Taylor & Francis
Taylor & Francis Group

Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: www.tandfonline.com/journals/ierr20

Real-world analysis of extended half-life product posology in hemophilia A: results from a retrospective analysis of medical chart and claims data

Cedric Hermans, John Waller & Steven R Lentz

To cite this article: Cedric Hermans, John Waller & Steven R Lentz (2025) Real-world analysis of extended half-life product posology in hemophilia A: results from a retrospective analysis of medical chart and claims data, Expert Review of Hematology, 18:7, 537-545, DOI: 10.1080/17474086.2025.2520312

To link to this article: https://doi.org/10.1080/17474086.2025.2520312

EXPERT REVIEW OF HEMATOLOGY
2025, VOL. 18, NO. 7, 537–545
https://doi.org/10.1080/17474086.2025.2520312

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Real-world analysis of extended half-life product posology in hemophilia A: results from a retrospective analysis of medical chart and claims data

Cedric Hermans [a], John Waller[b] and Steven R Lentz[c]

[a]Hemostasis and Thrombosis Unit, Division of Adult Haematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium; [b]Department of RWE Rare Disease, Novo Nordisk Health Care AG, Zurich, Switzerland; [c]Department of Internal Medicine, The University of Iowa Carver College of Medicine, Iowa City, IA, USA

ABSTRACT

Background: Extended half-life (EHL) products have changed the treatment landscape of patients with hemophilia as patients maintain protective FVIII levels with minimal occurrence of spontaneous bleeding.

Research design and methods: Two independent datasets from the multi-country patient record form (PRF)-based study and PicnicHealth/Komodo Health study were analyzed to understand the real-world use of EHL products for patients with hemophilia A (HA).

Results: Most patients receiving EHL prophylaxis were on per-label dosing. Those receiving individualized dosing had moderate to severe disease. EHL dose adjustment occurred in 20% of patients of which 14.3% experienced a second dose adjustment. Treatment efficacy was mainly monitored via annualized bleeding rate (ABR) with quality of life, tolerability, and treatment efficacy being the primary considerations for Healthcare Personnel when selecting treatment. Switching to a different EHL or standard half-life (SHL) product did not significantly reduce median ABR while switching to non-factor therapy significantly reduced median ABR from 5.2 to 0.94, $p < 0.0001$. Patients on individualized dosing had higher ABRs than those on per-label dosing both before index EHL treatment and while on EHL treatment, whereas individualization via dose adjustment was associated with significant median ABR reduction ($p < 0.0001$).

Conclusions: Individualization may support improved outcomes in patients unable to achieve satisfactory outcomes on a per-label dosing regimen.

ARTICLE HISTORY
Received 6 March 2025
Accepted 6 June 2025

KEYWORDS
Extended half-life; factor VIII; hemophilia; surveys and questionnaires; medical records

1. Introduction

Patients with hemophilia A (HA) have an increased tendency to bleed due to a mutation of the *F8* gene resulting in deficiency of coagulation factor VIII (FVIII) [1]. Prophylaxis with FVIII replacement therapies is used for the treatment and prevention of bleeds, improving quality of life (QoL), and minimizing treatment burden [2–4].

Standard half-life (SHL) FVIII replacement products have half-lives of approximately 8 – 12 h, which necessitates frequent intravenous (IV) infusions to keep baseline FVIII activity levels above 1%, leading to significant treatment burden and suboptimal treatment adherence [5–7]. To address these limitations of SHL products, recombinant FVIII products with extended half-lives (EHLs) have been developed, allowing for less frequent IV dosing and improvement of QoL in patients with HA [8,9]. Currently, there are five EHL FVIII treatment products available [10]. Efmoroctocog alfa is a Fc fusion product that functions by recycling via neonatal Fc receptors and exhibits a half-life of 19 h whereas damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol are PEGylated products that decrease renal filtration, proteolytic degradation, and receptor-mediated clearance, and exhibit half-lives of 18.7 h, 14.3 h and 19.0 h, respectively. Efanesoctocog alfa is a modified Fc fusion product with a half-life of 48.2 h in adults [11].

Pharmacokinetic (PK) differences between EHL FVIII products exist, which may influence the ability to optimize dosing regimens [12]. It has been noted that per-label dosing may not provide optimal protection from bleeding because the dose and frequency of FVIII replacement to minimize the number and severity of bleeding episodes vary between individuals and within the same individual over time [13]. Current labeling for EHL FVIII products is based on phase 3 studies where the dosing strategies were imposed by protocols. As a result, individual patients' needs to minimize the annualized bleeding rate (ABR) and optimize QoL may not be met since treatment is not individualized according to the real-life need of each patient.

Therapy may be individualized by adjusting dosing based on joint status, individual bleed pattern, anticipated physical

CONTACT Cedric Hermans Hermans.cedric@gmail.com Hemostasis and Thrombosis unit, Division of Adult Haematology, Cliniques Universitaires saint-Luc, Université Catholique de Louvain (UCLouvain), Avenue Hippocrate 10, Brussels 1200, Belgium

Supplemental data for this article can be accessed online at https://doi.org/10.1080/17474086.2025.2520312

activity, measured FVIII levels, and other factors. Individualization may help optimize patient outcomes allowing for greater patient engagement in treatment decisions [2,13] and overall improvement in the QoL of each individual patient [14].

