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"HE-RO-IS strategic cooperation in hematology"

F SEE 2014-2021 No. 19-COP-0031

Curricula in hemophilia

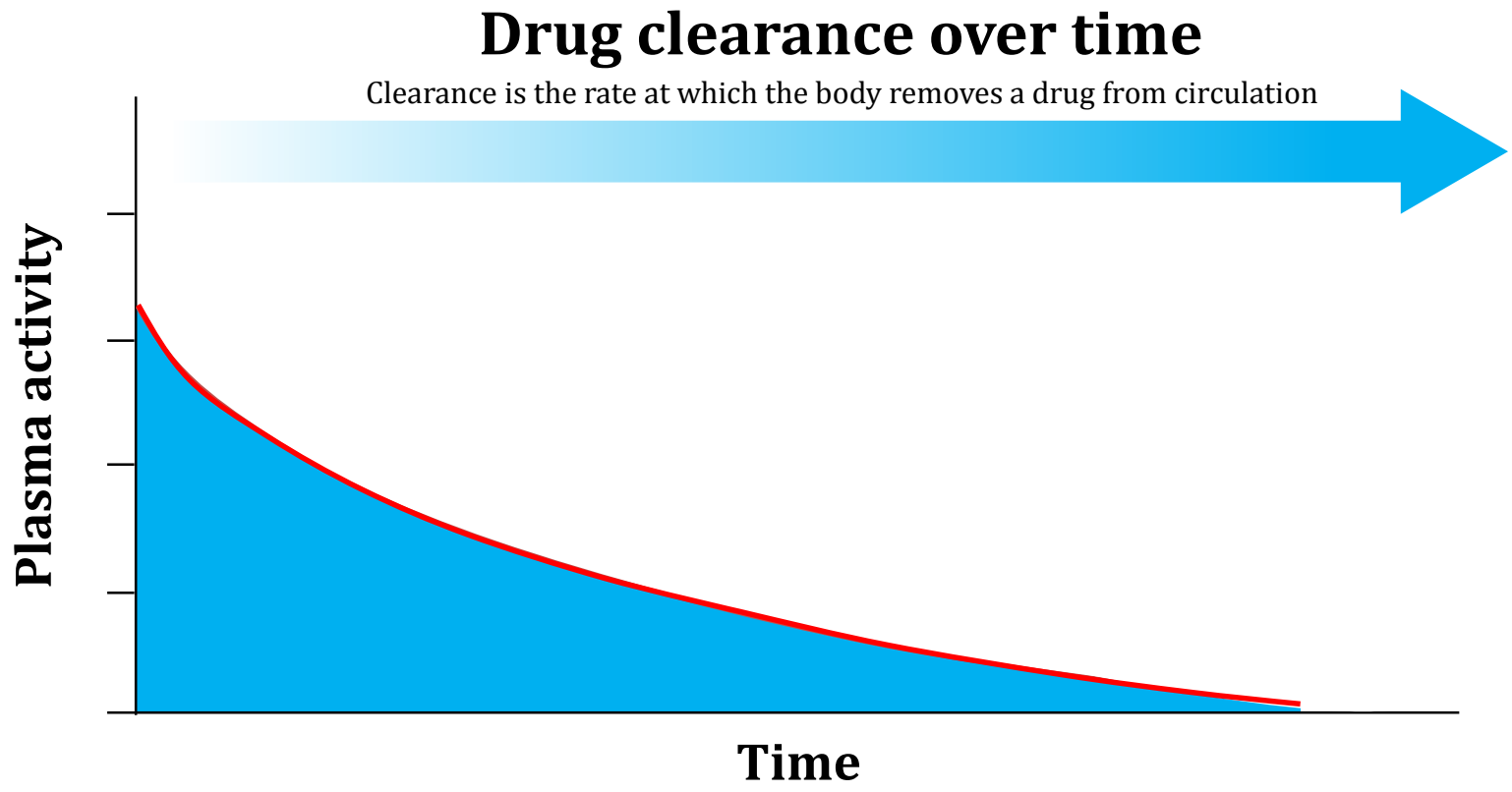
Disclaimer: This curricula was realised with the EEA Financial Mechanism 2014-2021 financial support. Its content (text, photos, videos) does not reflect the official opinion of the Programme Operator, the National Contact Point and the Financial Mechanism Office. Responsibility for the information and views expressed therein lies entirely with the authors.

