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ORIGINAL ARTICLE

Terminal half-life of FVIII and FIX according to age, blood group and concentrate type: Data from the WAPPS database

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Abstract

Background: Real-life data on pharmacokinetics of factor (F) VIII/IX concentrates, especially extended half-life (EHL), concentrates in large cohorts of persons with hemophilia are currently lacking.

Objectives: This cross-sectional study aimed to establish reference values for terminal half-life (THL) for FVIII/IX concentrates according to concentrate type, age, blood group and inhibitor history.

Patients/Methods: Data were extracted from the Web-Accessible Population Pharmacokinetics Service database. Groups were compared by nonparametric tests. THL was modelled according to patient characteristics and concentrate type.

Results: Infusion data (n = 8022) were collected from 4832 subjects (including 2222 children) with severe hemophilia (age: 1 month–85 years; 89% hemophilia A; 34% using EHL concentrates, 9.8% with history of inhibitors). THL of FVIII-EHL was longer than of FVIII standard half-life (SHL; median 15.1 vs. 11.1 h). FVIII-THL was dependent on age, concentrate type, blood group, and inhibitor history. THL of FIX-EHL was longer than of FIX-SHL (median 106.9 vs. 36.5 h). FIX-THL increased with age until 30 years and remained stable thereafter. FVIII-THL was shorter in subjects with blood group O. THL was decreased by 1.3 h for FVIII and 22 h for FIX in subjects with a positive inhibitor history.

Conclusions: We established reference values for FVIII/IX concentrates according to patient characteristics and concentrate type in a large database of hemophilia patients. These reference values may inform clinical practice (e.g., assessment of immune tolerance success), economic implications of procurement processes and value attribution of novel treatments (e.g., mimetics, gene therapy).

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KEYWORDS
extended half-life, factor IX, factor VIII, pharmacokinetics, prophylaxis, standard half-life

1 | INTRODUCTION

Severe hemophilia is a congenital disorder characterized by absence of coagulation factor VIII (FVIII, hemophilia A) or IX (FIX, hemophilia B). Intravenous replacement therapy has been the standard of care to prevent bleeding and its long-term consequences since its introduction. This has recently been complemented with nonreplacement therapy.[1]

Terminal half-life (THL) for coagulation concentrates is relatively short: 9–15 h for FVIII[2–4] and 17–33 h for FIX.[5–9] Consequently, frequent infusions are required to maintain minimum trough levels needed for effective prophylaxis.[10] These regular infusions pose a burden for persons with hemophilia. This may lead to poor adherence and less favorable treatment results.[11] To facilitate decreased infusion frequency and/or higher trough levels, longer acting clotting factor concentrates have been developed in recent years. These concentrates are referred to as extended half-life concentrates (EHL), as opposed to the traditional, largely unmodified standard half-life (SHL) concentrates. Mahlangu et al[12] defined EHL concentrates as a product that was designed to, and has an increase in area under the curve of at least 25% and a THL increase of at least 30%. Phase III studies with limited (range: 7–118 subjects) sample size have reported 1.5- to 2-fold increased terminal half-life values in FVIII EHL concentrates and 4- to 6-fold in FIX EHL concentrates.[10,13–16] However, these data need to be confirmed in clinical practice, both at group and individual levels.

Persons with hemophilia show a high interpatient variability in dosing and THL of FVIII and FIX to sustain desired trough levels.[9,17] Individual pharmacokinetics (PK) are relevant in the choice and design of prophylactic treatment regimens and perioperative management. Pharmacokinetics are dependent on age and anthropometric values[1,18–22] and, since the introduction of EHL concentrates, on type of concentrate, too.[9,23–25] Anthropometric assessments include several constructs (e.g., body weight, body mass index [BMI], body surface area [BSA], fat free mass [FFM]).[26] It remains unclear which of these constructs is the optimal predictor in PK.

The aim of this study was to estimate THL for various FVIII/IX concentrates and establish reference values according to concentrate type, age, blood group, and inhibitor status.

Essentials

- Real-life pharmacokinetic data of FVIII/IX concentrates in large cohorts are currently lacking.
- FVIII/IX reference values according to patient characteristics were created in a large dataset.
- Terminal half-life increases linearly for age across the entire life-span for FVIII concentrates.
- Terminal half-life increase increases up to age 30 years for FIX and remains constant afterwards.

2 | METHODS

2.1 | Design and setting

This multicenter analysis was performed in collaboration between the University Medical Centre Utrecht (Utrecht, the Netherlands), McMaster University (Hamilton, Ontario, Canada), and the University of Waterloo (Waterloo, Ontario, Canada) on behalf of the Pharmacokinetic Expert Working Group of the International Prophylaxis Study Group (IPSG). The data were collected as part of the Web Accessible Population Pharmacokinetic Service (WAPPS) project and consisted of PK data collected between September 2016 and March 2020 (downloaded: March 3, 2020). The WAPPS project aims to assemble a database of patients' PK data for all existing factor concentrates, develop and validate population PK models, and integrate these models within a Web-based calculator for individualized pharmacokinetic estimation in patients at participating treatment centers.[24,27,28] The data included patient characteristics, treatment-specific data, and calculated pharmacokinetic parameters. The WAPPS project was approved by the institutional review boards of McMaster University (#14-601-D) and University of Waterloo (#31977). The approval included using the collected data for modelling purposes and for investigating the determinants of factor concentrates pharmacokinetic variability, thus covering the analysis of the present study. All data were anonymized and did not include information on hemophilia treatment centers or date of assessment.

