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Biological mechanisms underlying inter-individual variation in factor VIII clearance in haemophilia

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Abstract

Previous studies have highlighted marked inter-individual variations in factor VIII (FVIII) clearance between patients with haemophilia (PWH). The half-life of infused FVIII has been reported to vary from as little as 5.3 hours in some adult PWH, up to as long as 28.8 hours in other individuals. These differences in clearance kinetics have been consistently observed using a number of different plasma-derived and recombinant FVIII products. Furthermore, recent studies have demonstrated that half-life for extended half-life (EHL-) FVIII products also demonstrates significant inter-patient variation. Since time spent with FVIII trough levels <1% has been shown to be associated with increased bleeding risk in PWH on prophylaxis therapy, this variability in FVIII clearance clearly has major clinical significance. Recent studies have provided significant novel insights into the cellular basis underlying FVIII clearance pathways. In addition, accumulating data have shown that endogenous plasma VWF levels, ABO blood group and age, all play important roles in regulating FVIII half-life in PWH. Indeed, multiple regression analysis suggests that together these factors account for approximately 34% of the total inter-individual variation in FVIII clearance observed between subjects with severe haemophilia A. In this review, we consider these and other putative modulators of FVIII half-life, and discuss the biological mechanisms through which these factors impact upon FVIII clearance in vivo.

KEYWORDS

clearance, factor VIII, haemophilia A, pharmacokinetics, von Willebrand factor

1 | INTRODUCTION

Haemophilia A is an X-linked inherited bleeding disorder caused by deficiency or dysfunction of procoagulant factor VIII (FVIII). Approximately 25 in 100 000 male births are affected by haemophilia A.¹ Consequently, there are estimated to be more than 1 million persons with haemophilia worldwide.¹ Patients with severe haemophilia A (PWH) have plasma FVIII <1 IU/dL

(<1% normal). These individuals typically develop spontaneous bleeding in joints and muscles from early childhood which result in progressive musculoskeletal deterioration.² In order to reduce bleeding, patients with severe haemophilia A require regular FVIII replacement treatment. Several studies have confirmed that FVIII prophylaxis reduces the number of spontaneous joint bleeds, thereby significantly attenuating haemophilic arthropathy.²

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Initial FVIII replacement studies first with single donations, and later with FVIII concentrates derived from human plasma, commenced in the 1950s based on the observation that spontaneous haemarthroses were much less common in patients with moderate haemophilia (FVIII 1-5 IU/dL; 1%-5%). Thus, patients with severe haemophilia were treated with the aim of maintaining trough FVIII levels >1%. From the 1990s, availability of recombinant FVIII products with standard half-life and later also modified FVIII with extended half-life enabled targeting higher trough levels of 3%, 5% or even 10%, which could further reduce the likelihood of bleeding and might improve the joint-health status of PWH.^{3,4} Based upon an estimated FVIII plasma half-life of approximately 12 hours, prophylaxis was typically administered as a dose of 25-40 IU/kg three times weekly. Critically however, accumulating data have demonstrated that this 'one size fits all' weight-based approach to haemophilia prophylaxis has inherent limitations.⁵ In particular, it is clear that in vivo clearance of FVIII varies markedly between different PWH.^{6,7} Despite this significant inter-individual variation in FVIII half-life, the mechanisms underlying FVIII clearance have remained poorly defined for many years. Recent studies have provided important insights into the biological mechanisms underpinning physiological and pathological FVIII clearance.^{8,9} In this manuscript, we review the molecular and cellular mechanisms responsible for modulating inter-individual variations in FVIII clearance in PWH, and consider its clinical significance.

