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Review

Optimising prophylaxis in haemophilia A: The ups and downs of treatment

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ABSTRACT

The classical goals of haemophilia A treatment are to prevent bleeds, minimise the risk of long-term complications associated with joint damage, and improve quality of life by maintaining appropriate factor VIII [FVIII] levels. The dose and frequency of FVIII replacement therapies required to reduce bleeds is now known to vary amongst individuals, and may change for the same individual over time, meaning that a standardised dose and regimen may not provide optimal protection to all patients. Here we review the evolving treatment landscape for haemophilia A, and discuss how an increased understanding of the pharmacology and pharmacokinetics underlying FVIII replacement and non-factor replacement therapies could improve patient outcomes. We also review the strengths and weaknesses of current treatments and explore the benefits of personalised therapy and review how this may best be achieved with current treatment options. The key points of our review are summarised in the accompanying short video.

1. The evolving haemophilia A treatment landscape

The overall goal of haemophilia A treatment is to provide patients with a normal life as much as possible, by (i) preventing and treating bleeds, (ii) minimising the risk of long-term complications associated with joint damage, and (iii) improving quality of life (QoL), while minimising treatment burden [1–3]. This can be achieved by maintaining appropriate factor VIII [FVIII] levels considering the patient's bleeding phenotype, joint status, clinical conditions (ie, need for surgery), and lifestyle [1–3]. Treatment may be given to prevent bleeds (prophylaxis) or on the occasion of a bleeding event (episodic treatment) [4]. Prophylaxis is the standard of care for both children and adults with haemophilia A, helping to reduce or abolish the frequency of bleeding events and maintain joint health [2,3,5]. Additional advantages of prophylaxis include reduced hospitalisations, less absenteeism from school or work, increased participation in physical/social activities, and improved health-related QoL [6,7].

For decades, physicians have aimed to keep the FVIII levels of patients with haemophilia A above a minimum level of 0.01 IU/mL (or 1%) by using fixed dosing regimens [3,8,9] based on early observations of the natural model of the disease where patients with moderate haemophilia (FVIII levels >1%) develop overt joint damage less frequently than patients with the severe form (FVIII levels ≤1%) [5,8,10]. More recently, it has been shown that patients with moderate haemophilia may also develop chronic arthropathy, based on results from the THUNDER study [11]; this suggests that it may be clinically prudent to target higher FVIII levels in these patients (emulating a mild haemophilia phenotype) in order to prevent joint damage. However, this approach, based only on trough levels, does not take into account inter- and intra-individual physiological variability or the variable needs of the patient based on lifestyle, physical activity, and joint status.

The dose and frequency of FVIII replacement therapies required to reduce bleeds is now known to vary amongst individuals, and may also vary for the same individual over time [12,13], meaning that a fixed regimen may not provide optimal protection from bleeding for all individuals. Reflecting this, in recent years a paradigm shift has occurred, with a recognition of the need to individualise therapy and to refocus efforts towards maintaining FVIII at optimal levels rather than above a minimal threshold [3,12,14,15]. PK parameters, such as the time spent in a therapeutic window or a 'normal and safe zone' between trough and peak thresholds, are now regarded as important concepts to define effective prophylactic regimens for individual patients [3,5,13]. Particular attention has been given to ensure that

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prophylaxis provides adequate protection for patients in relation to their preferred lifestyle and daily physical activities, including sports [14,16,17].

Prophylaxis with FVIII replacement therapies has been the standard of care treatment for patients with haemophilia A for many years, providing adequate bleeding control even in patients undergoing surgical procedures [2,3,6]. However, the half-life ($t_{½}$) of standard half-life (SHL) replacement FVIII therapies necessitates frequent intravenous infusions in order to keep levels above 1% [6,18]. Regular and frequent intravenous treatments can be challenging for all patients with haemophilia, but especially so for children and the elderly, leading to suboptimal adherence to treatment [6,18]. Recombinant FVIII concentrates with extended half-lives (EHLs) have been developed to address this need [6]. EHL FVIII therapies have thus far shown favourable safety profiles consistent with SHL FVIII therapies in pivotal trials [19–22]. Currently, there are four main EHL FVIII therapies available, which can be categorised into two main groups: (i) Fc-fusion treatments and (ii) PEGylated (conjugation of FVIII protein with polyethylene glycol [PEG]) treatments (Table 1) [6,23–27]. Ultra-long FVIII replacement therapies are also in development, but their impact on the treatment landscape remains to be seen [28]. Gene therapies, which have the potential to reduce treatment burden by eliminating the need for regular FVIII prophylaxis via the long-term expression of endogenous FVIII sufficient to normalise coagulation, are also in clinical development [29] although none, as yet, have been approved.

