Received: 27 May 2019 | Accepted: 20 September 2019

DOI: 10.1111/jth.14652

ORIGINAL ARTICLE

One piece of the puzzle: Population pharmacokinetics of FVIII during perioperative Haemate P®/Humate P® treatment in von Willebrand disease patients

Nico C. B. de Jager[1] | Laura H. Bukkems[1] | Jessica M. Heijdra[2] | Carolien H. C. A. M. Hazendonk[2] | Karin Fijnvandraat[3] | Karina Meijer[4] | Jeroen Eikenboom[5] | Britta A. P. Laros - van Gorkom[6] | Frank W. G. Leebeek[7] | Marjon H. Cnossen[2] | Ron A. A. Mathôt[1] | for the OPTI-CLOT group[†]

[1]Hospital Pharmacy - Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Paediatric Hematology, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands

[3]Amsterdam UMC, Emma Children's Hospital, Pediatric Hematology, University of Amsterdam, Amsterdam, Netherlands

[4]Department of Haematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[5]Department of Internal Medicine, Division of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands

[6]Department of Haematology, Radboud University Medical Center, Nijmegen, The Netherlands

[7]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Laura H. Bukkems, Amsterdam UMC, University of Amsterdam, P.O. 22660, 1100 DD Amsterdam, The Netherlands.
Email: l.h.bukkems@amc.uva.nl

Abstract

Introduction: Many patients with von Willebrand disease (VWD) are treated on demand with von Willebrand factor and factor VIII (FVIII) containing concentrates present with VWF and/or FVIII plasma levels outside set target levels. This carries a risk for bleeding and potentially for thrombosis. Development of a population pharmacokinetic (PK) model based on FVIII levels is a first step to more accurate on-demand perioperative dosing of this concentrate.

Methods: Patients with VWD undergoing surgery in Academic Haemophilia Treatment Centers in the Netherlands between 2000 and 2018 treated with a FVIII/VWF plasma-derived concentrate (Haemate® P/Humate P®) were included in this study. Population PK modeling was based on measured FVIII levels using nonlinear mixed-effects modeling (NONMEM).

Results: The population PK model was developed using 684 plasma FVIII measurements of 97 VWD patients undergoing 141 surgeries. Subsequently, the model was externally validated and reestimated with independent clinical data from 20 additional patients undergoing 31 surgeries and 208 plasma measurements of FVIII. The observed PK profiles were best described using a one-compartment model. Typical values for volume of distribution and clearance were 3.28 L/70 kg and 0.037 L/h/70 kg. Increased VWF activity, decreased physical status according to American

Nico C. B. de Jager and Laura H. Bukkems shared first authorship.

Marjon H. Cnossen and Ron A. A Mathôt both are last authors.

[†]See Appendix 1 for full list of members of the study group.

Manuscript handled by: Flora Peyvandi

Final decision: Flora Peyvandi, 20 September 2019

Society of Anesthesiologists (ASA) classification (ASA class >2), and increased duration of surgery were associated with decreased FVIII clearance.

Conclusion: This population PK model derived from real world data adequately describes FVIII levels following perioperative administration of the FVIII/VWF plasma-derived concentrate (Haemate® P/Humate P®) and will help to facilitate future dosing in VWD patients.

KEYWORDS

Haemate P, individualized medicine, pharmacokinetics, surgery, von Willebrand disease

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder diagnosed in humans.[1] This autosomally inherited disorder is characterized by quantitative or qualitative defects of Von Willebrand factor (VWF) and concomitant lower FVIII levels. Von Willebrand factor is essential for both primary and secondary hemostasis as it contributes to platelet adhesion and aggregation at sites of injury, resulting in platelet plug formation. Moreover, it acts as a chaperone protein for FVIII, protecting it from proteolysis in the circulation.[2,3]

The current VWD classification is based on observed VWF abnormalities. Whereas type 1 VWD describes a partial and type 3 VWD a complete quantitative VWF deficiency, type 2 VWD comprises several qualitative VWF defects. Von Willebrand disease is mainly characterized by mucocutaneous bleeding and bleeding after trauma or surgery. Available treatment focuses on normalization of VWF and FVIII levels in cases of acute bleeding, when trauma occurs, or in surgery. The VWF and FVIII levels can be increased by administration of desmopressin, which stimulates endogenous release, or by replacement therapy with intravenously administered exogenous VWF concentrate with or without FVIII.[4] Prophylactic treatment is rarely necessary and usually restricted to type 3 VWD patients.

A widely used plasma-derived VWF concentrate in patients with VWD is Haemate P® or Humate P®.[5] This concentrate contains both VWF and FVIII in a ratio of 2.4:1. Interindividual variability in achieved levels after infusion of this VWF/FVIII-containing concentrate has been reported by several investigators, both in the on-demand treatment of bleeding and in the surgical setting.[6-9] This variability can be explained by both the interindividual differences in PK of the exogenous VWF/FVIII-containing concentrate and the interindividual differences in residual endogenous VWF and FVIII levels. Moreover, endogenous FVIII levels, which are known to vary unpredictably because of FVIII release from the endothelium after induced stress, trauma, or surgery, can differ significantly within an individual patient and between individuals. This variability hampers adequate dosing of VWF/FVIII concentrate, leading to achieved levels that may be higher or lower than targeted.[6] Subsequently this may lead to an increased risk of thrombosis or bleeding, respectively. In addition, patient and societal burden of treatment are unnecessarily high as a result of frequent monitoring of plasma FVIII and VWF levels and more consumption of concentrate than necessary.[6]

Essentials

- In many Von Willebrand disease (VWD) patients, perioperative factor VIII (FVIII) and von Willebrand factor levels are outside set targets.
- A population pharmacokinetic model for Haemate P based on FVIII levels was developed.
- The FVIII levels after Haemate P administration were adequately described by the population pharmacokinetic model.
- The population pharmacokinetic model could facilitate more accurate perioperative dosing for VWD patients.

The current challenges to achieve the required target levels in VWD patients using this specific VWF/FVIII concentrate call for additional tools to dose more adequately. Population PK modeling and subsequent maximum *a posteriori* Bayesian analysis could be promising tools to reach individualize care in VWD patients who need to undergo surgery.

