeding and quality of life, even if it may not be suitable for every patient. Depending on the intensity of the prophylaxis regimen used as a comparator, PopPK-tailored prophylaxis may or may not result in a more effective use of health care resources.

Our study assembled a cohort of severe haemophilia A patients, irrespective of their previous treatment modality, estimated their individual PK profile using a limited sampling technique and a PopPK approach[9] and tailored their treatment regimens based on their individual PK profiles. We believe that prophylaxis should be offered to all patients, and we hypothesized that a tailored regimen could have been appealing both for patients already on prophylaxis but seeking a better regimen, and for patients on SP or OD, finding it a more acceptable regimen than regular prophylaxis. Our study confirmed that this was the case for some of the patients. Among the patients previously on prophylaxis, the tailored prophylactic regimen produced a median reduction of 2 bleed per year; those previously on SP, a median increase of 1 bleed per year; and those previously on OD a median reduction of 14 bleeds per year. The quality of life

Table 2 Median proportion of time spent with factor activity levels above 0.15 IU/mL, between 0.15 and 0.03 IU/mL and below 0.03 IU/mL

Treatment regimen (before PK-tailored)	*N*	Band (IU/mL)	12 months prior study Median % (Q1, Q3)	During study Median % (Q1, Q3)
Regular prophylaxis	11	> 0.15	27 (19, 35)	41 (33, 45)
		0.03–0.15	41 (34, 50)	50 (48, 53)
		< 0.03	34 (16, 46)	5 (2, 14)
Situational prophylaxis	5	> 0.15	16 (13, 19)	42 (41, 54)
		0.03–0.15	27 (21, 29)	46 (38, 58)
		< 0.03	57 (52, 66)	0 (0, 0)
On-demand	6	> 0.15	7 (2, 12)	41 (33, 45)
		0.03–0.15	8 (3, 19)	50 (48, 53)
		< 0.03	85 (69, 96)	5 (2, 19)

Abbreviation: PK, pharmacokinetics.

Table 3 Change in AJBR and Haemo-QoL-A scores

AJBR					
Treatment regimen (before PK-tailored)	***N***	**12 months prior study Median (Q1, Q3)**	**During study Median (Q1, Q3)**	**Rate reduction[a] (95% CI)**	***p*-Value**
Regular prophylaxis	11	2.0 (0, 4.0)	0.0 (0.0, 1.6)	0.31 (0.14, 0.68)	**0.003**
Situational prophylaxis	7	2.0 (2.0, 13.6)	3.0 (1.4, 7.2)	0.74 (0.47, 1.15)	0.183
On-demand	7	16.0 (13.0, 25.0)	2.3 (0, 5.0)	0.15 (0.04, 0.51)	**0.003**
Haemo-QoL-A score					
Treatment regimen (before PK-tailored)	***N***	**Baseline**	**End of study**	**Difference Median (Q1, Q3)**	***p*-Value**
Regular prophylaxis	12	83.7 (73.2, 87.7)	86.6 (83.4, 91.8)	+2.3 (1.1, 4.3)	**0.0414**
Situational prophylaxis	6	74.5 (54.3, 82.7)	81.8 (80.8, 84.5)	+3.3 (–0.9, 9.4)	0.1730
On-demand	7	73.3 (68.5, 92.7)	76.0 (71.3, 93.2)	+0.5 (–0.9, 7.5)	0.4990

Abbreviations: AJBR, annualized joint bleeding rate; CI, confidence interval; Haemo-QoL-A, haemophilia-specific quality of life questionnaire for adults; PK, pharmacokinetics; Q1, first quartile; Q3, third quartile.
Note: Bold *p*-Values imply statistically significant differences.
[a]Incidence rate ratio.

improved for 58% of patients previously on prophylaxis, 50% of those previously on SP and 29% of those previously on OD. As for factor utilization, patients on tailored prophylaxis required a median of approximately 3,500 IU/kg/year, which was needed to maintain each patient above 0.03 IU/mL for 93% of the time.

These results have to be considered with caution, as our sample was small and maybe not representative of the entire haemophilia population. However, they may be of interest to set expectations of doctors and patients considering the adoption of tailored prophylaxis. While it is unsurprising to see a clinical improvement in patients previously on OD, it may be interesting to note that some of them decided to start on prophylaxis when proposed the tailored regimen. For those previously on some form of prophylaxis, the observation that the larger improvement was seen in those previously on regular as compared with those on SP may be explained by the fact that SP is indeed a different approach to tailoring, and for some patients, probably a more efficient one.

