

ORIGINAL ARTICLE

Predictive performance of pharmacokinetic-guided prophylactic dosing of factor concentrates in hemophilia A and B

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Abstract

Background: Pharmacokinetic (PK)-guided dosing is used to individualize factor (F)VIII and FIX replacement therapy.

Objectives: This study investigates the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B.

Methods: In this multicenter, prospective cohort study, people of all ages with hemophilia received prophylactic treatment with factor concentrates based on individual PK parameters. During follow-up, at least 4 measured FVIII/FIX levels per patient were

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compared with corresponding predicted levels obtained by Bayesian forecasting. Predictive performance was defined as adequate when $\geq 80\%$ of measured FVIII/FIX levels were within $\pm 25\%$ of prediction (relative error). Additionally, mean absolute error and mean error were calculated. In post hoc analyses, predictive performance was assessed allowing maximum absolute errors of 1 (trough), 5 (mid), and 15 (peak) IU/dL. Five-point scale questionnaires addressed feasibility of PK guidance.

Results: We included 50 patients (median age, 19 years; range: 2-72 years). Median follow-up was 36 weeks. Seventy-one percent of levels (58% trough, 83% mid, and 80% peak) were within $\pm 25\%$ of prediction. Mean absolute errors were 0.8 (trough), 2.0 (mid), and 8.6 (peak) IU/dL. In post hoc analyses, 81% (trough), 96% (mid), and 82% (peak) of levels were within set limits. Patients reported low burden and high satisfaction.

Conclusion: PK-guided dosing was reliable according to post hoc analyses, based on low absolute errors that were regarded as clinically irrelevant in most cases. The predefined predictive performance was achieved in mid and peak factor levels but not in trough factor levels due to measurement inaccuracy. PK guidance also seemed feasible.

KEYWORDS

factor VIII, factor IX, hemophilia A, hemophilia B, pharmacokinetics, preventive medicine

Essentials

- Pharmacokinetic (PK) guidance of prophylaxis in hemophilia is used but not adequately validated.
- This prospective study investigates reliability and feasibility of PK guidance of prophylaxis.
- PK guidance of prophylaxis is reliable based on its low absolute and relative errors.
- Low burden and high satisfaction reported by patients and physicians suggest its feasibility.

1 | INTRODUCTION

Most people with severe and some with moderate hemophilia A and B receive prophylactic treatment with factor concentrates to alter their bleeding phenotype into a milder phenotype by maintaining higher factor trough levels [1]. Prophylactic treatment with factor concentrates prevents bleeding in joints and muscles and decreases joint damage, thereby lowering the risk of long-term disability due to hemophilic arthropathy [2].

Initial dosing of prophylaxis is often based on body weight. However, large interindividual variability in pharmacokinetics (PKs) can cause large differences in achieved factor levels [3-6]. During weight-based dosing, dose and/or dosing frequency are adjusted by the treatment team when subsequent (spontaneous) bleeding occurs. To shorten this dose-finding period with possible ineffective treatment or overconsumption of factor concentrate, targeted factor trough levels preferably should be established earlier. This can be achieved by application of PK-guided dosing [7]. This method uses Bayesian forecasting to estimate individual PK parameters using a population PK model by combining individually observed factor

activity levels and PK data from a population. Subsequently, estimated individual PK parameters are used to calculate a dosing regimen that maintains the desired factor levels. Target factor trough level should be at least >1 IU/dL; for the majority of patients, a factor level between 1 and 3 IU/dL is acceptable but most clinicians prefer a target factor trough level of $>3\%$ to 5% [8,9]. More recent insights advocate that target factor levels should be set individually, based on, for instance, bleeding phenotype and physical activities, aiming for true personalization of treatment [8,9].

Several studies indicate that PK-guided prophylaxis may optimize factor concentrate consumption and improve clinical outcomes [10-14]. Guidelines currently broadly recommend the use of PK-guided prophylactic dosing in hemophilia [9,15,16] and it is applied increasingly in daily clinical practice. The Web Accessible Population Pharmacokinetics Service-Hemophilia platform (WAPPS-Hemo) has analyzed the PK of almost 12,000 patients [17]. However, a survey reports that only 9.7% of the 70 responders of the ISTH Scientific and Standardization Committee factor VIII (FVIII) and factor IX (FIX) interest group routinely used Bayesian forecasting to tailor the dose when patients switch from standard half-life (SHL) to extended half-

life (EHL) factor concentrates [7]. In addition, patients and/or parents in a focus group study questioned the reliability of factor level estimates based on population PK analysis [18]. To our knowledge, only 1 study has indeed prospectively validated PK-guided dosing in clinical practice [10]. This study used the WAPPS-Hemo to estimate individual PK parameters. WAPPS-Hemo is one of the few available PK tools. Importantly, the choice of PK tool may influence the dosing advice given [19]. This highlights the necessity to further investigate the reliability of PK-guided dosing [10]. In addition, patient views on PK-guided dosing have only been described as discussed by focus groups in patients not treated with PK-guided prophylaxis [18]. Therefore, our study aims to investigate the predictive performance of PK-guided prophylactic dosing of factor concentrates in people with hemophilia A and B in daily clinical practice to establish both its reliability and feasibility for patients and treating physicians.

2 | METHODS

2.1 | Study design and patient population

The OPTI-CLOT TARGET study is a multicenter, nonrandomized, prospective cohort study that was performed in 2 hemophilia treatment centers in the Netherlands: the Erasmus University Medical Center Rotterdam and Amsterdam University Medical Centers. The Medical Ethical Committee of Erasmus University Medical Center Rotterdam approved the study and written informed consent was given. The trial is registered at the Dutch Trial register under trial number NTR7523 (www.trialregister.nl). OPTI-CLOT TARGET study design and detailed methods with figures have been described in an earlier publication [20]. People of all ages with hemophilia A and B on prophylaxis—both weight-based or PK-guided—or starting prophylaxis using SHL or EHL factor concentrates were eligible.

2.2 | Interventions

Study interventions are depicted in Figure 1. After infusion of a dose of 35 to 50 IU/kg FVIII or FIX concentrate, in line with Dutch guidelines, included patients underwent PK profiling with serial withdrawal of 3 to 6 blood samples [21–25]. No washout period was required since information with respect to 3 prior infusions was available. From patients' logbooks and medical files, we collected retrospective data on bleeds and dosing regimens over a 12-month period prior to inclusion to calculate annualized bleeding rate (ABR). The treating physicians set individual FVIII/FIX target levels based on bleeding phenotype (ABR), actual weekly physical activities, and prior FVIII/FIX levels (such as trough levels and levels during physical activities and at onset of bleeds). Based on aforementioned target level(s), PK profile, lifestyle, and patient dosing preferences, a trained clinical pharmacologist (within the OPTI-CLOT study group) individually advised a dosing regimen. These dosing regimens were calculated using published population PK models (Supplementary Table S1)

and maximum a posteriori Bayesian forecasting in NONMEM software (v7.4.1, Icon Development Solutions) [3,25–33]. This way, we performed transparent calculations.

Once agreement in treatment plans was obtained, patients received initial PK-guided treatment for 12 weeks. During this period, a minimum of 3 FVIII/FIX activity levels at varying time points after FVIII/FIX infusion were measured and compared with predicted levels to validate the suggested dosing regimen. The predictions were calculated using the individual PK parameters retrieved from Bayesian forecasting and population PK models. Therefore, these predictions relied on the known factor levels of a patient and characteristics of covariates (such as weight) used in the population PK models. Calculations were performed within a week after retrieving the measured factor levels. For every patient, we chose the population PK model that best matched the administered factor concentrate, patient characteristics, and measurement assay. Validation samples at any time point were allowed, but often trough and peak levels were sampled during 1 visit simultaneously to lower patient burden. If validation samples were not adequate or bleeding occurred, physicians could contact the OPTI-CLOT team for dosing adjustments.