2.2 | Data collected

Infusion data from persons with severe hemophilia that were included in the WAPPS database until March 3, 2020, were included in this study. At that time, 298 treatment centers in 47 countries were participating in WAPPS. Patient data were included in the WAPPS database when the treating physician wanted to estimate PK values for this patient. There was no targeted selection. Patients had to provide informed consent to have their data entered in the WAPPS database.

Patient characteristics (age, disease type and severity, weight, height, blood group, inhibitor status), treatment specific data (concentrate, dose administered, timing of laboratory samples), and calculated THL were collected. THL, calculated by the WAPPS Bayesian engine from the PK data, was the main outcome measure. THL was defined as the time required for the plasma concentration of concentrate to decrease by 50% after pseudo-equilibrium of distribution has been reached.[29] Inhibitor status was entered as formerly, currently, or never positive. This dataset contained inhibitor-negative patients only, including those with a history of inhibitors. Blood group was collected as a proxy for von Willebrand factor antigen (vWF:Ag), as vWF:Ag is lower in blood group O, and blood group is not an acute phase protein.[30–32] Blood group status was classified as O or non-O. Clotting factor concentrates were grouped as SHL or EHL concentrates (see Table S1).

Individual THL was derived from the PK parameters obtained from a Bayesian estimation model using concentrate specific models and according to concentrate types.[27] SHL factor concentrates were subdivided into plasma derived (PD) or recombinant (Rc) concentrates. All EHL concentrates are recombinant products. These were subdivided according to their chemical binding structure with FVIII or FIX, being Fc bound (Fc), Albumin bound (Alb), or glycoPEGylated (PEG). FVIII concentrates are limited to Fc and PEG, all three recombinant types exist in FIX. THL was assessed according to this subdivision as well by means of nonparametric testing.

2.3 | Statistics

Distribution of data was checked and outliers were removed to avoid overestimation in THL because of biased data. An outlier was defined as a value larger than the third quartile (Q3) + (1.5 × interquartile range [IQR]) or smaller than the first quartile (Q1) − (1.5 × IQR). Any value beyond these limits was discarded. Data are presented as median (IQR: P25-P75), mean (SD) or proportion (95% confidence interval [CI]) as appropriate.

Between-group differences in THL were compared by means of parametric and nonparametric testing, as appropriate. The data from each subset (age, type of concentrate, inhibitor history) were checked for normality by means of Kolmogorov-Smirnoff testing. Parametric (ANOVA) or nonparametric (Mann-Whitney, Wilcoxon) methods were used for analysis, as appropriate.

Anthropometric measures (BMI, BSA,[33] ideal body weight, and FFM[34,35]) were calculated from height, weight, and age (see Appendix A). The association between anthropometric variables and THL was determined by separate univariable regression analyses for FVIII and FIX.

Age (children [<18 years] vs. adults [≥18 years]) and BMI (underweight [BMI <18.5], normal weight [18.5–24], overweight [25–29], obese [30–40]) were treated as categorical variables. A univariable analysis of THL as a function of selected parameters (age, inhibitor status, anthropometric measures, concentrate type) was performed for FVIII and FIX separately to select variables for a multivariable regression model. Parameters with a (borderline) significant association (p value <.10) in the univariable analysis were included in the multivariable regression model.

Multivariable regression models were created for FVIII and FIX. A stepwise backwards linear regression model was used to predict estimated THL (inclusion criterion: $p < .05$; exclusion criterion: $p > .10$). A univariable regression analysis of THL in FIX showed an age-related increase in THL for subjects until the age of 30, whereas THL remained stable from the age of 30 onwards (see Results for details). Based on this, the models for the prediction of THL consisted of two separate formulas: one for persons younger than 30 and one for persons older than 30 years. The models were checked for collinearity by evaluating the variance inflation factor; collinearity was considered to be present when variance inflation factor was equal to 4 or more. Based on the regression coefficients, a formula was derived to allow estimation of THL based on patient characteristics.

Statistical significance levels were set at 5% ($p < .05$). The statistical analysis was performed using SPSS statistical software, version 25 (IBM Corp., Armonk. NY) and R (version 3.5.1.) and RStudio (version 1.1.456).[36]

2.4 | Data sharing statement

Original data can be accessed upon request from the original authors. Please contact wappshemo@mcmasterhkr.com.

3 | RESULTS

3.1 | Subjects and infusions

The selection process is shown in Figure 1. Data from 100 077 infusions (5767 participants) were available. After removal of persons with nonsevere (moderate and mild: FVIII/FIX >0.01 IU/ml) hemophilia (n = 610) and outliers on BMI (n = 200) and THL (n = 125), data from 4832 subjects with severe hemophilia (2222 children, 2610 adults) were included in the analysis. These subjects received 8022 infusions. Patient, disease, and treatment characteristics for children and adults are shown in Table 1. Median age was 8 years (IQR: 5–12) for children, including 13.7% younger than 6 years (4.5% younger than 2 years). Median age for adults was 33 (25–45) years. The median BMI was 17.4 (15.6; 20.2) for children and 24.7 (22.3; 27.7) for adults, indicating that nearly half of the adults in this study were overweight (BMI ≥25), 13.5% were obese (BMI ≥30). The majority (89%) of subjects had hemophilia A. EHL concentrates were used by 1619 subjects (34%). Table 2 shows patient characteristics according to diagnosis, age group, and concentrate type (SHL and EHL). Subject characteristics for adults and children were similar. However, more children reported a positive inhibitor history (13.5%; 95% CI: 12.1–14.9), as compared with adults (6.7% (5.8–7.7); $p < .01$).