Significant HRQoL improvements from baseline to the end of study were found for the Haemo-QoL-A total score and domain worry, showing improvements in 18 out of 25 evaluable patients for the total score and 17 out of 25 for the domain worry. We do not have a definitive explanation for this finding, but one might hypothesize that better understanding of the variations in the risk of bleeding and consequent reduction in the AJBR could translate into better performance on those domains. Similarly, we do not have a definitive explanation for why 7 patients treated on OD prior to study entry showed an improvement in AJBR but not in HRQoL. One hypothesis is that the beneficial effect of reducing bleeding and negative impact of increasing the burden of care had a negative balance. Unfortunately, we could not formally test this explanation. We found that factor utilization increased, including for patients already on prophylaxis; it has to be noted that our study population was on a very low intensity prophylaxis. In this perspective, our modelling analysis, though very exploratory due to the small sample

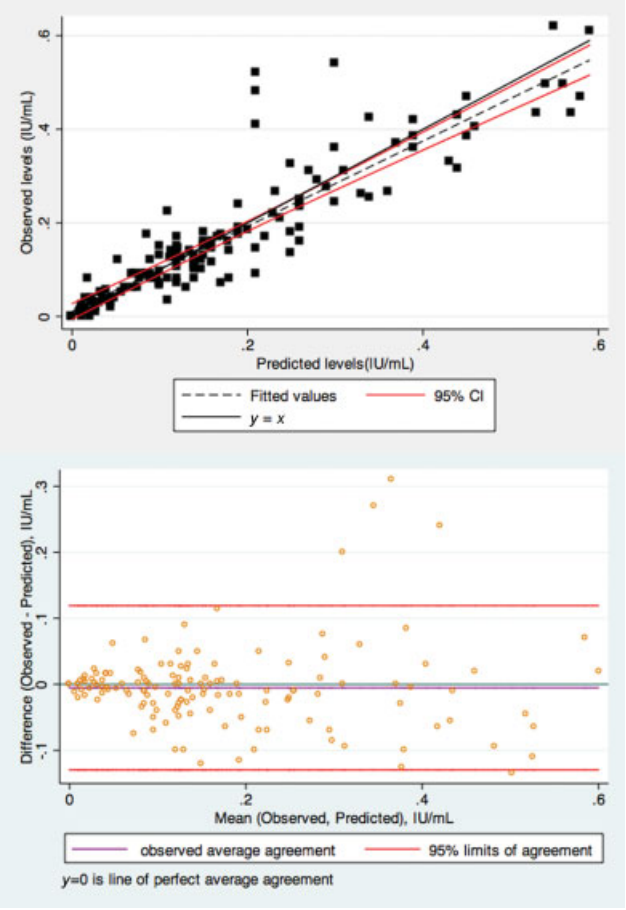


Fig. 3 Observed versus predicted factor VIII activity levels. Top panel: The plot shows the regression line (dashed line) of predicted versus observed measurements of plasma factor VIII activities. Solid red lines indicate the confidence intervals for the regression line. The black solid line indicates the identity line. R^2 for the regression was 0.82. Bottom panel: The figure shows a Bland–Altman plot of observed versus predicted plasma factor level activities. The difference between pairs of measurements (*y*-axis) is plotted against their means (*x*-axis). The horizontal solid line represents the average difference, the two red lines indicates the 95% confidence limits for the regression lines. A detail of the plot for the concentrations comprised between 0 and 0.05 IU/mL is presented in **Supplementary Material** (►**Supplementary Fig. S2**, available in the online version).

size and very simplified approach, may provide some evidence for those interested in understanding how tailored prophylaxis may impact factor utilization and its distribution among patients.

A valuable secondary objective of our study was to validate the accuracy of our PopPK and Bayesian forecasting approach to estimate individual profiles and support simulation of optimal treatment regimens. The accuracy of prediction was 93% with one critical over-prediction (out of 25 patients and 138 measurements). These results support and validate the use of PopPK tools like the Web-Accessible Population Pharmacokinetics Service (www.wapps-hemo.org) for the individualization of treatment in routine clinical practice.

Our study has some limitations. First, it did not account for variation in levels of physical activity. Even if more than 80% of patients reported some increase in their levels of physical

Table 4 Observed and predicted factor level activities

	Observed factor levels			
Predicted factor levels	**< 0.03 IU/mL**	**0.03–0.15 IU/mL**	**> 0.15 IU/mL**	**Total**
< 0.03 IU/mL	13	5	0	18
0.03–0.15 IU/mL	1	54	5	60
> 0.15 IU/mL	0	9	51	60
Total	14	68	56	138

Note: Agreement: 92.8%; kappa, 0.79, $p < 0.0001$.