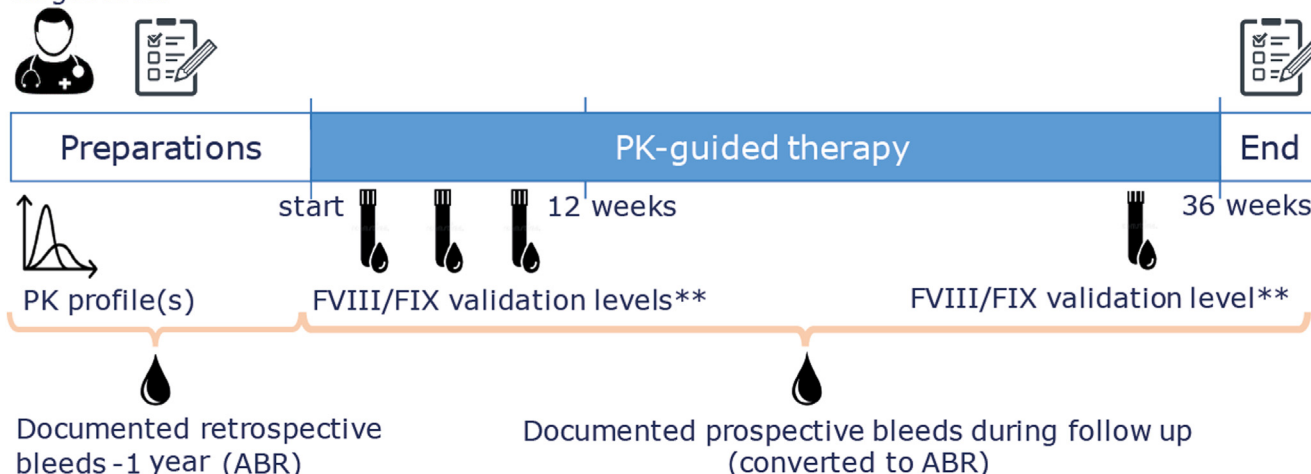
During the total follow-up period of 36 weeks, detailed data on bleeding events were recorded by patients and caretaker(s) in a personal treatment logbook. The treatment log was checked when validation levels were performed and additional questions were asked to complete bleeding documentation. Only if clinically indicated, additional FVIII/FIX levels were measured during prophylaxis or at the time of a bleed. At the end of the study period—per protocol 36 weeks after the start of PK-guided therapy—1 final blood sample at any random time after FVIII/FIX dosing was obtained for FVIII/FIX level assessment.

2.3 | Measurements

Laboratory measurements were performed according to local certified protocol. Specifications of the measurements can be found in Supplementary Table S2. The laboratory of the Erasmus University Medical Center measured all samples with both the chromogenic assay (CSA) and one-stage assay (OSA) and provided results in international units (IU) per deciliter, rounding off without decimals. In the Amsterdam Medical University Centers, FVIII was measured by CSA and FIX by OSA, and results were provided in IU per deciliter, rounding off with one decimal. For the dosing advice and validations, laboratory assays in the (published) population PK model that was used for Bayesian forecasting were matched with the assay applied in the study, and the rounding-off method was also matched.

For clinical purposes, we classified the FVIII/FIX levels into 3 categories of levels. Trough levels were FVIII/FIX levels determined within the last 24 hours of the dosing interval (both for SHL and EHL) with the exception of dosing intervals of ≤ 48 hours. In these cases, we categorized samples taken in the last 12 hours before the next prophylaxis dose as trough levels. Peak levels included factor levels within the first 4 hours after a factor concentrate dose. All other levels were categorized as mid levels.

Physician set individual FVIII/ FIX target level*



* Based on: previous FVIII/ FIX levels, physical activities and bleeding phenotype

** Measured levels compared to predicted levels by Bayesian analysis

FIGURE 1 Study design OPTI-CLOT TARGET. ABR, annualized bleeding rate; FIX, factor FIX; FVIII, factor FVIII; PK, pharmacokinetic.

We designed a short questionnaire using a visual analog scale of 1 to 5 to measure the feasibility of PK-guided dosing according to patient and/or caregiver and treating physician. Aforementioned stakeholders completed a questionnaire at study initiation and closure considering the burden of prophylaxis and study participation and expectations and satisfaction with PK-guided dosing. Patients who already received PK-guided dosing prior to study inclusion only completed the questionnaire at study closure, and their physicians were not required to complete the questionnaire. All patients received interactive visual PK curves. In this way, patients were able to check their factor level at any time after the last administered dose based on their regular dosing schedule. Patients were also informed about factor levels at the end of each day of the week and during their planned sport activities.

2.4 | Study endpoints

To investigate the predictive performance of PK-guided dosing, measured and predicted FVIII/ FIX levels were compared as primary endpoint. In the study protocol, we defined predictive performance as acceptable when at least 80% of measured FVIII/ FIX levels were within $\pm 25\%$ of the predicted FVIII/ FIX levels (relative error; measured/predicted level). Repeated measurements were not taken into account. Bias and accuracy were calculated using the mean error (ME; mean of predicted factor level - observed factor level) and mean absolute error, respectively. When 0 was included in the 95% CI of the ME, there was no statistically significant evidence that the bias was different from 0, and therefore, factor levels were not systemically underpredicted or overpredicted. For this primary endpoint analysis, FVIII/ FIX levels measured during a bleed were excluded as PK

parameters can be different in a different hemostatic setting. In addition, we explored differences between predicted and measured FVIII/ FIX levels during bleeds.

During the study period, the OPTI-CLOT steering committee—consisting of physicians from all Dutch hemophilia treatment centers—discussed what absolute errors (differences) between predicted and measured FVIII/ FIX levels are clinically acceptable. The committee achieved consensus to allow a maximum absolute error of 1 IU/dL for FVIII/ FIX trough levels, 5 IU/dL for mid levels, and 15 IU/dL for peak levels. We subsequently used these absolute errors to perform additional post hoc analyses.

As secondary endpoints, we explored differences between the retrospective and prospective study periods with regards to 1) predicted time spent with factor levels <1 and <5 IU/dL and 2) ABRs based on all patient-reported bleeds documented in patient logbooks and medical files. As the study was not powered to examine these secondary endpoints, we primarily described the outcomes and used statistical tests to explore potential differences.

2.5 | Statistical analysis

Analyses were performed in R (version 4.0.3, R Core Team). We used a paired permutation test to explore differences in time spent with factor levels <1 and <5 IU/dL and differences in ABRs between both study periods (retrospective vs prospective). We aimed to perform a negative binomial generalized linear mixed model with correction for follow-up time to explore differences in ABRs between the retrospective and prospective study periods, but because the model did not converge, we also used the paired permutation test to explore paired differences in

mean ABR. Prospective ABRs were estimated by extrapolating number of bleeds and individual follow-up time to 365.25 days.

