Review

Setting the stage for individualized therapy in hemophilia: What role can pharmacokinetics play?

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A R T I C L E   I N F O

A B S T R A C T

Replacement therapy with clotting factor concentrates (CFC) is the mainstay of treatment in hemophilia. Its widespread application has led to a dramatic decrease in morbidity and mortality in patients, with concomitant improvement of quality of life. However, dosing is challenging and costs are high. This review discusses benefits and limitations of pharmacokinetic (PK)-guided dosing of replacement therapy as an alternative for current dosing regimens. Dosing of CFC is now primarily based on body weight and based on its in vivo recovery (IVR). Benefits of PK-guided dosing include individualization of treatment with better targeting, more flexible blood sampling, increased insight into association of coagulation factor levels and bleeding, and potential overall lowering of overall costs. Limitations include a slight burden for the patient, and availability of closely collaborating, experienced clinical pharmacologists.

1. Hemophilia and current treatment

1.1. Background of the disease

Hemophilia A and B are X-linked inherited bleeding disorders characterized by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Prevalence is estimated at 1 in 5000 male births for hemophilia A and 1 in 30,000 male births for hemophilia B [1,2]. FVIII and FIX enhance formation of thrombin and consequently stabilize the hemostatic clot by increased fibrin formation. Disease severity is classified according to residual FVIII or FIX coagulation activity in plasma [3]. Mild hemophilia patients have FVIII or FIX levels of 0.05–0.40 IU mL^{-1}, moderate patients FVIII or FIX levels of 0.01–0.05 IU mL^{-1} and severe patients FVIII or FIX levels of < 0.01 IU mL^{-1}. Mild hemophilia is characterized by an increased risk of bleeding after trauma or surgery. Moreover, severe as well as moderate hemophilia patients suffer from spontaneous bleeding or bleeding after minimal trauma in muscles and/or joints, potentially resulting in disabling arthropathy [4]. Strikingly, bleeding phenotype differs between hemophilia patients with identical baseline FVIII or FIX levels and is probably influenced by inter-individual variation in patient characteristics such as age, body weight, modifying factors within the hemostatic system, behavioral factors and daily (sporting) activities and other yet unidentified factors [5–10]. In addition, it may be influenced by inter-individual variation of half-life of clotting factor concentrates (CFC) administered either prophylactically or on demand (Table 1).

1.2. Current treatment with replacement therapy

Replacement therapy with CFC can be given to prevent spontaneous or repetitive bleeding (prophylaxis), or "on demand" to treat acute bleeding and prevent bleeding at the time of dental or surgical procedures. Current CFCs are either of recombinant or plasma-derived origin. Prophylaxis is the mainstay of treatment in hemophilia. Its introduction has dramatically changed the lives of many hemophilia patients. Consequently, hemophilia has evolved from a crippling disease with a shortened life expectancy into a disease with a normal life expectancy, significantly less joint arthropathy and acceptable quality of life [11,12].

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Table 1
Factors influencing bleeding phenotype in hemophilia patients.

Patient characteristics	Hemostatic factors	Pharmacokinetics of treatment
Age[a]	FVIII and FIX plasma levels	Clearance (Cl)
Body weight	FVIII and FIX gene mutation	Volume of distribution (Vd)
Other morphometric variables	Blood group[a]	Half-life (T1/2)
Joint status	von Willebrand factor[a]	In vivo recovery (IVR)
General (muscle) condition	Thrombin generation and fibrinolysis	
Daily (sporting) activities	Unidentified hemostatic factors	
Behavioral factors		
Adherence to treatment		
Miscellaneous		

[a] Influencing factor for hemophilia A patients only.

1.2.1. Prophylaxis

Prophylaxis was introduced in 1965 by Ahlberg and is based on the observation that moderate hemophilia patients with FVIII or FIX levels above 0.01 IU mL^{-1} have far fewer joint bleeds and less subsequent arthropathy [13]. Therefore, it was reasoned that joint bleedings could be prevented in severe hemophilia by keeping FVIII and FIX levels above 0.01 IU mL^{-1}. To achieve this, CFCs must be regularly infused generally two to four times a week in hemophilia A and one to three times a week in hemophilia B [14–17]. Prophylactic treatment profoundly reduces frequency of bleeding and improves joint status as demonstrated by Manco Johnson et al. in a randomized controlled trial [11]. Various guidelines for prophylaxis are available of which Table 2 shows a selection of those most often applied. The efficacy of prophylaxis in preventing joint bleedings is largely dependent on maintaining minimal FVIII and FIX trough levels of 0.01 IU mL^{-1} in the patient. Moreover, time spent below trough levels is associated with number of bleeding events [18]. However, in standard clinical practice, trough levels are rarely measured and dose and frequency of prophylactic infusions are only adjusted when spontaneous or frequent bleeding occurs.