To gain a comprehensive understanding of the EHL treatment landscape in HA, we aimed to provide data on the real-world use of FVIII EHL, the drivers of treatment and dosing decisions, the degree of individualization, and the impact on ABR, by utilizing a triangulation approach to analyze two independent qualitative datasets. The first dataset is a multi-country study designed to investigate HA treatment patterns collected by online surveys of specialists directly involved in the treatment of HA. The specialists also provided data into patient record forms (PRFs) based on chart abstraction. The second dataset includes retrospective data from PicnicHealth/Komodo Health in the US, which evaluated prophylactic treatment with EHL products in patients with HA through electronic medical records (EMR) (PicnicHealth) and medical claims data (Komodo Health) to understand individualization of EHL dosing and the associated clinical outcomes of dosing changes. EHLs prescribed to patients with HA in the multi-country PRF-based study and the PicnicHealth/Komodo database included Efmoroctocog alfa, damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol. Efanesoctocog alfa was not available when the studies were conducted and therefore is not included in the analysis.

2. Patients and methods

2.1. Multi-country PRF-based study

The multi-country PRF-based study was a two-stage cross-sectional study which recruited adult and pediatric hemophilia specialists from the United Stated of America (U.S.A.), United Kingdom (UK), Italy, Germany, and Japan. Consent was not required as the study was conducted using a fully anonymized approach in accordance with EphMRA guidelines.

Eligible specialists were required to be directly responsible for treating HA, have 3 to 35 years of experience in this area, based in a Hemophilia Treatment Center (HTC) or, for the UK only, in other treatment settings, treat either adult or pediatric patients, and were required to have a certain number of current HA cases. An adult specialist was considered one that treats mostly patients aged 13 years and older. The number of current HA cases required to be eligible was defined as having more than ten patients with HA (all countries except Japan), or two patients with HA (Japan) for specialists based in an HTC. For specialists from treatment settings other than HTCs (UK only) six or more patients with HA were sufficient to be eligible. All specialists were required to prescribe at least two different EHL products and have four or more patients on a prophylaxis treatment with an EHL product.

Physicians were identified through targeted healthcare professional (HCP) panels and approached by a study vendor, Acuvia, to participate in the study. Participation was voluntary, and physicians received financial compensation for their time in accordance with local regulations and ethical standards. Stage one of the study comprised a 30-minute in-depth individual interview with a hematologist or hemophilia specialist. This qualitative element, which informed the development of the second quantitative phase of the study, is not included in this analysis. Stage two of the study, conducted between July 2022 and September 2022, consisted of a 30-minute web-assisted online survey and collection of patient characteristics from real PRFs for the four EHL products (Efmoroctocog alfa, damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol) among adult and pediatric hemophilia specialists in all countries, and pediatricians in the UK. The online survey distinguished between pediatric and adult specialty for all questions that were answered. It collected data asking questions around severity of disease (mild, moderate, severe), type of treatment (prophylaxis vs. on-demand) for each severity level, and, in case of prophylactic treatment, the percentage of patients receiving fixed dosing as per product label vs. individualized dosing for each severity level. It further asked questions regarding physicians' perceptions and attitude toward treatments and dosing including product awareness and availability, number of patients on specific products for prophylaxis vs. on-demand treatment and the importance of aspects such as effectiveness, safety, mechanism of action, compelling clinical data, patient characteristics or patient preferences, expected patient compliance, customizable dosing or convenience of therapy for physicians when choosing a treatment.

Physicians were also required to complete four unique PRFs on behalf of their patient(s). The patient characteristics collected through the PRFs by treating physicians included data on age, weight, severity at time of diagnosis, underlying conditions and comorbidities, activities during work or sports pursued by patients, dosage and frequency of current treatment, type of dosing and length of treatment with this regimen (fixed vs. individualized dose), patient's ABR, joint health status and Hemophilia Joint Health Score (HJHS) since treatment with a specific type of dosing and questions around treatment change from one type of dosing to another. The data were processed by Quintiles and IMS Health, Inc. (IQVIA), a health information technology and clinical research company, for the purpose of this study.

2.2. PicnicHealth/Komodo Health study

The non-interventional retrospective PicnicHealth/Komodo Health study identified patients with HA from various practice settings in the US receiving prophylactic treatment with an EHL product (Efmoroctocog alfa, damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol) and comprised two Cohorts.

Patients in Cohort 1 were identified in the PicnicHealth database, a platform containing de-identified information from patient medical records produced during standard clinical care in HTCs and other practice settings and transformed for analytical use. The EMR data contains information derived from medical records of any format. Data were collected between 1 June 2014 and 31 January 2022. Patients were required to have a HA diagnosis, prophylactic treatment with an EHL product (Efmoroctocog alfa, damoctocog alfa pegol, rurioctocog alfa pegol, and turoctocog alfa pegol), and

a minimum of three months of follow-up data after the index date in the PicnicHealth database. The index date was defined as the first EHL treatment in patients with a HA diagnosis (after three months of baseline collection of eligible patients). The study period was defined as the duration between diagnosis date (i.e. first visit date) and the last observed encounter (i.e. record) for each patient. This study adhered to reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE).