1.1 | Inter-individual variation in FVIII clearance between PWH

Numerous pharmacokinetic (PK) studies have consistently demonstrated marked inter-individual variations in FVIII clearance between PWH (Table 1).^{6,10-17} Collectively, these studies suggest that FVIII half-life may vary from as little as 5.3 hours in some PWH, up to as long as 28.8 hours in other individuals. These differences in clearance kinetics have been observed using a number of different plasma-derived and recombinant FVIII products (including full length and B-domain-deleted rFVIII) and appear to be independent of the dose of FVIII administered.¹⁰⁻¹² Moreover, similar inter-individual variations have been observed in studies of PWH from different ethnic and racial origins.¹⁴ FVIII clearance kinetics are significantly more rapid in young children compared to adult PWH.^{16,18} For example, Bjorkman et al¹⁶ found that the terminal half-life of FVIII in children aged 1-6 years was 9.4 hours compared to 11.1 hours in a combined group of adolescents and adults (aged 10-65 years). Nevertheless, significant inter-individual differences in FVIII clearance have also been reported in studies of paediatric cohorts.^{14,15} In contrast, for a given individual patient, FVIII half-life remains relatively consistent during adulthood at least until the age of 40 years.^{6,10,16,19} However, it has been shown that the half-life of infused FVIII is significantly reduced in PWH during acute bleeding episodes and in the perioperative period.²⁰

2 | FACTORS INFLUENCING INTER-INDIVIDUAL VARIATION IN FVIII CLEARANCE

2.1 | VWF levels and binding affinity

Under normal conditions, the majority of plasma FVIII circulates in high affinity complex ($K_d \sim 0.2$ - 0.5 nmol/L) with von Willebrand factor (VWF) (Figure 1).^{8,21} The plasma concentrations of FVIII and VWF are 200 ng/mL (0.8 nmol/L) and 10 μ g/mL (35 nmol/L), respectively. Consequently, under steady-state conditions there is a 50 Molar excess of VWF. In normal individuals, it has been estimated that approximately 95%-97% of FVIII is bound to VWF, whilst the remaining 3%-5% circulates as free FVIII.⁸ Importantly however, this interaction between VWF and FVIII is reversible and exists as a dynamic equilibrium.²² Interaction with VWF plays an important role in protecting FVIII against premature proteolytic degradation and clearance. In the absence of VWF binding, the half-life of free FVIII is reduced approximately sixfold. This enhanced clearance underlies the reduced plasma FVIII levels typically seen in patients with type 2N (characterized by reduced VWF binding to FVIII) or type 3 VWD (almost complete VWF deficiency). Conversely, VWF half-life is not affected by the presence or absence of FVIII.

Given this key role for VWF in regulating FVIII clearance in normal individuals, it is perhaps unsurprising that plasma VWF:Ag levels at time of FVIII treatment correlate with the half-life of infused FVIII. Several studies have demonstrated that FVIII half-life is significantly longer in PWH who have higher endogenous plasma VWF:Ag levels.^{10,12-15,17,21} This effect of VWF levels in regulating FVIII clearance is consistent for both pd- and rFVIII products.^{6,16} For example, in a study of 12 patients Fijnvandraat et al¹⁰ observed a strong correlation between pre-infusion VWF:Ag levels and half-life for a BDD-rFVIII product ($r = .87$; $P = .0003$). Subsequently in a larger cohort of 32 PWH, Vlot et al¹¹ confirmed a positive correlation between VWF:Ag levels and pd-FVIII half-life ($r = .52$; $P = .001$). Using linear regression analysis, the authors estimated that VWF levels accounted for approximately 25% of the total inter-patient variability observed in FVIII half-life.¹¹ Calculations suggest that each increase of 0.1 IU/dL VWF:Ag is associated with an increase of 16.6 (95% CI 9-24) minutes in the half-life of infused FVIII ($P < .01$).¹² Recent paediatric studies have showed that FVIII pharmacokinetics in children with haemophilia A are also significantly influenced by endogenous plasma VWF:Ag levels.^{14,15}