Historically, perioperative dosing of VWD patients with VWF/FVIII concentrates has been based on FVIII levels for a variety of reasons. First, generally FVIII plasma levels were presumed more important in preventing perioperative bleeding.[10] Second, product labels only contained information on FVIII potency. Finally, more practically, the more rapid availability of FVIII level results in most laboratories made FVIII-based dosing a more feasible guide for replacement therapy with VWF/FVIII concentrate. However, nowadays some researchers recommend that especially during the first 36 postoperative hours, VWF activity also needs to be measured because the presence of sufficient VWF activity can be important for the aggregation of platelets during primary hemostasis and therefore initial wound closure.[3,11] Sufficient FVIII levels are subsequently required for complete wound healing and are therefore often monitored during the whole perioperative period.[12-14] Dutch national guidelines have adopted these general principles and describe FVIII and VWF targets for the first 36 h after the surgery and FVIII targets for the further monitored postoperative period.[13]The aim of the study is to assess the population PK of FVIII activity levels after perioperative administration of a specific VWF/FVIII concentrate and to identify any patient, surgical, or treatment factors

correlating with the PK parameters of FVIII. The population model can be a starting point for the individualization of replacement therapy during the perioperative period in VWD patients and may be especially useful when only FVIII targets apply.

2 | METHODS

2.1 | Data

The data used to construct this population PK model were obtained from a multicenter retrospective cohort study performed by the OPTI-CLOT study group, conducted in five Academic Haemophilia Treatment Centers in the Netherlands.[6] This first data set is referred to as the *index data set* and was used for the development of this FVIII-based population PK model. Additionally, an extra data set from the Erasmus University Medical Center Rotterdam (n = 20) was collected; it was used for external validation of the developed FVIII-based population PK model. This data set will be referred to as the *validation data set*. The combination of both data sets was used to build the final FVIII-based population PK model. All data were collected between 2000 and 2018 and acquired in accordance with the Dutch rules and regulations for Good Clinical Practice.

All VWD patients included in this study underwent a surgical intervention requiring replacement therapy with VWF/FVIII concentrate (Haemate P®). The data consisted of FVIII plasma levels, patient demographics, surgical characteristics, and treatment information. Patient demographics included sex, age, height, weight, blood group, hemoglobin levels, baseline VWF:antigen (VWF:Ag), VWF activity (VWF:Act), and FVIII activity levels (lowest levels ever measured in the patient), renal function and hepatic function (characterized by aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, albumin, urea, and creatinine), type of VWD as diagnosed following the national guidelines, and surgical risk classification based on the ASA physical status classification system.[13] Surgical characteristics consisted of type, severity and duration of surgery.[15] Treatment information described timing and dosing of the concentrate and/or comedication with effect on hemostasis (nonsteroidal antiinflammatory drug, tranexamic acid, or heparin) and achieved FVIII, VWF:Act, VWF:Ag, and VWF:collagen binding levels. Perioperative dosing of the VWF/FVIII concentrate was based on FVIII levels, which were measured by one-stage clotting assays.[13] Dosages and levels obtained after additional desmopressin use were excluded, as FVIII pharmacokinetics after desmopressin were expected to deviate as a result of excessive endogenous FVIII release.[16] The included patients did not receive prophylactic treatment and when occasionally a dose was given before the loading dose of the surgery, this dose was included in the database. A more detailed overview of data characteristics is documented in Table 1.

2.2 | Population PK modeling

The population PK modeling approach analyzes the data from all patients simultaneously instead of modeling individual patients separately. An analysis provides typical (median) values of PK parameters and the corresponding interindividual and intraindividual variability. With this method sparse data with random sampling times, which usually are present during clinical data collection, can be analyzed.

A compartmental population PK model describing the PK of FVIII levels after administration of this specific VWF/FVIII concentrate in the perioperative setting was developed using nonlinear mixed effect modeling, as implemented in software package NONMEM version 7.4.2 (ICON Development Solution). Visualization and evaluation of the data and the developed FVIII PK model were achieved using R v3.4.1 and PsN v4.7.0 in combination with Piraña v2.9.6.[17-20] Factor VIII levels were log transformed and after analysis the PK parameters, their interindividual variability (IIV), and residual variability between observed and predicted FVIII were derived. In order to determine what number of compartments produced the best fit of the data, single and multiple compartment linear models were used to fit the FVIII versus time data. The PK parameters, volume of distribution (V) and clearance (CL), were estimated. When using, for example, a two-compartment model, estimation of the peripheral volume of distribution and intercompartmental clearance was included.

Baseline FVIII was estimated in the PK analysis and subtracted from the observed FVIII level in the modeling process, though, in 92 of the 180 surgeries, FVIII was measured before administration of the VWF/FVIII concentrate and these values did not always coincide with the measured baseline FVIII: That is, FVIII before administration was often higher than the lowest value ever measured in the patient. This difference is most likely caused by physiological variability in FVIII levels or by preoperative anxiety, increasing age, or presence of comorbidity.[21-23] For modeling purposes, a correction was introduced by administration of a fixed virtual dose with varying bioavailability to these patients prior to the time of measurement of the predose FVIII level. Application of this technique causes FVIII estimation to return to the lowest value ever measured instead of FVIII level before administration. The rationale of the use of this technique was strengthened by the presence of lower FVIII levels at the end of perioperative treatment than before dose FVIII was measured in 10 occasions. It was possible to estimate the bioavailability (F) and its variability as a correction without influencing estimations of other PK parameters.

Finally, as a wide variatiety of ages and weights was present in the data, the PK parameters were *a priori* scaled to a body weight of 70 kg using the allometric scaling principle.[24]

2.3 | Covariate modeling

In order to test the capability of the factors sex, age, height, blood group, duration and severity of surgical procedure, VWD type, ASA classification, (baseline) VWF:Act, (baseline) VWF:Ag, VWF:CB, use of nonsteroidal anti-inflammatory drugs, tranexamic acid and/or heparin, and altered hepatic function and/or renal function to explain the IIV or interoccasion variability in PK parameter estimates, a covariate analysis using a forward inclusion and backwardselimination method was performed. Using a univariate analysis, potential covariates could be identified and subsequently be included in

TABLE 1 Characteristics of the index data, validation data, and combination of all available data

