



## Full Length Article

# Bayesian pharmacokinetic-guided prophylaxis with recombinant factor VIII in severe or moderate haemophilia A

J.E. Megías-Vericat<sup>a,\*</sup>, S. Bonanad<sup>b</sup>, S. Haya<sup>b</sup>, A.R. Cid<sup>b</sup>, M.R. Marqués<sup>a</sup>, E. Monte<sup>a</sup>,  
S. Pérez-Alenda<sup>b,c</sup>, P. Bosch<sup>b</sup>, F. Querol<sup>b,c</sup>, J.L. Poveda<sup>a</sup>

<sup>a</sup> Pharmacy Department, Drug Clinical Area, University and Polytechnic Hospital La Fe, Avda. Fernando Abril Martorell 106, 46026, Valencia, Spain

<sup>b</sup> Haemostasis and Thrombosis Unit, University and Polytechnic Hospital La Fe, Avda. Fernando Abril Martorell 106, 46026, Valencia, Spain

<sup>c</sup> Department of Physiotherapy, University of Valencia, Valencia, Spain

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## ABSTRACT

**Introduction:** Personalised pharmacokinetics (PK) using Bayesian analysis with limited sampling is assumed to help to optimise prophylaxis in haemophilia A (HA) patients.

**Materials and methods:** Our prospective, observational study analysed the influence of PK parameters on clinical variables (bleeding rates, joint status, adherence, and consumption) using myPKFIT<sup>®</sup> in a cohort of twenty-one severe and moderate HA patients on prophylaxis with recombinant FVIII (Advate<sup>®</sup>) in two periods of one year, the first before PK-based tailoring and the second after PK-guided prophylaxis. Intra-individual and inter-individual coefficients of variation (CV) of half-life ( $t_{1/2}$ ) were calculated.

**Results:** A total of 73 PK estimations were performed in both periods, resulting in 17.2% inter-individual CV in mean  $t_{1/2}$ , and 4.9% intra-individual CV. Before PK-based tailoring a significant association between joint bleeds and  $t_{1/2}$  was found ( $P = 0.010$ ), especially in patients with short  $t_{1/2}$ . This finding was reproduced ( $P = 0.013$ ) after withdrawal of two patients with bleeding phenotype related to their advanced arthropathy but normal  $t_{1/2}$  and trough levels. Patients with joint bleeds weighed less ( $P = 0.039$ ) and required higher doses ( $P = 0.032$ ) than patients with zero joint bleeds. These associations were not observed in the second period after the adoption of PK-guided prophylaxis. There were no differences between the two periods, although a tendency to fewer spontaneous bleeds was suggested after PK-based tailoring.

**Conclusions:** PK-guided prophylaxis facilitates an adequate level of bleeding control in patients with HA, maintaining clinical variables and patient convenience in an integrative manner, without increasing FVIII consumption.

## 1. Introduction

Prophylaxis with factor VIII (FVIII) has been shown to be more effective than on-demand treatment to prevent bleeding and joint damage in severe and moderate haemophilia A (HA), where dosing is based on body weight, in vivo recovery (IVR), or bleeding phenotype. However, these regimens do not protect all patients from developing chronic joint damage due to spontaneous bleeding or physical activity [1–4]. Inter-patient variability in FVIII pharmacokinetics (PK) is thought to be the main determinant of uncertainty in standardised prophylaxis and provides justification for individualisation [5,6].

The individual PK profile of FVIII varies considerably from patient to patient, and this can have significant clinical implications for treatment. The PK variability of FVIII can be attributed to age, weight, von

Willebrand factor (VWF) level, and blood group [7]. An important determinant of prophylaxis efficacy is the length of time an individual spends with FVIII levels  $< 1$  IU/dL, and these trough levels (TLs) are clearly related to spontaneous bleeds [5,6]. Higher TLs may be desirable for managing target joints, patients with high physical activity, or those more vulnerable to bleeding. In contrast, lower levels may be sufficient in patients with few bleeds [8,9]. Adequate peak FVIII levels help to reduce the risk of bleeding related to repetitive physical activity [10–12] and the area under the curve (AUC) has been related to a lower risk of subclinical bleeds [12]. Knowledge of the individual PK helps to determine dosing frequency to achieve optimal FVIII levels.

According to International Society on Thrombosis and Haemostasis (ISTH) guidelines, the measurement of individual FVIII PK requires 9 to 11 samples in adult patients and 5 samples in children, and a washout

\* Corresponding author.

E-mail address: [megias\\_jua@gva.es](mailto:megias_jua@gva.es) (J.E. Megías-Vericat).

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period of 72 h [13,14]. The Bayesian estimation method uses a population PK (PopPK) model based on FVIII levels from a large population of patients as a mathematical/statistical framework to estimate the PK in a patient from minimal data. The first studies in HA employing PopPK with sparse sampling demonstrated a very good correlation in PK estimates [15–19]. A comparative study showed that PK-guided dosing is equally as effective as standard dosing, with similar annualized bleeding rate (ABR), FVIII consumption, and adverse event rates but fewer infusions [20]. Different PopPK tools have been developed to predict the PK parameters in HA patients with FVIII prophylaxis [21–26]. This methodology can facilitate measurement of PK parameters in routine clinical practice, reducing inconvenience to the patient. Furthermore, this approach is potentially more cost-effective [22,24,27].

The aim of this study is to analyse whether the implementation of PK-guided prophylaxis using myPKFiT® results in clinical improvement in a cohort of severe and moderate HA patients treated with Advate®. Our hypothesis is that PK-guided prophylaxis integrated with clinical variables will allow for better bleeding control without increasing FVIII consumption when two 1-year periods are compared.

## 2. Material and methods

A prospective, open-label, observational, single-centre study was conducted including adult subjects with severe and moderate HA without inhibitors on prophylaxis with recombinant FVIII (rFVIII) Advate® (Baxalta Incorporated, Bannockburn, IL). Patients were recruited between January and December 2016. This study was conducted in accordance with the Declaration of Helsinki, approved by the local Clinical Research Ethics Committee and all participants gave written informed consent (NCT02622646).