Table 5 Comparison of the amount of factor concentrate utilization on tailored prophylaxis with the theoretical amount which would have been used by applying local and international guidelines for weight-based dosing

Comparator	Median variation (Q1, Q3) IU/kg/y
Utrecht, lower band[24] (15 IU/kg 3 × /wk)	857 (–21, 2,043)
Austrian guidelines, lower bound[25] (25 IU/kg 3 × /wk)	–698 (–1,575, 486)
Highest recommended dose in international guidelines[7] (40 IU/kg Q4 8 h)	–4,106 (–4,981, –2,914)

Abbreviations: IU, international unit; Q1, first quartile; Q3, third quartile.
Note: The median yearly usage of factor concentrates in our study was very similar to the amount resulting by adopting the 25 IU/kg suggested as the lower dose in the Austrian guideline, and significantly lower than adopting the 40 IU/kg contemplated by most guidelines as the upper end of the range.

activity and a more enjoyable lifestyle, we did not formally measure physical activity and could not therefore assess if tailored prophylaxis was or was not impacting the ability to reach the desired level of activity, neither if bleeding rates were associated with different activity levels. Second, our modelling exercise for factor utilization was not a formal simulation study, due to the small sample size. The results on resource utilization have to be considered approximate and preliminary. Third, it is likely that intra- and inter-patient laboratory variability in the measurement of factor VIII plasma activity levels may impact the applicability of tailoring prophylaxis, both when simply using trough levels and when using a PopPK approach. Our study was not designed to provide any direct evidence to this topic. Fourth, for 15 out 36 patients the follow-up period was less than the expected 12-month period due to study closure. In most published studies reporting on the adoption of prophylaxis, ABJR improves over time, and so does HRQoL, and therefore our results should be robust to the early stopping. However, we cannot exclude that a longer follow-up would have shown a larger or smaller difference in the study outcomes. Fifth, the patients' understanding of the tailoring process was not formally assessed. Each patient received an individualized treatment hand-out with a graphical representation of plasma factor VIII activity and indicating when it was safer to exercise or when

extra infusions may be indicated. Judging upon occasional feedback received from the patients, the treatment schedule helped them understanding the principle of prophylactic treatment and integrating it into their daily lives. However, this remains a hypothesis requiring further study. Finally, as in any study without a parallel active control, we cannot exclude that the improvements in HRQoL might be related to the *Hawthorne effect*[28] and a more intensive follow-up of patients in this study could have resulted in a better HRQoL outcome. A similar improvement was found in the placebo arm of randomized, placebo-controlled clinical trial in patients with dementia.[28]

In summary, this study demonstrates that PK-tailored prophylaxis is a suitable option for adult patients with severe haemophilia, may improve ABJR and HRQoL and optimize usage of health care resources.

What is known about this topic?

- The use of prophylaxis regimens based on individual pharmacokinetics estimates in patients with haemophilia has been recommended for years, but rarely up taken in clinical practice.
- The availability of web-based population pharmacokinetics forecasting tools, enabling limiting blood sampling to two to three flexible time points, have made individual pharmacokinetics profiling widely accessible.

What does this paper add?

- Haemophilia treatment tailoring based on individual pharmacokinetics profiles on limited sampling data was performed in 36 patients.
- Tailored prophylaxis reduced bleeding frequency and affected health-related quality of life in a more or less pronounced way depending on the treatment modality at study entry (prophylaxis, situational prophylaxis, on-demand).
- Bayesian individual pharmacokinetics profiling accurately predicted post-infusion factor activity level in $>$ 90% of cases, including for critical levels.
- Tailored prophylaxis resulted in increased factor usage as compared with the previous prophylaxis regimen and would have been cost-neutral to adoption of intermediate dose prophylaxis.

Authors' Contributions

M.S. and A.I. designed the study. M.S. coordinated the study. M.S. and K.K. conducted the study in Munich and collected the data. F.K. and E.S. performed the PK studies and laboratory assays. A.M.K. and A.N.E. performed the PopPK modelling and individual PopPK estimations. S.v.M. analysed the Haemo-QoL-A data. M.S., A.I., C.H.T.Y. and F.G. drafted the manuscript, analysed and interpreted the data. All the authors critically revised the manuscript and gave final approval to the current version.

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Conflict of Interest

M.S. has received honoraria for participating in scientific advisory panels, consulting and speaking engagements for Baxter/Baxalta, Bayer Health Care, Biotest, CSL Behring, Novo Nordisk and Pfizer. Other authors have no other conflict of interest to disclose.

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