3 | RESULTS

3.1 | Patients

We included 50 patients between July 22, 2019, and November 30, 2021, of whom 37 patients (74%) completed the entire study at study closure in October 2022. Thirteen patients withdrew early from the study due to either a switch to emicizumab treatment ($n = 12$)—which was introduced in the hospitals during the study—or long-term hospitalization requiring dosing adjustments ($n = 1$). Median study period was 36 weeks (IQR, 31–39 weeks). At study initiation, 5 patients were treated on demand, 29 patients received standard body weight-based prophylaxis, and 16 patients already received PK-guided prophylaxis. Besides people with severe hemophilia, 6 people with moderate hemophilia with a median endogenous FVIII/FIX level of 2.5 IU/dL (range, 1–3 IU/dL) participated in the study. All age groups were represented (range, 2–72 years). Almost half of the included patients were children (<18 years). Other patient and treatment characteristics are presented in the [Table](#).

3.2 | Predictive performance

A total of 206 FVIII/FIX levels were collected during follow-up visits to investigate the reliability of PK-guided dosing. We excluded 8 levels from analysis because levels were sampled during a bleed or no exact timing of dosing or sampling was available. The median number of collected validation samples per patient was 4 (IQR, 4–4). Median observed factor levels for trough, mid, and peak levels were 2.2 (IQR, 1.5–4.9; $n = 91$), 11.8 (IQR, 6.9–17.2; $n = 52$), and 47.0 (IQR, 28.5–82.0; $n = 55$) IU/dL. [Supplementary Figure S1](#) presents the difference between predicted and measured levels. The median of the absolute relative error of all levels was 15% (IQR, 5%–29%). In total, 71% of the remaining 198 measured factor levels were within $\pm 25\%$ of the predicted FVIII/FIX levels ([Figure 2](#)). More specifically, 58% of the 91 trough levels, 83% of 52 mid levels, and 80% of 55 peak levels were within the $\pm 25\%$ of the predictive levels (relative error). The predictive performance was comparable between age groups, between levels measured by CSA (72% correct of 82 levels) and OSA (70% correct of 116 levels), between FVIII concentrates (73% correct) and FIX concentrates (64% correct), and between the different factor concentrates ([Figure 2](#) and [Supplementary Table S3](#)). [Figure 3](#) depicts the absolute error between predicted and measured factor levels. The mean absolute error and ME were 0.8 IU/dL (95% CI, 0.6–1.0) and 0.0 IU/dL (95% CI, –0.3 to 0.2) for trough, 2.0 IU/dL (95% CI, 1.3–2.6) and –0.1 IU/dL (95% CI, –0.9 to 0.7) for mid, and 8.6 IU/dL (95% CI, 6.4–10.9) and 3.9 IU/dL (95% CI, 0.8–6.9) for peak levels, respectively. The 95% CIs of the ME and [Figure 3](#) demonstrate that the predictive performance of trough and mid levels is not biased, in contrast to the

peak levels that are slightly overpredicted. According to the post hoc analysis, 85% of total levels were within set limits. Specifically, for 81% of trough levels, the absolute error was <1 IU/dL; for 96% of mid levels, the absolute error was <5 IU/dL; and for 82% of peak levels, the absolute error was <15 IU/dL.

In addition to our primary analysis, we explored the predictive performance of 34 FVIII/FIX levels collected during a bleed. These levels were not scheduled as validation levels, but were clinically indicated to monitor adequate treatment of the bleeding. In total, 69% of these levels were within $\pm 25\%$ of the predicted factor levels ([Supplementary Figure S2](#)).

3.3 | Dosing regimens

The dose was tailored to the individual patient using PK-guided dosing. The median target trough as set by treating physician was 1 IU/dL (IQR, 1–3; range, 1–6 IU/dL). [Figure 4](#) provides an overview of the time patients spent with factor levels <1 and <5 IU/dL during the retrospective and prospective study periods of data collection. Patients spent less time ($P < .001$) with factor levels <1 IU/mL in the prospective, PK-guided time period (median, 0 hours; IQR, 0–1 hours) compared with the retrospective time period (median, 0 hours; IQR, 0–18 hours). Likewise, time spent with factor levels <5 IU/dL decreased ($P = .03$) from a median of 68 hours (IQR, 22–99 hours) in the retrospective time period to a median of 55 hours (IQR, 23–75 hours) in the prospective time period. For 29 patients who received weight-based prophylaxis in the retrospective time period, time spent with factor levels <1 IU/dL was significantly reduced while on PK-guided dosing in the prospective period ($P = .001$), whereas time spent with factor levels <5 IU/dL seemed to be reduced but did not differ significantly ($P = .54$) between the 2 periods. “Most patients switched to an alternative factor concentrate at the start of PK-guided treatment. Eight patients continued prophylaxis with the same factor concentrate. Three of these continued on the exact prophylactic dosing regimen and five were prescribed a higher dose or a higher dosing frequency, resulting in a higher trough level.”

During the PK-guided follow-up period, dosing regimens of 7 patients were adjusted due to varying reasons. Firstly, we intensified the SHL FVIII treatment plan for bleeds for 1 patient as a result of a high absolute error in 2 validated peak levels (predicted, 68 IU/dL and 57 IU/dL; measured, 32 IU/dL and 34 IU/dL, respectively). Secondly, we adapted the dosing regimen of another patient because of changes in weekly sport activities. Thirdly, dosing regimens for 5 patients were (temporarily) adjusted due to recurrent bleeding or synovitis.

3.4 | Bleeding

In total, 100 bleeds occurred in 35 patients during study inclusion, of which 23 spontaneous bleeds occurred in 11 patients. ABR for all bleeds was 1.9 (IQR, 0.0–4.4), and ABR for spontaneous joint and muscle bleeds was 0.0 (IQR, 0.0–1.4). Twenty-five patients switched from body weight–

TABLE Patient and treatment characteristics.

Characteristics	Value, number (n; %) or median (IQR; range)
Patient characteristics	
Total number of patients	50
Follow-up time (wk)	35.5 (31.1-38.5; 3.4-60.0)
Hemophilia A	34 (68%)
Hemophilia B	16 (32%)
Severe hemophilia (FVIII/FIX, <1 IU/dL)	44 (88%)
Baseline FVIII/FIX level in people with nonsevere hemophilia (IU/dL)	2.5 (2.0-3.0; 1.0-3.0)
Age (y)	19.4 (11.3-29.6; 2.3-71.8)
Number of pediatric patients	
Aged <18 y	24 (48%)
Aged <12 y	14 (28%)
Aged <6 y	7 (14%)
Height (cm)	176 (143-182; 85-197)
Body weight (kg)	70.2 (37.9-81.5; 13.0-117.0)
Body mass index (kg/m ²)	22.4 (18.3-24.9; 14.40-37.35)
Lean body mass (kg) ^a	62.0 (52.6-69.7; 17.1-78.8)
Mode of treatment before study initiation	
On demand—with indication to start prophylaxis	5 (10%)
Standard (body weight-based) prophylaxis	29 (58%)
Pharmacokinetic-guided prophylaxis	16 (32%)
Factor concentrate specifications	
Factor concentrate during study	
EHL FVIII	
Elocta	11 (22%)
Adynovi	9 (18%)
Jivi	1 (2%)
SHL FVIII	
Kovaltry	4 (8%)
NovoEight	7 (14%)
ReFacto AF	2 (4%)
EHL FIX	
Alprolix	12 (24%)
Idelvion	4 (8%)

(Continues)

TABLE (Continued)

Characteristics	Value, number (n; %) or median (IQR; range)
Switching of factor concentrate at study initiation	27 (54%)
Switching from SHL to EHL at study start initiation	22 (44%)

EHL, extended half-life; FIX, factor IX; FVIII, factor VIII; SHL, standard half-life.