In the PicnicHealth/Komodo Health study, natural language processing was used to convert structured and unstructured ABR data extracted from medical records for ABR assessment. Total ABR was analyzed using Generalized Linear Models (GLM) with Poisson distribution and log link to estimate the ABR changes for before and after a treatment switch or EHL dose change. Both least square means with 95% confidence intervals (CIs) and p-values were reported. For patients who received an EHL treatment and started on a dose consistent with label instructions and remained on this dose, total ABR was summarized by Poisson rate with 95% CIs. GLMs with Poisson distribution and log link were used to estimate the association of ABR and the starting dose. Both least square means with 95% CIs and p-values were reported for different starting doses.

Cohort 2 was comprised of patients in Cohort 1 who were linked to the Komodo Health claims database to provide the details of healthcare resource utilization (HCRU), costs, and identify patients with HA who were treated prophylactically with an EHL product from 1 January 2015 to 31 January 2022. Inclusion criterion was a minimum of 3 months of claims activity after the index date derived from PicnicHealth database. All participants in the PicnicHealth/Komodo health study provided informed consent for the use of their data.

Analysis focused on evaluating data derived at treatment-class level and not product level analysis.

2.3. Definitions (as used in the study questionnaires or databases)

The multi-country PRF-based study used the following definitions:

- Prophylaxis: Regular administration (intravenously, subcutaneously, or otherwise) of a hemostatic agent/agents to enhance hemostasis and effectively prevent bleeding in people with hemophilia.
- On-demand: Administration of clotting factor concentrates only at the time of a bleed.
- Fixed dosing, referred to as per-label dosing in this paper, regimen entails keeping the same dosage and interval of product at every injection, without the need to monitor FVIII levels before every new injection.
- Individualized dosing regimen is a customized approach that allows changing dosing and intervals at certain injection periods based on individual PK parameters and patient factors such as bleeding phenotype, lifestyle, and joint status [15]. This requires monitoring very closely the clinical response after every injection and before the new one, to adjust dosing accordingly.
- ABR is the number of bleeds per year. It can also be measured as the number of reported bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12 [16].

The PicnicHealth/Komodo Health study used the following definitions:

- Standard dose/per-label dose is defined as the dose as given in the labels of the respective products.
  - A ±10% window was allowed in accordance with the National Hemophilia Foundation's Medical and Scientific Advisory Council's (MASAC) recommendations for factor dosing standard of care. The window is a range of 90%–110% of the standard dose schedule. If a range is provided, the lower bound is considered for the 90% threshold and the upper bound for the 110% threshold.
  - Only dosage schedules listed as twice weekly or once every 4 days were considered as potential candidates for per-label dose.
- The lag period is defined as the number of days between the end of the index EHL medication era, a continuous period of medication use, and the date of last contact in the PicnicHealth data.
- A drug is defined as concomitant if the patient begins the medication before the index date and ends the medication after the index date. Drugs that are either started or stopped on the index date were not considered concomitant.
- ABR is calculated as the number of reported bleeding events divided by the number of months in the reporting time window (3 months to 12 months) and multiplied by 12 [16].

3. Results

3.1. Study cohorts and EHL dosing patterns

In the multi-country PRF-based study, a total of 111 specialists participated in the online survey and provided data into PRFs based on chart abstraction for 623 patients. Of the 623 patients of whom PRFs were included in the analysis, 515 were adult (aged ≥13 years) and 108 were pediatric patients (aged ≤12 years) with HA, respectively (Table 1). Across countries, the HCPs surveyed had a comparatively lower caseload of pediatric patients compared to adult patients, except for Japan where the caseload of adult and pediatric patients was similar (Table 1).

According to survey data ($N = 111$), 94.6% ($N = 105$) of total physicians reported primarily practicing at HTCs whereas 5.4% physicians reported practicing at non-HTCs such as academic/teaching hospitals or community-based hospitals (Supplementary Table S1). Survey data showed that 83.0% of patients (adult and pediatric) were treated with EHLs as a prophylactic treatment; the majority were on per-label dosing (66.0%) compared with individualized dosing (34.0%) (Table 2). The country with the highest rate of individualized dosing was

Table 1. Sample sizes from phase 2 of the multi-country PRF-based study.

	Online Survey		PRFs	
Total (N)	Adult[a]	Pediatric[b]	Adult[a]	Pediatric[b]
U.S.A	25	4	143	18
Germany	15	3	114	19
United Kingdom	13	4	80	11
Italy	17	4	118	16
Japan	15	11	60	44
Total	85	26	515	108

[a]Adult specialists treat patients where most patients are aged ≥13 years. [b]Pediatric specialists treat patients where most patients are aged ≤12 years. PRF, Patient Record Forms; U.S.A., United States of America.

Table 2. Distribution of EHL treatment in the multi-country PRF-based study.

	All (*N* = 111)	U.S.A. (*n* = 29)	Germany (*n* = 18)	United Kingdom (*n* = 17)	Italy (*n* = 21)	Japan (*n* = 26)
Percentage (%) of patients (adult + pediatric) receiving prophylactic EHL treatment	83.0	94.0	98.0	94.0	64.0	78.0
Treatment type						
Per label, %	66.0	67.0	61.0	88.0	39.0	58.0
Individualized, %	34.0	33.0	39.0	12.0	61.0	42.0

EHL, extended half-life; N, number of patients; PRF, Patient-Record Form; U.S.A., United States of America.

Italy, which reported 39.0% on per-label dosing and 61.0% on individualized dosing.