Individual PK estimation was performed using myPKFiT® (Baxalta Incorporated, Bannockburn, IL, [www.myPKFiT.com](http://www.myPKFiT.com)) [28], a web-based medical device based on PopPK models of Advate®. The PK parameters analysed were clearance (Cl), steady-state volume (Vss), plasma half-life ( $t_{1/2}$ ), TL at 48 h (TL48) and 72 h (TL72), and time to reach rFVIII < 1% (T1%). PK parameters previous to patient inclusion were estimated with available retrospective data for rFVIII levels from January 2014 to December 2015, mostly TL48 and TL72 (all the included patients, except patients #7, #10 and #13 who had on-demand treatment before 2016). Initially, we employed myPKFiT® version 1.0 until September of 2016, when version 2.0 was implemented. This new version improves upon the myPKFiT® algorithm and uses an adjustment of the prior version, such as for patients whose FVIII activity shows a  $t_{1/2}$  shorter than typically expected [28].

We compared data from two years of follow-up (Fig. 1): before PK-based tailoring without prophylaxis adjustment (January to December 2016) and a second year when PK-guided prophylaxis was applied to regimen adjustment (January to December 2017). In the second period, PK estimations obtained from myPKFiT® were employed for prophylaxis tailoring. Patients with arthropathy, a bleeding phenotype or bleeding risk associated with physical activity were adjusted to obtain TL of 2%–3%, whereas well-controlled patients, sedentary patients or patients without bleeding were adjusted to 1% TL.

The primary endpoint was a difference in clinical variables and PK parameters between the two periods, before and after PK-guided prophylaxis was applied. Secondary endpoints included: a) comparisons between categorized  $t_{1/2}$  and clinical variables in each study period; b) comparisons between categorized annualized joint bleeding rate (AJBR) and clinical variables and PK parameters in each study period; c) comparisons between categorized  $t_{1/2}$  and categorized AJBR in each study period.

Collected variables were anthropometric characteristics (age, weight), disease characteristics (severity, coinfection, mutation), prophylaxis regimen (regimen, dosing frequency, and rFVIII dose [IU/Kg]), Haemophilia Joint Health Score (HJHS), physical activity, bleeding

episodes (AJBR, ABR, including location and cause (spontaneous or provoked)), rFVIII consumption, and Adherence Index (AI) [29]. AI was calculated as the IU administered, based on pharmacy dispensing data and hospital infusion records, divided by the IU prescribed, multiplied by 100.

Data was described using the mean, standard deviation (SD), median, and interquartile range (IQR) for quantitative variables and relative and absolute frequencies for categorical variables. The Kruskal-Wallis test was used to compare PK parameters and clinical variables. The  $t_{1/2}$  was categorized as short (< p25), normal (p25–p75), and long (> p75) and these subgroups were compared to clinical variables using the Kruskal-Wallis test. Furthermore, AJBR was categorized as zero against  $\geq 1$  joint bleed and compared with clinical variables and PK parameters using the Kruskal-Wallis test, and with the categorized  $t_{1/2}$  using the  $\chi^2$  test. Intra-individual and inter-individual coefficients of variation (CV) of  $t_{1/2}$  were calculated. Comparisons between parameters of the two periods were performed using Wilcoxon signed-rank test. P-values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS® statistical package version 19. The sample size of 20–25 patients was calculated to provide 90% power to detect a mean treatment difference of one ABR or AJBR episode with two-sided  $\alpha = 0.05$ , assuming a standard deviation (SD) of two ABR or AJBR episodes in 1 year, using NQUERY version 7.0 (Statistical Solutions, Saugus, MA, USA).

## 3. Results

Twenty-one patients were included in the study, whose baseline characteristics are summarised in Table 1. All patients had severe HA, except one with moderate disease with a previous history of bleedings and controlled with prophylaxis. At recruitment, median age was 33.0 years (IQR = 26.5–42.5), median weight was 70.0 kg (IQR = 61.5–80.5), and median rFVIII dose was 69 IU/kg/week (IQR = 56.3–79.5). Eight patients received prophylaxis three times a week, seven twice a week, one patient every 48 h and one patient every 120 h. Three patients were on demand (OD) treatment at recruitment and changed to prophylaxis during the study.

We performed a total of 141 PK estimations with myPKFiT®, 68 for the retrospective period, 39 before and 34 after PK-based tailoring (mean 6.7 estimations/patient and 1.7 estimations/patient/year). The median values of the PK parameters including all the determinations were: Cl 3.1 mL/h/kg (IQR = 2.5–3.3); Vss 50.0 mL/kg (IQR = 50–55);  $t_{1/2}$  13.7 h (IQR = 12.1–15.5); TL48 3.9 IU/dL (IQR = 2.5–7.0); TL72 1.3 IU/dL (IQR = 0.5–2.3) and T1% 72.0 h (IQR = 63.5–87.5).

The intra-individual variability calculated with mean CV of  $t_{1/2}$  was 4.9% (SD: 0.03; range 1.0–11.3%). A corrected mean intra-individual CV of 3.5% (SD: 0.03; range 0.6–7.7%) was calculated after the removal of PK estimates evaluated with myPKFiT® version 1.0. Inter-individual CV mean  $t_{1/2}$  among patients was 17.2% (19.5% if restricted to myPKFiT® version 2.0).

The clinical variables and PK parameters of each patient before PK-based tailoring are summarised in Table 2. The PK parameters with two patients receiving OD treatment during this period were not analysed (#7, #10). A significant association between AJBR and categorized  $t_{1/2}$  was noted (P = 0.010, Table 3A). Similar results were observed when AJBR was categorized as zero against  $\geq 1$  joint bleed and compared with the categorized  $t_{1/2}$  (P = 0.001, Table 4A). Joint bleeds in four patients were related to low TL48 and short  $t_{1/2}$  (#1, #8, #11, #21). Patients #6 and #15 suffered one joint bleed with long  $t_{1/2}$  and were not related to arthropathy. However, in two patients with severe arthropathy and with HJHS  $\geq 40$  joint bleeds were reported, whereas their estimated TL and  $t_{1/2}$  were appropriate (#13, #19). If these two patients were excluded from the analysis, the association between AJBR and  $t_{1/2}$  was maintained (P = 0.013; Table 3B), and the  $\chi^2$  test reproduced the relationship between joint bleeds and short  $t_{1/2}$  (P = 0.003; Table 4B).