3.2 | Terminal half-life according to concentrate type in FVIII and FIX

In total, 37 FVIII-SHL concentrates were included in the data set (including 10 recombinant and 27 plasma-derived concentrates) and 13 FIX-SHL concentrates (including 2 recombinant and 11

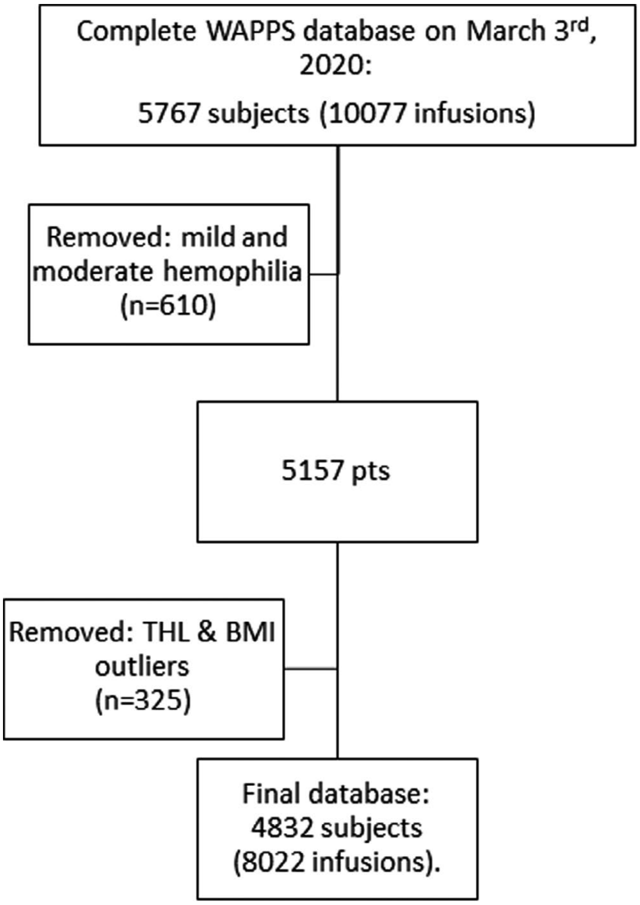

FIGURE 1 Overview of available subjects and selection process of final database. Elimination of subjects with moderate and mild hemophilia reduced the number of included subjects (n = 610). Subsequent elimination of outliers in body mass index (BMI) and terminal half-life (THL) reduced the total number of 4832 subjects with 8022 infusions

plasma-derived concentrates). Table S1 shows the number of EHL and SHL concentrates for FVIII and FIX and their respective frequencies.

For SHL concentrates, THL was similar for FVIII-PD (n = 1103) and FVIII-Rc (4177) concentrates (median 11.0 [IQR: 8.7; 13.8] vs. 11.0 [8.8; 13.7] hours; p = 0.86). THL was longer for FIX-Rc (n = 155) than FIX-PD concentrates (n = 75): median 38.3 (32.3–42.9) vs. 33.7 (29.3–41.8) h; p = 0.02.

Terminal half-life was similar for both types of FVIII-EHL concentrates (PEG): median (15.0 [IQR: 12.1; 18.4] vs. Fc: 15.0 [12.0–18.9] h; p = 0.41), whereas THL was shorter for FIX-Fc (90.0 [71.0–116.0] h) than for FIX-Alb (128.3 [106.8–157.0] h; p < .01) and FIX-PEG (150.8 [138.8–164.8] h; p < .01). THL was similar in FIX-Alb (128.3 [106.8–157.0]) and FIX-PEG (150.8 [138.8–164.8]; p = 0.76). Despite a large absolute difference (~22 h; 15%), no significance was reached. This was likely due to a lack of statistical power (FIX-PEG: n = 21; FIX-Alb: 149; FIX-Fc: 249). Therefore, THL was modelled separately for FIX-Fc and FIX-Alb/PEG.

Median THL for FVIII was 1.4 times longer for EHL concentrates (from 10.9 [8.7–13.6] to 15.1 [12.0–19.0] h; p < .01). The same accounts for FIX: median THL was 2.9 times longer for EHL concentrates (from 36.5 [31.2; 42.6] to 106.9 [81.1; 134.2] h; p < .01).

3.3 | Terminal half-life according to age

Table 3A shows the results of the multivariable regression analysis of THL. THL increased 0.9 (95% CI: 0.8–0.9) hours in 10 years for FVIII and 12 hours/10 years (8–17) for FIX in subjects younger than 30. THL was not associated with age in FIX in subjects older than 30.