PRF data (*N* = 623) showed that 39.2%, 37.7%, and 22.0% of the total patient population had severe, moderate, and mild HA, respectively at the time of diagnosis; in 1.1% of patients the diagnosis was not known (Table 3). 54.5%, 29.6%, and 15.0% of patients that received individualized dosing had severe, moderate, and mild HA, respectively; in 0.9% of patients the diagnosis was not known. Conversely, 31.2%, 42.0%, and 25.6% of patients receiving per-label dosing had severe, moderate, and mild HA, respectively; in 1.2% of patients the diagnosis was not known.

The PicnicHealth research database contained 354 US patients with HA, of which 105 patients were treated with EHL products and met the inclusion criterion of a minimum of three months follow-up post-index during the study period (Cohort 1) (Supplementary Figure S1). PicnicHealth's EMR data were linked to Komodo Health claims for an estimated 83 patients, 37 of whom met the requirement of having medical and prescription insurance coverage on the index date and for at least 90 days after the index date (Cohort 2).

By creating a window of ± 10% around the per-label dose in Cohort 1, 49.5% of patients received per-label EHL dosing compared to 34.3% on precise per-label dosing as listed in the protocol (Supplementary Figure S1). A total of 47.6% patients received individualized EHL dosing and 3.0% patients had missing dose information.

During the follow-up period after starting an EHL product, 23.8% of patients in Cohort 1 remained on their index EHL dose, while 20.0% had a dose adjustment from the index EHL dose by either altering dose value or frequency of dose administration (Table 4). 23.8% discontinued their index EHL treatment and 32.4% patients switched from EHL to non-factor therapy, SHL products, or other EHL products. Of the 20.0% with an EHL dose adjustment, 14.3% experienced a second dose adjustment (Table 4). Most dose adjustments were increases in either the dose value or frequency of administration. Among the patients with two dose adjustments (14.3%), two of three patients had a dose increase at both the first and second adjustment. 18.1% (19/105) of patients had evidence of concomitant SHL use with their EHL treatment.

3.2. Annualized bleeding rates and effects of switching/adjustment

In the multi-country PRF-based study, median ABR [Interquartile range (IQR)] was similar in patients on individualized (2 [1 – 3]) and per-label (2 [1 – 4]) dosing (Table 5). Mean ABR (standard deviation [SD]) was 2.12 (5.47) and 3.87 (9.43) in patients on

Table 3. Distribution of disease severity and dosing regimen in the multi-country PRF-based study.

	Total	Adult	Pediatric	Total		
	Total Sample N (%)	Total N (%)	Total N (%)	Total Sample N (%)	Total individualized N (%)	Total per-label N (%)
Base: All Respondents	623 (100)	515 (100)	108 (100)	623 (100)	213 (34.2)	410 (65.8)
Mild	137 (22.0)	116 (22.5)	21 (19.4)	137 (22.0)	32 (15.0)	105 (25.6)
Moderate	235 (37.7)	201 (39.0)	34 (31.5)	235 (37.7)	63 (29.6)	172 (42.0)
Severe	244 (39.2)	192 (37.3)	52 (48.2)	244 (39.2)	116 (54.5)	128 (31.2)
Do not know	7 (1.1)	6 (1.2)	1 (0.9)	7 (1.1)	2 (0.9)	5 (1.2)
Total mentions	623 (100)	515 (100)	108 (100)	623 (100)	213 (100)	410 (100)

N, number of patients; PRF, Patient-Record Form.

Table 4. Dose adjustment and product switching in the PicnicHealth Cohort.

	All patients (N = 105)
Still On Index Dose[a], N (%)	25 (23.8)
Adjusted Dose from Index, N (%)	21 (20.0)
Stopped Index Drug, no further record of medication[b], N (%)	25 (23.8)
Switched From Index Drug to Other Drug, N (%)	34 (32.4)
Non-factor therapy, N (%)	19 (55.9)
SHL products, N (%)	11 (32.4)
Different EHL product, N (%)	4 (11.8)
Patients with No EHL Tx Dose Adjustments, N (%)	84 (80.0)[c]
Patients with EHL Tx Dose Adjustments, N (%)	21 (20.0)
Patients with 1 EHL Tx Dose Adjustment, N (%)	18 (85.7)
Patients with 2 EHL Tx Dose Adjustments, N (%)	3 (14.3)
Time to First EHL Tx Dose Adjustment in months, N (mean)	21 (24.0)
Time to Second EHL Tx Dose Adjustment in months, N (mean)	3 (9.3)

[a]As of last available follow-up date in PicnicHealth data. [b]Patients who have no further record of hemophilia A medication (EHL, SHL, non-factor, or bypass) have a mean lag period of 523.6 days, a median lag period of 419 days (IQR: 238 – 689), and the lag period ranged from 0 days to 1883 days. The lag period is defined as the number of days between the end of the index EHL medication era and the date of last contact in the Picnic Health data. [c]The 80% of patients with no dose adjustment consist of the patients still on index (24%), patients that switched from index drug to other drugs (32%), and the patients who stopped index drug (24%). EHL, extended half-life; IQR, interquartile range; N, number of patients; SHL, standard half-life; Tx, treatment.

Table 5. Annualized bleeding rates (ABR) pre-switch to individualized treatment and on current treatment in the multi-country PRF-based study.