In addition to the importance of pre-infusion plasma VWF:Ag levels in regulating the half-life of FVIII therapy in PWH, recent studies have demonstrated that alterations in the FVIII-binding capacity of VWF may also contribute to inter-individual variations in FVIII clearance. Swystun et al¹⁵ investigated FVIII-binding activity in 43 paediatric PWH. Sequencing of the FVIII-binding region of VWF identified five patients heterozygous for two low-frequency variants (p.Arg826Lys and p.Arg852Glu) both of which were shown to attenuate FVIII binding. Another study suggested that structural elements of the huge VWF protein chains and the degree of multimerization may

TABLE 1 Examples of studies investigating FVIII half-life determinants in PWH

Study	n	Age range	Haemophilia	FVIII product	PK study	Half-life (Average) (h)	Half-life (Range) (h)	Significant determinants
Fijnvandraat et al ¹⁰	12	25-44 y (mean = 32)	Severe	rFVIII	11 time points	12.5	6-28.8	Pre-infusion VWF
Vlot et al ¹¹	32	15-43 y	Severe (n = 30) Mild (n = 2)	pd-FVIII & rFVIII	11 time points	18.2 & 17.6	13.2-23.2; 13.5-21.7	Pre-infusion VWF ABO group Age (P = .08)
van Dijk et al ¹²	42	15-43 y (mean = 28.8)	Severe	pd-FVIII & rFVIII	10 time points	11.8	7.4-20.4	Pre-infusion VWF ABO group Age
Barnes et al ⁶¹	20	4-18 y (mean = 12.8)	Severe (n = 16) Moderate (n = 4)	rFVIII	11 time points 5 time points	10.7	7.8-15.3	Pre-infusion VWF Low titre inhibitors
Fischer et al ¹³	38	10-47 y (mean = 26.3)	Severe	pd-FVIII & rFVIII	10 time points	12.9	7.4-20.4	Pre-infusion VWF ABO group VWF:pp/Ag ratio
Kepa et al ¹⁷	42	24-44 y (median = 25.7)	Severe (n = 37) Moderate (n = 5)	pd-FVIII & rFVIII	11 time points	10	6.2-20.7	Pre-infusion VWF ABO group Age
Chen et al ¹⁴	36	4-16 y (median = 7.8)	Severe	pd-FVIII & rFVIII	5 time points	11.0	5.5-20.0	Pre-infusion VWF ABO group
Swystun et al ¹⁵	43	6-17 y (median = 10.6)	Severe	rFVIII	5 time points	10.4	5.3-18.4	Pre-infusion VWF ABO group VWF:pp/Ag ratio

Abbreviation: n, number.

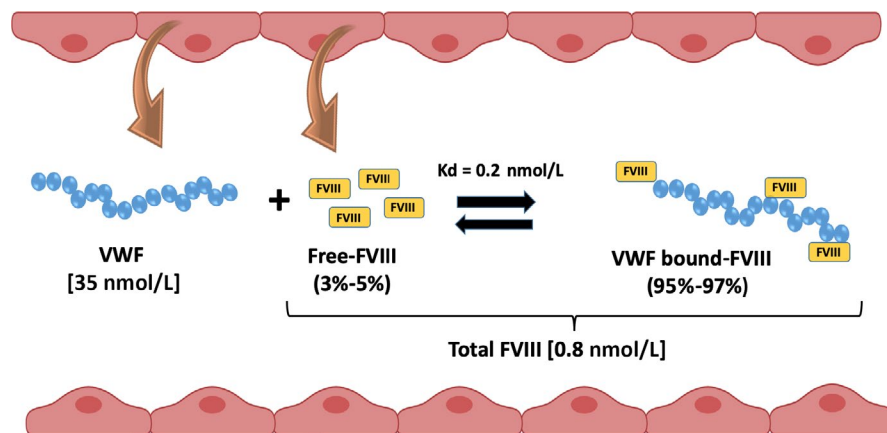


FIGURE 1 FVIII interaction with VWF in normal plasma. VWF and FVIII are both expressed in EC and secreted into plasma. Normal plasma concentrations for VWF and FVIII are 35 and 0.8 nmol/L, respectively. The majority of plasma FVIII (approximately 95%-97%) circulates as part of a high-affinity complex with VWF. Thus, free-FVIII and VWF-bound FVIII exist in dynamic equilibrium [Colour figure can be viewed at wileyonlinelibrary.com]