	Subset					
Demographics	index data		Validation data		All available data	
Number of patients	97	-	20	-	117	-
Female sex	66	(68%)	12	(60%)	78	(67%)
Age (y)	50	(0.5-82)	48.5	(6.0-76.0)	50	(0.5-82)
Height (cm)[a]	173	(69-194)	170	(120-183)	172	(69-194)
Weight (kg)	76.0	(8.8-118.0)	83.0	(24.0-112.0)	77.0	(8.8-118.0)
Blood group O[a]	49	(51%)	9	(45%)	58	(50%)
Baseline FVIII level ($IUmL^{-1}$)	0.41	(0.01-0.97)	0.40	(0.1-0.7)	0.41	(0.01-0.97)
Baseline VWF:Act level ($IUmL^{-1}$)	0.16	(0.0-0.58)	0.11	(0.05-0.31)	0.15	(0.0-0.58)
Baseline VWF:Ag level ($IUmL^{-1}$)	0.28	(0.0-0.93)	0.22	(0.07-0.56)	0.28	(0.0-0.93)
Liver function disorders[a]	18	(19%)	1	(5%)	19	(16%)
Surgical characteristics						
Number of patients undergoing						
1 surgery	69	(71%)	13	(65%)	82	(70%)
2 surgeries	16	(16%)	5	(25%)	21	(18%)
3 surgeries	10	(10%)	1	(5%)	11	(9%)
4 surgeries	0	(0%)	0	(0%)	0	(0%)
5 surgeries	1	(1%)	1	(5%)	2	(2%)
6 surgeries	1	(1%)	0	(0%)	1	(1%)
Duration of procedure (min)	71	(7-470)	48	(10-387)	65	(7-470)
Number of occasions/surgeries	141	-	31	-	172	-
Diagnosis per occasion						
Number of VWD-type diagnoses						
1	66	(47%)	15	(48%)	81	(47%)
2A	34	(24%)	12	(39%)	46	(27%)
2B	8	(6%)	2	(6%)	10	(6%)
2M	17	(12%)	2	(6%)	19	(11%)
2N	8	(6%)	0	(0%)	8	(5%)
3	8	(6%)	0	(0%)	8	(5%)
Number of ASA classifications[a]						
II	99	(82%)	27	(87%)	126	(83%)
III	21	(17%)	4	(13%)	25	(16%)
IV	1	(1%)	0	(0%)	1	(1%)
Severity of surgical procedure						
Minor	37	(26%)	12	(39%)	49	(28%)
Major	104	(74%)	19	(61%)	123	(72%)
Treatment information						
Haemate P® dosages per occasion	5	(1-30)	7	(2-20)	5	(1-30)
FVIII dose (IU/kg)	22.1	(5.5-66.1)	16.7	(5.6-50.0)	20.8	(5.5-66.1)
Tranexamic acid use during occasion	59	(42%)	9	(29%)	68	(40%)
NSAID use during occasion	6	(4%)	3	(10%)	9	(5%)
Heparin use during occasion	58	(41%)	12	(39%)	70	(40%)

Note: Data expressed as frequency (%) or median (range).

Abbreviations: ASA, American Society of Anesthesiologists; FVIII, factor VIII; NSAID, nonsteroidal antiinflamatory drug; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen; VWF:Act, von Willebrand factor activity.

[a]Missing data were present in 4.3% height, 4.3% blood group, 18.8% altered hepatic functioning, and 11.6% ASA classifications of all available data.

a multivariate analysis.[25] Factors to be included in the covariate analysis were selected when respective data were available in ≥50% of patients. Therefore, in our study hemoglobin was ultimately excluded from the covariate analysis. For the time-varying covariates VWF:Act, VWF:Ag, and VWF:CB, the last observation carried forward method was applied. This method assumes the last measured observation until a new observation is known. Periods when a virtual loading dose was estimated were handled separately, as no VWF/FVIII had been administrated yet. A more in-depth overview of the population pharmacokinetic modeling can be found in Supplement 1 in Appendix S1.

2.4 | Model evaluation and validation

The predictive performance of the model was evaluated by visual inspection of the goodness-of-fit plots. Furthermore, visual predictive checks were performed in order to validate the model internally. The evaluated model generated (n = 1000) simulations of the observed data, where after the simulated data were compared with the observed data.

Subsequently, this intermediate PK model based on 97 patients was externally validated in 20 other patients by fitting the validation data set without reestimating model parameter estimates. Visual inspection of goodness-of-fit plots was performed and the predictive performance of the intermediate FVIII PK model was determined by calculating the mean percentage error (Equation 1) and mean absolute percentage error (Equation 2), respectively, representing bias and inaccuracy.

$$\mathrm{MPE}\,(\%) = \frac{1}{n}\sum_{j=1}^{n}\left(\frac{C_{\mathrm{pred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right) \times 100\% \quad (1)$$

$$\mathrm{MAPE}\,(\%) = \frac{1}{n}\sum_{j=1}^{n}\left|\frac{C_{\mathrm{ipred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right| \times 100\% \quad (2)$$

where C_{pred} represents the population predication, C_{ipred} the individual predication, and C_{obs} the observed FVIII for a total number of observations (n). The bias is regarded as non-significant when 0 is included in the confidence interval. Inaccuracy below the arbitrary chosen 25% was accepted.

Subsequently, the FVIII PK model was fully developed after reestimation of all parameter values using all data resulting in the final FVIII PK model. Finally, a bootstrap method was applied, using 1000 data subsets resampled from the complete original data.

3 | RESULTS

From a total of 97 patients, 684 FVIII measurements were collected and used for model building, while the remaining 208 FVIII samples of 20 patients were used for external validation of the developed model. Factor VIII levels after administration of the VWF/FVIII concentrate ranged from 4.70 IU/mL as highest top level to 0.01 IU/mL over time. Bolus infusion dosages ranged from 5.5 to 66.1 IU FVIII/ kg body weight, while 4.7% of the dosages were given as continuous infusion with doses ranging from 0.19 to 4.2 IU/h/kg body weight. Samples were collected within a period of 146 h before surgery and 524 h postoperatively; the majority of the samples were collected up to 168 h after the surgery. Each patient received at least one bolus or continuous infusion and was monitored for a period ranging from 1 to 22 days after surgery. The median number of FVIII measurements during hospitalization was 5 (ranging from 1 to 14). Younger patients were underrepresented, as only seven children with a median age of 14 years (range: 0.5-16 years) and median body weight of 54 kg (range: 8.8-107 kg) were included. None of the FVIII samples was below the lower limit of quantification (0.01 IU/mL). Hemostatic complications during surgery were limited, as no thrombotic events were reported and a clinically relevant bleeding occurred in only five surgeries. Additional information can be found in the article describing the data.[6]

3.1 | Structural model

A one-compartment linear model best described FVIII PK after administration of the VWF/FVIII concentrate in a perioperative setting. Allometric scaling for body weight was applied to V and CL. Parameter F successfully corrected for the difference in the baseline FVIII level and the FVIII level observed prior to the surgical procedure without influencing the estimation of the other PK parameters. The IIV was identified in PK parameters V and CL, whereas the interoccasion variability was identified in F. Furthermore, a correlation coefficient was estimated between the variability of V and CL. Estimated values of this structural FVIII PK model can be found in Table 2.