Non-factor replacement (NFR) therapies that can be administered subcutaneously are also being evaluated as a treatment option [6,15]. To date, the only NFR treatment available for haemophilia A is emicizumab-kxwh (Hemlibra®, ACE-910), a recombinant, humanised, bispecific monoclonal antibody, which binds to activated factor IX (FIXa) and factor X (FX), thereby mimicking the cofactor function of activated FVIII. Emicizumab is indicated for routine prophylaxis in adult and paediatric patients with haemophilia A (from newborn and older) with and without factor VIII inhibitors, following HAVEN 1–4 trial results [30,31]. It is administered subcutaneously every 7, 14, or 28 days (Table 1) [32–36]. Other NFR therapies in development include the RNA interference agent fitusiran (ALN-AT3), which aims to be administered subcutaneously, once monthly, and targets antithrombin to promote thrombin generation and restore haemostasis [37]; the anti-tissue factor pathway agents (anti-TFPI) concizumab (mAb-2021; NN-7415; NNC-172-2021) and marstacimab (PF 06741086), are monoclonal antibodies under investigation as subcutaneous once-daily to once-weekly treatments, which promote Factor Xa generation through a FVII tissue factor (FVII-TF) complex to provide effective haemostasis in the absence of functional activated FVIII [38,39].

In this review we discuss the importance of prophylaxis in all patients with haemophilia and the different PK profiles of current treatments, alongside other factors that contribute to clinical decision-making when selecting the right treatment for the right patient.

2. Optimising prophylaxis using early initiation and pharmacokinetics

As treatment goals have expanded beyond targeting low annual bleeding rates (zero bleeds if possible) to include long-term outcomes such as prolonged joint protection, improved patient-reported QoL, and the ability to participate in physical activities [2,3], the focus has been on developing prophylactic therapies not only to achieve these goals, but also to enable less frequent (including once-weekly) dosing that still maintains sufficient protection from bleeds. The individual tailoring of therapy based on PK profiling and disease phenotype, as well as early initiation of prophylaxis, are key to achieving these treatment goals [2,3].

Table 1
Summary of currently available EHL FVIII and NFR prophylactic treatments [6,23].

Name	Alteration	EHL mechanism	Half-life (h)	Study	Overall ABR (dosing regimen)
EHL FVIII treatments					
Damoctocog alfa pegol (Jivi®; BAY 94–9027) [25]	PEGylated (60 kDa) B-domain-deleted FVIII	Decreased renal filtration, proteolytic degradation, and receptor-mediated clearance	18.7	PROTECT-VIII [22]	3.9 (weekly) 1.9 (twice weekly) 1.9 (every 5 days) 23.4 (episodic)
Efmoroctocog alfa (Elocta®; Eloctate™; rFVIII-Fc) [27]	Fc (IgG1) fusion to B-domain-deleted FVIII	Neonatal Fc receptor recycling	19.0	A-LONG [21]	1.6 (individualised) 3.6 (weekly) 33.6 (episodic)
Rurioctocog alfa pegol (Adynovi®; Adynovate®; BAX 855) [24]	PEGylated (20 kDa) to full-length FVIII	Decreased renal filtration, proteolytic degradation, and receptor-mediated clearance	14.3	PROLONG-ATE [20]	1.9 (twice weekly) 41.5 (episodic)
Turoctocog alfa pegol (Esperoct®, N8-GP) [26]	PEGylated (40 kDa) B-domain-truncated FVIII	Decreased renal filtration, proteolytic degradation, and receptor-mediated clearance	19.0	Pathfinder 2 [19]	1.33 (every 4 days) 30.9 (episodic)
NFR treatments					
Emicizumab[a] (Hemlibra®; ACE-910, emicizumab -kxwh) [35]	N/A	N/A	640.8	HAVEN 3 [32]	2.5[b] (weekly) 2.6[b] (every 2 weeks)

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ABR, annualised bleeding rate; EHL, extended half-life; rFVIII, recombinant Factor VIII; NFR, non-factor replacement.
[a] Emicizumab may also be administered every 4 weeks (6 mg/kg); ABR data for this dosing regimen was not captured in the HAVEN 3 trial.

[b] All bleeding events, regardless of treatment with FVIII.