A Practical Guide to Pharmacokinetics in Haemophilia

Pharmacokinetics (PK)

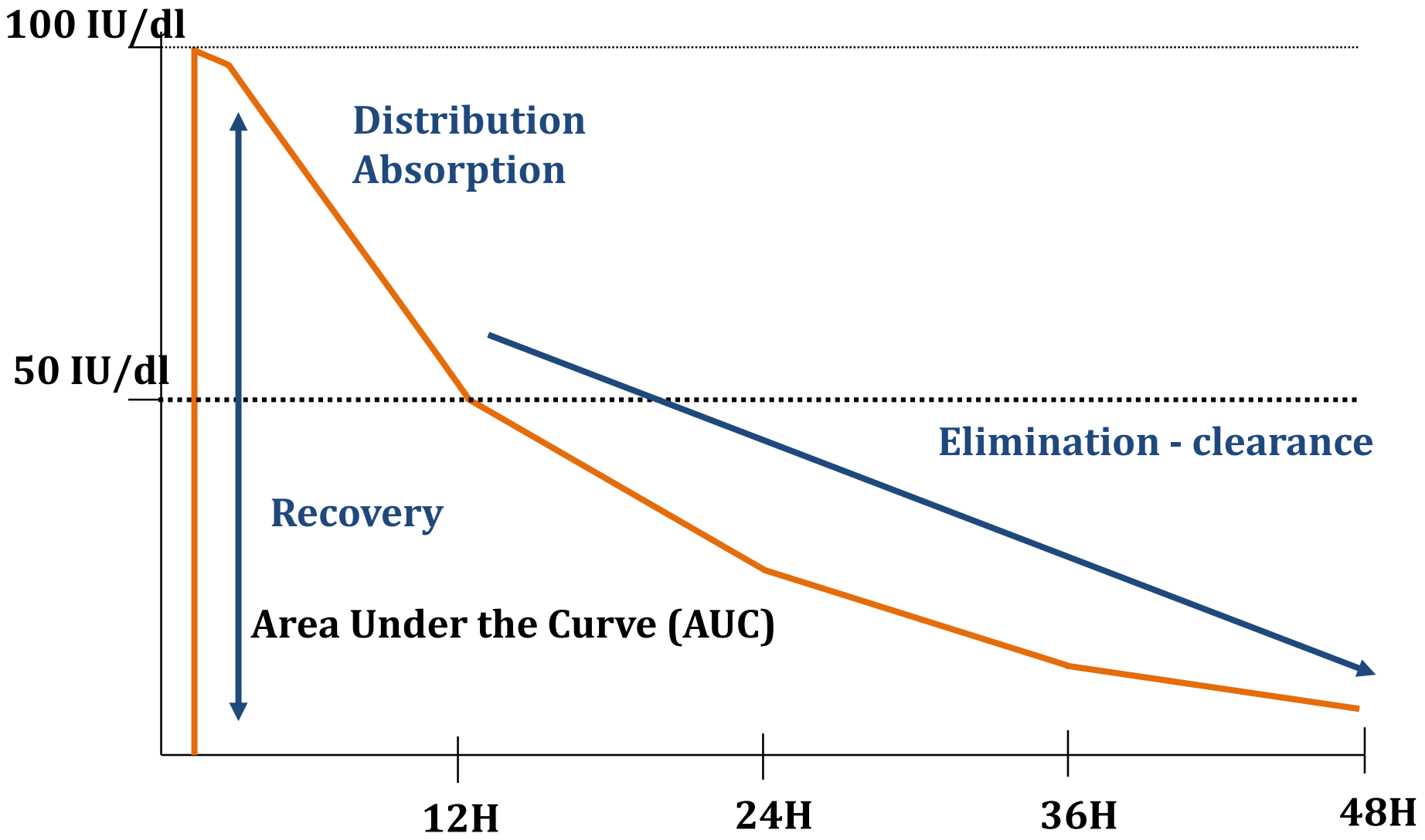
- Describes the movement of drugs in the body
- Based on measurements of plasma concentrations
- The effects of FVIII is directly related to plasma concentrations.