Figure 2A shows the association between age and THL in FVIII for SHL and EHL concentrates. THL showed a steady, linear increase with age in both SHL and EHL FVIII concentrates across the entire age rage (0–85 years). THL increased consistently by 1.0 hour/10 years (regression coefficient: 0.10 [CI: 0.09–0.10] for FVIII-SHL and by 1.2 hours/10 years (0.12 (0.10–0.13) for FVIII-EHL across all ages. Table 3B shows the results of an additional analysis with age as a categorical variable in children (age groups: 0–5; 6–11; 12–17 with the youngest age group as reference group). This showed the increase in THL with age was indeed linear in children (increase: 1.07 years/age group). Figure 2B shows the association between age and THL in FIX. THL increased by 2.5 h/10 years for subjects younger than 30 in FIX-SHL (0.25 [CI: 0.07–0.42]) and 22 h/10 years in FIX-EHL (2.2 [CI: 1.7–2.7]), showing an additional 2 h/y increase compared to those on FIX-SHL. THL remained stable from age 30 onwards.

3.4 | Terminal half-life according to blood group

Figure 3A (SHL) and 3B (EHL) show the association between age and THL in FVIII for subjects with blood groups O or non-O. Only infusions with blood group data (5331 infusions [62%] in 2769 subjects [57%]) were included in this analysis. Overall median THL was ~2 h shorter for hemophilia A subjects with blood group O compared with non-O (10.7 [8.5–13.8] vs. 13.0 [10.4–16.4] hours; p < .01). This was observed for both FVIII-SHL and FVIII-EHL concentrates. FVIII-THL was shorter in subjects with blood group O using SHL concentrates (Figure 3A): median 9.8 (8.0–12.2) vs. 11.9 (9.6–14.5) hours in subjects with non-O; (p < .01), and in subjects using FVIII-EHL (median 13.6 [11.3–17.2] for blood group O vs. 17.6 [13.9–21.3] hours for those with blood group non-O; p < .01). For FIX, THL was not associated with blood group (Spearman's rho: 0.31; p = .20).

3.5 | Terminal half-life according to body composition

To determine which parameter of body composition should be included in the estimation of THL, we compared the variance explained (adjusted R^2) by weight, BMI, BSA, and FFM in univariable regression models for THL of FVIII and FIX. The individual results are presented in Table A1 in Appendix A. For FVIII, all parameters had similar R^2 values. Therefore, the parameter "weight" was chosen for

TABLE 1 Subject, disease, and treatment characteristics

	Overall		Children (0–17)		Adults (18–85)	
	4832		2222		2610	
N	*n* (%) or Median (IQR)	Range	*n* (%) or Median (IQR)	Range	*n* (%) or Median (IQR)	Range
Age (years)	19 (9–35)	0–85	8 (5–12)	0–17	33 (25–45)	18–85
<2 year	205 (4.5%)		205 (4.5%)			
<6 year	625 (13.7%)		625 (13.7%)			
Weight (kg)	63 (32–78)	4–146	30 (19–49)	4–103	76 (67–86)	29–146
BMI (kg/m^2)	22 (18–26)	8–36	17 (16–21)	8–29	25 (22–28)	15–36
Blood group O	1233 (26%)		578 (26%)		655 (25%)	
Blood group missing	2063 (43%)		973 (44%)		1090 (42%)	
Positive inhibitor history	473 (9.8%)		298 (13%)		175 (7%)	
Disease and infusion characteristics						
Hemophilia A	4316 (89%)		2026 (91%)		2290 (88%)	
Extended half-life concentrate	1619 (34%)		683 (31%)		936 (36%)	
Infusions (*n*)	8022		3365 (42%)		4657 (58%)	
Infusions/patient	1.7		1.4		1.8	

Abbreviations: BMI, body mass index; IQR, interquartile range (25th-75th percentile).

its ease of application. For FIX, weight turned out to be the poorest predictor of THL. Adjusted R^2 was similar for BMI, BSA, and FFM. Therefore, BMI was chosen as the body composition parameter for FIX for the ease of practical application.

3.6 | Terminal half-life according to inhibitor history

A positive inhibitor history was reported for 473 (9.8%; FVIII: 454 [10.5%]; FIX: 19 [3.7%]) subjects, who underwent a total of 893 (10.4%) PK assessments. Subjects with a positive inhibitor history reported a shorter median THL for both FVIII (10.4 [8.1–13.3] hours for ex-inhibitor subjects vs. 12.1 [9.5–15.6] for others) and FIX (median 38.6 [30.1–72.5] vs. 81.1 [41.1–121.2] hours). Subjects with a positive inhibitor history were younger in both users of FVIII (15.4 [7.6–29.0] vs. 24.3 [11.3–39.8]) and FIX (13.7 [7.3–16.0] vs. 22.0 [10.0–41.1]). Multivariable regression analysis showed that a history of inhibitors was independently associated with a shorter THL (regression coefficient: −0.9 [95% CI: −1.2 to −0.6]) for FVIII, but not for FIX (−0.15 [−10 to +9]; $p = 0.98$). Although there was a shorter THL in subjects with a positive history of FIX inhibitors, the number of observations was limited ($n = 19$) and significance was not reached because of a lack of statistical power.

3.7 | Establishing reference values

Reference values according to patient characteristics were based on multivariable regression analyses. For FVIII, these analyses showed that THL was independently associated with age, body weight, concentrate type, a positive inhibitor history and blood group. However, because of the limited independent significance of body weight (+0.2 hours/10 kg), body weight was not included in the final model for FVIII. This limited clinical significance is likely caused by the correlation between body weight and age. The proposed final formula for FVIII-THL estimation according to patient characteristics is shown in Table 4. FVIII-THL could be estimated by age (+1 hour/10 years), blood group (−1.4 h for blood group O), history of inhibitors (−0.9 h when positive), and concentrate type (+4.4 h when on EHL).