influence FVIII binding.²³ Collectively, these findings suggest that subtle reductions in the FVIII-binding capacity of endogenous VWF have the potential to lead to enhanced clearance of infused FVIII in PWH.

2.2 | ABO blood group

Although traditionally regarded as red blood cell antigens, the carbohydrate structures that constitute the ABO blood group system (A, B and H determinants) are actually expressed on a number of other tissues and cell types including endothelial cells (EC) and platelets. Recent evidence suggests that the majority of plasma VWF and FVIII are derived from constitutive EC secretion. Prior to this secretion, VWF and FVIII undergo complex post-translational modification that includes significant glycosylation.²⁴ Unlike the vast majority of other plasma proteins, mass spectrometry studies have demonstrated that plasma VWF and FVIII both express covalently linked ABO(H) structures on their glycan structures. This is important because ABO blood group has a major effect on plasma levels of the VWF-FVIII complex. In particular, blood group O individuals have VWF:Ag levels that are approximately 20%-30% lower compared to non-O individuals.²⁵ ABO group has similar effects on plasma FVIII:C levels in normal individuals, although these effects appear to be predominantly mediated via the changes in VWF levels. The mechanism(s) through which ABO blood group influences plasma VWF:Ag levels has not been fully elucidated, but current evidence suggests that VWF clearance is significantly enhanced in group O compared to non-O individuals.²⁶ Interestingly, platelet VWF does not carry AB blood group determinants and levels are not influenced by ABO blood group.²⁷

Given the major effect of plasma VWF:Ag levels in determining the half-life of infused FVIII in PWH, it is perhaps unsurprising that several studies have reported that ABO blood group also influences FVIII pharmacokinetics.^{11,13,17} Vlot et al¹¹ showed that FVIII half-life was significantly reduced in group O PWH compared to group A PWH (15.3 vs 19.7 hours respectively; $P = .003$). Similarly, Fischer et al¹³ observed significantly enhanced FVIII clearance in group O compared to non-O adult PWH (11.5 vs 14.3 hours; $P = .004$). This later study further observed that plasma VWF:Ag levels correlated more strongly with FVIII half-life in non-O compared to group O PWH. Despite the fact that ABO blood group prevalence varies between racial groups,

the ABO effect in modulating FVIII clearance in PWH has been consistently observed in studies that have enrolled a variety of different ethnicities. Finally, although FVIII clearance is significantly faster in children compared to adult PWH,¹⁸ nonetheless an ABO effect on FVIII half-life is still apparent in paediatric PK studies.^{14,15}

2.3 | Age

It is well recognized that plasma VWF:Ag levels increase progressively with age. This observation has been reported in normal individuals, as well as in patients with VWD.^{28,29} Indeed, plasma VWF:Ag levels have been shown to correct into the normal range with advancing age in many patients with mild quantitative VWD.³⁰ Furthermore, significant age-related increases in plasma VWF levels have also been observed in PWH. van Dijk et al¹² demonstrated that every 10-year increase in age in PWH was associated with a 0.16 IU/dL increase in VWF:Ag levels. Interestingly, the age-related increase in plasma VWF:Ag has also been reported to be more marked in non-O compared to group O individuals.²⁸