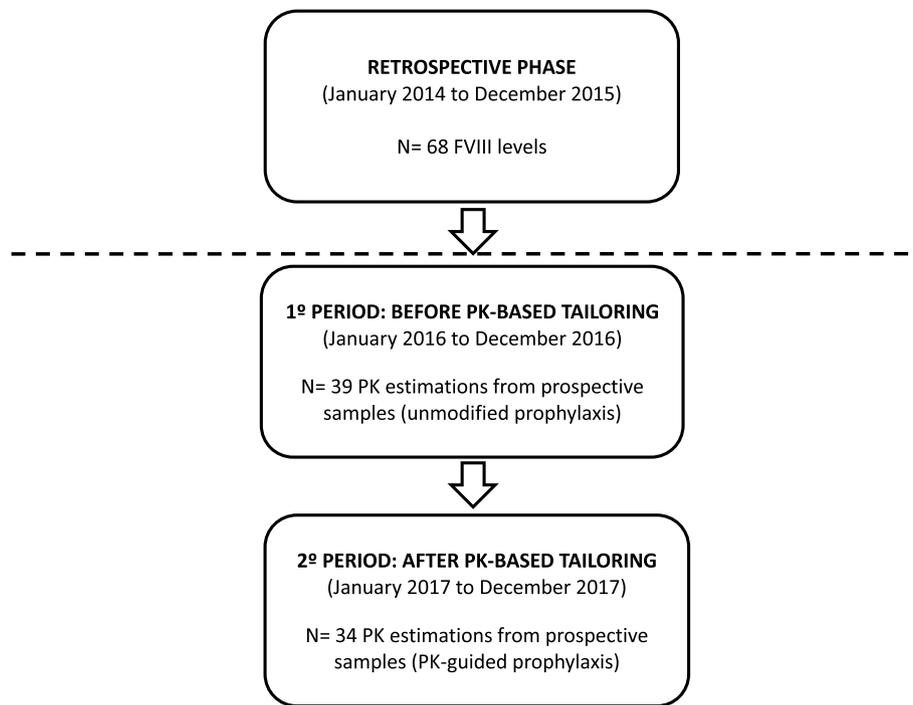


Fig. 1. Diagram of the study design and the distribution of the study phases.

When we compared short against normal or long  $t_{1/2}$  we observed associations between short  $t_{1/2}$  and AJBR, and provoked bleeds ( $P = 0.012$ ,  $P = 0.024$ ; Table 3C), and a trend to higher ABR ( $P = 0.057$ ). Furthermore, dose/kg/week was related to the  $t_{1/2}$ , showing higher doses in patients with short  $t_{1/2}$  than in patients with normal/long  $t_{1/2}$  ( $P = 0.045$ ). The influence of short  $t_{1/2}$  in joint bleeds was more evident when this analysis was repeated combining normal and long  $t_{1/2}$  ( $P = 0.012$ ; Table 4C).

The analysis of categorized AJBR found that patients with joint bleeds had lower weight and more dose/kg/week than patients with zero joint bleeds ( $P = 0.039$ ,  $P = 0.032$ , Table 5). A similar trend was reported with Vss ( $P = 0.068$ ), another variable related to weight. No associations were shown with  $t_{1/2}$ , despite lower median  $t_{1/2}$  being observed in patients with AJBR  $\geq 1$  (11.7 vs. 14 h), especially after withdrawal of the two patients with severe arthropathy.

After one year of follow-up, treatment was adapted in the clinical

Table 1  
Baseline characteristics of the patients included in the study.

Patient #	Age (years)	Weight (kg)	Severity	Coinfection	Mutation	Regimen	Dose (IU/kg/week)	Dosing frequency (IU)	HJHS
1	25	53	Severe	No	INTRON-24 c.6723 + 1G > A	P	75.5	2000 (T/F)	14
2	44	56	Severe	HIV/HCV	EXON-24 c.6682C > T (p.R2228*)	P	71.4	2000 (M/TH)	5
3	36	83	Severe	HIV/HCV	EXON-17 c.5815G > A (p.Ala1939Thr)	P	72.3	3000 (T/S)	21
4	30	76	Severe	No	EXON-17 c.5815G > A (p.Ala1939Thr)	P	65.8	2500 (T/S)	33
5	16	67	Severe	No	INTRON-22 inversion	P	67.2	1500 (M/W/F)	0
6	29	63	Severe	No	INTRON-22 inversion	P	79.4	1500/1500/2000 (M/W/F)	7
7	33	88	Severe	No	EXON-24 c.6682C > T (p.Arg2228Ter)	OD	NA	OD	5
8	14	50	Severe	No	EXON-14 c.4841_4841delA (p.K1614Rfs*7)	P	90.0	1500 (M/W/F)	0
9	37	97	Moderate	No	EXON-15 c.5286 T > A (p.F1762 L)	P	28.9	2000/120H	36
10	28	78	Severe	No	EXON-14 c.4450_4450delA (p.S1484Vfs*83)	OD	NA	OD	6
11	46	63.5	Severe	HIV/HCV	EXON-14 c.4428_4431delAGAG (p.E1477Lfs*89)	P	82.7	1500/48H	24
12	28	70	Severe	No	INTRON-22 inversion	P	50.0	1000–1500-1000 (T/TH/SU)	7
13	68	60	Severe	HCV	EXON 15–22 large deletion	OD	NA	OD	40
14	32	149	Severe	HCV	EXON-8 c.1263_1264insC (p.D422Rfs*2)	P	60.4	3000 (M/W/F)	15
15	37	83	Severe	No	INTRON-22 inversion	P	57.2	2250–2500 (W/S)	15
16	35	70	Severe	No	EXON-18 c.5879G > A (p.R1960Q)	P	53.6	1750–2000 (T/F)	12
17	18	66	Severe	No	EXON-13 c.1990C > G (p.Q664E)	P	75.8	1500–1500-2000 (M/W/F)	11
18	41	72	Severe	HIV/HCV	INTRON-22 inversion	P	62.5	1500 (M/W/F)	21
19	49	75	Severe	HIV/HCV	INTRON-22 inversion	P	80.0	2000 (M/W/F)	44
20	46	78	Severe	HIV/HCV	EXON-21 c.6243G > A (p.W2081*)	P	41.7	1500–1750 (W/S)	39
21	23	53	Severe	No	EXON-14 c.4895_4895delT (p.I1632Kfs*10)	P (OD)	84.9	1500 (M/W/F)	15

HCV, hepatitis C virus; HIV, human immunodeficiency virus; HJHS, Haemophilia Joint Health Score; IU, international units; NA, not applicable; OD, on-demand; P, prophylaxis. Dosing frequency: M/TH, Monday/Thursday; M/W/F, Monday/Wednesday/Friday; T/F, Tuesday/Friday; T/S, Tuesday/Saturday; T/TH/SU, Tuesday/Thursday/Sunday; W/S, Wednesday/Saturday.