1.2.2. On demand treatment

When patients are treated "on demand" either for acute bleeding or in a dental and/or surgical setting, dosing of CFC is aimed to achieve FVIII and FIX levels above a certain threshold/trough and below a certain maximum to avoid waste of CFC and high costs without clinical effect according to various guidelines (Table 3).

More specifically, when acute bleeding occurs FVIII and FIX peak levels are generally considered particularly important, although they are rarely monitored. Targeted peak levels are dependent on both severity and location of bleeding. In Dutch guidelines [14], FVIII or FIX peak levels of 0.30 IU mL^{-1} for minor bleeds, 0.50 IU mL^{-1} for severe bleeds and 1.00 IU mL^{-1} for life threatening bleeds are targeted. In severe or life threatening bleeds, it is more important to take trough levels into account. These FVIII and FIX levels are sometimes monitored but often merely estimated, and maintained based on the opinions of the treating physician. In the perioperative setting, mainly trough levels are considered important. Although, at initiation of surgery a specific peak FVIII and FIX range is targeted according to all guidelines. Overall, targeted perioperative FVIII and FIX trough levels depend on the invasiveness of the dental and/or surgical procedure and postoperative day, with e.g. Dutch guidelines prescribing FVIII or FIX trough levels of 0.80–1.00 IU mL^{-1} during the first 24 h after surgery; 0.50–0.80 IU mL^{-1} 1 to 5 days (24–120 h) after surgery; and 0.30–0.50 IU mL^{-1} > 5 days after surgery (Table 3).

Peak FVIII and FIX levels are estimated based on average in vivo recovery (IVR) of FVIII or FIX concentrates and amounts of CFC (IU) infused per kilogram body weight. This IVR-based dosing originates from studies that show that each infused unit of CFC per kilogram results in a mean increase of 0.02 IU mL^{-1} for FVIII and 0.01 IU mL^{-1} for FIX [9,19]. Application of this formula only provides a rough estimate of the maximum plasma concentration of FVIII and FIX after infusion. More explicitly, it does not take the pharmacokinetics (PK) of administered CFC of the individual patient into account, e.g., clearance, volume of distribution, and half-life (Fig. 1). Application of these PK parameters results in a more precise estimate of peak FVIII and FIX but also enables calculation of FVIII or FIX levels and the formulation of recommendations on frequency and timing of dosing of FVIII and FIX concentrates.

When describing PK of the various CFC in hemophilia, differences

Table 2
Prophylactic dosing regimens for hemophilia A and B.

Prophylaxis	Hemophilia A		Hemophilia B	
	Dose (IU kg^{-1})	Frequency dosing (n/week)	Dose (IU kg^{-1})	Frequency dosing (n/week)
Utrecht protocol-Dutch (Low dose prophylactic regimen) [14]	15–30	Three	15–30	Two
Malmö protocol – Nordic (High dose prophylactic regimen) [17]	25–40	Three	25–40	Two
UKHCDO [16]	25–50	Four	Not provided[a]	
WFH [15]	According to Utrecht or Malmö protocol		According to Utrecht or Malmö protocol	

[a] Recommendations for patients with hemophilia B are not provided given the paucity of published evidence.