3.2 | Covariate modeling

During the forward inclusion of the covariate analysis, statistically significant (P < .05) associations were identified between covariates surgery duration, ASA classification and VWF:Act levels over time, and the PK parameter CL. Backward exclusion revealed all associations to be statistically significant (P < .01). When surgery duration increased from 45 to 106 min (interquartile range), CL decreased with 38%. Additionally, when the VWF:Act increased from 0.78 to 2.21 U/mL (interquartile range of all measured VWF:Act levels), CL decreased with 29%, presumably caused by prevention of degradation of FVIII by binding to VWF. The associations between these exponentially modeled covariates and CL are visualized in Figure 1A. In Figure 1C interindividual variability in CL is plotted against VWF activity level and surgery duration. These plots should show no trend, as this indicates that the covariates explain the variability well. Finally, patients in ASA class III or IV exhibited a 44% decrease of CL in comparison to patients in ASA class II.

TABLE 2 Parameter estimates of the structural, intermediate, and final FVIII-based PK model of a specific VWF/FVIII concentrate (Haemate P®/Humate P®)

	Structural FVIII PK model			Intermediate FVIII PK model			Final FVIII PK model			Bootstrap	
Parameter	Estimate	RSE (%)	Shr. (%)	Estimate	RSE (%)	Shr. (%)	Estimate	RSE (%)	**Shr. (%)**	**Estimate**	**95% CI**
Volume of distribution (L/70 kg)	3.31	4.4		3.27	4.4		3.28	3.8		3.28	(3.05-3.55)
Clearance (L/70 kg/h)	0.044	9.8		0.044	9.8		0.037	10.9		0.038	(0.029-0.048)
Bioavailability virtual dose	0.193	21.3		0.221	21.5		0.200	16.2		0.203	(0.138-0.288)
Surgery duration on CL	-	-		−0.435	24.6		-0.416	25.2		−0.419	(−0.669-−0.236)
ASA class III or IV on CL	-	-		0.553	15.4		0.555	14.1		0.581	(0.437-0.822)
VWF activity on CL	-	-		−0.303	43.2		-0.263	47.1		−0.253	(−0.578-−0.001)
Interindividual variability (%CV)											
(IIV) Volume of distribution	33.1	13.4	19.6	34.6	12.6	18.1	30.9	12.1	19.3	30.39	(22.34-38.32)
IIV Clearance	82.0	11.4	16.8	65.1	12.7	17.7	84.1	12.7	16.6	84.37	(59.85-114.53)
Correlation between V and CL	53	-		51	-		47	-		56.27	(25.27-85.20)
IOV Bioavailability virtual dose	172.5	21.9		160.0	24.3		154.5	19.0		146.69	(67.35-280.65)
Proportional residual variability (%)	22.5	7.2		21.3	7.6		20.3	6.6		20.1	(17.6-22.9)

Note: Bootstrap results are based on 1000 data subsets sampled from the original data with resampling.

$$CL = \theta_{CL} \times \left(\frac{Weight_i}{70}\right)^{0.75} \times \left(\frac{Surgery\ duration_i}{81}\right)^{-0.416} \times \left(\frac{VWF{:}Act_{ij}}{1.65}\right)^{-0.263} \times 0.555_{ASAclass3,4} \times e^{\eta_{CL}}.$$

$$V = \theta_V \times \left(\frac{Weight_i}{70}\right)^{1} \times e^{\eta_V}.$$

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; CL, clearance; CV, coefficient of variation calculated as $\sqrt{(\exp(\omega 2) - 1)} * 100$; FVIII, factor VIII; IIV, interindividual variability; IOV, interoccasion variability; PK, pharmacokinetic; RSE, relative standard error; Shr, shrinkage; V, volume of distribution; VWF, von Willebrand factor.

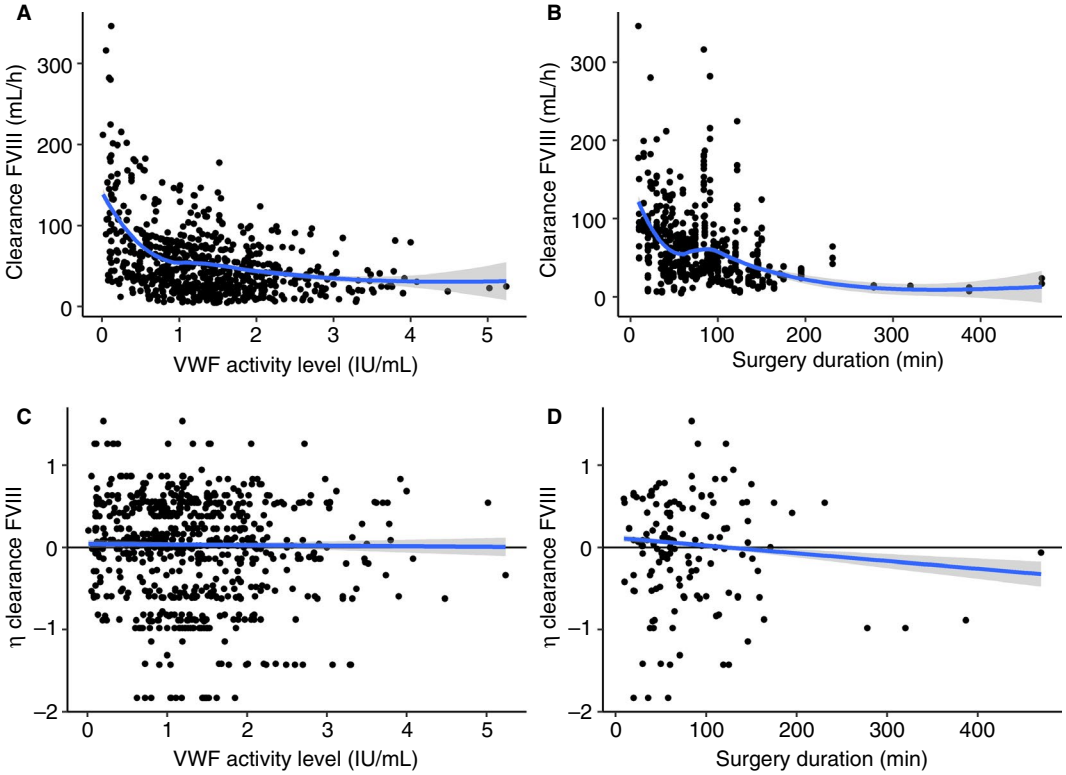

FIGURE 1 Relation between clearance and A, the VWF activity level and B, the duration of surgery in the population PK model for a specific VWF/FVIII concentrate (Haemate P®/ Humate P®). The interindividual random effects for interindividual variability (η) show no trend when plotted against VWF activity level C, and duration surgery D, demonstrating the appropriateness of the covariates to explain variability. FVIII, factor VIII; PK, pharmacokinetics; VWF, von Willebrand factor