**Table 2**  
Characteristics, clinical variables and pharmacokinetic parameters before PK-based tailoring.

Patient #	Weight (kg)	Dose (IU/kg/week)	Dosing frequency (IU)	Physical activity	Consumption (IU/year)	Adherence index (%)	Cl (mL/h/kg)	V <sub>ss</sub> (mL/kg)	t <sub>1/2</sub> (h)	TL48 (IU/dL)	TL72 (IU/dL)	TT1% (h)	AJBR	Other MSK bleeds	ABR	SP/PR
1	53	69.8	2000 (T/F); 1500 (T/F) since 13/09/16	Swimming 2–3 TAW	132,443	68.6	4.0	50	10.2	0.8	< 0.5	57	1 (R. Ankle)	0	1	1/0
2	56	71.4	2000 (M/TH)	Walking > 1 h every day	187,843	90.0	2.8	50	14.4	5.5	1.7	83	0	0	0	0/0
3	83	72.3	3000 (T/S)	Swimming 3 TAW, Cycling 2 TAW	313,934	100.3	2.7	50	14.8	6.1	2	86	0	0	0	0/0
4	76	65.8	2500 (T/S)	Swimming 3–4 TAW	205,417	78.7	1.8	50	21.6	12	5.9	127	0	0	0	0/0
5	67	67.2	1500 (M/W/F) <sup>a</sup>	Cycling + Hiking 2–3 TAW	193,612	82.5	3	50	13.2	2.6	< 0.5	66	0	1 (Pain & edema L. Ankle)	1	1/0
6	63	79.4	1500/2000 (M/W/F)	Sedentary	263,893	101.1	2.6	50	15.2	4.6	1.5	81	1 (R. Elbow)	0	1	1/0
7	88	NA	OD	Home exercises	57,000	NA	NA	NA	NA	NA	NA	NA	0	2 (Trunk/ Superior limbs)	2	2/0
8	50	90.0	1500 (M/W/F)	Basketball 2 TAW	204,041	86.9	3.9	60	11.6	3.1	< 0.5	67	1 (Finger R. Foot)	0	1	1/0
9	97	28.9	2000/120H	Walking and Cycling	158,107	108.2	2.4	40	14.6	4.1	3 <sup>b</sup>	77	0	1 (Sinovitis R. Ankle)	1	1/0
10	78	NA	OD	Sedentary	24,000	NA	NA	NA	NA	NA	NA	NA	3 (Finger R. Foot/ R. Wrist/ R. Ankle)	0	3	3/0
11	63.5	82.7	1500/48H	Swimming 6 TAW, Gym	284,474	103.8	3.8	50	11	1.7	< 0.5	56	0	0	1	0/1
12	70	50.0	1000–1500-1000 (T/TH/SU)	Sedentary	176,839	96.8	3.3	50	12.6	2.3	< 0.5	63	0	0	0	0/0
13	60	52.6	OD; 1500 (T/F) since 09/05/16	Sedentary	177,716	175.7	2.1	50	18.5	15.2	4.6	112	4 (L. Knee/R. Ankle/ R. Knee/R. Ankle)	0	4	4/0
14	149	60.4	3000 (M/W/F)	Sedentary	435,017	92.6	3.8	50	11.1	1.5	0.9	53	0	0	0	0/0
15	83	57.2	2250–2500 (W/S)	Swimming 1 TAW,	184,953	74.6	2.2	50	16.5	9.4	3.4	101	1 (L. Ankle)	0	1	1/0

(continued on next page)

Table 2 (continued)

Patient #	Weight (kg)	Dose (IU/kg/week)	Dosing frequency (IU)	Physical activity	Consumption (IU/year)	Adherence index (%)	CI (mL/h/kg)	Vss (mL/kg)	t <sub>1/2</sub> (h)	TL48 (IU/dL)	TL72 (IU/dL)	T1% (h)	AJBR	Other MSK bleeds	ABR	SP/PR
16	70	53.6	1750–2000 (T/F)	cycling 2 TAW Walking 4 TAW	195,670	100	3	50	13.2	8.4	5.9	71	0	0	0	0/0
17	66	75.8	1500–1500-2000 (M/W/F)	Sedentary	215,463	82.6	3	50	12.2	3.2	1.3	68	0	0	0	0/0
18	72	62.5	1500 (M/W/F)	Bowling 1 TAW, home exercises 4	237,804	101.3	2.8	50	14	3	0.8	70	0	0	0	0/0
19	75	80.0	2000 (M/W/F)	TAW Sedentary	361,133	115.4	2.6	50	14.8	5.5	1.8	84	1 (L. Ankle)	0	1	0/1
20	78	41.7	1500–1750 (W/S)	Sedentary	184,611	108.9	2.9	50	14.3	2.8	1.6	69	0	0	0	0/0
21	53	84.9	1500 (M/W/F) <sup>c</sup>	Sedentary	76000 <sup>b</sup>	32.4 <sup>b</sup>	3.8	60	11.8	3	< 0.5	66	3 (R. Elbow/L. Knee/R. Elbow)	0	3	2/1
Median (IQR)	70.0 (61.5–80.5)	67.2 (53.6–79.4)	3 doses per week	NA	193,612 (167473–250,848.5)	96.8 (82.5–103.8)	2.9 (2.6–3.8)	50 (50–50)	14.0 (11.8–14.8)	3.2 (2.6–6.1)	1.3 (< 0.5–2.0)	70 (66–84)	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–0)

ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; CI, clearance; IQR, interquartile range; IU, international units; MSK, musculoskeletal; NA, not applicable; OD, on-demand; PR, provoked; SP, spontaneous; t<sub>1/2</sub>, half-life; T1%, time to reach rFVIII < 1%; TAW, times a week; TL48, trough level at 48 h; TL72, trough level at 72 h; Vss, steady state volume.

Dosing frequency: M/TH, Monday/Thursday; M/W/F, Monday/Wednesday/Friday; T/F, Tuesday/Friday; T/S, Tuesday/Saturday; T/TH/SU, Tuesday/Thursday/Sunday; W/S, Wednesday/Saturday.

<sup>a</sup> Patient non completely adherent to prophylaxis, who reported that sometimes administered rFVIII 2 times a week.

<sup>c</sup> Patient with moderate haemophilia and baseline FVIII levels of 3.0 IU/dL.

<sup>b</sup> Patient non-adherent to prophylaxis, with limited infusions OD most of the year and low rFVIII consumption.

**Table 3**  
Comparisons between half-life categorized and clinical variables using Kruskal-Wallis test at two periods of PK study.