2.1. Early initiation of prophylaxis

To prevent joint damage, prophylaxis should commence before joint disease starts and ideally before the first joint bleed occurs [2]. As the average age of a first joint bleed in severe haemophilia is 1.5 years, and age at the start of prophylaxis older than 3 years has been found to significantly increase the risk of developing arthropathy, it is important that prophylaxis is initiated as early as possible [2,3,40]. A Cochrane database review of six randomised controlled trials ($N = 142$; five trials in haemophilia A and one in haemophilia B) showed that prophylaxis started early in childhood reduced the number of total bleeds and joint bleeds, preserving joint function, and improving QoL compared with on-demand treatment [41]. Based on evidence such as this, primary prophylaxis for severe haemophilia is recommended in early childhood, at the latest before the second joint bleed or the age of 3 years [2]. Primary prophylaxis is possible with both FVIII replacement products and NFRs (emicizumab), however several factors need to be considered for the first-choice prophylactic agent, and this decision should be personalised and reviewed at key stages. Switching from FVIII replacement to NFR products (and vice versa) should be discussed with the patient (and their guardian if applicable), with consideration given to changes in lifestyle (especially engaging in high-impact activities) and in the case of surgery/trauma [2,6]. Early and optimized prophylaxis is essential because clinical studies have shown that FVIII replacement and NFR (emicizumab) treatments do not fully eliminate the bleeding rate in patients with haemophilia and subclinical bleeding episodes have been proposed to occur [33,42,43]. Moreover, while the FDA has approved the use of PEG-EHLs (eg, rurioctocog alfa pegol, Adynovate®) in patients under 12 years old, the European Medicines Agency has restricted these products to older patients (older than age 12 years), resulting in regional approval differences in this treatment type [24,36,44]. Additionally, the long-term efficacy and safety of emicizumab in the first year of life is still to be evaluated in the HAVEN 7 trial [45].

Nevertheless, with optimized primary prophylaxis, the expected outcome is that children with haemophilia A will reach adulthood with normal joint function and live a full and active life in the absence of bleeding events [2].

2.2. Utilising pharmacokinetics to optimise prophylaxis

It is broadly established that the risk of bleeding events is greatly correlated with FVIII levels and that there is considerable inter- and intra-individual variability in factors that can affect these levels [3]. As such, PK assessment is a crucial tool to tailor prophylaxis regimens to meet the range of treatment goals in patients with haemophilia A [5]. PK parameters such as incremental recovery, area under the concentration-time curve (AUC), clearance (CL), and subsequently, $t_{½}$ are now considered important surrogate efficacy endpoints for FVIII replacement therapies [12], and can be utilised to individualise dosing with respect to patient lifestyle and activities, distinguish between prophylactic FVIII treatments (Fig. 1), and optimise treatment selection for the individual patient [13,46]. Moreover, it is well established that FVIII PK parameters and clinical outcomes are correlated with endogenous levels of von Willebrand factor antigen (VWF:Ag), and seems to be similar across modified and unmodified FVIII product [47]. PK assessments are not frequently used to optimise early initiated prophylaxis owing to the need for blood sampling, which can be problematic in young children, and dosing is based on pragmatic experience. However, it is possible to use PK tools, which require less burdensome PK assessment when starting prophylaxis or during first years of life, leaving full PK measurements for later on in order to optimise factor consumption and, factor levels and manage bleeding phenotype [48]. In general, for any given molecule the PK plasma concentration curve generated after an intravenous injection shows a peak and a trough concentration reached over time and according to a decay curve with variable slopes [5]. In contrast to this 'up and down' concentration curve, NFR therapies such as emicizumab provide, after a loading phase, a steady-state concentration over time (ie, without peak and troughs), thought to be equivalent to a FVIII level of 9–15 IU/dL (9–15%) [49–51]. Indeed, according to the natural model, FVIII levels of 15 IU/dL (15%) can provide effective protection from the majority of spontaneous bleeds [16,49,52,53]. However, this level of bleeding control, while it may mimic the mild haemophilia phenotype, is not sufficient to control acute bleeding events and may not be sufficient to protect from all bleeds, particularly subclinical bleeds and those associated with traumas, surgery, and/or intense physical activity [6,16].

EHL recombinant FVIII therapies were developed to address these issues, as their PK profiles offer more convenient dosing regimens than the SHL FVIII replacement therapies, with longer intervals between dosing and/or maintenance of higher FVIII levels with the same dosing interval (ie, enlarging FVIII AUC and optimising the time spent within the FVIII range best suited to each individual's needs; Fig. 1) [3,6]. Increasing the time spent with FVIII levels >15 IU/dL (15%), with the option of increasing levels up to 40–50 IU/dL (40–50%), may be an important factor in protecting against haemarthrosis and other bleeding episodes, particularly during periods of high levels of physical activity and/or in cases of chronic synovitis or in the presence of target joints [3,7,14,53]. Indeed, given the wide inter-patient variability in PK, lifestyle and physical activity levels, the ability to adjust FVIII levels and provide