All patients on per-label dosing prior to switching to individualized dosing	Median	2.5
	Q1	2
	Q3	3
	Mean	3.99
	Standard deviation	9.58
All patients on individualized dosing	Median	2
	Q1	1
	Q3	3
	Mean	2.12
	Standard deviation	5.47
All patients on per label dosing	Median	2
	Q1	1
	Q3	4
	Mean	3.87
	Standard deviation	9.43

Calculated retrospectively from source data in response to survey question Q23C. [ABR with current treatment] What is this patient's ABR since treated with a per-label/an individualized dosage of [. . .]? ABR, annualized bleeding rate; PRF, Patient-Record Form; Q1, 1st quartile; Q3, 3rd quartile.

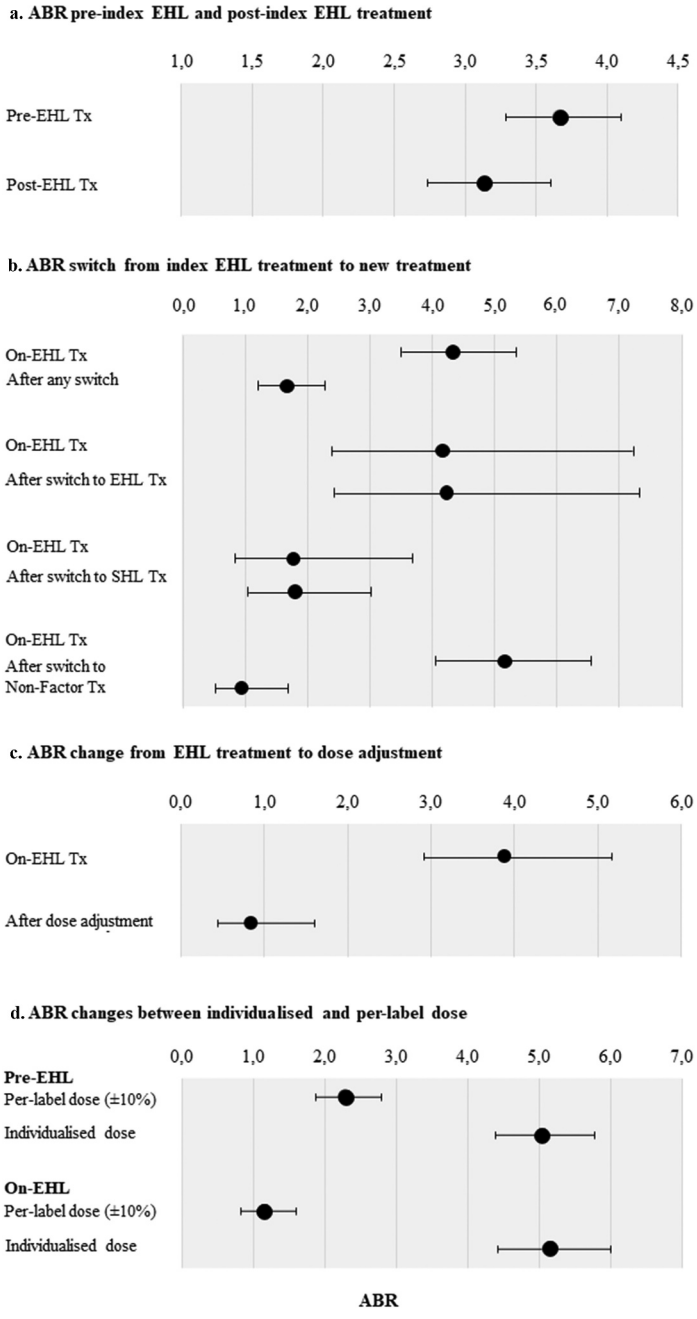
individualized and per-label (3.87 [9.43] dosing, respectively. Pre-switch to individualized treatment was 2.5 (IQR 2 – 3) (Table 5).

In the PicnicHealth Cohort, a non-significant reduction in median ABR was observed during the follow-up period after starting the index EHL treatment ($p > 0.05$); patients experienced 3.7 bleeds per year prior to EHL treatment initiation, and approximately 3.1 bleeds per year following EHL treatment (Figure 1(a)). Reductions in ABR for patients switching treatment from index EHL therapy to other treatments were driven by switch from EHL treatment (median ABR 5.2) to non-factor treatments (median ABR 0.94), $p < 0.0001$ (Figure 1(b)). Small sample sizes limited the assessment of switches from index EHL to other EHL or SHL products. A statistically significant reduction in ABR from approximately 4 bleeds to less than 1 bleed per year was observed after EHL treatment dose adjustment ($p < 0.0001$) (Figure 1(c)). Patients on individualized dosing had higher ABRs compared to patients on per-label dosing (±10%) both before index EHL treatment and while on EHL treatment (Figure 1(d)).

3.3. Treatment monitoring and treatment decisions

Supplementary Figure 2 shows the factors used to monitor treatment efficacy by HCPs that participated in the multi-country PRF-based study. The most common assessment was ABR, except in the US and Germany, where improved FVIII levels (76%) and resolving recurrent target joint bleedings (67%), respectively, were considered more important factors for monitoring treatment efficacy.