Clinical Variables	3A) Half-life categorized in short/normal/long (after excluding OD)						3B) Half-life categorized in short/normal/long (cohort after excluding OD and severe arthropathy)						3C) Half-life categorized in short/normal/long (cohort after excluding OD and severe arthropathy, n = 17)					
	First period: before PK-based tailoring (n = 19)			Second period: after PK-based tailoring (n = 21)			First period: before PK-based tailoring (n = 17)			Second period: after PK-based tailoring (n = 19)			First period: before PK-based tailoring (n = 17)			Second period: after PK-based tailoring (n = 19)		
	Short t <sub>1/2</sub>	Normal t <sub>1/2</sub>	Long t <sub>1/2</sub>	P-value	Short t <sub>1/2</sub>	Normal t <sub>1/2</sub>	Long t <sub>1/2</sub>	P-value	Short t <sub>1/2</sub>	Normal t <sub>1/2</sub>	Long t <sub>1/2</sub>	P-value	Short t <sub>1/2</sub>	Normal t <sub>1/2</sub>	Long t <sub>1/2</sub>	P-value		
Age (years)	25	36	36.5	0.272	25	34	36.5	0.213	25	33	36	0.603	25	33	36	0.503		
Weight (kg)	53	70	75.5	0.236	54	71.8	75.8	0.101	54.5	71.5	81	0.204	54.5	71.5	81	0.101		
HJHS	15	11.5	27	0.246	15	9	27	0.181	15	7	21	0.789	15	7	21	0.181		
Dose (IU/kg/week)	82.7	69.8–84.9	58.1	0.062	83.9	62.1–84.7	76.8	0.277	83.3	60.5	65.4	0.071	83.3	60.5	65.4	0.277		
Consumption (IU/year)	204,041	132,443–284,474	190,727.5	0.426	249,500	151,431–270,269	227,451	0.230	249,500	151,431–270,269	174,528	0.411	249,500	151,431–270,269	174,528	0.230		
Adherence index (%)	86.9	68.6–92.6	98.4	0.327	97.6	92.1–98.7	98.4	0.834	97.6	88.9	92.3	0.331	97.6	88.9	92.3	0.834		
AJBR	1	0	1	0.010	1	0	0.5	0.422	1	0	0	0.013	1	0	0	0.422		
ABR	1	0	1	0.104	1	0	0.5	0.427	1	0	0	0.125	1	0	0	0.427		
Spontaneous bleeds	1	0	0.5	0.359	0	0	0	0.627	0	0	0	0.363	0	0	0	0.627		
Provoked bleeds	0	0	0	0.173	0	0	0	0.788	0	0	0	0.077	0	0	0	0.788		
Age (years)	25	36	36.5	0.316	25	34	36.5	0.286	25	33	36	0.603	25	33	36	0.503		
Weight (kg)	53	70	75.5	0.091	54.5	71.8	75.8	0.064	54.5	71.5	81	0.204	54.5	71.5	81	0.101		
HJHS	15	11.5	27	0.874	15	9	27	0.889	15	7	21	0.789	15	7	21	0.181		
Dose (IU/kg/week)	82.7	69.8–84.9	58.1	0.045	83.9	62.1–84.7	76.8	0.116	83.3	60.5	65.4	0.071	83.3	60.5	65.4	0.277		
Consumption (IU/year)	204,041	132,443–284,474	190,727.5	1.0	249,500	151,431–270,269	182,304	0.355	249,500	151,431–270,269	174,528	1.0	249,500	151,431–270,269	174,528	0.355		
Adherence index (%)	86.9	68.6–92.6	98.4	0.246	97.6	92.1–98.7	98.4	0.547	97.6	88.9	92.3	0.246	97.6	88.9	92.3	0.547		
AJBR	1	0	1	0.012	1	0	0.5	0.213	1	0	0	0.012	1	0	0	0.213		

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**Table 5**  
Results of the analysis of clinical variables and PK parameters with the presence or absence of joint bleeds at two periods of PK study.

Variables	First period: before PK-based tailoring						Second period: after PK-based tailoring					
	N	Zero joint bleeds		1 or more joint bleeds		P-value	N	Zero joint bleeds		1 or more joint bleeds		P-value
		Median	IQR	Median	IQR			Median	IQR	Median	IQR	
Age (years)	21	34	29–39	29	25–46	0.972	21	34	29.5–42.5	28	23–37	0.455
Weight (kg)	21	74	68.5–85.5	63	53–75	<b>0.039</b>	21	71.8	64.5–79.5	66	54.5–76	0.303
HJHS	21	13.5	6–27	15	7–24	0.722	21	13.5	7–22.5	15	6–36	0.887
Dose (IU/kg/week)	19	62.5	51.8–69.3	79.7	63.5–83.8	<b>0.032</b>	21	68.4	57.9–77.6	60.5	57.2–80.0	0.776
Consumption (IU/year)	21	194,641	180,725–226,633.5	184,953	132,443–263,893	0.619	21	196,947	174,264–263,869.5	170,000	121,434–185,157	0.177
Adherence index (%)	19	96.8	86.3–100.8	94.0	71.6–109.6	0.869	21	98.1	79.7–99.0	92.1	72.4–105.5	0.776
Cl (mL/h/kg)	19	2.9	2.8–3.0	3.2	2.4–3.9	0.678	21	3.1	2.7–3.3	2.9	2.4–3.7	0.858
Vss (mL/kg)	19	50	50–50	50	50–55	0.068	21	50	50–50	50	50–60	0.496
t <sub>1/2</sub> (h)	19	14	12.9–14.5	13.3	11.3–15.9	0.863	21	13.6	12.5–15	13.7	11.8–15.5	0.887
t <sub>1/2</sub> (h) <sup>a</sup>	17	14	12.9–14.5	11.7	11–15.2	0.269	19	13.6	12.5–15	13.3	11.6–14.2	0.583
TL48 (IU/dL)	19	3.2	2.7–5.9	3.9	2.4–7.5	0.869	21	4	2.5–7	3.9	2.9–5.7	0.972
TL72 (IU/dL)	13	1.6	1.3–2.0	2.6	1.7–4.0	0.353	15	2	1.3–2.4	1.7	1.2–3.4	0.594
T1% (h)	19	70	67–80	74	61.5–92.5	0.967	21	67	63.5–87.5	74	65–87	0.722

Cl, clearance; HJHS, Haemophilia Joint Health Score; IQR, interquartile range; IU, international units; t<sub>1/2</sub>, half-life; T1%, time to reach rFVIII < 1%; TL48, trough level at 48 h; TL72, trough level at 72 h; Vss, steady state volume.