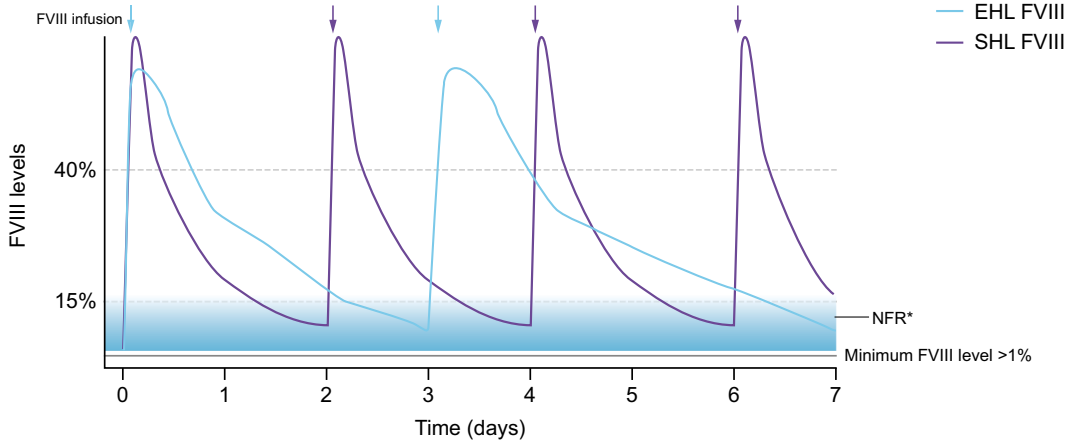

Fig. 1. Illustrative comparison of the pharmacokinetic profiles of currently available prophylactic treatment options (peaks vs steady state) [46].
*For NFR treatments the absolute FVIII level would be zero, but the haemostatic potential provided is thought to be equivalent to 9–15% FVIII levels. Dosing adjustments and bleed protection may be provided by additional, situational factor supplementation.
EHL, extended half-life; FVIII, Factor VIII; NFR, non-factor replacement; SHL, standard half-life.

appropriate bleeding protection to suit a given situation (something that is not possible with current NFR treatments) may be a crucial factor in the treatment decision-making process. PK-guided dosing with EHL recombinant FVIII has been shown to be efficacious in terms of bleeding control [23], and licensed EHL agents recommend tailoring the dose to the individual patient's FVIII responses as well as their bleeding status and clinical condition [54–57]. However, because there are no head-to-head studies comparing EHL factor replacement treatments with NFR therapies in patients with haemophilia A, direct comparisons cannot be made and the relative risks and benefits of available treatment options need to be assessed for each individual patient [2,3,58].

2.3. Modelling analysis of extended half-life versus standard half-life FVIII replacement therapy

In order to model the difference in bleeding protection provided by EHL and SHL FVIII replacement products, the time spent above certain FVIII levels was compared. In silico PK simulations by means of a population PK approach were conducted using damoctocog alfa pegol (Jivi®; BAY 94–9027) [55] as a representative example for an EHL model and using the SHL FVIII population PK model by McEneny-King et al. for the SHL model (see Supplementary Fig. 1) [59]. Recombinant FVIII replacement products share some key PK properties, for example, the relationship between patient characteristics and PK, such as the differences in half-life between paediatric and adult patients and the range of inter-individual PK variability, making this analysis a suitable representative example of these therapies.

For these in silico simulations, a virtual severe haemophilia A population was generated by randomly drawing patient characteristics from the damoctocog alfa pegol clinical development program data pool ($N = 151$; >12 years of age; severe haemophilia A population) [60]. For each virtual individual, the EHL and SHL model was then used to simulate the PK profile for a 40 IU/kg, twice-weekly dosing regimen of damoctocog alfa pegol, and the corresponding SHL profile calculated using a generic model developed for SHL FVIII replacement treatments [59]. The 40 IU/kg treatment was chosen as it can be found across SHL and EHL labels.

In this comparison, for EHL products, CL is considerably reduced compared with SHL therapy (median 47% reduction), with only a minor difference in V1 (median 15% reduction) that was potentially attributable to between-study assay differences between the two studies [59]. The proportion of patients above a specific FVIII level was also found to be consistently greater with EHL compared with SHL FVIII replacement therapy (Table 3, Supplementary Fig. 2). In addition, the median FVIII levels remain constantly above 1% in the EHL group, and were also calculated to be sustained for a high percentage of the week above a range of levels (20 IU/dL: 49.9% of the week; 50 IU/dL: 24.4% of the week; 60 IU/dL: 19.4% of the week; Table 3). The in silico approach was qualified with clinical PK data obtained in the PROTECT Phase 1 study [61], where for all patients, PK was determined for an SHL (Kogenate®, octocog alfa) followed by an EHL (Jivi®, damoctocog alfa pegol) product. For illustration, three individuals each representing a patient with an average PK profile in this population, a 'poor' PK profile (fast CL and a short-half-life compared with average values), and a 'good' PK profile (slow CL and long half-life compared with average values) were selected (Fig. 2, Supplementary Table 1). As predicted with the in silico approach, FVIII levels are maintained above 20% for approximately half of the week with the EHL product. The individual PK for the SHL and EHL products were described by employing the respective population PK models.