3.3 | Model validation and evaluation

The intermediate PK model based on the index data set was validated with an external data set. The bias and inaccuracy, described by the MPE and MAPE, were found to be −10.2% (95% CI: −14.3 to −6.2) and 13.0% (95% CI: 11.6-14.4). Therefore, the predictive performance of the model in the validation data set showed a small bias and acceptable inaccuracy. The goodness-of-fit plots of the validation (Supplement 1 in Appendix S1) depict the same results and visualize the small bias seen in population prediction versus the observed levels plot and acceptable inaccuracy in the population prediction as well as the individual prediction versus observed levels plot.

Following reestimation of the parameters using all data, goodness-of-fit plots (Figure 2) indicated that the final FVIII population PK model adequately describes FVIII levels of the total study population. In these plots the trend lines are close to the line of identity, indicating that no bias is present and the data are randomly distributed around the line $y = x$. Figure 2A shows the predicted FVIII levels based on the population PK parameters with covariate adjustment. Since IIV is not taken into account, large deviations from the line $y = x$ are observed. Figure 2B displays the individual predicted FVIII levels compared to the observed levels. The individual predicted levels are calculated by using the individual PK parameters estimated by Bayesian analysis. Smaller deviations around the line $y = x$ are observed as IIV of the PK parameters is taken into account. However, residual error is still present. In Figure 2C, D the conditional weighted residuals, representing the difference between the observed and predicted FVIII levels, versus population prediction or time after dose are shown. The vast majority of the points are between −2 and +2 SD without a trend, indicating sufficient model performance.

Adequate model performance of the final FVIII PK model is visualized using a prediction-corrected visual predictive check (Figure 3). Bootstrap confirmed the robustness of the parameter estimates obtained in the final FVIII PK model. Estimated parameters of the intermediate and final validated FVIII PK model parameters and bootstrap values can be found in Table 2.

4 | DISCUSSION

The aim of this study was to develop a population PK model describing FVIII levels after administration of a specific VWF/FVIII concentrate (Haemate P®/Humate P®) in a perioperative setting. Additionally, using covariate analysis, any patient, surgical, or treatment factors correlating with the PK parameters of the developed model were identified.

A one-compartment PK model was able to fit the available data describing FVIII levels after administration of the VWF/FVIII