<sup>a</sup> After excluding cohort after excluding 2 patients with severe arthropathy. Results with statistical significance are in bold.

setting according to patients' behaviour and PK estimations, and variables were measured again (Table 6). After PK-based tailoring we estimated the PK parameters for all the patients, after the switch of the two OD treatments to prophylaxis. The association between joint bleeds and t<sub>1/2</sub> disappeared in this period (Table 3), as well as the associations between joint bleeds, weight, and dose/kg/week (Table 5).

No significant associations were obtained when the two periods were compared (Table 7). Despite this, several relevant changes in dosage, PK parameters, and clinical variables were reported (Tables 2 and 6). Considering the individual PK profile, seven modifications in dosing frequency were performed after PK-based tailoring: dosage was increased for three patients (#1, #8, #13), dosage was reduced for one patient (#5), two patients with OD treatment initiated prophylaxis (#7, #10), and an OD treatment was reintroduced for convenience in an HA moderate patient (#9) with non-bleeding phenotype and previous prophylaxis every 5 days. The other patients did not require modifications in their prophylaxis.

A relevant increase in AI was obtained in four patients (#1, #7, #8, #14), whereas the majority of patients showed similar adherence in both periods. Four patients who suffered bleeds reported high consumption and AI > 105% at the first period (#9, #13, #19, #20) had decreased AI and consumption after based tailoring. Further, we detected three non-adherent patients (#7, #10, #21, AI < 50%), patients who had previously rejected prophylaxis. Moreover, lower rFVIII consumption was reported in fifteen patients (median reduction of annual FVIII consumption: 10611 IU; IQR = 6423–19,001). Regarding physical activity, improvements of at least 1 day of weekly physical activity frequency were reported in five patients during the second year (#1, #3, #4, #5, #11). PK profile was employed as an educational tool to adjust physical activity for patient #5. Although PK parameters were similar in both periods, we observed an increase in t<sub>1/2</sub> (mean 0.3 h; range 0.1–0.7 h) and TL48 (mean 0.2 IU/dL; range 2.3–0.2 IU/dL) in nine patients, and a decrease in t<sub>1/2</sub> in five patients, but only two of them had reduced TL48.

Analysing bleeding episodes, in fifteen patients similar AJBRs were registered in both periods, whereas AJBRs were reduced in three patients (#6, #10, #11) and increased in another three (#5, #9, #19). These findings were reproduced with ABR: fourteen patients had the same number of bleeding episodes, four had fewer (#6, #7, #10, #11) and three experienced more bleeding episodes (#5, #8, #19). A tendency to fewer spontaneous bleeds was observed after PK-guided

prophylaxis in five patients (#1, #6, #7, #10, #15; P = 0.08; Table 7). In contrast, a higher number of provoked bleeds was reported in six patients (#1, #5, #8, #10, #15, #19).

#### 4. Discussion

Personalised medicine has been proposed as a new approach in a large number of diseases, including haemophilia [30]. In this study, we analysed whether the adoption of PK estimates in the clinical setting resulted in clinical improvement in our cohort of severe and moderate HA patients on prophylaxis with Advate®.

The standard prophylaxis based on weight or IVR, and adjusted by bleeding phenotype, may result in underdosing (ineffective and unsafe prophylaxis) in some patients or overdosing (waste of resources). The use of PK should contribute to identifying the best prophylaxis regimen. The justification for performing an individual PK for each patient is relevant inter-individual variability, > 30% in some studies [7,17,31]. In our cohort, we obtained a relevant inter-individual CV of 17.2% in mean t<sub>1/2</sub>, whereas the intra-individual CV was relatively low (4.9%). In addition, the differences reported with myPKFit® version 2.0, showing lower intra-individual and higher inter-individual CV, demonstrated that in version 2.0 the influence of patient rFVIII levels was higher than the population model in comparison to the previous version.

The novelty that our study provides is the integrated management of all the factors that can modify the success of prophylaxis, not just the individualised PK. The inclusion of only adult patients avoided the discrepancies in PK parameters between adults and children. The t<sub>1/2</sub> is lower in children, related to higher FVIII clearance, lower in vivo recovery and lower VWF levels [32]. Previous published experience using myPKFit® suggested the potential benefits to tailoring prophylaxis [23,24,33] are to help in patient's education and adherence [23], reduce costs [24] and help in physical activity monitoring [33]. Only a recent cohort of 36 severe HA patients demonstrated a clinical benefit of PK-driven prophylaxis, but no differences in FVIII consumption were observed [34].

A clear association between joint bleeds and t<sub>1/2</sub> was observed during before PK-based tailoring. We detected two different kinds of patients with joint bleeds. Patients with short t<sub>1/2</sub> were more prone to bleeding, because they were exposed to higher periods of time with rFVIII plasma levels < 1 IU/dL [5,6], and PK-guided prophylaxis would

**Table 6**  
Characteristics, clinical variables and pharmacokinetic parameters after PK-based tailoring.

Patient #	Weight (kg)	Dose (IU/kg/week)	Dosing frequency (IU)	Physical activity	Consumption (IU/year)	Adherence index (%)	Cl (mL/h/kg)	V <sub>ss</sub> (mL/kg)
1	54.5	57.8	1500 (T/F); 1500/2000 (T/F) since 05/09/17	Sedentary	151,431	92.1	4.0	50
2	56	71.4	2000 (M/TH)	Walking > 1 h every day	174,528	83.6	2.5	50
3	81	74.1	3000 (T/S)	Gym and Swimming 4 TAW	307,164	98.1	3.1	60
4	76.5	65.4	2500 (T/S)	Cycling every day 1 h	197,432	75.7	1.8	50
5	66	60.5	1500 (M/W/F); 2000 (M/TH) since 05/01/17	Gym 4 TAW	185,157	88.9	3.1	60
6	63	79.4	1500/1500/2000 (M/W/F)	Sedentary	257,470	98.7	2.5	50
7	95	94.7	3000 × 3 times at week	Home exercises	81000 <sup>a</sup>	17.2 <sup>a</sup>	2.9	50
8	54	83.9	1500 (M/W/F); 2000/1500/1500 (M/TH/S) since 27/11/17	Basketball 2 TAW	249,500	105.5	4.2	70
9	99	28.3	2000/120H; 3000 OD since 12/05/17 <sup>b</sup>	Walking and Cycling	121434 <sup>b</sup>	92.3 <sup>b</sup>	2.4	40
10	76	26.3	2000 × 2 times at week <sup>a</sup>	Sedentary	32500 <sup>a</sup>	11.1	2.9	50
11	62	84.7	1500/48H	Swimming every day, gym, walking	270,269	98.7	3.9	60
12	71.5	49.0	1000–1500–1000 (T/TH/SU)	Sedentary	18,625	100	3.3	50
13	57	80.0	1500 (T/F); 2000 (M/W/F) since 23/06/17	Sedentary	340,113	143	2.1	50
14	145	62.1	3000 (M/W/F)	Sedentary	458,122	97.6	3.3	40
15	83	57.2	2250–2500 (W/S)	Swimming 1 TAW, cycling 2 TAW	179,452	72.4	2.2	50
16	70	53.6	1750–2000 (T/F)	Walking 4 TAW	191,676	98	3.2	50
17	66	75.8	1500–1500–2000 (M/W/F)	Sedentary	196,462	75.3	3.1	50
18	72	62.5	1500 (M/W/F)	Bowling 1 TAW, home exercises 4 TAW	233,012	99.2	3.1	50
19	75	80.0	2000 (M/W/F) <sup>c</sup>	Sedentary	170000 <sup>c</sup>	112.7	2.6	50
20	78	41.7	1500–1750 (W/S) <sup>d</sup>	Sedentary	174000 <sup>d</sup>	102.6	2.9	50
21	53	84.9	1500 (M/W/F) <sup>a</sup>	Sedentary	59000 <sup>a</sup>	25.1	3.7	60
Median (IQR)	71.5 (59.5–79.5)	65.4 (55.4–80.0)	3 doses per week	NA	185,157 (136432–253,485)	97.6 (75.5–99.6)	3.1 (2.5–3.3)	55 (50–55)