2.4. Patient engagement, education, and adherence

Patient understanding, engagement, and motivation is key to informing treatment choice and promoting adherence [3]. As such, it is recommended that the choice of prophylactic treatment should involve shared decision-making between the patient/caregiver and physician (and the wider multidisciplinary care team, where possible), incorporating patient preferences, values, and personal experiences to determine the best individualised treatment option [2,3]. As part of this decision-making process, it is essential that patients receive education about: (i) the nature of the disease; (ii) possible complications associated with the disease; (iii) the reasons why different patients may have different outcomes with the same treatments; and (iv) PK concepts, which can help them to understand the different types of therapies available; how they work; their key differences and their expected effects and limitations; how to administer them and monitor treatment progress; and which of them may be the most important to meet their individual needs with regard to tolerability, convenience, lifestyle, and levels of physical activity [3]. This, in turn, may help to improve treatment adherence and compliance [3,12,62]. Considerations for patients are summarised in the accompanying Plain Language Summary. While the multidisciplinary clinical care team plays a crucial role in this education [3], digital tools are also becoming available that can support patients in not only understanding the PK profile of their factor replacement product, but also in monitoring and/or adjusting their treatment based on their planned activities [12], thereby increasing their engagement with therapy. While it must be noted that the utility of these tools has not been formally validated, they include smartphone products such as the myWAPPS (https://mywapps.org/) and MicroHealth (https://microhealth.org/pages/learn-more.html) apps, and medical devices such as the MyPKFit (https://www.advatepro.com/about-mypkfit) package.

In addition to clinical factors (eg, efficacy, side effects), some of the key factors that influence treatment selection and adherence to therapy are ease of use such as route and frequency of administration [3,63]. EHL FVIII replacement treatments can help reduce the frequency of intravenous infusions compared with SHL FVIII replacement therapies while maintaining haemostatic efficacy [58]. NFR agents, such as emicizumab, cannot only be administered less frequently than SHL FVIII replacement therapies but can also be administered subcutaneously [35], which is less invasive and more convenient for patients [58].

3. Prophylaxis and physical activity

Historically, patients with severe haemophilia A have been advised to refrain from strenuous exercising. However, the reality is that many people with haemophilia A do take part in physical activities, including contact sports [35,64]. There is also an increasing recognition of the benefits of physical activity for people with haemophilia A, such as improved QoL, better muscle tone, and increased bone strength (with the associated protection from potential bleeds) [3,65,66]. Further, the ability to undertake physical activity has been shown to be important for the general health status and psychological well-being of people with haemophilia [67]. Enabling the participation in desired activities and sports while maintaining a reduced risk of bleeding events, especially joint bleeds, is therefore a key goal in the management of severe haemophilia A.

Increasing the dose/dose frequency of prophylactic therapy to maintain specific FVIII levels and to reduce the risk of serious bleeding events prior to surgical procedures is an established part of the management of patients with haemophilia [5,14], and the same reasoning may also be applied to participation in physical activity. Reflecting this, it is becoming increasingly accepted that prophylactic regimens must recognise a patient's level of physical activity, not only with regard to sporting activities, but also everyday activities such as housework, gardening, or playing musical instruments [14,16,68]. While no formal studies have been undertaken, expert opinion suggests that higher minimum and ideal coagulation factor levels are required as the physical risk of injury and bleeding associated with an activity increases [14,16,17].

A 2017 Delphi consensus statement by Iorio et al. recommended tailoring the target FVIII levels according to various factors, including physical activity [14]. Consensus was reached that FVIII levels of 3–5 IU/dL (3–5%) were appropriate for mild physical activity and FVIII levels of 5–15 IU/dL (5–15%) were appropriate for higher-risk physical