QoL, tolerability/safety and treatment efficacy were the primary reasons for selecting the current treatment product for the specific patient by the HCPs (Supplementary Table S2). HCPs selected 'improving QoL' as the reason for selecting the current EHL product in 29.1% of patients (30.7%, 26.8%, and 27.7% with severe, moderate, and mild disease, respectively). 'Improving QoL' was selected as the reason for selecting the current treatment product in all adult patients (30.1%) and adult patients with severe (29.7%), moderate (30.3%), and mild (27.6%) disease, respectively. 'Effective in any severity level' was selected as the reason for selecting current treatment in all pediatric patients (32.4%) and in



	Number of subjects in model	Number of observations in model
ABR, Pre- and Post- EHL		
Total subjects within model[1]	87	149
Pre-EHL	85	85
On-EHL	64	64
Switched to any therapy		
Total subjects within model[1]	29	43
On-EHL	20	20
Post-EHL	23	23
Switched to an EHL therapy		
Total subjects within model[1]	4	6
On-EHL	3	3
Post-EHL	3	3
Switched to an SHL therapy		
Total subjects within model[1]	9	12
On-EHL	4	4
Post-EHL	8	8
Switched to a Non-Factor therapy		
Total subjects within model[1]	16	25
On-EHL	13	13
Post-EHL	12	12
Total subjects within model	15	23
On-EHL	12	12
Post-EHL	11	11
Total subjects within model	15	23
On-EHL	12	12
Post-EHL	11	11

Figure 1. Annualized bleeding rates (ABR) in the PicnicHealth Cohort.

(a) ABR reduction (not statistically significant) was observed following index EHL treatment. (b) Switches to non-factor replacement therapy drove overall reduction in ABR. (c) Statistically significant reduction in ABR was observed after an EHL treatment dose adjustment. (d) Higher ABRs observed in patients on individualized dosing compared to per-label dosing both before index EHL treatment and while on EHL treatment.

[1]Subjects may have contributed to both Pre-EHL and On-EHL time periods if they had requisite follow-up time and data were available, resulting in the total number of observations included in the model. Poisson regression models were used to compare ABR between subject groups. ABR, annualized bleeding rate; EHL, extended half-life; SHL, standard half-life; Tx, treatment.

those with severe (36.5%) and moderate (38.2%) disease, respectively; Effective even in cases when patients develop FVIII inhibitors' was selected as the reason for selecting current treatment product in pediatric patients with mild (42.9%) disease. When asked whether HCPs consider patient preferences in the treatment decisions, 26.0%–37.0% of HCPs reported a score of at least 8 out of 10; a score of 10/10 being 'I fully take them into consideration' (Supplementary Table S3).

4. Discussion

The common use of EHLs has changed the treatment landscape for patients with HA by allowing for less frequent dosing compared to SHLs and the potential for improved QoL [8,9]. Use of EHLs may require individualization due to several factors such as variation in a patient's PK profile, bleeding phenotype, physical activity/lifestyle, and joint status [17]. In this report, we analyzed two independent real-world datasets to

explore and understand the patterns of EHL FVIII treatment use for HA in current clinical practice.

To date, research on the real-world treatment landscape of EHL dosing is limited and as a result, this observational study required a unique data collection approach. The multi-country PRF-based study sought to understand the drivers of EHL treatment and dosing decisions and the extent to which patient preference influences treatment decisions through the collection of quantitative online surveys among specialists. The specialists who participated in this research also provided real patient cases, through PRFs, to help derive insights on EHL usage and outcomes. The study design not only allowed researchers to gain insights into the EHL HA treatment landscape but also provided an opportunity to gain an understanding of the physician's viewpoint when making treatment changes and decisions which had been little examined previously.

The PicnicHealth/Komodo Health study was included in this analysis to overcome the issue of missing data in real-world datasets. PicnicHealth collects data retrospectively from health records in any format and processes it through the platform to produce a complete timeline of health records [18]. Health records are processed using PicnicHealth's novel approach of task-specific machine learning and software tool assortment allowing for research of large patient populations [18]. This study leveraged the structured, longitudinal datasets provided by PicnicHealth and could filter the HA population based on several inclusion and exclusion criteria to conduct research on a unique HA patient population ($n = 105$).

In the multi-country PRF-based study, 34% of patients were on individualized dosing of whom the majority had severe HA (54.5%).

We found that HCPs monitor multiple factors to determine dosing, including ABR, FVIII levels, and resolving recurrent target joint bleedings. EHL treatment decisions were also found to be driven by patient QoL, guideline recommendations, and tolerability/safety, with the majority of HCPs reporting that they consider patient preferences when making treatment decisions.

In the multi-country PRF-based study, there were no significant differences between patients on individualized vs. per-label treatment, or for patients who switched from per-label dosing to individualized dosing.

Results in Figure 1(a) from the PicnicHealth/Komodo Health study showed that while there was a lower ABR following EHL treatment compared to prior to EHL treatment, the difference was not statistically significant. A study by Ay et al., which evaluated bleeding outcomes after switching to an EHL product for prophylaxis in HA in Austria, showed that the switch from an SHL treatment to an EHL treatment was associated with an improved clinical outcome, reflected by a significantly reduced ABR [19]. Several real-world studies evaluating the switch to EHL products have shown that ABR is either decreased [17,20] or comparable [21] which is similar to what was observed in the PicnicHealth/Komodo Health study.