Table 3
Target ranges with peak and trough FVIII and FIX levels and duration of administration according to a selection of available guidelines.

|		Hemophilia A		Hemophilia B	
		Predefined target ranges (IU mL^{-1})	Duration (days)	Predefined target ranges (IU mL^{-1})	Duration (days)
Dutch [14]	Major surgery				
	Preoperative	0.80–1.00		0.80–1.00	
	Postoperative	0.80–1.00	1	0.80–1.00	1
		0.50–0.80	2–5	0.50–0.80	2–5
		0.30–0.50	> 6	0.30–0.50	> 6
	Minor surgery				
	Preoperative	0.80–1.00		0.80–1.00	
	Postoperative	> 0.50	Depending on procedure	> 0.50	Depending on procedure
Nordic [17]	Major surgery				
	Preoperative	0.70–1.00		0.70–1.00	
	Postoperative	0.60–0.80	1–3	0.60–0.80	1–3
		0.40–0.60	4–6	0.40–0.60	4–6
		0.30–0.40	7–9	0.30–0.40	7–9
	Minor surgery				
	Preoperative	> 0.50		> 0.50	
	Postoperative		1–5 depending on procedure		1–5 depending on procedure
WFH [15]	No significant resource constraints				
	Major surgery				
	Preoperative	0.80–1.00		0.60–0.80	
	Postoperative	0.60–0.80	1–3	0.40–0.60	1–3
		0.40–0.60	4–6	0.30–0.50	4–6
		0.30–0.50	7–14	0.20–0.40	7–14
	Minor surgery				
	Preoperative	0.50–0.80		0.50–0.80	
	Postoperative	0.30–0.80	1–5	0.30–0.80	1–5
	Significant resource constraints				
	Major surgery				
	Preoperative	0.60–0.80		0.50–0.70	
	Postoperative	0.30–0.40	1–3	0.30–0.40	1–3
		0.20–0.30	4–6	0.20–0.30	4–6
		0.10–0.20	7–14	0.10–0.20	7–14
	Minor surgery				
	Preoperative	0.40–0.80		0.40–0.80	
	Postoperative	0.20–0.50	1–5	0.20–0.50	1–5
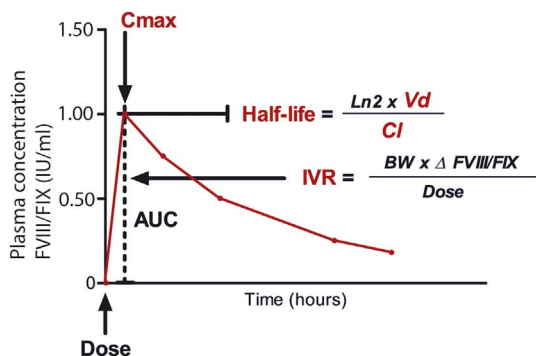
Fig. 1. Description of pharmacokinetic (PK) parameters using non-compartmental principles. After bolus infusion of clotting factor concentrate, FVIII or FIX plasma levels increase until the maximum concentration is reached (**Cmax**). The in vivo recovery (**IVR**) is calculated by body weight (**BW**) (kilograms) x observed increase in FVIII/FIX plasma levels divided by the dose. **Half-life** is derived from the clearance (**Cl**) and volume of distribution (**Vd**) and is defined as the time required for the concentration to halve. Finally, area under de curve (**AUC**) is the integral of the concentration-time curve.

are apparent between products. In both recombinant and plasma-derived FVIII concentrates, average half-life is estimated at 10.4 h [95% CI 7.5–16.5] in adults and 9.4 h [95%CI 7.4–13.1] in children [20]. This lower half-life in children can be explained by a higher clearance of FVIII in childhood probably due to the fact that VWF levels increase with age [21]. Contrastingly, no relationship between age and terminal half-life is observed for FIX concentrates [22]. Differences in PK of current FVIII and FIX concentrates are also significant. FVIII clearance is lower than FIX clearance (2.4–3.4 mL h^{-1} kg^{-1} versus 3.8–8.4 mL h^{-1} kg^{-1}) [23], due to the binding of FVIII to its carrier

protein VWF which protects FVIII from proteolytic degradation [24,25].

Although, FVIII has a lower clearance in comparison to FIX, FIX has a much larger volume of distribution (Vd). This larger volume of distribution of FIX is due to FIX binding to the vascular endothelium and diffusion into interstitial fluid on account of its lower molecular weight when compared to FVIII (FIX: 57 kDa; FVIII: 280 kDa) [26,27]. This results in a longer half-life for FIX compared to FVIII (18–34 h and 11–16 h, respectively) as half-life is calculated roughly by t1/2 = (0.693 ∗ Volume of distribution (Vd))/clearance (CL) [23].