Basic principles of PK

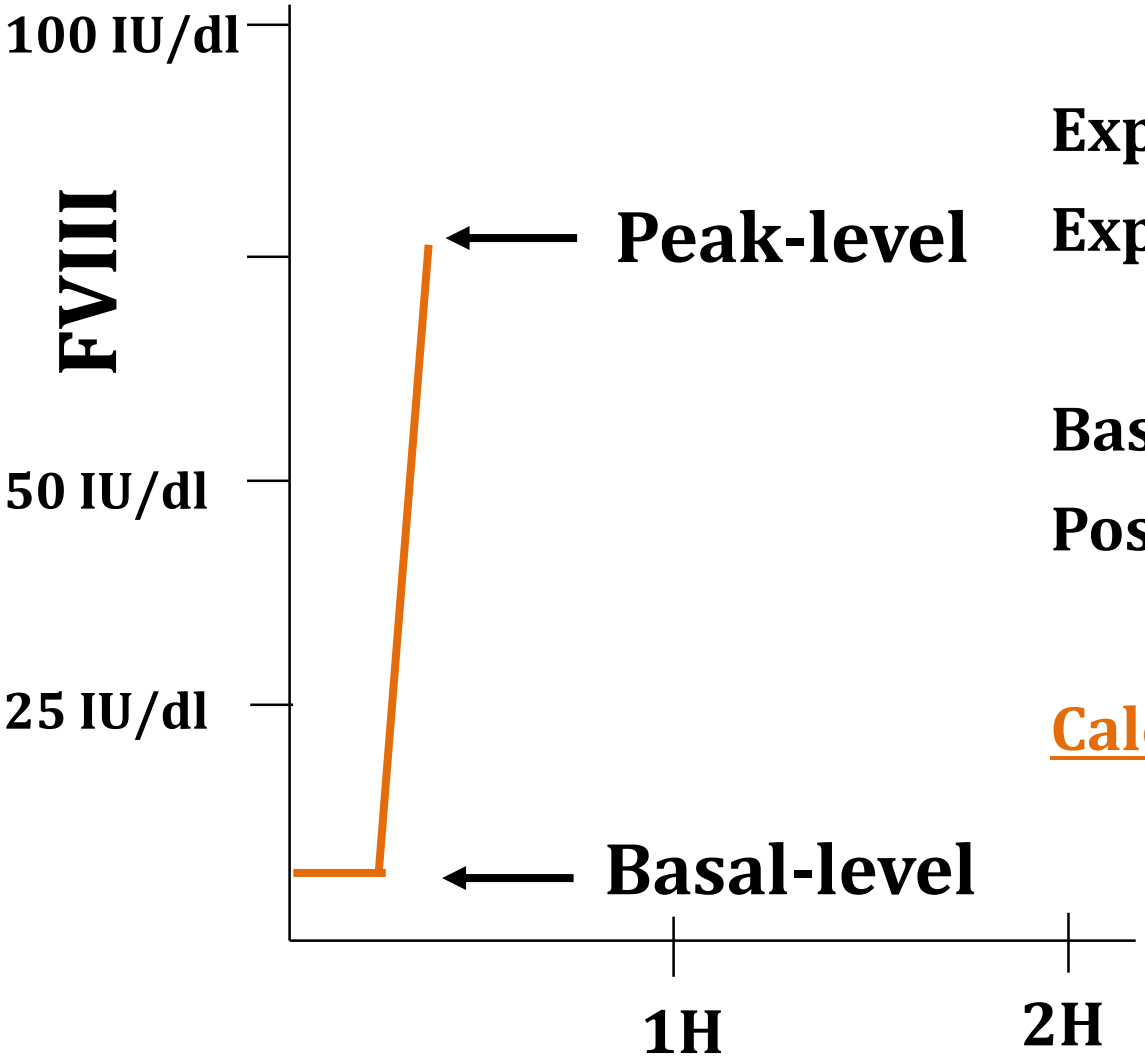


Buxton I, Benet L. In: Brunton I et al. **The Pharmacological Basis of Therapeutics** 12th ed. New York, NY 2011:17–39.