Patient #	t <sub>1/2</sub> (h)	TL48 (IU/dL)	TL72 (IU/dL)	T1% (h)	AJBR	Other MSK bleeds	ABR	SP/PR
1	10.2	0.8	< 0.5	57	1 (R. Shoulder)	0	1	0/1
2	14.5	7.0	2.2	88	0	0	0	0/0
3	15.5	6.2	2.0	87	0	0	0	0/0
4	20.8	12.3	5.5	123	0	0	0	0/0
5	13.3	3.7	1.1	72	3 (L. Elbow/Finger/R. Shoulder)	0	3	1/2
6	15.9	6.9	2.4	92	0	0	0	0/0
7	13.8	4.9	1.3	77	0	0	0	0/0
8	11.8	2.9	< 0.5	65	1 (R. Forearm)	1 (Hematoma L. Arm)	2	1/1
9	14.6	4.1	3.0 <sup>b</sup>	77	1 (L. Ankle)	0	1	1/0
10	13.7	3.9	1.2	74	1 (R. Knee)	1 (Psoas hematoma)	2	1/1
11	11.3	1.9	< 0.5	58	0	0	0	0/0
12	12.6	2.3	< 0.5	63	0	0	0	0/0
13	18.8	10.5	4.3	111	4 (4 episodes in R. Knee)	0	4	4/0
14	11.0	1.5	0.9	54	0	0	0	0/0
15	16.5	9.4	3.4	101	1 (R. Ankle)	0	1	0/1

(continued on next page)

Table 6 (continued)

Patient #	t <sub>1/2</sub> (h)	TL48 (IU/dL)	TL72 (IU/dL)	T1% (h)	AJBR	Other MSK bleeds	ABR	SP/PR
16	12.7	7.7	5.0	66	0	0	0	0/0
17	12.4	2.7	1.3	64	0	0	0	0/0
18	13.3	3.0	< 0.5	66	0	0	0	0/0
19	15.5	5.7	2.0	87	2 (L. Ankle)	0	2	0/2
20	14.3	2.8	1.4	68	0	0	0	0/0
21	11.4	2.3	< 0.5	61	3 (R. Elbow/L. Elbow/ R. Knee)	0	3	3/0
Median (IQR)	13.7 (12.1–15.5)	3.9 (2.5–7.0)	2.0 (< 0.5–2.3)	72 (63.5–87.5)	0 (0–1)	0 (0–0)	0 (0–2)	0 (0–1)/0 (0–1)

ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; CI, clearance; IQR, interquartile range; IU, international units; MSK, musculoskeletal; NA, not applicable; OD, on-demand; PR, provoked; SP, spontaneous; t<sub>1/2</sub>, half-life; T1%, time to reach rFVIII < 1%; TAW, times at week; TL48, trough level at 48 h; TL72, trough level at 72 h; Vss, steady state volume.

Dosing frequency: M/TH, Monday/Thursday; M/W/F, Monday/Wednesday/Friday; T/F, Tuesday/Friday; T/TH/SU, Tuesday/Thursday/Sunday; W/S, Wednesday/Saturday.

<sup>a</sup> Patient non-adherent to prophylaxis, with limited infusions OD most of the year and low rFVIII consumption.

<sup>b</sup> Patient moderate (baseline FVIII levels of 3.0 IU/dL) with non-bleeding phenotype with 1 dose every 5 days who prefer to come back to OD treatment increasing the medical visit frequency.

<sup>c</sup> Patient with rFVIII prophylaxis until 30/05/17, when switch to clinical trial to non-substitutive therapy. The consumption, adherence index, PK parameters and bleeding rates have been calculated only during the rFVIII prophylaxis.

<sup>d</sup> Patient with rFVIII prophylaxis until 11/12/17, when switch to clinical trial to non-substitutive therapy. The consumption, adherence index, PK parameters and bleeding rates have been calculated only during the rFVIII prophylaxis.

be adequate. On the other hand, severe arthropathy has been demonstrated to be a risk factor for joint bleeds in two cases, despite appropriate t<sub>1/2</sub> and TL. Furthermore, patients with bleeds, arthropathy, and long t<sub>1/2</sub> were older than patients with bleeds and short t<sub>1/2</sub> (median age 49 vs. 24 years). In vitro studies suggested that joints in older patients were less vulnerable to break-through bleeds than those in young haemophiliacs [35–37]. Associations between short t<sub>1/2</sub> and AJBR were reproduced after withdrawal of the two patients with advanced arthropathy. Similar findings were observed with AJBR and ABR comparing short against normal/long t<sub>1/2</sub>. Moreover, short t<sub>1/2</sub> and joint bleeds were associated with lower weight and higher values of dose/kg/week. A possible cause is that the patients with short t<sub>1/2</sub> and joint bleeds were younger and less adherent, with lower weight and higher dose/kg/week in proportion than patients with zero bleeds and normal/long t<sub>1/2</sub>. Further, this association reflects the use of standard prophylaxis based on body weight and modified by bleeding episodes before PK-guided prophylaxis.