1.2.3. Limitations of current treatment guidelines

Underlying the presently used dosing calculations is the assumption that all patients demonstrate similar PK of administered CFCs. However unfortunately, this is not the case. Bjorkman et al. were the first to report the significant inter-individual variations in PK after the administration of a standard bolus of FVIII or FIX concentrate in a large population. Significant differences were observed with regard to in vivo recovery (IVR), clearance and half-life with FVIII half-life varying from 6 to 25 h and FIX half-life from 25 to 56 h between individuals [8,20,28,29]. Collins et al. showed that the efficacy of prophylactic treatment is based on time spent above certain FVIII trough levels [30] and that therefore half-life and frequency of CFC dosing is more important than IVR of CFCs. Despite these findings, current treatment guidelines for replacement therapy are still based on IVR-based dosing regimens, which do not take the inter-individual variation of pharmacokinetics of CFCs into account.

Furthermore, as is observed in the general population, obesity also increasingly occurs in hemophilia patients [31]. This will result in in higher FVIII and FIX consumption if prophylactic and on demand

treatment is persistently based on body weight and IVR-based dosing regimens. Importantly, increasing body weight is not linearly associated with increasing volume of distribution as assumed by IVR-based dosing regimens [32]. Therefore, these higher costs of treatment may not be necessary to safeguard hemostasis. Obviously, current global constraints of health care budgets, obligates hemophilia communities worldwide to generate dosing algorithms in hemophilia with optimal results for patients and minimal costs for society.

Moreover in the perioperative setting, we recently demonstrated that current dosing leads to significantly lower and higher FVIII and FIX levels than targeted in hemophilia A and B [33], (Hazendonk et al. in preparation). In moderate and severe hemophilia A patients, a large proportion of trough and steady state FVIII levels were found to be below or above predefined target ranges. Specifically, 45% of FVIII measurements were below the FVIII target range within first 24 h after surgery and 75% above the target range during hospitalization more than six days after surgery [33]. Potentially, more optimal maintenance of perioperative target ranges could result in a reduction of 44% of CFC consumption, when ignoring logistical aspects of care [33]. In a recent retrospective study on perioperative management in moderate and severe hemophilia B patients, 60% of FIX measurements were below target and 59% FIX levels above target during hospitalization more than six days after surgery (Hazendonk et al. in preparation). Although the terminology of under- and overdosing suggests putting the patient at risk which is not the case as perioperative complications were minimal, these data do underline the limitations of current dosing algorithms primarily based on body weight using IVR-based dosing, as well as potential cost-effectiveness of alternative algorithms.
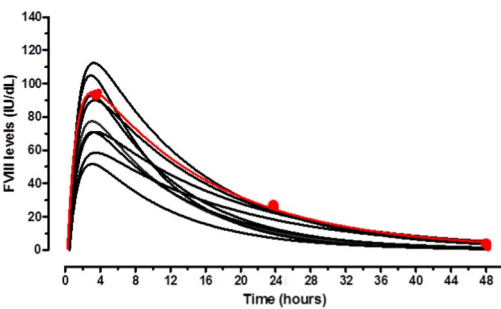
2. Pharmacokinetic (PK)-guided dosing in hemophilia

2.1. Principles of PK-guided dosing

To address inter-individual differences in PK of CFC and to employ more effective dosing, PK-guided dosing is a potential strategy. PK-guided dose-calculations are based on individual PK parameters in relationship to the population PK model and obtained by Bayesian analysis using statistical software (NONMEM®). In a population PK model for CFC, relationships between dose and achieved FVIII or FIX levels are described by PK parameters of all individuals in the population under review. This makes it possible to describe both inter-individual and intra-individual variability within this population dataset. In general, an important condition for implementing PK-guided dosing, is that intra-individual variability is smaller than inter-individual variability. Identified covariates explaining variability can be used to further improve constructed models, while unknown factors are labeled as residual errors. The principal strength of PK-guided dosing is that a population PK model not only represents identified covariates influencing PK parameters, but also takes the unknown modifiers of PK into account as they are described by the population data included in the model.