^aLean body mass was not measured in 9 patients aged 71, 15, 8, 5, 6, 2, 2, 2, and 2 years.

based dosing to PK-guided dosing and completed the follow-up period. Bleeds of this subgroup of patients are presented separately (Figure 5), to be able to compare bleeds between the 2 dosing strategies. Supplementary Table S4 presents the ABR of patients both in the retrospective period and in the prospective study period. According to the permutation test that we used to explore differences, no differences were found in ABRs of all patients and patients switching from weight-based to PK-guided dosing ($N = 25$) for all bleeds ($P = .51$ and $P = .76$, respectively), joint and muscle bleeds ($P = .13$ and $P = .98$, respectively), and spontaneous joint and muscle bleeds ($P = .07$ and $P = .096$, respectively).

3.5 | Feasibility

Figure 6 shows the patient- and physician-reported outcomes of the questionnaire developed to evaluate the feasibility of PK-guided dosing. At both study initiation and closure, the majority of patients reported no difficulties in combining prophylaxis with daily life and traveling. In contrast to physicians' expectations, patients did not report an experienced (high) burden due to additional hospital visits and/or blood sampling as required for PK guidance. High expectations of satisfaction with the PK-guided dosing intervention at study initiation were fulfilled during the study. Strikingly, Figure 6 shows that the majority of patients (72%) and physicians (94%) were satisfied or very satisfied with PK guidance of prophylaxis. Sixty-seven percent to 71% of patients and physicians considered knowledge on approximate factor activity levels during the week important or very important. When switching to an alternative factor concentrate in the future, 56% of patients reported to be willing, with 26% definitely willing, to repeatedly construct a PK profile. In total, 86% of patients (definitely) recommended PK-guided dosing to other patients. Nearly all physicians (96%) would (definitely) like to apply PK-guided dosing to other patients as well.

4 | DISCUSSION

Our study was designed to investigate the predictive performance of PK-guided prophylactic dosing of factor concentrates in people with

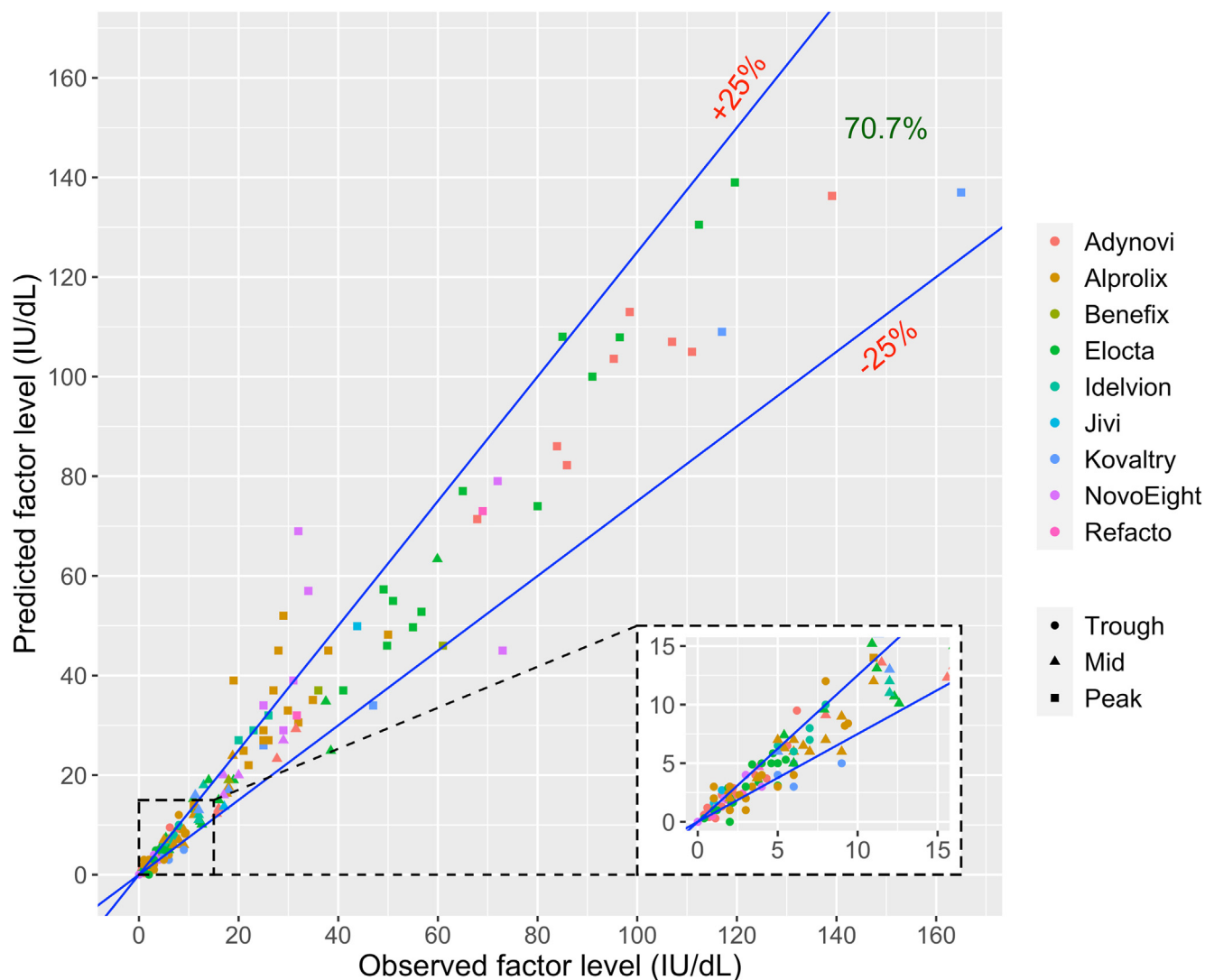


FIGURE 2 Predictive performance of follow-up factor levels during pharmacokinetic-guided dosing. The predicted factor levels based on the individual pharmacokinetic parameters are plotted against the observed factor levels. The blue lines represent $\pm 25\%$ limits of deviation, and in green (top right), the percentage of samples within these limits is depicted (70.7%). The various factor concentrates are depicted in different colors. No obvious differences between factor concentrates are observed. The shape of the markers characterizes the nature of the factor level according to time after dose and dosing schedule (trough, mid, and peak). For readability, factor levels < 15 IU/dL are enlarged in the right corner of the plot. As is demonstrated, more trough levels fall outside the limits in the detail of this figure.

hemophilia A and B and to establish reliability and feasibility of this approach. According to the study protocol, predictive performance was deemed adequate when at least 80% of the measured FVIII/FIX levels were within the $\pm 25\%$ of the predicted FVIII/FIX levels (relative error). Predictive performance was adequate for mid (83%) and peak levels (80%) but inadequate for trough levels (57%). In total, 71% of factor levels were within limits.

In our opinion, not achieving the target of 80% is explained by the relatively high coefficient of variation (CV) of FVIII/FIX trough level measurements. [Supplementary Table S2](#) shows a CV of 3% to 8% for factor levels ≥ 26 IU/dL. It is well known that CVs of these assays at lower FVIII/FIX levels are higher. van Moort et al. [34] confirmed high assay CVs when measuring lower FVIII levels as factor levels < 5 IU/dL showed CVs ranging from 9.9% to even 121% in quality control

studies by the External quality Control of diagnostic Assays and Tests (ECAT) Foundation. For clinical purposes, it is important to validate trough factor levels. However, the high CV of these measurements should be taken into account when validating dosing regimens with these low factor levels. To overcome these difficulties, physicians may be inclined to measure a mid factor level instead of a trough level. The trough factor level can subsequently be extrapolated on basis of the individual PK parameters as obtained by Bayesian forecasting.