The ABRs from time on index EHL treatment were compared to those after a switch to another EHL, SHL, or non-factor treatment. Switch to another EHL treatment or SHL therapy showed no significant change in ABR, although these comparisons were limited by the small sample sizes. In contrast, a significant reduction in ABR was driven by switch from EHL to non-factor therapy, $p < 0.0001$.

Furthermore, patients on individualized dosing had higher ABRs compared to patients on per-label dosing (±10%), both before index EHL treatment and while on EHL treatment. Interestingly, a significant reduction in ABR from approximately 4 bleeds per year to less than 1 ($p < 0.0001$) bleed per year was observed following an EHL dose adjustment which reduced the ABR to a non-significant difference vs. per-label dosing. This shows that desired ABRs can be achieved with further individualization approaches in patients with HA.

The ABR results from both studies demonstrate that patient outcomes can be favorable and successful on per-label and/or individualized dosing and that individualization can achieve desired outcomes regardless of whether the patients were previously on per-label or non-label use.

The value of individualized treatment has been emphasized by recent guidelines and recommendations [4,22]. Several studies obtained improved clinical outcomes by aiming to set a fixed target trough level for patients with different bleeding phenotypes or joint status [23,24], while another study demonstrated an overall FVIII consumption reduction and possibility of extending the dosing interval when tailoring prophylaxis according to PK [25]. Unfortunately, fixed target trough levels translate into a lack of true individualization in determining personalized FVIII levels, further highlighting the need to individualize treatment based upon each individual patient's need. To date, various assessment tools have been developed to assist in the process of individualization including population PK profiling, MRI/joint status imaging, and QoL scores [26]. Individualization may support improved outcomes in those patients who are unable to achieve satisfactory outcomes on a per-label dosing regimen, allow HCPs to amplify the hemostatic benefits of EHLs and address the ultimate goal of achieving zero bleeds, preserving joint health, and improving patients' overall QoL.

As with all studies using real-world data, the insights of this study are limited by selection and reporting biases and inherent noise in the data. The incidence of participants with mild, moderate and severe HA reported in the multi-country PRF-based study may not accurately reflect global representation which may suggest a degree of enrollment bias.

The PicnicHealth/Komodo Health study has several limitations, including a relatively small sample size which may have contributed to the lack of significance observed during the follow-up period after starting the index EHL treatment. Not all patients with dose adjustments had adequate data to input into the model to determine ABRs which further limits the interpretation of the findings. Furthermore, differences in the use of bleed definition and selection of bleeding phenotype across physicians may limit the interpretation of ABR within the PicnicHealth dataset. Treatment adherence, which has been demonstrated to be poorer in adult patients than pediatric patients [27], was not taken into consideration. The follow-up time was limited due to some EHL-FVIII products being commercially available for only a short time period. Damoctocog alfa pegol and turoctocog alfa pegol were approved in 2018 and 2019, respectively, and as

a result, fewer patients in our analysis received turoctocog alfa pegol and damoctocog alfa pegol compared to rurioctocog alfa pegol and efmoroctocog alfa. Additionally, there are limitations inherent to the source data from the PicnicHealth research database, as data collected retrospectively from medical records may be incomplete, non-standardized, and vary in the quality of information recorded by physicians. Further studies with a larger sample size are needed to confirm these results and the benefits of other EHL products.

5. Conclusions

EHL products for the treatment of HA have shown beneficial effects overcoming current prophylaxis limitations. The individualization of EHL treatment, including dose adjustments, may amplify the hemostatic benefits. Future in-depth research into factors that drive the need for individualization is needed across all treatment classes, not just EHL, due to the heterogeneity of HA.

Funding

This manuscript was funded by Novo Nordisk Health Care AG, Zurich, Switzerland.

Declaration of interest

C Hermans has received grants or contracts from Sobi and Bayer; consulting fees from Novo Nordisk, Bayer, Takeda, CSL Behring, Sobi, Octa Pharma, and LFBCS; payment or honoraria from CSL Behring, Sobi, and Octa Pharma; support for attending meetings and/or travel from LFB, Sobi, and CSL Behring and participated in data safety monitoring or advisory boards for CSL Behring. J Waller is an employee and stockholder of Novo Nordisk. SR Lentz has received grants or contracts from Novo Nordisk and Sanofi and consulting fees from Novo Nordisk, Sanofi, and Argenx. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

J Waller acquired the data. All authors equally contributed to the conception and design, analysis and interpretation of data, drafting and critical revision of the manuscript, and approved the final version.

Acknowledgments

The authors thank the hemophilia specialists and patients for their participation and support in the multi-country PRF-based study and the PicnicHealth/Komodo Health study, respectively. Medical writing support was provided by Ashfield MedComms GmbH (Mannheim, Germany), an Inizio company, and funded by Novo Nordisk Health Care AG, Zurich, Switzerland.