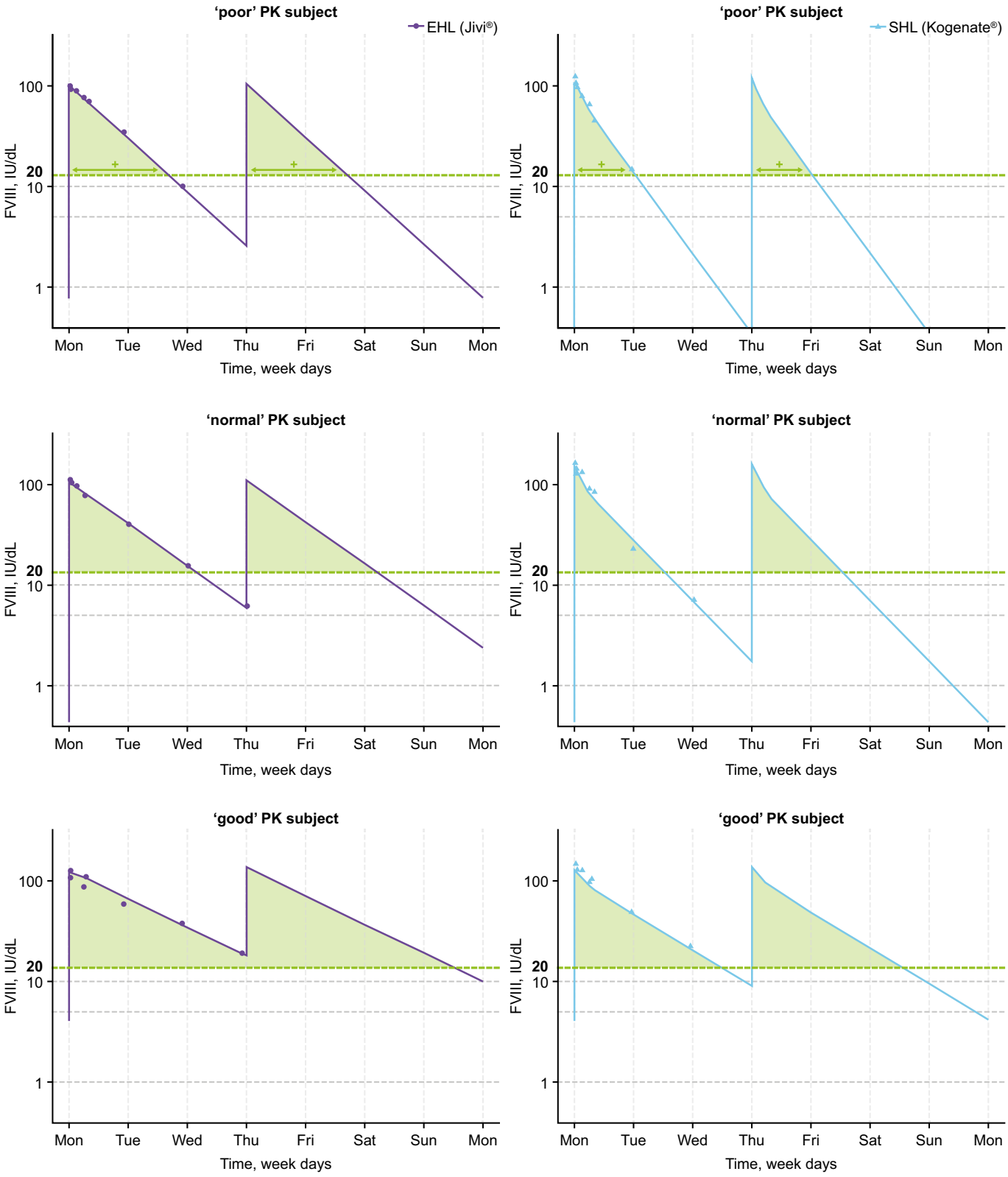

Fig. 2. Population PK modelling simulation of the time above specific FVIII levels provided by EHL versus SHL FVIII replacement therapies in patients with a 'poor' PK profile (a fast CL and a short half-life compared with average values), an average PK profile, and a 'good' PK profile (a slow CL and long half-life compared with average values), shown independently for each product.
CL, clearance; EHL, extended half-life; FVIII, Factor VIII; PK, pharmacokinetic; SHL, standard half-life; for illustration purposes, the observed FVIII concentrations, obtained with different doses, were scaled (assuming dose-linear PK) to the 40 IU/kg dose of interest.

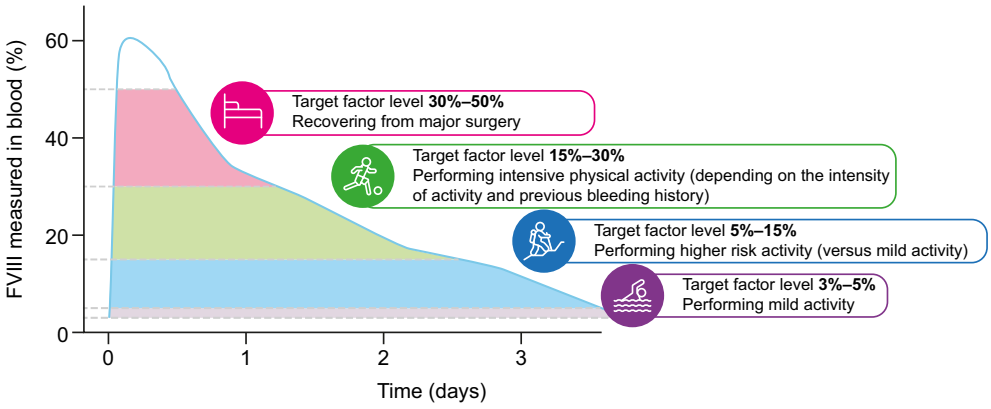

Fig. 3. Recommended target FVIII levels for varying types of physical activity [14].
FVIII, Factor VIII.

Table 2
Summary of physical activities and their associated risks [14,17,65,16].