Additionally, the very low absolute error that is permitted when maintaining $\pm 25\%$ limits (relative error) may have also impacted the lower predictive performance in the FVIII/FIX trough levels. For instance, with an observed level of 1 IU/dL, predicted levels ranging from 0.75 to 1.25 IU/dL (absolute error, 0.25 IU/dL) will fall within limits. Such small differences however are hardly measurable by the

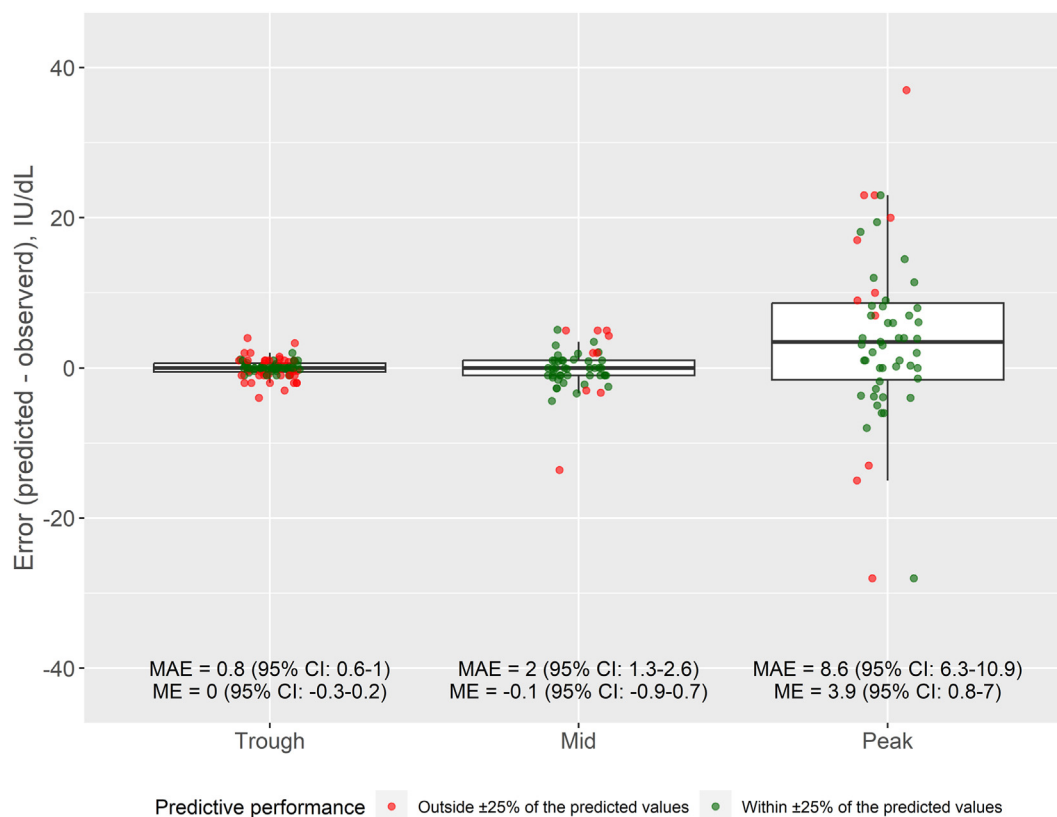


FIGURE 3 The absolute error is presented for trough, mid, and peak factor (F)VIII/FIX levels. Observed factor levels that were within $\pm 25\%$ of the predicted values are depicted in green, while levels outside these boundaries are red. Median observed factor activity levels for trough, mid, and peak levels were 2.2 (IQR, 1.5-4.9), 11.8 (IQR, 6.9-17.2), and 47.0 (IQR, 28.5-82.0) IU/dL, respectively. The mean absolute error (MAE, accuracy) and mean error (ME, bias) and including 95% CIs are presented in the bottom of the plot. The figure shows that the proportion of adequately predicted factor levels (in green) is higher for peak levels, though the absolute error is low for trough levels. Furthermore, in the prediction of the peak levels, a significant bias is observed. These predicted levels are generally overestimated.

participating hemostasis laboratories, and numbers behind the decimal point are not communicated in all laboratories.

Errors in Bayesian forecasting in general, as well as discrepancies of data used to develop the population PK models (eg, laboratory specifications such as varying reagents), may also have contributed to lower predictive performance in all types of levels. Therefore, when possible, we used population PK models that were based on data with similar characteristics as the populations in our study. Other sources of errors may be corrections for residual factor levels of previously administered factor concentrates as no washout period was used during PK profiling.

In the post hoc analysis, the total predictive performance of all FVIII/FIX levels was 85%. In this analysis, acceptable absolute errors were set at 1, 5, and 15 IU/dL for trough, mid, and peak levels, respectively. Importantly, we believe that this post hoc analysis represents the overall predictive performance of PK-guided prophylaxis in hemophilia in daily clinical practice more optimally. Our approach shows similarities with a report by Stemberger et al. [10]. Stemberger et al. [10] coded 138 measured factor levels as concordant/discordant with 3 predicted factor windows. The study reported 72% concordant levels in the window < 3 IU/dL, 90% in the window 3 to 15 IU/dL, and 85% in the window > 15 IU/dL. As in our study, these estimates

increased with increasing factor levels. If these windows are subsequently compared with our classifications of trough (median observed factor level, 2.2 IU/dL), mid (median, 11.8 IU/dL), and peak (median, 47 IU/dL) levels, it can be concluded that Stemberger et al. [10] accepted larger differences between measured and predicted levels in all 3 documented windows, although our predictive performance results of the post hoc analysis were comparable and even higher (81% for trough levels, 96% for mid levels, 82% for peak levels). "Although both studies report good predictive performance, we believe our approach applies more clinically acceptable cut-off values. As an example, a measured trough level of a patient in the study by Stemberger et al. with a predicted trough between 3-15 IU/dL was categorized as concordant even though the trough level deviated 12 IU/dL, while this difference has relevant clinical consequences."

Interestingly, predictive performance of factor levels measured during bleeds was similar to the predictive performance of factor levels measured in the normal prophylactic setting (68% vs 71% within $\pm 25\%$ of prediction, respectively). Importantly, the severity of bleeding was patient-reported and most of the bleeds in which factor levels were measured were severe bleeds. Furthermore, as only 34 FVIII/FIX levels were measured during a bleed, more research is necessary to examine the differences in PK characteristics in these varying hemostatic settings.