ORCID

Cedric Hermans http://orcid.org/0000-0001-5429-8437

References

1. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet (London, England). 2003;361(9371):1801–1809. doi: 10.1016/S0140-6736(03)13405-8
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1–47. doi: 10.1111/j.1365-2516.2012.02909.x
3. Iorio A, Edginton AN, Blanchette V, et al. Performing and interpreting individual pharmacokinetic profiles in patients with hemophilia A or B: Rationale and general considerations. Res Pract Thromb Haemost. 2018;2(3):535–548. doi: 10.1002/rth2.12106
4. Rayment R, Chalmers E, Forsyth K, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. Br J Haematol. 2020;190(5):684–695. doi: 10.1111/bjh.16704
5. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of haemophilia. Ther Adv Hematol. 2018;9(9):295–308. doi: 10.1177/2040620718796429
6. Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. Haemophilia. 2001;7(4):392–396. doi: 10.1111/j.1365-2516.2001.00534.x
7. Petrini P. Identifying and overcoming barriers to prophylaxis in the management of haemophilia. Haemophilia. 2007;13(Suppl 2):16–22. doi: 10.1111/j.1365-2516.2007.01501.x
8. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. Lancet. 2016;388(10040):187–197. doi: 10.1016/S0140-6736(15)01123-X
9. Wyrwich KW, Krishnan S, Auguste P, et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. Haemophilia. 2016;22(6):866–872. doi: 10.1111/hae.12987
10. Okaygoun D, Oliveira DD, Soman S, et al. Advances in the management of haemophilia: emerging treatments and their mechanisms. J Biomed Sci. 2021;28(1):64. doi: 10.1186/s12929-021-00760-4
11. Bioverativ Therapeutics Inc. Altuviiio precsribing information. Waltham MA, USA; 2023. https://www.marylandphysicianscare.com/wp-content/uploads/2024/03/Altuviiio-RX.PA_.086.MPC-ver-Feb-24.pdf
12. Bukkems LH, Preijers T, van Spengler MWF, et al. Comparison of the pharmacokinetic properties of extended half-life and recombinant factor VIII concentrates by in silico simulations. Thromb Haemost. 2021;121(6):731–740. doi: 10.1055/s-0040-1721484
13. Iorio A. Using pharmacokinetics to individualize hemophilia therapy. Hematol Am Soc Hematol Educ Program. 2017;(1):595–604. doi: 10.1182/asheducation-2017.1.595
14. Ljung R, Fischer K, Carcao M, et al. Practical considerations in choosing a factor VIII prophylaxis regimen: role of clinical phenotype and trough levels. Thromb Haemost. 2016;115(5):913–920. doi: 10.1160/TH15-08-0664
15. Hermans C, Dolan G. Pharmacokinetics in routine haemophilia clinical practice: rationale and modalities-a practical review. Ther Adv Hematol. 2020;11:2040620720966888.c. doi: 10.1177/2040620720966888
16. Liao NS, Dusendang JR, Bissel MCS, et al. Methods of estimating annualized bleed rates from medical records among patients with hemophilia A. Value in Health. 2023;26(12):S549.
17. Brennan Y, Parikh S, McRae S, et al. The Australian experience with switching to extended half-life factor VIII and IX concentrates: on behalf of the Australian haemophilia centre directors' organisation. Haemophilia. 2020;26(3):529–535. doi: 10.1111/hae.13970
18. Hanson G, Chitnis T, Williams MJ, et al. Generating real-world data from health records: design of a patient-centric study in multiple sclerosis using a commercial health records platform. JAMIA Open. 2022;5(1). doi: 10.1093/jamiaopen/ooab110

19. Ay C, Feistritzer C, Rettl J, et al. Bleeding outcomes and factor utilization after switching to an extended half-life product for prophylaxis in haemophilia a in Austria. Sci Rep. 2021;11(1):12967. doi: 10.1038/s41598-021-92245-5
20. Wang C, Young G. Clinical use of recombinant factor VIII Fc and recombinant factor IX Fc in patients with haemophilia A and B. Haemophilia. 2018;24(3):414–419. doi: 10.1111/hae.13432
21. Tagliaferri A, Matichecchia A, Rivolta GF, et al. Optimising prophylaxis outcomes and costs in haemophilia patients switching to recombinant FVIII-Fc: a single-centre real-world experience. Blood Transfus. 2020;18(5):374–385. doi: 10.2450/2019.0220-19
22. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6(S6):1–158. doi: 10.1111/hae.14046
23. Megías-Vericat JE, Bonanad S, Haya S, et al. Bayesian pharmacokinetic-guided prophylaxis with recombinant factor VIII in severe or moderate haemophilia a. Thromb Res. 2019;174:151–162. doi: 10.1016/j.thromres.2018.12.027
24. Mingot-Castellano ME, Parra R, Núñez R, et al. Improvement in clinical outcomes and replacement factor VIII use in patients with haemophilia a after factor VIII pharmacokinetic-guided prophylaxis based on Bayesian models with myPKFiT®. Haemophilia. 2018;24(5):e338–e343. doi: 10.1111/hae.13540
25. Lissitchkov T, Rusen L, Georgiev P, et al. PK-guided personalized prophylaxis with Nuwiq(®) (human-cl rhFVIII) in adults with severe haemophilia A. Haemophilia. 2017;23(5):697–704. doi: 10.1111/hae.13251
26. Poon MC, Lee A. Individualized prophylaxis for optimizing hemophilia care: can we apply this to both developed and developing nations? Thromb J. 2016;14(Suppl 1):32. doi: 10.1186/s12959-016-0096-y
27. Mason JA, Parikh S, Tran H, et al. Australian multicentre study of current real-world prophylaxis practice in severe and moderate haemophilia A and B. Haemophilia. 2018;24(2):253–260. doi: 10.1111/hae.13375