Since endogenous VWF levels have an effect in regulating infused FVIII half-life in PWH, several groups have investigated whether age may also have an effect. Some inconsistency in results has been observed between studies, which may reflect limited sample numbers, as well as other differences in study design. Nevertheless, a number of studies have reported that FVIII clearance is reduced in older patients.^{11,13,17,19} For example, Vlot et al¹¹ observed a trend towards increased FVIII half-life with age, although this failed to achieve statistical significance ($P = .08$). In addition, Fischer et al¹³ demonstrated a weak positive correlation between age and FVIII half-life on univariate analysis (Pearson rank = 0.5; $P = .028$). More recently, Kepa et al¹⁷ also showed that age had a significant association with FVIII clearance. When patients were grouped into age decades, the authors noted that this age effect was considerably more evident in PWH aged >40 years. Importantly, regression analysis confirmed that the association between age and FVIII clearance was not just attributable to increased VWF levels, as age remained an independent predictor even following correction for VWF. Although the biology

underlying this age-related increase in VWF has not been fully defined, recent data suggest that age may impact upon both the secretion and clearance of VWF.²⁸

2.4 | Additional factors

It is well established that neutralizing high-titre FVIII-specific antibodies in PWH result in the rapid clearance of infused FVIII. These polyclonal antibodies tend to be IgG1 or IgG4 and are high-affinity in nature.³¹ Non-neutralizing anti-FVIII antibodies can also be identified in a significant number of PWH who do not have clinically evident inhibitors.³² These antibodies are commonly IgG1 or IgG3 and bind FVIII with low-to-moderate affinity. In a recent study of 42 adult PWH, Hofbauer et al³³ investigated whether these non-neutralizing FVIII-specific antibodies had any effect on the clearance of infused FVIII. Overall, 15 (37%) of these patients studied were found to have FVIII-binding antibodies with titres $\geq 1:20$. Moreover, in nine of these subjects, the titre of FVIII-specific antibodies was $\geq 1:40$. Interestingly, FVIII half-life was significantly reduced in this cohort with high titre non-neutralizing FVIII-specific antibodies (median 7.8 vs 10.4 hours, respectively; $P = .004$). The effect of the non-neutralizing antibodies was independent of VWF:Ag levels and was estimated to account for 17% of the total inter-individual variability in FVIII half-life.³³

The fact that ABO blood group influences FVIII clearance has led to the suggestion that other blood groups may also be important. Vlot et al¹¹ found that Rhesus phenotype (RhD), a blood group system determined by a protein in the red blood cell membrane, had no effect on FVIII pharmacokinetics in PWH. In contrast, the

Secretor carbohydrate blood group shares some similarities with the ABO system in that it is defined by the presence or absence of specific terminal sugar residues on glycan chains. A number of groups have reported a weak association between Secretor blood group and plasma VWF:Ag levels.^{34,35} Further studies will be required to determine whether this effect on VWF levels translates into a secondary effect on FVIII half-life in PWH. Finally, studies have investigated whether FVIII PK may be influenced by FVIII genotype in PWH.¹⁷ However, no significant difference in FVIII recovery or clearance was observed between patients with *F8* gene inversions, deletions or point mutations, respectively.

3 | CLEARANCE OF FREE-FVIII COMPARED TO VWF-BOUND FVIII

As previously discussed, under normal steady-state conditions, approximately 95%–97% of plasma FVIII circulates bound to VWF.^{8,36} The remaining 3%–5% circulates in plasma as free-FVIII. Consequently, it seems likely that the majority of infused FVIII in PWH will be cleared in complex with endogenous VWF. Importantly, although the amount of free-FVIII in plasma at any particular time point is limited, this fraction of FVIII has a very short in vivo half-life (~2 hours compared to ~12 hours for VWF-bound FVIII). Consequently, as much as 25% of total infused FVIII in PWH may actually be cleared in the form of free-FVIII.³⁷ The relative proportion of infused FVIII cleared as free-FVIII will clearly be highly dependent upon the affinity of the FVIII-VWF-binding interaction (Figure 2).