Risk category	Risk interpretation [65,16]	Physical activity type examples [17]
0	Activities considered to have no risk.	Inactivity, reading, watching television, bathing, home duties (eg, cleaning, cooking, gardening)
1	Even though an activity may be rated as '1,'or low risk, there is still no guarantee that the patient will be injury-free or that a particular '1' activity may be the best one for the patient. For example, someone with a target shoulder may have difficulty swimming.	Walking, jogging, sprinting, light play, non-contact sports (eg, golf), dancing, gym activities, unspecified PE, non-contact ball games, low risk water activities (eg, swimming)
2	Even though activities rated as '2' or '2.5' have more risks, this does not mean that you need to avoid all of them. For example, if you wear appropriate safety gear and choose not to slide into bases, the injury risk when playing baseball may be in the '1.5–2' range. In contrast, if you choose to routinely slide into bases or play catcher, the risk level could be in the '2–2.5' range.	Moderate-risk water activities (eg, surfing), park/playground activities (eg, climbing), gymnastics, low-risk riding activities (eg, cycling, horse riding), wilderness activities (eg, rock climbing), hard ball games, running games, jumping activities, racquet sports, moderate-to-low-risk contact sports (eg, soccer, basketball)
3	These activities contain aspects that can be dangerous for ANYONE who participates, regardless of a bleeding disorder. The risks of these activities are due to the physical contact with other players, equipment, or hard surfaces that may result in serious traumatic injury.	Snow sports (eg, skiing, ice-skating, snowboarding), martial arts, contact/collision sports (eg, rugby), motor sports, moderate-risk riding activities (eg, skateboarding), rough play (eg, wrestling)

PE, physical education.

activity (Fig. 3), though specific risk ratings for physical and sporting activities were not defined [14]. However, the National Haemophilia Foundation has previously reported bleeding risk ratings for sporting activities [65,69], and Broderick et al. have since expanded upon these categories, providing risk factors for other daily physical activities (Table 2) [16,17]. Martin et al. subsequently used these categories to conduct an expert opinion survey into the minimally acceptable and ideal FVIII levels at which a bleed could be avoided for each type of activity, revealing increasing ideal FVIII levels with increasing risk, up to 40–50% with the highest-risk activities [16]. However, there are still no formally defined minimum or ideal FVIII levels for specific physical activities and further research is warranted, as knowledge of their own appropriate FVIII levels based on type of activity and risk of bleeding would greatly benefit the patient.

Table 3
Proportion of time per week spent above a specific FVIII level for EHL versus SHL recombinant FVIII replacement therapies with 40 IU/kg twice weekly.

Threshold (IU/dL)		Time spent above threshold/ week (%), median	Time spent above threshold/ week (%), 5th percentile	Time spent above threshold/ week (%), 95th percentile
1	SHL	90.6	63.1	100
	EHL	100	81.9	100
2	SHL	80.2	52.9	100
	EHL	100	69.9	100
3	SHL	71.4	46.7	99.8
	EHL	94.4	62.9	100
5	SHL	60.4	39.1	91.3
	EHL	87.2	54.1	100
10	SHL	45.1	28.8	73.2
	EHL	69.0	42.1	100
15	SHL	36.3	22.8	59.8
	EHL	57.8	34.9	96.2
20	SHL	30.0	18.4	50.4
	EHL	49.9	29.8	89.1
40	SHL	15.1	8.2	27.9
	EHL	30.6	17.3	58.6
50	SHL	10.6	5.2	21.0
	EHL	24.4	12.9	48.6
60	SHL	7.2	2.9	15.3
	EHL	19.4	9.2	40.3

Simulations were performed in silico using clinical study patient characteristics representative of a severe haemophilia A patient population.
EHL, extended half-life; FVIII, Factor VIII; SHL, standard half-life.

4. Non-factor replacement therapies

In contrast to replacement therapies, NFR treatments (eg, emicizumab) potentially provide a continuous/steady-state level of haemostatic protection without variations over time and with infrequent subcutaneous injections. The HAVEN 1–4 trials showed a consistent reduction in bleeding events (79% reduction in HAVEN 1) and more than half of patients reporting no bleeds requiring treatment (77% in HAVEN 2, 56% in HAVEN 4) [32–34,36]. In the HAVEN 3 Phase 3 controlled trial by Mahlangu et al., steady-state plasma levels thought to be equivalent to 9–15 IU/dL (9–15%) of FVIII levels were reported for emicizumab, which can be delivered at a maintenance dose of either 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks [32,49,50].

Unfortunately, however, it is not possible to determine an exact equivalence between the steady-state levels of emicizumab and FVIII levels, particularly given the substantial inter-patient variability of trough emicizumab levels and inconsistency of assays [49,50,70]. As such, a degree of uncertainty remains over the precise level of bleeding protection provided by specific doses of emicizumab [6,49,50,58]. In addition, the HAVEN 3 trial data have showed no superiority over factor replacement as evidenced by equivalent ABRs when comparing emicizumab to adherent FVIII use [32].