Importantly, Bayesian adaptive dosing is only possible when population PK models are representative of the individual patient and her or his specific clinical setting. Constructed models should therefore comprise a wide variation in patient-related (age, body weight, endogenous baseline FVIII/FIX, blood group) and circumstance-related factors (prophylaxis, on demand dosing during hemostatic challenges such as acute bleeding and surgery). For example, the recently published perioperative FVIII population PK model showed a significantly larger peripheral volume of distribution in comparison to the prophylactic PK model by Bjorkman et al. (1180 mL/68 kg versus 240 mL/68 kg) [8,34]. Further, to optimize current population models it is important to include often underrepresented patient populations, such as children and overweight/obese patients since PK parameters in these populations may differ significantly.

Table 4
Limited blood sampling strategies to construct individual PK curves.

	Bolus infusion (IUkg^{-1})	FVIII or FIX measurements
Factor VIII (FVIII) (Björkman et al.) [35]	50	$T = 4$, $T = 24$, $T = 48$ h
Plasma derived Factor IX (FIX) (Brekkan et al.) [37]	50	$T = 48$, $T = 72$ h or $T = 54$, $T = 78$ h
Recombinant Factor IX (FIX) (Preijers et al.) [36]	100	One sample post infusion, two samples between $T = 72$ and $T = 80$ h.

The upper panel shows a graphic example of a Factor VIII (FVIII) concentrate PK profile. A FVIII concentrate bolus is administrated followed by FVIII measurements (red points). Using a population PK model, FVIII plasma levels (red line) are calculated using individual PK parameter estimates derived from Bayesian analysis. To estimate FIX PK, similar principles are applied, although FIX blood sampling occurs at different longer time points as FIX concentrate half-life is longer.

2.2. Construction of individual PK profiles and population PK models

Extensive work performed by Bjorkman et al. has made PK-guided prophylactic dosing with limited blood sampling in hemophilia possible [35]. Prior to the construction of these population PK models, individual PK curves were constructed through extensive blood sampling (> 10 samples), with an obligatory wash-out period, leaving the patient at potential risk of bleeding. Currently, individual PK profiles for FVIII and FIX can fortunately be constructed with limited blood sampling and without a wash out period (Table 4) [35–37]. Different PK sampling models exist for rFIX and pdFIX, as it was already previously shown, that the PK of these two products differ [9]. Using Bayesian analysis and a representative population PK model, individual PK estimates can be iteratively updated, providing prophylactic dosing advice and prediction of achieved FVIII and FIX levels [38].

Perioperatively, several research groups have estimated preoperative loading doses of FVIII and FIX after constructing individual PK profiles [39–43]. However, until recently it was not possible to iteratively dose patients in the perioperative setting owing to the lack of population PK models for this specific setting. Construction of perioperative PK population models for both moderate and severe hemophilia A [34] and B, mild hemophilia A [44] and in the near future for von Willebrand disease [45] will eventually make this possible for several bleeding disorders.

The most important covariate in FVIII population PK models for hemophilia A patients, will most likely be von Willebrand factor (VWF) as patients with blood group O have 25% lower VWF levels. This is supported by findings that blood group O versus non-O is a significant covariate of clearance in the perioperative setting, with 26% higher clearance rates for patients with blood group O [45]. Furthermore, it was also shown by Kepa et al. that blood group was associated with FVIII half-life [46]. However, this effect of blood group O was not previously observed in a steady state prophylactic setting [47] and therefore not considered to be a covariate in available prophylactic population PK models. Most likely, this difference can be explained by

an increase of VWF due to inflicted endothelial damage and its role in the acute phase reaction after surgery [48].

Pharmacogenomics may also play an important role in the PK of coagulation factor concentrates. Many genes are known to modify the hemostatic system and the clearance of coagulation factors. As VWF serves as carrier protein for FVIII, mutations in the binding site of VWF to FVIII can result in lower levels of FVIII, also known as von Willebrand disease type 2N. In addition, the R1205H mutation in the D3 domain of VWF, also known as VWD Vicenza, results in reduced plasma VWF levels with ultra-large VWF multimers and therefore leading to an accelerated clearance of both VWF and FVIII [49]. Although, not only mutations in the *VWF* gene influence FVIII levels as ABO blood group has also a strong relation with FVIII levels. Blood group O is associated with lower FVIII levels compared to other blood types even when adjusted for VWF antigen [44]. In addition, the CHARGE has consortium reported multiple genetic loci in clearance receptors of VWF and/or FVIII which were associated with FVIII levels, for example *STXBP5* and *SCARA5*[50]. Furthermore, polymorphisms in one of the clearance receptors of FVIII/VWF, *LRP1* gene, are also associated with both FVIII and VWF plasma levels [51].