Factor VIII/FIX decay curve



Calculation of recovery in a 50 kg patient treated with 2000 IU factor VIII



Expected recovery: 2

Expected rise: 80 %

Basal level: 5 %

Post-infusion level: 75 %

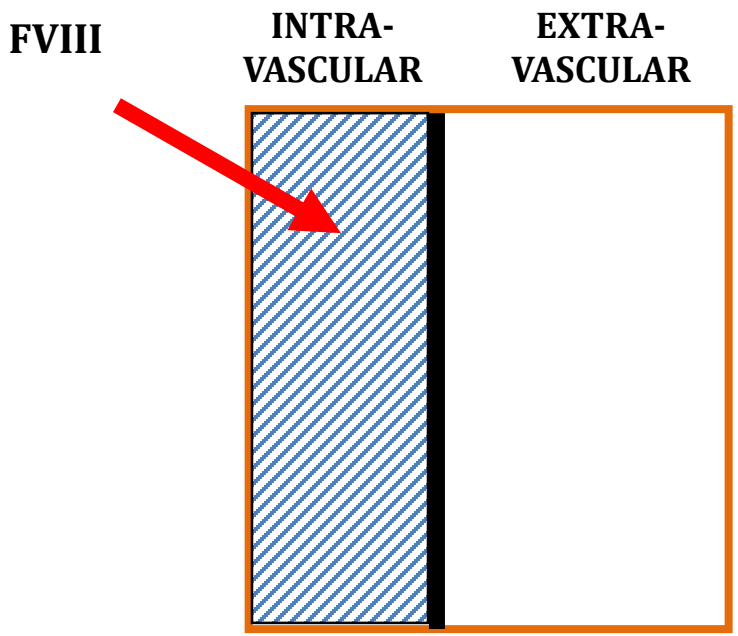
Calculated recovery : 1.75

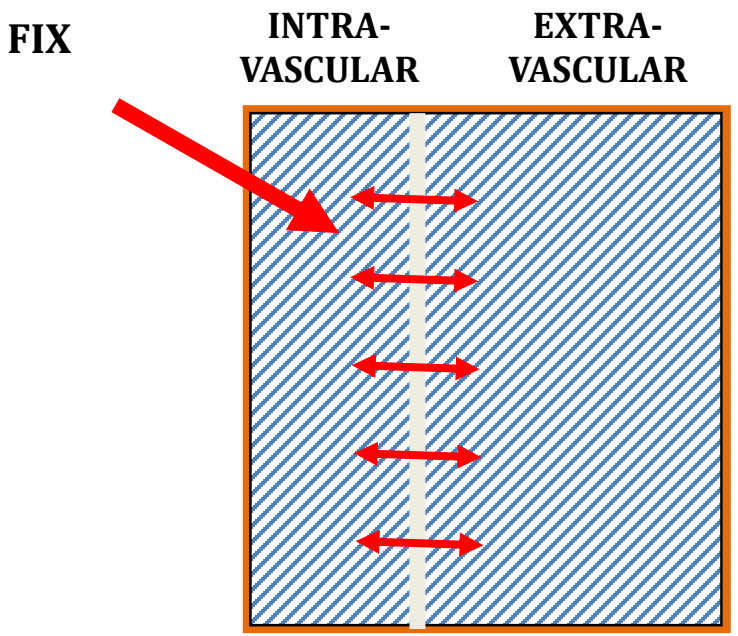
Factors affecting recovery

- Quantity of factor infused (potency, labeling)
- Volume of distribution -dilution (vd)
  - Recovery lower if Vd larger
  - Vd larger for smaller molecules (FIX >>> FVIII)
  - Plasma volume as a fraction of body weight decreases with body weight
- Timing of peak value (10 to 15 min)
- Factor assay after infusion

Influence of the molecular weight of FVIII and FIX on recovery

The distribution of FVIII and FIX between intra and extravascular spaces is influenced by their respective molecular weights