NFR therapies are designed as prophylactic agents to be used according to fixed dosing schedules; therefore, individualised tailoring of treatment to meet the physical needs of the patient is not possible [6]. For this reason, NFR agents are not considered suitable as monotherapy (the only drug taken to manage the patient's condition) because patients on prophylaxis with such therapies would require additional haemostatic support in the case of major surgery, trauma, or for treating acute breakthrough bleeding episodes [6,35,42]. Moreover, due to the nature of new drugs, long-term safety data for NFR products is still lacking.

For many patients with haemophilia, FVIII replacement therapy may not be an option due to barriers such as vascular access difficulties, lack of adherence/aversion to intravenous medication, an unfavourable PK profile, and persistence of haemarthrosis despite well-conducted prophylaxis [71]. In these cases, NFR therapies such as emicizumab could be considered as second-line therapy, and as a first-line therapy for patients with persistent FVIII inhibitors [2,3,72]. Overall, despite the intravenous treatment burden it places upon the patient, FVIII replacement prophylaxis still provides important advantages over NFR and gene therapies, including flexibility of dosing, the potential for personalised treatment, and the ability to achieve time-limited total correction of FVIII deficiency [72].

5. Conclusions and future considerations

Prophylaxis with replacement FVIII agents remains an important treatment option for many patients with haemophilia A. However, the reality is that some patients may not be able to receive these treatments, may not tolerate frequent intravenous infusions, or may experience bleeds despite well-conducted prophylaxis [72]. EHL FVIII replacement therapies and NFR therapies go some way to address these issues, providing less frequent and/or subcutaneous administration while maintaining haemostatic efficacy [54–56,58,72]. NFR therapies such as emicizumab may also provide more convenient subcutaneous administration than FVIII therapies, which could potentially improve adherence [3,63]. However, long-term efficacy and safety data (eg, the long-term risks of sub-clinical bleeding) are still lacking, and unlike FVIII replacement products, NFR therapies do not allow for corrections to adjust the haemostatic potential in specific situations. Given the considerable inter- and intra-individual variability, tailoring prophylaxis to the individual may help to optimise patient outcomes by adjusting for patient preference, clinical status, physical activity levels, and individual PK and treatment responses [2,3]. Overall, EHL FVIII replacement and NFR therapies provide benefits over conventional prophylaxis for the treatment of haemophilia A.

6. Enhanced publication content

Infographic: Plain language summary of current treatment options for patients with haemophilia A.

Video: Overview of the evolving haemophilia A treatment landscape.

Practice points

- Different haemophilia A treatments may provide varying levels of bleeding protection over time
- The maximum achievable (ie, peak) FVIII level that can be reached and the amount of time in a therapeutic window or a 'normal and safe zone' varies by product, and is an important consideration for some patients
- Where possible, treatment should be personalised in accordance with individual clinical characteristics, patient preferences, and lifestyle
- Introducing tools that allow patients to understand their own PK, aligned with bleeding phenotype and supported by practical technologies, may enhance patients' responsibility towards treatment, thereby improving outcomes
- Early prophylactic treatment remains a cornerstone in haemophilia A management
- NFRs such as emicizumab that provide a partial correction of haemophilia A cannot be used as the only drug to manage the condition (monotherapy), and adjunctive intravenous treatment with FVIII concentrates remains indicated in many situations, such as trauma, invasive procedures, and some physical activities
- Administration of FVIII concentrates or emicizumab by patients with haemophilia A at home, initiated as soon as possible in life, remains an important aspect of haemophilia treatment

Research agenda

- Studies to determine the optimal target FVIII levels for a range of activities
- Further investigation of PK characteristics of FVIII replacement and NFR therapies under variable conditions
- Assessment of the feasibility and benefits of personalised therapy in haemophilia A
- Investigations to better understand predictive factors for bleeding phenotypes
- Research into supporting digital technologies/algorithms and how these can improve personalised treatment
- Long-term assessment of joint health, as well as research into the detection of subclinical bleeding, and its role, both with NFR therapies and the higher FVIII levels achievable with EHL FVIII replacement therapies
- Investigations into the effect of treatment on patient quality of life and patient preferences across different treatment modalities

Author contributions

Erik Berntorp: Conceptualisation, Writing – review & editing, Writing – original draft; Cédric Hermans: Conceptualisation, Writing – review & editing, Writing – original draft; Alexander Solms: Visualisation, Methodology; Writing – review & editing, Writing – original draft; Lone Poulsen: Writing – review & editing, Writing – original draft; Maria Elisa Mancuso: Conceptualisation, Writing – review & editing, Writing – original draft.

Declaration of competing interest

EB has acted as a consultant for Bayer, Takeda, CSL Behring, and Novo Nordisk.

CH reports consulting honoraria for participation in advisory boards and/or speaker bureaus for Bayer, Biogen, CAF-DCF, CSL Behring, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, and SOBI; research funding from Bayer, Shire, and Pfizer.

AS is an employee and shareholder of Bayer.

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Appendix A. Supplementary data

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