FIX-THL was increased with age until the age of 30, and was modelled according to two age categories to promote interpretation of regression analyses. For subjects younger than 30 years, FIX-THL could be predicted by age (+12 hours/10 years) and concentrate type, with an added THL for FIX-Fc (+65.7 h) and FIX-Alb (+98.7 h), while from age 30 onwards, THL remained stable and was only predicted by concentrate type (i.e., FIX-Fc [+91.4 h] or FIX-Alb [≥30 years: +109.6 h]). Although BMI showed a significant association with FIX-THL, it was not identified as a significant predictor in the multivariable model for FIX-THL. A positive inhibitor history did not contribute significantly to the model in FIX, despite the significant decrease in THL for subjects with a positive inhibitor history in the univariable analysis.

4 | DISCUSSION

4.1 | Principal findings

This study of 8022 infusions in 4832 subjects represents the largest series of pharmacokinetic assessments in persons with hemophilia to date. It is the first study to include more than 600 children

TABLE 2 Infusion (n = 8022) characteristics according to diagnosis, age group. and concentrate type

N = 8022	FVIII				FIX			
	Children (0–17)		Adults (18–85)		Children (0–17)		Adults (18–85)	
	SHL	EHL	SHL	EHL	SHL	EHL	SHL	EHL
n (%) or median (IQR)								
n	2134	941	3146	1152	106	184	124	235
Age (years; median [IQR])	8.6 (5.4–12.6)	10.6 (6.6–14.0)	35.9 (27.5–46.3)	35.5 (26.8–47.1)	9.7 (5.7–13.8)	9.0 (5.3–13.4)	34.2 (23.7–49.3)	37.4 (27.4–52.2)
Weight (kg; median [IQR])	29.5 (20.0–45.7)	37.0 (22.7–56.2)	75.0 (67.0–85.0)	77.0 (66.0–86.0)	36.4 (23.5–51.0)	30.3 (19.5–51.9)	77.0 (66.0–86.8)	80.0 (69.0–90.0)
BMI (kg/m^2; median [IQR])	17.3 (15.5–20.2)	18.2 (15.921.3)	24.3 (22.0–27.3)	24.5 (22.1–27.7)	18.5 (16.0–20.8)	17.5 (15.6–20.5)	25.8 (22.6–29.0)	25.3 (23.1–28.0)
Positive inhibitor history (N [%])	304 (14.2)	113 (12.0)	237 (7.5)	96 (8.3)	16 (15.1)	13 (7.1)	5 (4.0)	2 (0.9)
Blood group O (N [%])	639 (29.9)	234 (24.9)	945 (30)	296 (25.7)	31 (29.2)	31 (16.8)	28 (22.6)	42 (17.9)
THL (hours; median [IQR])	9.3 (7.7–11.3)	13.3 (10.9–16.4)	12.2 (10.0–14.9)	16.7 (13.4–20.2)	34.1 (29.3–39.0)	87.7 (66.2–111.7)	39.6 (33.4–44.1)	127.1 (99.0–153.0)

Abbreviations: EHL, extended half-life; IQR, interquartile range; FIX, factor IX; SHL, standard half-life.

younger than 6 years. It is the first to show that THL increases linearly with age across the entire age span for FVIII concentrates and increased up to age 30 years for FIX concentrates. The prolongation of THL for extended half-life FVIII/IX concentrates was confirmed and quantified in this study. THL of FVIII was dependent on age, weight, blood group, inhibitor status, and concentrate type. THL of FIX concentrates was dependent on age and concentrate type.

By demonstrating the linear effect of age on PK, this study may allow simplifying the design and conduct of future studies in the field by releasing the specific sampling of children in the age bands 0–6, 6–12, and 12–18. Indeed, PK data can be confidently pooled across all ages increasing the power of analysis while simplifying enrollment, usually difficult to achieve for a rare disease like hemophilia. By providing reference values for THL for FVIII and FIX, this study promotes effective treatment decision making in hemophilia.

4.2 | Strengths and limitations

This study analyzed THL and its determinants in the largest multicenter, multinational database currently available (WAPPS) so far. All data were collected and recorded in a standardized way and FVIII/IX activity levels were measured according to local laboratory standards. As the database includes data from 298 centers, its data are subject to inter-laboratory variation. the model was not corrected for individual centers as these real-world data are representative of a large proportion of users of factor concentrates globally, thus increasing the external validity of our results.

Classical PK assessments are very demanding, which is why most previous studies addressing PK in hemophilia have relied on adults or children older than age 6 years. Population-based Bayesian PK models can provide estimates based on a limited number of samples, making PK assessment much more accessible.[18,27,28,37–41] This is well illustrated in the WAPPS database.[23,24,42–44] As a result, this study included subjects of all ages (13.7% below 6), including very young children (4.5% below 2) as well. This large number of young children adds to the existing data and allows for assessment of the effects of age on THL.

Blood group was missing in a substantial proportion (43%) of the subjects in this study. However, the distribution of the remaining blood group data was similar to the global distribution, suggesting absence of bias. The analysis of those with blood group data indicate that blood group is an important covariate, particularly in persons with hemophilia A. The remaining dataset, however, was sufficiently large to generate reliable results.