2.3. Benefits of PK-guided treatment

As early as 1997, Carlsson et al. showed benefits of a PK-guided dosing approach for prophylaxis [7]. This small study was designed as a randomized cross-over study comparing PK-guided dosing of prophylaxis with standard prophylactic dosing in 14 individuals during a period of two times six months. Strikingly, a reduction of CFC administration of 30% was achieved. The number of reported bleedings was similar in both treatment arms [7]. Such a reduction can have a significant financial impact, since annual costs for replacement therapy in the Netherlands amount to > 126 million euros [52]. Before drawing conclusions, however, it is important to prospectively evaluate these outcomes of PK-guided dosing in adequately designed and powered studies [53]. Currently, a randomized controlled trial comparing PK-guided perioperative treatment of CFC in moderate and severe hemophilia A patients is in place to analyze the amount of CFC administered, time spent to achieve targeted FVIII levels, as well as staff investment and costs, all in accordance with the economic health principles established by Hakkaart-van Rooijen [53,54]. This study may result in clear conclusions regarding the cost effectiveness of PK-guided dosing.

Another benefit of PK-guided dosing is that both prophylactic and "on demand" dosing will be based on actual FVIII and FIX trough and peak levels or FVIII and FIX levels predicted by population PK models, instead of current FVIII and FIX estimates based on IVR-based dosing. Furthermore, FVIII and FIX sampling can be made flexible and not necessarily fixed at certain time points before or after infusion, once models are in place. Moreover, PK-guidance will optimize dosing as knowledge will increase with regard to the relationship between FVIII and FIX levels and bleeding in individual patients and patient groups. In addition, an increase in dosing will not only depend on actual bleeding and a reduction of dosing can be considered by the treating professional in consultation with patients and parents. Importantly, the dose and frequency of CFC of patients on prophylaxis should only be reduced if clinically justified and impact should be monitored with regard to bleeding events, bleeding pattern and joint status (Table 5).

Over time, more exact targeting of FVIII and FIX levels may also lead to reliably lowering of target levels of treatment. Especially in hemophilia B, studies and clinical experience suggest that lower target levels may be acceptable [15,55]. In a recent retrospective study on perioperative management in moderate and severe hemophilia B patients, 60% of FIX measurements were below target, without clinical relevant bleeding and independent of the severity of surgical procedures (Hazendonk et al. in preparation). Srivastava et al. showed that lower trough FVIII (0.20–0.40 IU mL^{-1}) and FIX (0.15–0.30 IU mL^{-1}) levels 0–72 h after surgery were not accompanied by bleeding

complications since only one patient experienced bleeding due to a lack of surgical hemostasis [55]. Furthermore, International WFH guidelines for perioperative treatment in hemophilia A and B patients recommend FIX levels 0.20 IU mL^{-1} lower than FVIII levels (Table 3) [15]. In countries with significant financial constraints, even lower FIX target ranges are suggested [15]. Interestingly, various European guidelines do not differ regarding perioperative target ranges for hemophilia A and B [14,17,56] as reported in a survey by the European Therapy Standardization Board in 2009 [57].

PK-guided dosing will also facilitate individualization of dosing according to individual lifestyle and activities, therefore achieving true personalization of treatment. When targeting weekly FVIII and FIX levels, personal activities and preferences should be taken into account, as bleeding risk is closely related to these factors [58–60]. Moreover, non-adherence should be discussed as implementation of minimal dosing schemes may lead to an increased risk of bleeding [61–63]. Patients and families should be aware of time points when factor concentrate levels are low or high and consider additional dosing when bleeding risk is significant.

All benefits of PK-guided dosing are also applicable with regard to upcoming enhanced half-life (EHL) products. Moreover, costs of treatment will directly depend on the dose and frequency of treatment and therefore on individual PK and population PK parameters. Furthermore, the ongoing discussion of the association of trough levels and the role of peak levels with regard to bleeding will be made more transparent. This is especially relevant in EHL products as higher troughs will be possible and treatment peaks will be less frequent [64].