After PK-based tailoring, associations between joint bleeds and t<sub>1/2</sub>, weight, and dose/kg/week disappeared. This change could be related to the adoption of PK-driven prophylaxis replacing a standard prophylaxis based on body weight and bleeding phenotype. This observation was repeated when we compared the clinical variables and PK parameters of the two years without significant relationships. Although the majority of the patients maintained their dosing frequency, two changes were performed during before PK-based tailoring, and seven changes and one educational intervention were performed after PK individualization. This approach is especially useful in patients with short t<sub>1/2</sub>, however a better knowledge of the PK profile could help to tailor prophylaxis, although it is not essential in all patients.

Despite the absence of statistical significance, probably related to the small sample size, we observed slight improvements in clinical outcomes after PK-based tailoring. The measurement of adherence was affected by over-consumer patients with bleeds and non-adherent patients (two of them only included in the second period). Median rates of AI were elevated in both periods (96.8 and 97.6%), and higher than in previous studies (89–64%) [6,29], but the influence of adherence on bleeding risk was not reproduced. Furthermore, the use of AI based on pharmacy dispensary data and hospital infusion records did not necessarily reflect adherence objectively. Similarly, the physical activity of the patients was not objectively measured and it was not included in the statistical analysis. A trend to lower rFVIII consumption was observed with PK-driven prophylaxis, in accordance with previous reports [22,24,27].

No differences were observed in PK parameters between the two periods studied. It may be that myPKFiT<sup>®</sup> employed all the available samples of each patient for creating the simulations, increasing the influence of individual FVIII levels compared to the population model. We could not compare PK estimates obtained before and after tailoring treatment, as the estimations done after also included measurements taken before. Recently, the ISTH has recommended using a 2–3 samples protocol (at 4–8, 16–28, and 40–60 h) and combining time points from multiple infusions in PK estimates [38,39]. Including a large number of PK samples could explain why we obtained a small inter-individual CV and no differences between periods.

The most clinically-relevant change observed with PK-tailored prophylaxis was the reduction of the spontaneous bleed rate, whereas the rate of provoked bleeding showed a trend to higher values. However, ABR and AJBR were similar in both periods, because these ratios included spontaneous and provoked bleeds and were inverted in these two years. The previous reports of PK-driven prophylaxis obtained similar bleeding rates to standard prophylaxis [20,27], and the first experiences with myPKFiT<sup>®</sup> did not analyse bleeding rates [23] or sample sizes were too small to perform statistical analysis [24,33]. Recently, in the largest cohort of severe HA patients individualised with myPKFiT<sup>®</sup>, a significant decrease in ABR and AJBR was obtained after adjustment, especially in patients older than 15 years [34]. These

**Table 7**  
Comparisons between clinical variables and PK parameters of the two periods of PK study (Wilcoxon test).

Variable	N	Before PK-based tailoring		After PK-based tailoring		P-value
		Mean	SD	Mean	SD	
Weight (kg)	21	73.8	21.1	74.0	20.6	0.78
Dose (IU/kg/week)	19	65.6	15.7	65.9	15.7	0.85
Consumption (IU/year)	21	203,331.9	95,315.3	192,778.4	103,660.7	0.48
Adherence index (%)	21	94.8	27.1	92.6	22.5	0.43
Cl (mL/h/kg)	19	3.0	0.6	3.0	0.7	0.58
Vss (mL/kg)	19	50.5	4.0	52.1	7.1	0.19
t <sub>1/2</sub> (h)	19	14.0	2.8	14.0	2.7	0.67
TL48 (IU/dL)	19	5.0	3.8	4.9	3.3	0.85
TL72 (IU/dL)	12	2.7	1.8	2.6	1.5	0.90
T1% (h)	19	76.7	19.2	16.8	19.4	0.87
AJBR	21	0.8	1.2	0.8	1.2	0.82
ABR	21	1.0	1.2	0.9	1.3	0.79
Spontaneous bleeds	21	0.8	1.1	0.5	1.1	0.08
Provoked bleeds	21	0.1	0.4	0.4	0.7	0.14

ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; Cl, clearance; HJHS, Haemophilia Joint Health Score; IQR, interquartile range; IU, international units; SD, standard deviation; t<sub>1/2</sub>, half-life; T1%, time to reach rFVIII < 1%; TL48, trough level at 48 h; TL72, trough level at 72 h; Vss, steady state volume.

associations were in accordance with our results, although the cause of bleeding (spontaneous/provoked) was not analysed. Besides, a study with a fourth-generation rFVIII suggested a reduction in ABR with personalised prophylaxis compared to standard prophylaxis, but adequate statistical analysis was not performed [40].

The benefits of PK-guided prophylaxis previously described [41] and those observed in our study were: better adjustment of dosing frequency and target TL, flexibility and variety in sampling, a more rational basis for the association between rFVIII coverage and bleeding episodes to recommendations for performing physical activity, and a potential reduction in overall costs and weekly doses. The inclusion of patient preferences is the key to achieving the implementation of PK-guided prophylaxis, as a recent survey suggested [42]. Furthermore, we also valued the empowering educational role of PopPK simulations and graphs [23] for our cohort. Along these lines, we are promoting the use of patient reported outcomes and specific programmes for physical activity monitoring [33].

Some limitations of this study should be addressed. First, the sample size was small, although this size could be relevant, taking into account that HA is a rare disease. Second, the heterogeneity of severity of disease, age, and joint status of the HA patients could influence the findings reported and they should be interpreted with caution. Third, the conclusions regarding PK estimates obtained with myPKFIT® are only valid for Advate® [28], although the benefits of PK-driven prophylaxis could be extended to other FVIII. Finally, adherence and rFVIII consumption were measured using pharmacy and hospital records but validated questionnaires (VERITAS-Pro scale) [43] and cost-effectiveness studies were not performed.

In conclusion, we propose a new approach of individualised prophylaxis to include individual PK, clinical variables, and patient convenience in an integrated manner, which allows better control of disease. We reported significant associations between joint bleeds and short t<sub>1/2</sub>, which disappeared after the adoption of personalised prophylaxis, probably related to a reduction in spontaneous bleeds. We did not find that PK-guided prophylaxis was associated with increased consumption of rFVIII. Several ongoing clinical trials and prospective studies with larger populations should validate the available PopPK tools with different FVIII and FIX concentrations (including extended t<sub>1/2</sub> products), clearly demonstrating the clinical benefits of this approach, as well as its positive economic impact.

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#### Author contributions

JM designed, performed, analysed and wrote this paper, SB designed, analysed and corrected this paper, SH, AC and SPA corrected and reviewed this paper, RM, EM, PB, FQ and JLP supported and reviewed this paper.

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