4.3 | Comparison with other studies

This study confirmed the reported 1.4-fold prolongation of THL for FVIII-EHL concentrates and 3-fold (range: 2.4 [Fc]-4.0 [PEG]) prolongation of THL for FIX-EHL as reported in previous studies.[15,16,45] However, these previous studies were generally

TABLE 3A Regression coefficients (with 95% confidence interval) for multivariable regression analysis of terminal half-life

	FVIII (All Ages)	FIX (<30)	FIX (≥30)
Constant	9.9 (9.4–10.1)	15.8 (0.03–31.6)	43.4 (4.9–82.0)
Age (per year)	0.09 (0.08–0.09)	1.2 (0.8–1.7)	NS
Extended half-life (reference = SHL)	4.4 (4.2–4.5)	65.7 (60.2–71.2)	91.4 (83.1–99.6)
Positive inhibitor history (yes = 1)	−0.9 (−1.2–−0.7)	NS	NS
Blood group (O = 1; non-O = 0)	−1.4 (−1.6; −1.3)	-	-

Note: Regression coefficients from a multivariate linear regression of THL for FVIII and FIX (<30 and ≥30). Only statistically significant parameters are specified. Age, dose, weight, and body mass index were included as continuous variables. Concentrate type, positive inhibitor history, child/adult, and blood group were included as dummy variables, with SHL, no history, child, and blood group O as reference values.

TABLE 3B Regression coefficients (with 95% confidence interval) for multivariable regression analysis of THL in children with age as a categorical variable, corrected for inhibitor history, concentrate type and blood group

	FVIII (Children)
Age: 0–5 (reference category)	0
Age: 6–11	1.07 (0.78; 1.35)
Age: 12–17	2.14 (1.84; 2.44)

Abbreviations: NS, nonsignificant; SHL, standard half-life; THL, terminal half-life

smaller in size (<100 subjects). Data on FIX-Fc concentrates and FIX-albumin concentrates were considered individually. Fc-fusion concentrates accounted for an additional prolongation of 65.7 h in subjects below 30 years and 98.7 h in subjects over 30 years while albumin-fusion concentrates accounted for extensions of 91.4 and 109.6 h, respectively. These increases were more pronounced than those presented in a review of data in 518 subjects by Mannucci et al,[46] who reported an 82.1 h increase in THL for FIX-Fc (123 subjects) and 92 h in FIX-Alb concentrate (25 subjects).[46] However, the differences were relatively small (10% and 16%, respectively), especially given the differences in sample size.

This study showed a linear age-related increase in THL in FVIII, independent of product type over the entire age range of this study (0–85 years). The linear correlation between age and THL has the potential to simplify estimation of THL across age groups, particularly in combination with the proposed regression model for FVIII.[47] This increase in THL may be explained with a recently suggested age-related increase in vWF:Ag.[48] In contrast to earlier reports, this study showed that THL increased with age in FIX, but this increase was only observed for subjects up to 30 years. Björkman reported stable THL with increasing age in a series of 56 subjects (46 severe, aged 4–56, number of assessments not reported).[20]

This study reported a 2-h reduction of THL of FVIII in subjects with blood group O in a subgroup of 2769 subjects (5331 infusions). This was a confirmation of previous studies performed in small groups of <40 subjects/assessments. Vlot et al[32] (*n* = 32, age range: 13–63) and Fischer et al[49] (*n* = 38; mean age: 28 ± 10) reported THL being 4.4 and 2.8 h shorter in subjects with blood group O compared with blood group non-O, respectively. Two other studies Tiede et al[22] (*n* = 35; mean age: 37 ± 10) and Carcao et al (*n* = 25, age range: 12–18) reported shorter THL in subjects with blood group O as well without specifying the magnitude of the difference.[22,50]

Although we could not identify any published reports, many clinicians have suggested that subjects with a positive inhibitor history show a shorter THL in both FVIII and FIX, which was confirmed in this study. Although the proportion of subjects with a history of inhibitors in the present study was relatively small (FVIII: 454 [10.5%]; FIX: 19 [3.7%]) compared with other studies,[51,52] it represents the largest dataset available to study the association between inhibitor history and THL. The proportion of subjects with a positive history of inhibitors was about one-third of the 30% reported cumulative inhibitor incidence for severe hemophilia A[51] and the 10% reported for severe hemophilia B.[52] A selection bias or information bias cannot be excluded because of the low number of subjects with a history of inhibitors and/or that these subjects were generally younger. Multivariable regression showed the independent effect of inhibitor history on THL of FVIII, but not on FIX-THL, probably due to lack of statistical power.

Body composition parameters have been under discussion in PK research. This study suggested that body weight (FVIII) and BMI (FIX) seem sufficient for the modelling of THL. Although FFM might be performing better in modelling,[23,25] body weight or BMI seems to be sufficient for clinical purposes as well as more practical for clinicians. However, several studies indicated the importance of other body composition parameters (e.g., BMI, FFM, BSA) with regard to PK.[22,26,53] Henrard et al[54] showed the importance of BMI and ideal body weight in dosing of under- and overweight in FVIII in 201 persons with hemophilia A, whereas Tiede et al[22] reported that clearance and recovery were more associated with BMI than with other body composition parameters (e.g., BSA and LBW) in 35 adult subjects (mean age 37.4; mean BMI: 28.6; 66% overweight or obese), but THL was not associated with BMI. FIX is present in extravascular tissues, whereas FVIII seems to be limited to the vascular system.[55] This could explain that PK modelling of FIX relies more on total body predictors (e.g., BMI, BSA) than on body weight.