Recent studies have provided significant insights into the biological pathways involved in regulating the clearance of both free-FVIII and VWF-bound FVIII.^{8,9} These data have demonstrated that

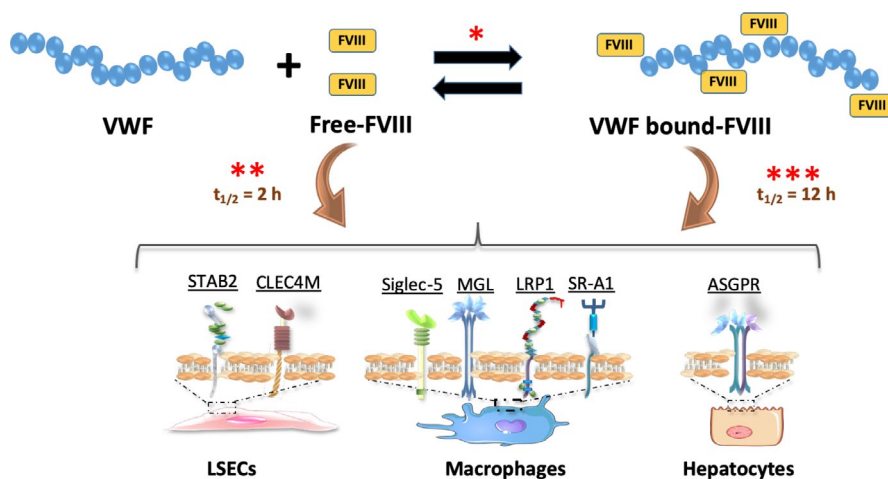


FIGURE 2 Inter-individual variation in FVIII clearance in PWH. Previous studies have highlighted marked inter-individual variations between PWH in terms of clearance rates for infused FVIII therapy. Although recent data have provided important insights into the cellular and receptors involved in the clearance of both free-FVIII and VWF-bound FVIII, the biological mechanisms responsible for the variation in FVIII half-life remain poorly understood. This may be due to (a) variability in the VWF-FVIII-binding affinity*; (b) variation in the clearance of Free-FVIII** and/or (c) variation in the clearance of VWF-bound FVIII***. ASGPR, asialoglycoprotein receptor; CLEC4M, C-type lectin domain family 4 member M; LRP1, low-density lipoprotein receptor-related protein-1; LSECs, liver sinusoidal endothelial cells; MGL, macrophage galactose-type lectin; SR-A1, scavenger receptor class A member I; STAB2, stabilin-2 [Colour figure can be viewed at wileyonlinelibrary.com]



hepatic macrophages and liver sinusoidal EC (LSECs) play key roles in regulating *in vivo* clearance of VWF and FVIII.³⁸⁻⁴⁰ In addition, a number of cell surface receptors have also been implicated in modulating VWF-FVIII-binding interactions.⁹ On macrophages, these include the low-density lipoprotein receptor-related protein-1 (LRP1),⁴¹ the scavenger receptor class A member I (SR-A1)⁴² and the macrophage galactose-type lectin (MGL).⁴³ Additional receptors expressed on LSECs that may be important include stabilin-2 (STAB2)⁴⁰ and C-type lectin domain family 4 member M (CLEC4M).⁴⁴ A number of other miscellaneous receptors have also been reported to bind FVIII *in vitro*. These include the asialoglycoprotein receptor (ASGPR) which is predominantly expressed on hepatocytes, as well as LDLR, CD206, Siglec-5 and heparin sulphate proteoglycans (HSPGs).⁸ Although the relative importance of these different clearance receptors in terms of regulating the clearance of free- and VWF-bound FVIII remains unclear, many of them have been shown to be able to bind and internalize VWF and FVIII. Interestingly, for some of these clearance receptors (eg LRP1 and ASGPR), the ability of FVIII to interact with the receptor is significantly attenuated when FVIII is in complex with VWF.⁸ Nevertheless, significant correlations between some receptor polymorphisms and human FVIII levels have been reported.^{45,46} In addition, Lunghi et al⁴⁷ recently reported that a polymorphism in the LDLR (c.1773C/T) was associated with differences in the initial phase of FVIII distribution in PWH. All together, based on current evidence, it seems that variation in clearance pathways for free- and VWF-bound FVIII is highly likely to contribute to inter-individual variations in FVIII clearance in PWH (Figure 2).^{9,48}