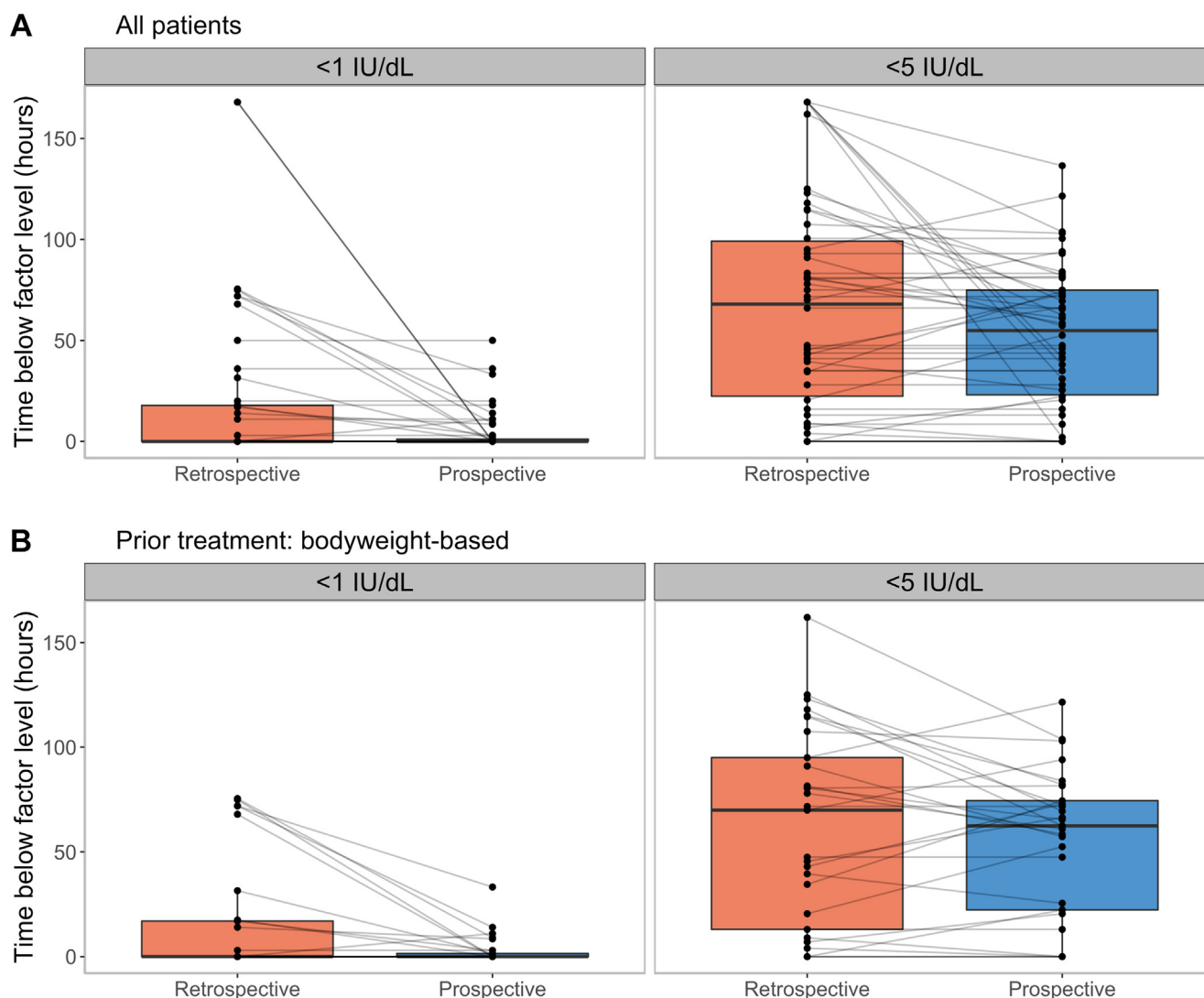


FIGURE 4 Time with factor levels <1 and <5 IU/dL during the prospective and retrospective study periods for (A) all patients and (B) patients previously treated with body weight-based therapy. The boxes of the boxplots present the median (middle line) and IQR with whiskers extending to the first quartile or third quartile + 1.5 IQR. The lines represent individual patients, and darker lines indicate multiple patients. For (A) all patients, time spent with factor levels <1 and <5 IU/dL decreased in the prospective period ($P < .001$ and $P = .003$, respectively). For 29 patients who were previously on body weight-based prophylaxis (B), time spent with factor levels <1 IU/dL reduced in the prospective period in comparison with the retrospective period ($P = .001$). The time spent with factor levels <5 IU/dL did not differ between the 2 periods in this group ($P = .54$).

The explored differences in ABRs between the retrospective and prospective periods must be interpreted with caution. Firstly, the study was not powered to investigate differences in ABRs. Secondly, we cannot control for the following confounding factors: 1) almost half of study patients switched from SHL to EHL factor concentrate and 2) almost one-third of the patients initiated PK guidance of treatment before study inclusion. Moreover, the number of bleeds occurring in the 36 weeks (or less) of follow-up had to be converted to ABRs. Lastly, it is plausible that the extent of documentation of bleeds in logbooks was higher during the prospective period than during the retrospective period. After all, patients were instructed to keep a detailed logbook at study inclusion and the study investigator asked for occurred bleeds every study visit. Importantly, patients spent less time with factor levels <1 IU/mL and <5

IU/mL when PK-guided dosing was applied, which is associated with a decreased rate of bleeds [12,35].

The strengths of this study consist of the design and its reflection of the real-world setting. Similar to daily clinical practice, the study used local protocols of the specialized hemostasis laboratories in both hemophilia treatment centers, as well as varying SHL and EHL factor concentrates and individual preferences in dosing regimens. Furthermore, the included study population is a true representation of the heterogeneity encountered in people with hemophilia. However, data on sociocultural determinants were not collected as impact on the primary outcome was not expected. Moreover, despite withdrawal of a number of patients due to unforeseen circumstances, 198 validation samples were included. To our knowledge, this is also the first report on patients'