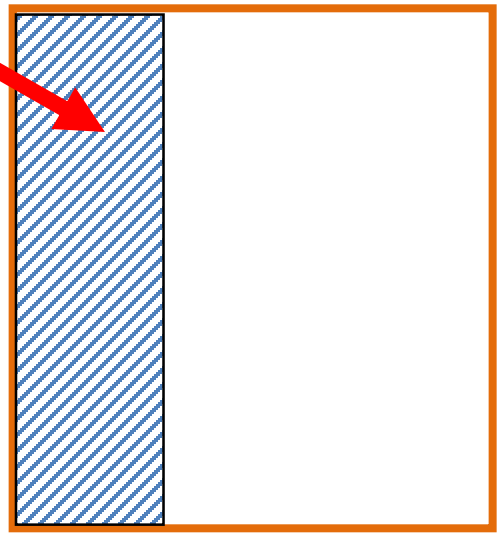


Effects of body weight / surface on recovery

ADULTS

FVIII

Plasma volume

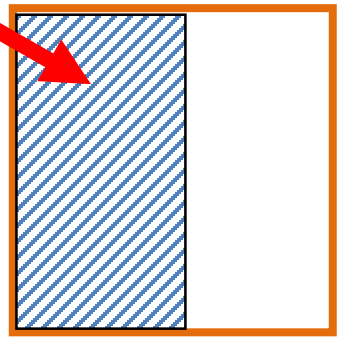


K = 2

CHILDREN

FVIII

Plasma volume



K = 1.5

Body surface < 1.7 m^2
Weight < 40 kg

Am. J Pathol 1982; 35 : 289

Clinical case: A 45-year-old male with severe HA and obesity

- Severe haemophilia A
- Diffuse arthropathy
- Hypertension
- Obesity
  - Body weight: 120 kg
  - Height: 177 cm
  - Body mass index (BMI): 38 kg/m^2
  - Body fat (impedance): 40.7%
  - Ideal body weight: 70 kg
- Measurement of FVIII *in vivo* recovery
  - Dose of FVIII given: 1960 units
  - FVIII before infusion: 11%; after infusion: 56%

$$\textbf{Recovery} = \frac{\textbf{45 x 120}}{\textbf{1960}} = \textbf{2.75} = \textbf{Much higher than 2 Over-treatment?}$$

Impact of underweight and overweight on FVIII dosing in people with hemophilia A

- Study shows that **BMI** is a **strong predictor** of FVIII **recovery**

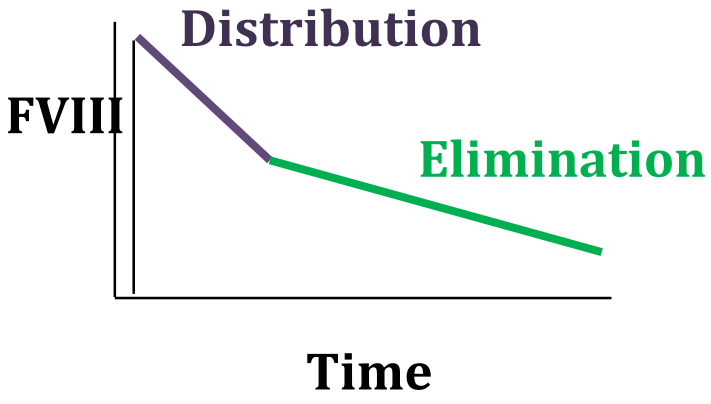
- In theory, the dose of FVIII needed to reach a specific FVIII target level should be adapted in underweight (BMI ≤ 20 kg/m^2) and overweight (BMI ≥ 30 kg/m^2) patients

Ingram GI. *Br J Haematol* 1981;48(2):351-354.

Analysis of the decay curve

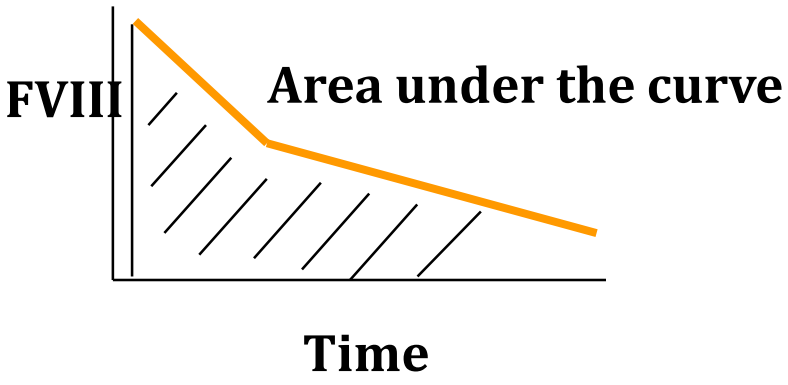
Model-dependent approach

- Relies on a model relating ***time after infusion*** to factor level
- Most studies have shown the FVIII activity–time curve follows a two-compartment model (distribution and elimination phases)
- Kinetic parameters :
  - Half-lives