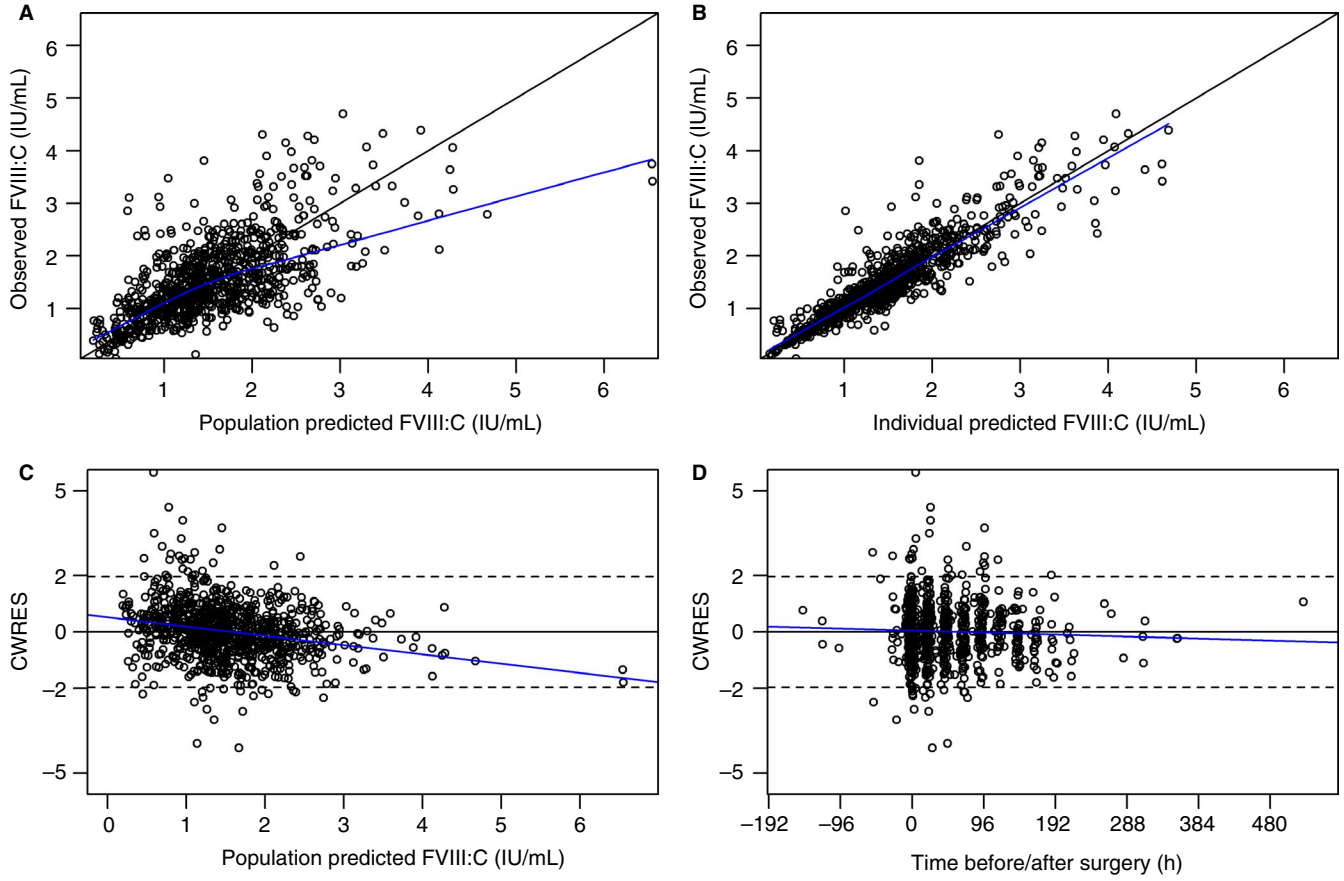

FIGURE 2 The goodness-of-fit plots of the final FVIII population pharmacokinetic model for a specific VWF/FVIII concentrate (Haemate P®/Humate P®). A, Population predicted and B, individual predicted FVIII levels are compared to observed FVIII levels. Conditional weighted residuals (CWRES) representing the difference between the observed and predicted FVIII levels are compared to the C, population predicted levels and D, time before/after surgery. The individual data (black circles) are visualized as a trend line (blue solid line) that approximates the line of identity (black solid line). The blue line should be close to the line of identity, indicating that no bias is present in the pharmacokinetic model. FVII, factor VIII; VWD, von Willebrand factor

concentrate in the perioperative setting. Almost all achieved FVIII levels of included study patients were well above predefined targets as stated by national guidelines, specifically 95.2% during the first 36 h and 98.9% in the subsequent period.[13] Twenty-five of the included patients showed excessive FVIII levels (>2.5 IU/mL) during the perioperative period, indicating the potential benefit of PK-guided dosing. Some studies have already examined application of PK-guided dosing of this specific VWF/FVIII concentrate following surgery.[14,26] The prospective multicenter trial of Lethagen et al[14] demonstrated feasibility in selection of the loading dose prior to elective surgery based on the PK profile of the patient. However, the study of Di Paola et al. observed a poor correlation between the presurgical and postsurgical In Vivo Recovery (IVR) values, questioning the potential profit of PK-guided dosing. However, our approach is likely superior to the study by Di Paola et al[26], in which PK-guided dosing of this VWF/FVIII concentrate with a standard two-compartment PK model was evaluated without taking the prior information of the population and influences of covariates into account.[26] A covariate analysis is important as various international guidelines recommend specific FVIII target levels depending on the type and extent of the surgical procedure.[11,13,27] Unfortunately, correlation between the presurgical and postsurgical IVR values could not be estimated in this study as presurgical PK profiles were not available.

The effects observed in this study that increasing surgery duration is linked to decreased CL of FVIII, is possibly indicative of an enhanced production or release, or decreased clearance of FVIII (and possibly primarily of VWF) to safeguard hemostasis during longer-lasting hemostatic challenges with greater tissue damage. Patients in ASA class III or IV showed a decreased FVIII CL compared to patients in ASA class II. This can possibly be linked to earlier findings that patients with comorbidities exhibit higher VWF and FVIII levels.[23] However, as FVIII baseline levels are included in this population PK model, a decreased FVIII clearance for these patients with more comorbidities would mean that their FVIII levels would rise more during the surgery than those of patients without comorbidities. This has not yet been observed. In the data used for the covariate analysis no patients were classified in ASA class V (moribund patient not expected to survive 24 hrs with or without an operation) and therefore this class could not be included in the final FVIII population PK model.[28]

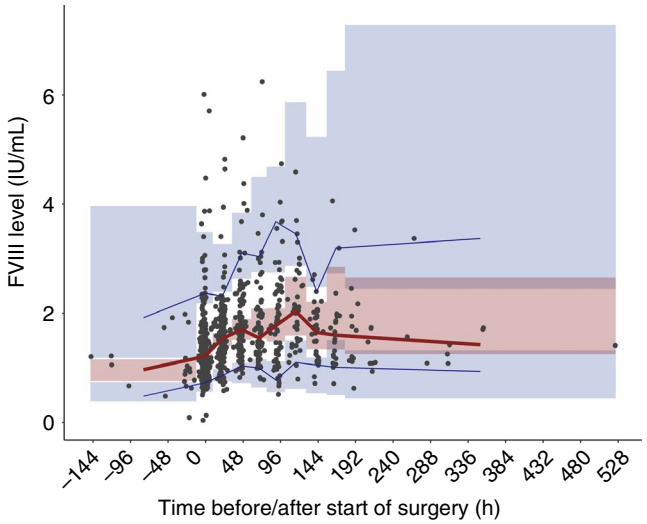

FIGURE 3 Prediction-corrected visual predictive check (VPC) of the final FVIII-based pharmacokinetic model of a specific VWF/FVIII concentrate (Haemate P®/Humate P®). The median (red line) and 95% CI (blue lines) of the observed data are plotted against the simulated data (n = 1000) indicated as highlighted areas (red area: median; blue area: 95% prediction interval). Individual observations in the data are shown as black dots. A model predicts the concentrations adequately when the blue and red lines run through the corresponding areas CI, confidence interval; FVIII, factor VIII; VWF, von Willebrand factor

The interaction between VWF and FVIII is complex, considering the variations in the VWF-interactive region located on the light chain of FVIII and possible underlying genetic mutations.[29,30] Since VWF acts as a chaperone for FVIII, the observed effect of higher VWF:Act levels resulting in decreased FVIII clearances seems logical.[31] Nonetheless, it should be noted that the influence of VWF:Act on FVIII in this PK model is only based on the measured VWF:Act levels, which were assumed to be constant until the next measured level, while in fact VWF:Act levels are expected to change constantly over time after the administration of the VWF/FVIII concentrate. Furthermore, the high relative standard error (RSE = 51%) of the parameter estimate describing the relationship implies that this observation may be inaccurately estimated. This inaccuracy can be caused by the heterogeneity of VWD types or the absence of sufficient data to describe this association fully. The effect of VWF:Ag on FVIII PK was also evaluated; however, against expectations this influence was insignificant (Objective Function Value −3.54, P = .05).