4 | INTER-INDIVIDUAL VARIATIONS IN VWF CLEARANCE PATHWAYS

As detailed above, current findings suggest that VWF represents the most important determinant of inter-individual variation in FVIII clearance in PWH. In keeping with this hypothesis, the effects of ABO blood group and age on FVIII half-life seem to result predominantly via their respective effects upon VWF levels. The observation that pre-infusion plasma VWF:Ag levels positively correlates with FVIII half-life in PWH is interesting. One simple explanation for this correlation would be that in PWH with higher endogenous VWF levels, more infused FVIII therapy is able to bind to VWF.¹³ Consequently, since there is less free-FVIII in plasma, overall FVIII clearance rate is attenuated. A number of lines of evidence suggest that this may not be the case. First, VWF is present in huge molar excess in plasma compared to the infused FVIII.³⁶ Second, several studies have demonstrated that induced increases in plasma VWF levels prior to FVIII infusion do not affect FVIII half-life in haemophilic plasma. In a murine model of haemophilia, Fischer et al¹³ showed that treatment with rIL-11 resulted in a 1.7-fold increase in plasma VWF levels compared to untreated controls. Subsequently, the half-life of infused FVIII was assessed in the rIL-11-treated and control cohorts. Despite the higher basal VWF levels in the rIL-11-treated group, no difference in FVIII half-life was observed.¹³

Similarly, human studies have shown that DDAVP administration can significantly increase endogenous plasma VWF:Ag levels in PWH. However, DDAVP pre-treatment 2 hours prior to infusion of FVIII had no significant effect on FVIII clearance.⁴⁹

Some plasma-derived FVIII concentrates also contain VWF in substantial and pharmacologically relevant amounts. Nevertheless, pharmacokinetics of such FVIII-VWF concentrates seem not to be essentially different from pharmacokinetics of FVIII products devoid of VWF. Both groups of products, plasma-derived with and without VWF and recombinant FVIII concentrates, all without VWF are considered to have virtually indistinguishable pharmacokinetics of FVIII.^{14,50}

An alternative mechanism that could explain the positive correlation between plasma VWF levels and FVIII half-life in PWH is that the VWF level is really a surrogate measure of endogenous VWF clearance rates. Hence, PWH with slower VWF clearance rates will tend to have higher basal plasma VWF:Ag levels. According to this hypothesis, these PWH would also have longer FVIII half-lives since the majority of infused FVIII is cleared through VWF-dependent clearance pathways. This mechanism is consistent with the data demonstrating that targeted increased in plasma VWF levels before FVIII administration do not prolong FVIII half-life.^{13,49} Several studies have attempted to assess endogenous VWF clearance rates in PWH using VWF propeptide to antigen (VWF:pp/VWF:Ag) ratios. Swystun et al¹⁵ recently reported a strong association between FVIII pharmacokinetics in PWH and the VWF:pp/VWF:Ag ratio ($P < .0001$). In particular, the VWF:pp/VWF:Ag ratio negatively correlated with FVIII half-life in non-O paediatric PWH.¹⁵ Similarly, Fischer et al¹³ observed a strong correlation between VWF:pp/VWF:Ag ratio and FVIII half-life in blood group O PWH (Pearson rank = 0.7; $P = .001$). Collectively, these findings emphasize the fact that FVIII half-life in PWH is critically dependent upon inter-individual variations in clearance rates for endogenous VWF. The factors responsible for regulating variability in VWF clearance between individual patients with haemophilia remain to be defined but likely relate in part to (a) variations in VWF glycosylation^{51,52} and/or (b) variations in VWF clearance pathways.^{9,48}