Model-independent approach

- Does not rely on a model relating time after infusion to factor level
- Based on the calculation of the Area Under the Curve (AUC)
- Kinetic parameters :
  - Clearance
  - Volume of distribution
  - Mean Residence Time



Kinetic parameters

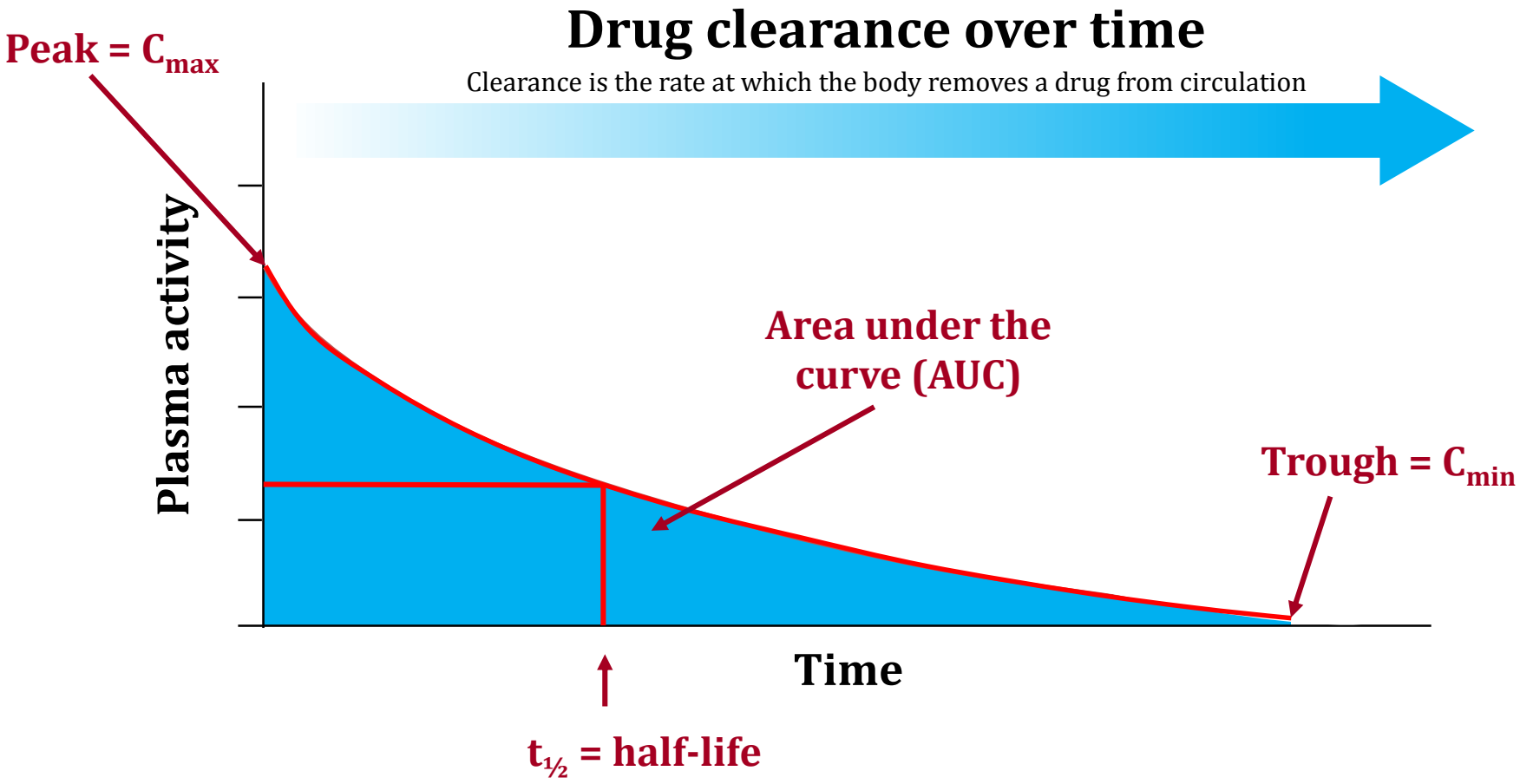
Model-dependent approach

- **Distribution phase**
  - Extravasation, binding to endothelial cells …
  - Half-life alpha (initial T1/2)
- **Elimination phase**
  - Half-life beta (terminal or **biological T1/2**)