Remaining covariates included in the covariate analysis showed no significant associations with PK parameters present in the final FVIII PK model. Minor or major surgery severity was identified as a significant covariate; however, the ASA classification system and surgery duration achieved a higher statistical significance in the multivariate analysis. Von Willebrand disease type was also expected to have a significant influence on the PK parameters. During univariate analysis, this covariate showed a significant association with CL, as type 2 and type 3, respectively, showed a 54% and 74% higher clearance relative to type 1 patients. However, this effect was not significant when the other covariates were also included in the model. An earlier study evaluating the PK of the VWF/FVIII concentrate in elective surgery also showed no difference between VWD types and the PK of individual patients.[14] However, we cannot directly compare this study with our current study, as a different PK approach was used and a different loading dose was administrated. One possible explanation could be that VWD type has less effect on the FVIII clearance than expected after administration of VWF/FVIII concentrate as (functional) VWF is simultaneously administrated. On the other hand, it should be noted that the majority of the patients included in this population PK model were type 1 and 2A and 2M patients and that the model contains fewer data on other VWD types, for example, the data of only eight VWD type 2B, eight type 2N, and eight type 3 patients. Therefore, the model is expected to be less applicable to these patients. Patient characteristics height, age, sex, blood group, and renal functioning and hepatic functioning were not associated with any PK parameters in the final FVIII-based PK model for this VWF/FVIII concentrate.

The large estimated IIV in CL indicates a clinically relevant variability in FVIII clearance after administration of this specific VWF/FVIII concentrate between VWD patients. The estimated IIV of CL became smaller when interoccasion variability was taken into account. The latter quantifies the intrapatient variability of CL. Unfortunately, inclusion of interoccasion variability on CL resulted in an unstable model and it was therefore excluded. The large IIV on CL could, however, be partially explained by introduction of the statistically significant covariates. However, after reestimation of the PK parameters using both subsets, IIV on CL increased again. This can be explained by the fact that the *validation data set* differed from the *index data set* as the *validation set* was not composed randomly from all data, but solely included data from one center during a certain period. Differences between the data sets included lower average surgery durations, a higher percentage of patients in ASA class II, less tranexamic acid administration, and fewer patients with blood group O in the validation data set. Moreover, one patient with a genetically proven VWD type 1 Vicenza, which is associated with a high clearance, was present in this data set. Overall, clearance in this validation subset was highly variable.

A limitation of the study is that the developed PK model could not distinguish endogenous FVIII from exogenous FVIII, as it is not possible yet to detect endogenous FVIII as a separate entity. The terminal half-life calculations can be misleading, because of subsequent increases in endogenous FVIII after increase of exogenous and endogenous VWF after administration of this specific VWF/FVIII concentrate in the perioperative period.[32,33] The median calculated FVIII half-life of 57.7 h is compatible with a rise in endogenous FVIII, as this is longer than the generally reported FVIII half-life of approximately 12 h.

The population PK of FVIII after perioperative dosing of the specific VWF/FVIII concentrate in patients diagnosed with VWD can be adequately described by the model outlined in this paper. Increased

VWF activity or surgery duration and classification in a higher ASA class are correlated with a decrease in FVIII CL. As individual predicted FVIII over time profiles can be established using this model, this could be a first step into the direction of PK-guided dosing in VWD patients undergoing surgery treated with this specific VWF/FVIII concentrate. With the developed model the FVIII levels can be tailored to the individual patient, which is especially useful when only FVIII targets apply. Development of new population PK models for the various other VWF/FVIII concentrates is necessary as the PK of these concentrates differs, because of varying VWF/FVIII ratios and multimer patterns. Furthermore, a VWF-based population PK model for this specific concentrate is currently under development, and the ultimate goal is to provide a model describing both VWF and FVIII and the VWF and FVIII interaction, to facilitate PK-guided dosing based on VWF as well as FVIII levels. Eventually this overall approach may result in more accurate individualized therapy and therefore in increased quality and cost-effectiveness of care for patients with VWD.

ACKNOWLEDGMENTS

This study was performed by the international multicenter OPTI-CLOT research consortium, "Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates and desmopressin in bleeding disorders." The OPTI-CLOT consortium aims to implement PK-guided dosing of clotting factor concentrates and desmopressin by (I) initiating studies emphasizing the impact of PK-guided dosing, (II) constructing prophylactic and on-demand population PK models, and (III) evaluating the cost-effectiveness of a PK-guided approach. In Appendix 1 a complete list of members of the OPTI-CLOT group can be found.

CONFLICT OF INTEREST

J. M. Heijdra has received an award from CSL Behring outside the submitted work. K. Fijnvandraat has received unrestricted research grants from CSL Behring, Bayer, and Novo Nordisk, and her institution has received consultancy fees from Shire, Roche, Novo Nordis,k and Bayer. B. Laros-van Gorkom has received unrestricted educational grants from Baxter and CSL Behring. K. Meijer has received research support from Bayer, Sanquin, and Pfizer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS, and Aspen; and consulting fees from uniQure. J. Eikenboom received research support from CSL Behring and has been teacher at educational activities of Roche. F. W. G. Leebeek has received unrestricted research grants from CSL Behring and Shire, outside the submitted work, and is a consultant for Shire, uniQure, and Novo Nordisk (DSMB). He is a DSMB member for a study sponsored by Roche. M. H. Cnossen has received unrestricted research grants for investigator-initiated studies and educational as well as travel grants from Pfizer, Baxalta/Shire, Bayer, CSL Behring, Novo Nordisk, Novartis, Nordic Pharma, and for advisory board activities from Bayer and Roche. R. Mathôt has received travel grants from Shire and Bayer. The remaining authors declare no competing financial interests. All unrestricted research grants, awards, educational grants, and consultancy fees have been forwarded to the respective institutions.

AUTHOR CONTRIBUTION

N. C. B. de Jager, L. H. Bukkems, and R. A. A. Mathôt performed the analyses and developed the population pharmacokinetic model. N.C.B. de Jager and L.H. Bukkems wrote the manuscript, with assistance of J. M. Heijdra. R.A. A. Mathôt and M. H. Cnossen supervised the study, while F.W. G. Leebeek gave critical guidance. H.C.A.M. Hazendonk and J.M. Heijdra collected the clinical data jointly. Patient inclusion was monitored by H.C. A. M. Hazendonk, K. Fijnvandraat, K. Meijer, B. A. P. Laros-van Gorkom, F.W. G. Leebeek, and M.H. Cnossen. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

ORCID

Laura H. Bukkems https://orcid.org/0000-0001-7967-1023
Jessica M. Heijdra https://orcid.org/0000-0003-1069-8097
Jeroen Eikenboom https://orcid.org/0000-0002-3268-5759