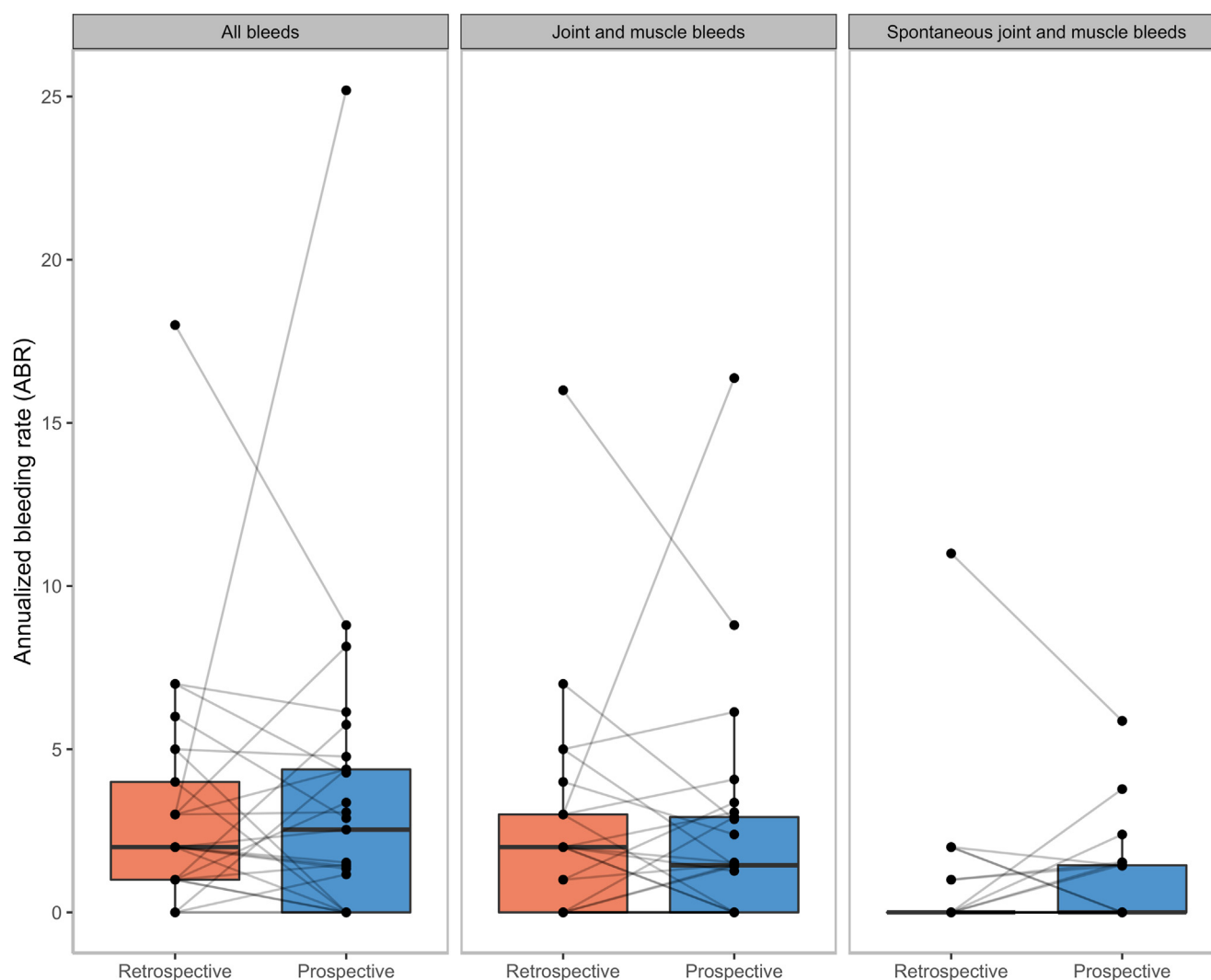


FIGURE 5 Annualized bleeding rates (ABRs) of 25 patients who switched from body weight-based therapy in the retrospective study period to PK-guided dosing in the prospective study period and completed follow-up. The first panel shows ABRs of all bleeds, the second panel shows ABRs of joint and muscle bleeds, and the third panel shows ABRs of spontaneous joint and muscle bleeds. The boxes of the boxplots present the median (middle line) and IQR with whiskers extending to Q1 or Q3 + 1.5 IQR. The lines represent the individual bleeding rates. The ABR of the prospective period was calculated and extrapolated, since the follow-up period was shorter than an entire year. Overall, a minimal fluctuation is observed, and no statistically significant differences were found between study periods for all bleeds ($P = .76$), joint and muscle bleeds ($P = .98$), and spontaneous joint and muscle bleeds ($P = .96$).

and physicians' experiences with PK-guided dosing. In general, patients reported low burden of required extra hospital visits and/or blood sampling. Also, both patients and physicians expressed high satisfaction with PK-guided dosing. The fact that nearly all patients and physicians would recommend PK-guided dosing to others and would commit to repeated PK profiling in the future further underlines patients' and physicians' support for this intervention and will contribute to the broader implementation of PK-guided dosing in clinical practice. Another strength of this study is that trained pharmacologists within the OPTI-CLOT study team gave dose advices. They checked if individual-fitted PK profiles were fitted correctly and adapted dosing times according to timing of physical activities. Recently, the OPTI-CLOT web portal has been initiated to provide such personalized consultation.

An important study limitation is the aforementioned high laboratory inaccuracy in the measurement of FVIII/FIX trough levels. Unfortunately, 13 of 50 patients withdrew early from the study mostly due to switching to subcutaneous nonfactor replacement medication. However, as evaluation of the predictive performance was our primary aim and 198 factor levels were included from 50 patients, we do not believe that this impacts our study endpoints. Lastly, since feasibility was only addressed in patients (and physicians) who participated in the study, the results may have been subject to selection bias. "Most mentioned reasons to decline study participation were either a large distance to the hospital complicating study visits and/or trust in current therapy and unwillingness to change." Notwithstanding these limitations, this study offers valuable insights