5 | VARIATION IN FVIII CLEARANCE—CLINICAL SIGNIFICANCE

Understanding the molecular mechanisms responsible for the marked inter-individual variability in FVIII clearance kinetics observed between individual PWH has major clinical significance. In particular, Collins et al¹⁸ demonstrated that for patients with severe haemophilia A on prophylaxis, increasing time per week with plasma FVIII <1% was associated with significantly increased risk for bleeding episodes. This finding was true for both haemarthroses and total bleeds. Moreover, the observation was consistent for both children and adult PWH. For example, in 99 patients aged between 10 and 65 years, each hour spent with FVIII levels below 1% was associated with a 1.4% increase in annual bleed rate (CI 0.21-2.62%).¹⁸

Subsequent modelling studies have shown that FVIII half-life and frequency of infusions are critical determinants of the amount of time each PWH spends per week with trough FVIII levels <1%.⁷ In contrast, in vivo FVIII recovery and infused FVIII dose per kg were less important. Cumulatively, these data have led to the concept that personalized treatment regimens for PWH should be considered. Defining individual-specific FVIII PK parameters constitutes a critical first step in terms of developing any precision-medicine approach to the treatment of haemophilia. This approach has already been investigated in a number of clinical studies and has become significantly more practical with the recent introduction of population-based PK studies. This subject has been addressed in a number of recent comprehensive review articles.^{53,54}

With respect to optimization of treatment for PWH, it is also important to highlight that a number of different extended half-life (EHL-) rFVIII treatments have been developed in recent years that use a variety of different genetic engineering strategies to extend the half-life of FVIII.⁵⁵ Interestingly however, significant inter-individual variation in clearance of these long-acting FVIII preparations has already been reported.⁵⁶⁻⁵⁸ In the clinical context, knowledge of individual pharmacokinetics for EHL-FVIII is likely to be of even greater translational importance.⁵⁹ Although the biological factors responsible for mediating inter-individual variation in clearance of different EHL-rFVIII products remain poorly understood, it is interesting that associations with endogenous plasma VWF levels and ABO blood group have already been reported.^{57,60} These data are consistent with the concept that EHL-FVIII molecules are still being cleared in complex with endogenous VWF.

6 | CONCLUSIONS

In conclusion, numerous studies have highlighted the fact that marked inter-individual variation in FVIII clearance rates exists between PWH. This variation has direct clinical relevance in that it impacts the efficacy of weight-based FVIII prophylaxis regimens.¹² Current state-of-the-art data suggest that endogenous VWF levels, ABO blood group and age all play important roles in regulating FVIII half-life in PWH. Critically however, multiple regression analysis suggests that cumulatively VWF, ABO group and age can only explain 34% of the total inter-individual variation in FVIII clearance observed between subjects with severe haemophilia A.¹⁷ Further adequately powered studies that include deep clinical phenotype, detailed PK analysis and genomic data will be necessary to elucidate the biological mechanisms responsible for the remaining 66% in FVIII clearance variability.

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DISCLOSURES

PLT is full-time employee of Baxalta Innovations GmbH, a member of the Takeda group of companies, and shareholder of Takeda Pharmaceutical Company Limited. JMJ has served as a consultant for CSL Behring and Octapharma and has received research grant funding from Octapharma. SWP has served as a consultant to Apicintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, and uniQure. JSO'D has served on the speaker's bureau for Baxter, Bayer, Novo Nordisk, Boehringer Ingelheim, Leo Pharma, Takeda and Octapharma. He has also served on the advisory boards of Baxter, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, Takeda and Pfizer. JSOD has received research grant funding awards from Baxter, Bayer, Pfizer, Shire (now part of Takeda), Takeda and Novo Nordisk.

AUTHOR CONTRIBUTION

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