REFERENCES

1. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost*. 2000;84:160-174.
2. Roberts JC, Morateck PA, Christopherson PA, et al. Rapid discrimination of the phenotypic variants of von Willebrand disease. *Blood*. 2016;127:2472-2481.
3. Leebeek F, Eikenboom J. Von Willebrand's disease. *N Engl J Med*. 2016;375:2067-2080.
4. Sadler JE, Mannucci PM, Mazurier C, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the subcommittee on von Willebrand factor. *J Thromb Haemost*. 2006;4:2103-2114.
5. Berntorp E. Haemate P/Humate-P: a systematic review. *Thromb Res*. 2009;124:S11-S14.
6. Hazendonk H, Heijdra JM, de Jager N, et al. Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: identifying the need for personalized treatment. *Haemophilia*. 2018;24:460-470.
7. Franchini M. Surgical prophylaxis in von Willebrand's disease: a difficult balance to manage. *Blood Transfus*. 2008;6:s33-s38.
8. Castaman G. Treatment of von Willebrand disease with FVIII/VWF concentrates. *Blood Transfus*. 2011;9:9-13.
9. Berntorp E, Archey W, Auerswald G, et al. A systematic overview of the first pasteurised VWF/FVIII medicinal product, Haemate P/Humate -P: history and clinical performance. *Eur J Haematol Suppl*. 2008;70:3-35.
10. Rodeghiero F, Castaman G, Meyer D, et al. Replacement therapy with virus-inactivated plasma concentrates in von Willebrand disease. *Vox Sang*. 1992;62:193-199.
11. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom haemophilia centre doctors organization guideline approved by the British committee for standards in haematology. *Br J Haematol*. 2014;167:453-465.

12. Ewenstein BM. Use of ristocetin cofactor activity in the management of von Willebrand disease. *Haemophilia*. 2001;7:10-15.
13. Nederlandse Vereniging van Hemofiliebehandelaars (NVHB). *Richtlijn: diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen*. Amsterdam, The Netherlands: Alphen aan den Rijn: Van Zuiden Communications B.V.; 2009.
14. Lethagen S, Kyrle PA, Castaman G, et al. von Willebrand factor/factor VIII concentrate (Haemate® P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost*. 2007;5:1420-1430.
15. Koshy BM, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. Cooperative study of sickle cell diseases. *Blood*. 1995;86:3676-3684.
16. Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost*. 2003;1:682-689.
17. Keizer RJ, van Benten M, Beijnen JH, et al. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed*. 2011;101:72-79.
18. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit - a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed*. 2005;79:241-257.
19. Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN) - A perl module for NONMEM related programming. *Comput Methods Programs Biomed*. 2004;75:85-94.
20. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.
21. Lee LJ, John K, Wu M-CP, Shannon J An increase in factor VIII levels with increasing age in a subgroup of individuals with mild hemophilia A. *Blood*. 2011;118:2278.
22. Koch B, Luban NL, Galioto FM, Rick ME, Goldstein D, Kelleher JF. Changes in coagulation parameters with exercise in patients with classic hemophilia. *Am J Hematol*. 1984;16:227-233.
23. Atiq F, Meijer K, Eikenboom J, et al. Comorbidities associated with higher von Willebrand factor (VWF) levels may explain the age-related increase of VWF in von Willebrand disease. *Br J Haematol*. 2018;182:93-105.
24. Anderson BJ, Holford N. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008;48:303-332.
25. Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. *Pharm Res*. 1998;15:1463-1468.
26. Di Paola J, Lethagen S, Gill J, et al. Presurgical pharmacokinetic analysis of a von Willebrand factor/factor VIII (VWF/FVIII) concentrate in patients with von Willebrand's disease (VWD) has limited value in dosing for surgery. *Haemophilia*. 2011;17:752-758.
27. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the national heart, lung, and blood institute (NHLBI) expert panel report (USA). *Haemophilia*. 2008;14:171-232.
28. Visnjevac O, Davari-Farid S, Lee J, et al. The effect of adding functional classification to ASA status for predicting 30-day mortality. *Anesth Analg*. 2015;121:110-116.
29. Terraube V, O'Donnell JS, Jenkins PV. Factor VIII and von Willebrand factor interaction: biological, clinical and therapeutic importance. *Haemophilia*. 2010;16:3-13.
30. Miesbach W, Berntorp E. Interaction between VWF and FVIII in treating VWD. *Eur J Haematol*. 2015;95:449-454.
31. Leyte A, Verbeet MP, Brodniewicz-Proba T, et al. The interaction between human blood-coagulation factor VIII and von Willebrand factor: characterization of a high-affinity binding site on factor VIII. *Biochem J*. 1989;257:679-683.
32. Dobrkovska A, Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P® in von Willebrand disease. *Haemophilia*. 1998;4:33-39.
33. Van Dijk K, Van Der Bom JG, Lenting PJ, et al. Factor VIII half life and clinical phenotype of severe hemophilia A. *Haematologica*. 2005;90:494-498.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: de Jager NCB, Bukkems LH, Heijdra JM, et al. OPTI-CLOT group. One piece of the puzzle: Population pharmacokinetics of FVIII during perioperative Haemate P®/Humate P® treatment in von Willebrand disease patients. *J Thromb Haemost*. 2020;18:295–305. https://doi.org/10.1111/jth.14652

APPENDIX

Steering Committee, the Netherlands: M. H. Cnossen (principal Investigator and chair OPTI-CLOT), F. W. G. Leebeek, Rotterdam; K. Fijnvandraat, R. A. A. Mathôt, Amsterdam; K. Meijer, Groningen.

Local principal investigators, other local collaborators, and PhDs, the Netherlands: M. J. H. A. Kruip, S. Polinder, J. Lock, H. C. A. M. Hazendonk, I. van Moort, J. M. Heijdra, M. C. H. J. Goedhart, Rotterdam; M. Coppens, M. Peters, T. Preijers, NCB de Jager, LH Bukkems, Amsterdam; R. Y. J. Tamminga, Groningen; B. A. P. Laros-van Gorkom, P. Brons, Nijmegen; F. J. M. van der Meer, H. C. J. Eikenboom, Leiden; R. E. G. Schutgens, K. Fischer, Utrecht; M. H. E. Driessens, Nijkerk. Trial bureau: C. M. Zwaan, I. van Vliet, Rotterdam. Principal investigators and local collaborators in the United Kingdom: P. W. Collins, Cardiff; R. Liesner, P. Chowdary, London; D. Keeling, Oxford. We thank all hemophilia and research nurses for their dedication and support for this project.