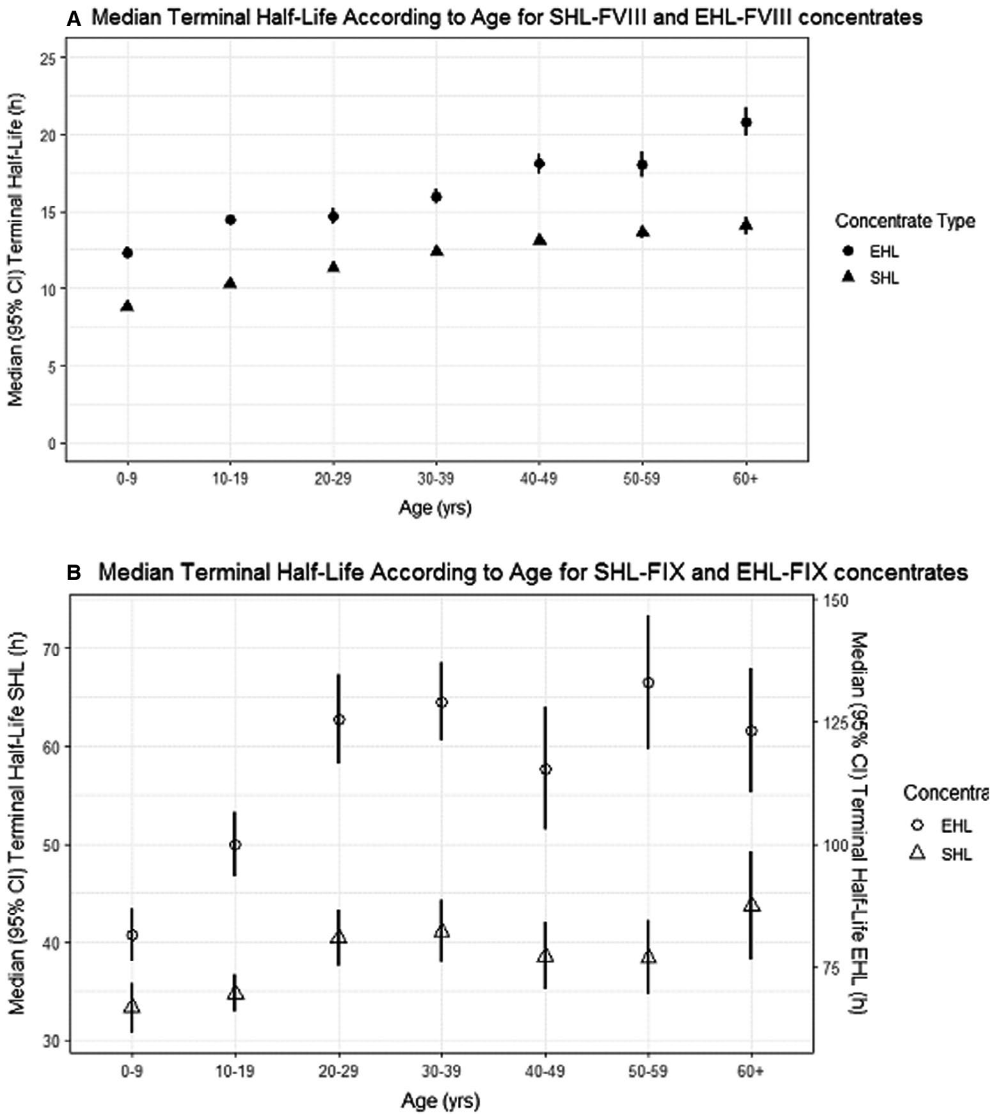

FIGURE 2 Terminal half-life was associated with age in both factor (F) VIII and FIX. (A) Association between THL and age for FVIII-SHL (solid triangles) and FVIII-EHL (solid circles). (B) Association between THL and for FIX-SHL (open triangles) and FIX-EHL (open circles). Displayed error bars represent 95% confidence intervals. EHL, extended half-life; SHL, standard half-life; THL, terminal half-life

4.4 | Clinical relevance and future research

The clinical use of EHL in hemophilia treatment is increasing, urging researchers to study the mechanisms and benefits of these concentrates. Population-based PK modelling can be a valuable tool to estimate THL in persons with hemophilia.[24,38] Particularly in the absence of measured data, or when subjects and caregivers consider switching to EHL concentrates, population-based models based on elementary patient data (e.g., age, body weight/BMI, type of concentrate, inhibitor history, blood group)[22,26] can assist in establishing dose, choice of concentrate, and dosing intervals. In addition, results from the formula can be used to establish reference values. Reference values are especially important for setting standards around surgery and determining the return to normal THL during immune tolerance therapy in subjects with inhibitors.[1]

In addition, reference values provide essential information in the assessment of the economic impact of procurement processes and value attribution of novel treatment modalities such as mimetics or gene therapy. Clinicians can determine the reference values of THL, including the 95% confidence intervals, using the new calculator provided In the WAPPS system (www.wapps-hemo.org).

This study showed that subjects with blood group O in FVIII had lower THL than those with blood group non-O, which emphasizes the need to routinely assess blood group type in persons with hemophilia A. Subjects with blood group O may require a different initial dosing when starting prophylaxis.

This study was performed at population level. Within the age of personalized medicine, individualized PK assessments seem more appropriate. Our next project will be to analyze the effects of switching from SHL to EHL in individual subjects.