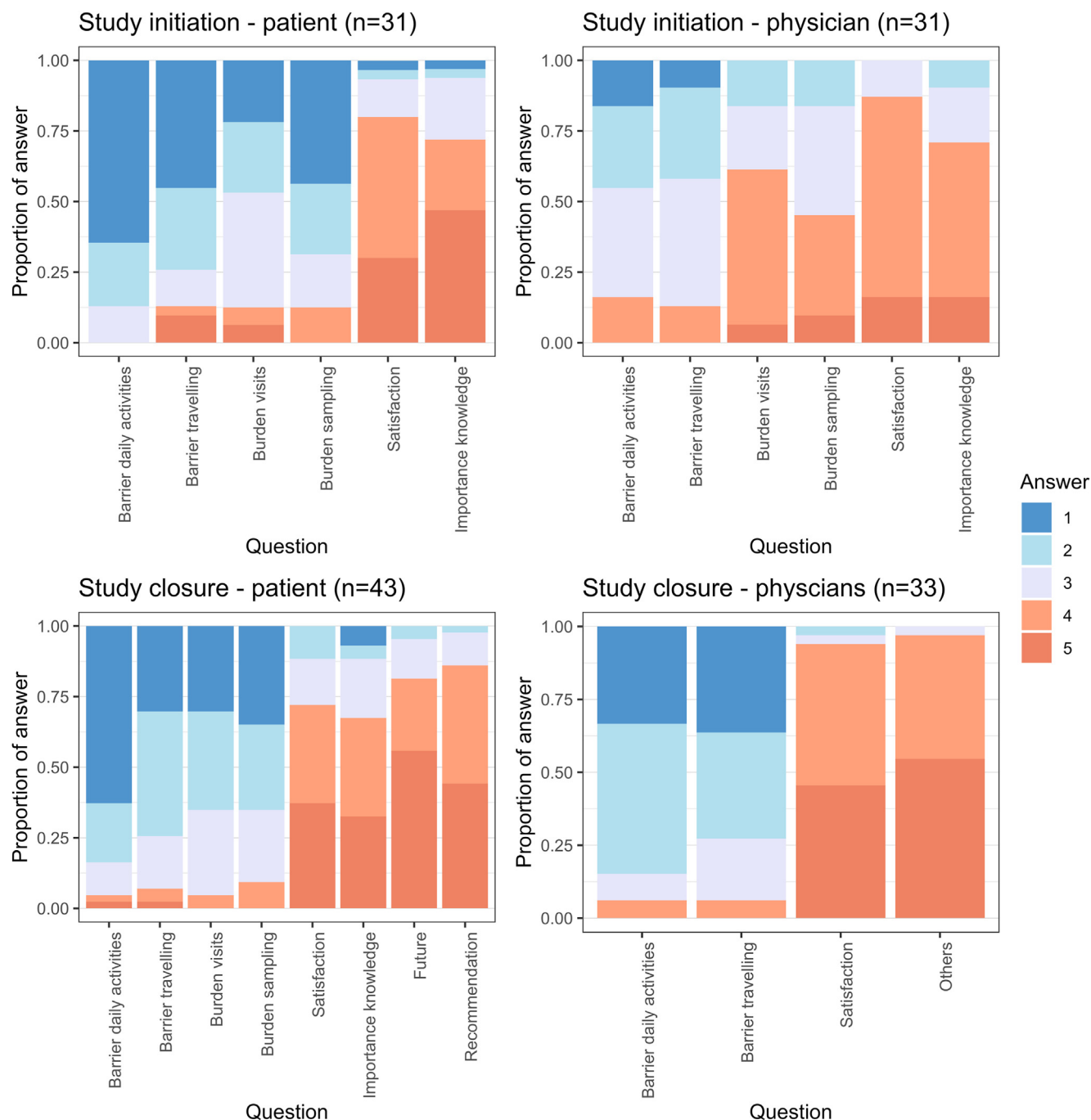


FIGURE 6 Patient- and physician-reported outcomes regarding the feasibility of pharmacokinetic (PK)-guided dosing. All questions utilized a 1- to 5-point visual analog scale, ranging from very low/very easy (1) to very high/very difficult (5). At study initiation and closure, patients answered questions in the following domains: 1) difficulties combining prophylaxis with daily activities (barrier daily activities), 2) difficulties combining prophylaxis with traveling (barrier traveling), 3) extent of the burden of additional hospital visits for PK profiling (burden visits), 4) extent of the burden of additional blood sampling (burden sampling), 5) expectations and satisfaction with PK-guided dosing (satisfaction), and 6) importance of knowledge of factor levels during the week (importance knowledge). At study closure, patients answered 2 additional questions regarding 7) willingness to construct PK profiles in the future in case of a factor VIII/IX concentrate switch (future) and 8) if the patient would recommend PK-guided dosing to other patients (recommendation). Physicians were asked the same questions as patients at study initiation. At study closure, questions 1, 2, and 5 were repeated and physicians answered the following additional question: Would the physician like to dose other patients under PK guidance as well (others)? It is apparent from this graph that the burden of PK guidance is low (blue) and the satisfaction with PK guidance is high (orange).

into the predictive performance of PK-guided prophylaxis in daily clinical practice.

The next step within the OPTI-CLOT TARGET study is to further personalize dosing based on not only PK parameters but also pharmacodynamic (PD) parameters and construct population PK-PD models for prophylaxis. PD describes how the drug affects the body, and in hemophilia PD describes bleeding or coagulation parameters. As we clearly see that patients necessitate different (trough, mid, and peak) factor levels to not bleed, this may be challenging. Therefore, individual bleeding risk as an endpoint may be more feasible [36,37]. Attempts at population PK-PD modeling have already been made for hemophilia A, combining PK of FVIII with thrombin/plasmin generation parameters and/or with information on past bleeds [36,38–40].

5 | CONCLUSION

We conclude that, according to post hoc analysis based on absolute errors, PK-guided dosing is reliable in clinical practice. Our pre-specified predictive performance, based on relative errors, was not completely achieved due to higher relative errors in trough FVIII/FIX levels. These errors can be explained by measurement inaccuracy in lower factor ranges as has been reported by many. Importantly, PK-guided dosing seemed feasible according to reported low burden and high satisfaction in both patients and physicians.

APPENDIX

SYMPHONY: Dr M.H. Cnossen (principal investigator), Dr S.H. Reitsma, Erasmus MC Sophia Children's Hospital, Rotterdam; according to Theme and workpackage: Prof Dr M. de Haas, Dr M. van den Biggelaar, Sanquin, Amsterdam, Prof Dr M.P.M de Maat, R.A. Arisz, Erasmus MC, Rotterdam, Prof Dr R.E.G. Schutgens, Dr R.T. Urbanus, M. Zivkovic, UMCU, Utrecht, Prof Dr F.W.G. Leebeek, Prof Dr H.F. Lingsma, E.S. van Hoorn, Erasmus MC, Rotterdam, Prof Dr R.A.A. Mathot, L.H. Bukkems, M.E. Cloesmeijer, A. Janssen, S.F. Koopman, Amsterdam UMC, Amsterdam, M.C.H.J. Goedhart, L.G.R. Romano, W. Al Arashi, C. Mussert, Erasmus MC, Rotterdam, Dr S.C. Gouw, M.R. Brands, Amsterdam UMC, Amsterdam, R.M.T. ten Ham, UMCU, Utrecht, D.M. Prameyllawati, Erasmus MC, Rotterdam, Prof Dr K. Meijer, UMCG, Groningen, Prof Dr A.L. Bredenoord, EUR, Rotterdam, Dr R. van der Graaf, L. Baas, UMCU, Utrecht, Prof Dr J.J. Voorberg, Sanquin, Amsterdam, Prof Dr K. Fijnvandraat, Amsterdam UMC, Amsterdam, Prof Dr A.B. Meijer, J. Del Castillo Alferes, Dr E. van den Akker, H. Zhang, Sanquin, Amsterdam, Dr R. Bierings, Erasmus MC, Rotterdam, Prof Dr H.C.J. Eikenboom, LUMC, Leiden, Dr I. van Moort, Erasmus MC, Rotterdam, S.N.J. Laan, LUMC, Leiden. Advisory Board: Prof Dr C.A. Uyl-de Groot (EUR, Rotterdam), C. Smit, G. Wijffjes (NVHP), Dr M.H.A. Bos (NVTH), Prof Dr V.W.V. Jaddoe (Erasmus MC, Rotterdam), Prof Dr P.J. Lenting (Université Paris-Saclay, France), Prof Dr M. Makris (University of Sheffield, England),

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ETHICS STATEMENT

The Medical Ethical Committee of Erasmus University Medical Center Rotterdam approved the study, and written informed consent was given.

AUTHOR CONTRIBUTIONS

T.M.H.J.G. enrolled patients, performed blood sampling for pharmacokinetic analysis and validation, and collected the data. L.H.B. performed the Bayesian forecasting and gave the dosing advices. T.M.H.J.G. and L.H.B. jointly performed (statistical) data analyses and are the main authors of the manuscript. A.-F.Z. aided in study logistics and blood sampling at the Amsterdam UMC. R.A.A.M. and M.H.C. designed and supervised the study and helped write the manuscript. All authors substantially contributed to group discussions, wrote and critically revised the manuscript, and approved the final draft.

RELATIONSHIP DISCLOSURE

M.H.C.'s institution has received investigator-initiated research grants, travel grants, and speaker fees from the Netherlands Organization for Scientific Research (NWO) and Netherlands National research Agenda (NWA), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch Innovatiefonds Zorgverzekeraars, Baxter/Baxalta/Shire/Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma and M.H.C. has served as a steering board member for Roche, Bayer, and Novartis. Fees go to the Erasmus MC as an institution. She is furthermore an active member of the European Reference Network EuroBloodNet. R.A.A.M. has received grants from governmental and societal research institutes such as NWO, ZonMw, and Dutch Kidney Foundation and Innovation Fund and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, Sobi, and CelltrionHC. He has served as advisor for Bayer, CSL Behring, Merck Sharp & Dohme, and Baxter/Baxalta/Shire/Takeda. All grants and fees were paid to the institution. M.C. has received financial support for research from Bayer, Roche, uniQure, and Novo Nordisk and honoraria for lecturing or consulting or travel support from Alexion, Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, Sobi, and Viatrix. All payments were made to the institution. The institution of K.F. has received unrestricted research grants from CSL Behring and Novo Nordisk and her institution received consultancy fees from Sobi, Grifols, Takeda, Novo Nordisk, and Roche. S.E.M.S. received a research grant from Bayer. F.C.J.I.H.-M. received a research grant from Bayer. K.M. reports speaker fees from Alexion, Bayer, and CSL Behring; participation in trial steering committee for Bayer; consulting fees from uniQure; and participation in data monitoring and endpoint adjudication committee for Octapharma; all payments go to

her institution. F.W.G.L. received unrestricted research grants from CSL Behring, Takeda, Sobi, and uniQure. He is a consultant for CSL Behring, Takeda, BioMarin, and uniQure, the fees from which go to the university. He has been a Data and Safety Monitoring Board member of a study sponsored by Roche. Other authors have no conflict of interest to declare for this paper.

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SUPPLEMENTARY MATERIAL

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