2.4. Limitations of PK-guided treatment

Important limitations with regard to PK-guided dosing include the requirement of close collaboration with a clinical pharmacologist with expertise in PK modeling. Furthermore, time investments by patients, parents and medical professionals may be substantial as individual PK profiles must be performed regularly (every three to four years depending on patient characteristics) and perioperative PK-guided iterative dosing requires daily dosing recommendations. Solutions to overcome these limitations are the availability of web portal-based consultancies for PK-guided dosing advice, as established by Iorio [21], for instance, and as developed by a pharmaceutical company for the prophylactic setting [65]. Both initiatives to implement a closer collaboration and to educate both professionals and patients are valuable for future patient care. Transparency and reliability of the data used to construct underlying population models are of course of crucial importance in such settings.

3. Future role for PK-guided dosing of factor concentrates in hemophilia care and research perspective

Replacement therapy has led to the high standard of hemophilia care in high-income countries. However, recent studies show that treatment is suboptimal; although bleeding is rare, both under- and overdosing of CFC occur. We believe that PK-guided dosing as the alternative to body weight and IVR-based dosing, will play an important role in further individualization of therapy. We have summarized the anticipated improvements in Table 5.

Future research should include studies prospectively validating constructed population PK models but also combining PK with pharmacodynamic data (e.g. bleeding events, global hemostatic test results) and simulations to determine minimal FVIII and FIX levels required for adequate hemostasis in the individual patient and in populations. These data may subsequently support studies aiming at lower target levels in specific bleeding disorders.

There are no suggestions that implementation of PK-guided dosing will lead to an increased risk of inhibitor development. It is well-known that risk factors of development are peak treatment moments in

Table 5
Benefits and limitations of PK-guided dosing based on population PK models as alternative for body weight and IVR-based dosing regimens.

Advantages	Conditions and remarks
1. Better targeting of FVIII and FIX levels with minimal burden to patients.	Although limited blood sampling decreases frequency of blood sampling, two/three samples for individual PK profile are still obligatory.
2. More flexible blood sampling	Population PK models should however be representative of population and specific setting. Once PK-guided dosing is in place.
3. Insight into association of FVIII and FIX trough and peak levels and bleeding Future possibilities to construct both PK and pharmacodynamic (PD) models and to further understand pathophysiology of hemostasis	Further development of global hemostatic assays measuring hemostatic potential also essential.
4. Possibility to potentially lower FVIII and FIX target values, due to more reliable targeting	Intensive collaboration between experienced clinical pharmacologist and (pediatric) hematologist necessary. Realization of risks and intensive monitoring of clinical impact of lowering of FVIII and FIX levels obligatory.
5. Facilitation of actual personalization of treatment according to lifestyle	Continuous adaptation of dosing regimen according to lifestyle also necessary. Individual PK profiles must be potentially repeated every 3–4 years. Adherence must be discussed.
6. Potential reduction of overall treatment costs	Prospective studies to evaluate actual impact on costs are obligatory.
7. Further enrichment of population PK models	Intensive collaboration between experienced clinical pharmacologist and (pediatric) hematologist necessary.

younger children, which is often the case in the perioperative period. Use of PK-guided dosing may be able to prevent extreme peaks. However, future studies will be needed to prove such a hypothesis.

4. Conclusion

We believe that PK-guided dosing deserves attention as a means of ensuring the individualization of treatment in hemophilia since benefits are significant and limitations can be overcome. The burden for patients and parents appears to be minimal. Accordingly, we call on patients, medical professionals, clinical pharmacologists, hemostatic laboratories and pharmaceutical companies to join hands in applying this approach for all CFCs, in hemophilia and other bleeding disorders requiring CFC replacement therapy.

Practice points

- Replacement therapy with clotting factor concentrates (CFC) is the mainstay of treatment in hemophilia.
- However, dosing is challenging and costs are high.
- Current dosing is based on body weight and in vivo recovery (IVR) of CFC.
- PK-guided dosing will enable individualization of treatment with better targeting of coagulation factor levels.

Research agenda

- Prospective studies are warranted validating constructed population PK models
- Future studies combining PK with pharmacodynamic data (e.g. bleeding events, global hemostatic test results)
- Simulation analyses to objectify minimal FVIII and FIX levels required for adequate hemostasis in individual patients and specific patient populations.

Disclosure of conflicts of interest

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interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2018.01.001.

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