Model-independent approach

- **AUC:** The integral of the concentration–time curve
- **Clearance:** Dose given / AUC (ml/h/kg)
- **Mean Residence Time (MRT):**
  AUMC / AUC (hours)
  MRT = time for 63.2 % of excretion
  MRT = 1.443 x T1/2 (Monophasic)
- **Volume of distribution** (ml/kg):
  CL x MRT

Basic principles of PK



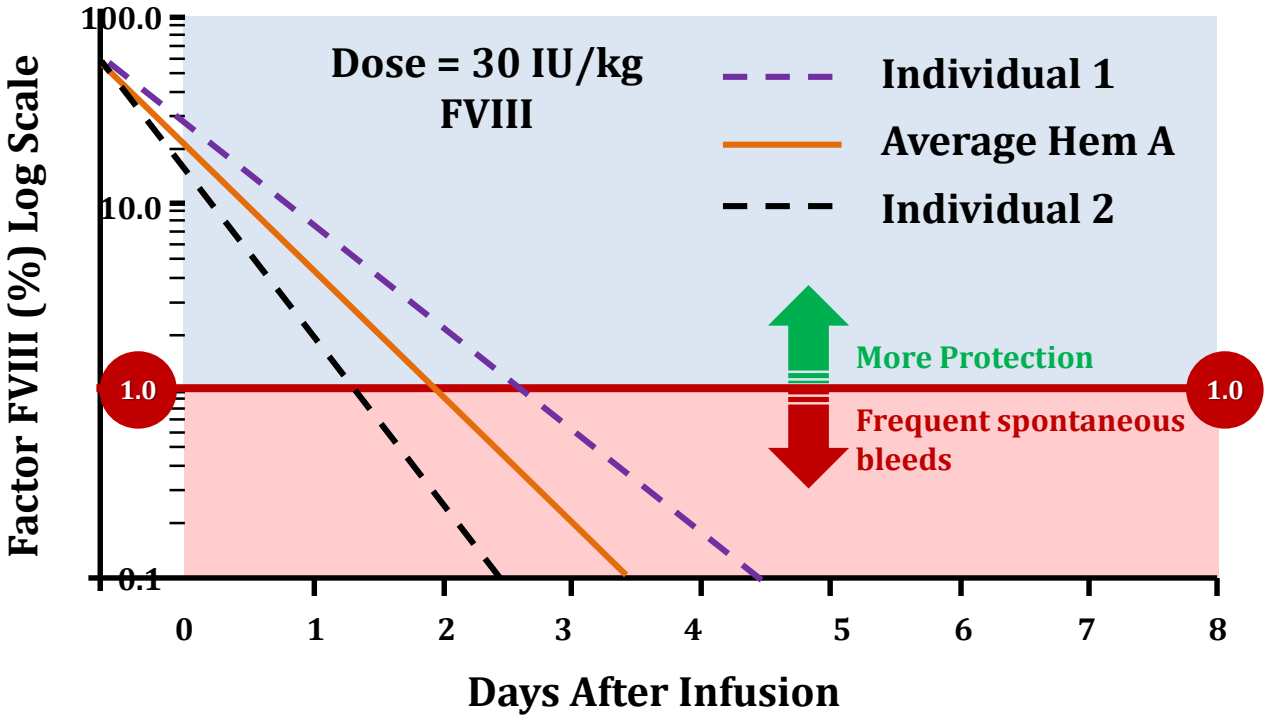
Buxton I, Benet L. In: Brunton I et al. **The Pharmacological Basis of Therapeutics** 12th ed. New York, NY 2011:17–39.