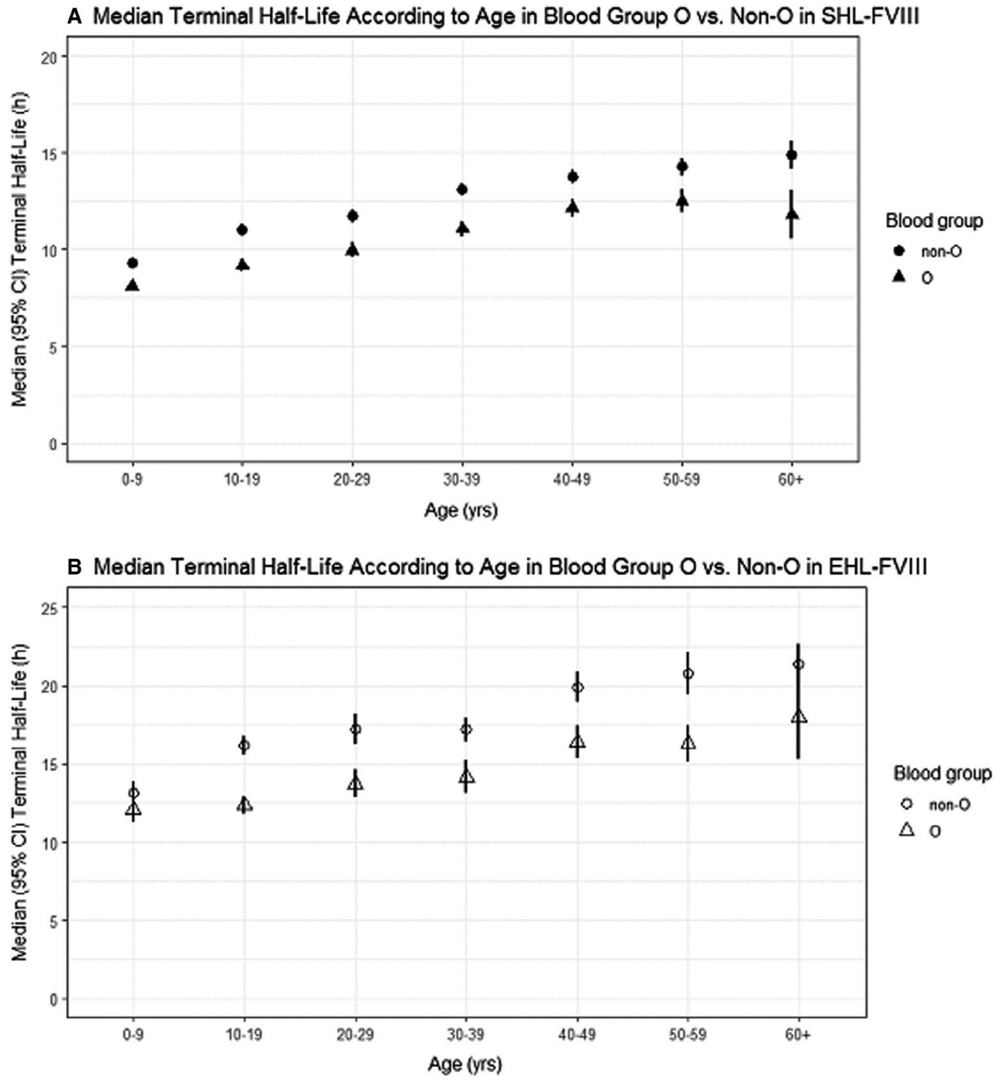

FIGURE 3 Terminal half-life (THL) in subjects with blood group O was lower than those with blood group non-O for both FVIII-SHL and FVIII-EHL concentrates. (A) THL for FVIII-SHL in blood group O (solid triangles) and non-O (solid circles). (B) Median THL for blood group O (open triangles) and non-O (open circles). Displayed error bars represent 95% confidence intervals. EHL, extended half-life; F, factor; SHL, standard half-life

TABLE 4 Regression formulas for THL (in hours) for FVIII and FIX

		THL Formula (in hours)
FVIII	All ages	=9.9 + 0.09 x age (years) + 4.4 (if on EHL) −0.9 (if positive inhibitor history) −1.4 (if blood group O)
FIX	<30 years	= 15.8 + 1.2x age (years) + 65.7 (if on FIX-Fc) + 98.7 (If on FIX-Alb)
	≥30 years	= 43.4 + 91.4 (if on FIX-Fc) + 109.6 (if on FIX-Alb)

Abbreviations: EHL, extended half-life; F, factor; THL, terminal half-life.

5 | CONCLUSIONS

Terminal half-life increased linearly with age across the entire lifespan for FVIII concentrates. For FIX concentrates, THL increased up to age 30 years and remained stable afterwards. Furthermore, THL was shorter in subjects with a history of an inhibitor against FVIII. FVIII-THL was shorter in subjects with blood group O. The extension of THL for EHL concentrates was confirmed. FIX-THL was longer in recombinant FIX than in plasma-derived FIX. These results have the potential to give clear clinical guidance to clinicians for establishing long-term treatment strategies in daily life, around surgery or when treating subjects with ITI.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in the design of the study. Olav Versloot, Emma Iserman, Pierre Chelle, and Kathelijn Fischer analyzed the data and wrote the initial version of the report. All authors were involved in data interpretation. All authors reviewed and approved the final version of the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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