Half-Life of FVIII

Individual 1
$t_{1/2}$ for FVIII
= 15 hours

Average half-life
($t_{1/2}$) for FVIII
= 12 hours

Individual 2
$t_{1/2}$ for FVIII
= 9 hours



- Other factors also determine individual bleeding frequency, but half-life of clotting factor is a major determinant for trough level
- Factor activity can be measured; thus individual PK profile can be determined and time to 1% trough level can be predicted

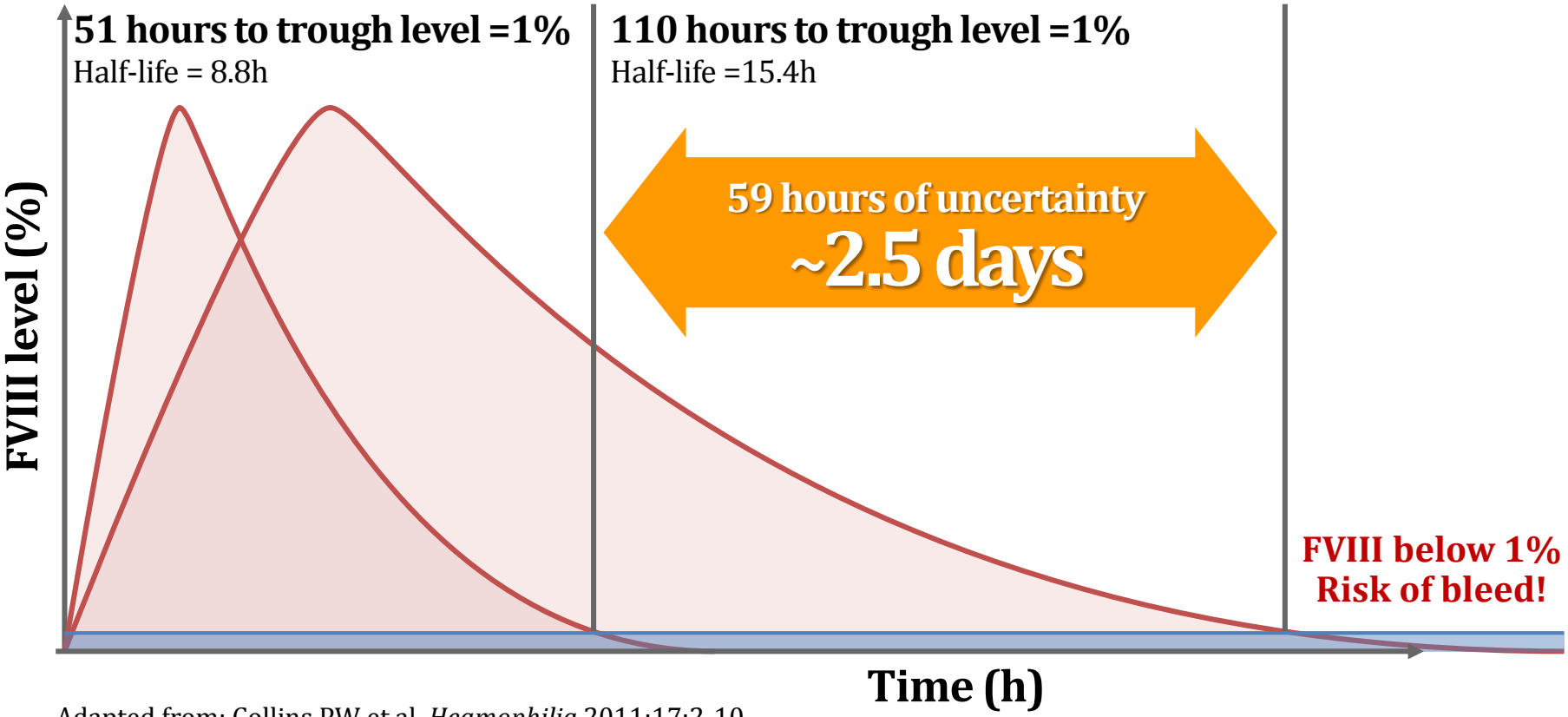
Collins PW et al *J Thromb Haemost*. 2010; 8:269-75

Why is PK-guided prophylaxis important?

PK varies widely among patients and with age

POSSIBLE VARIANCE

Adolescents/Adults 10-65 years old; e.g. 70 kg, 30 IU/kg of the same FVIII product



Adapted from: Collins PW et al. *Heamophilia* 2011;17:2-10.

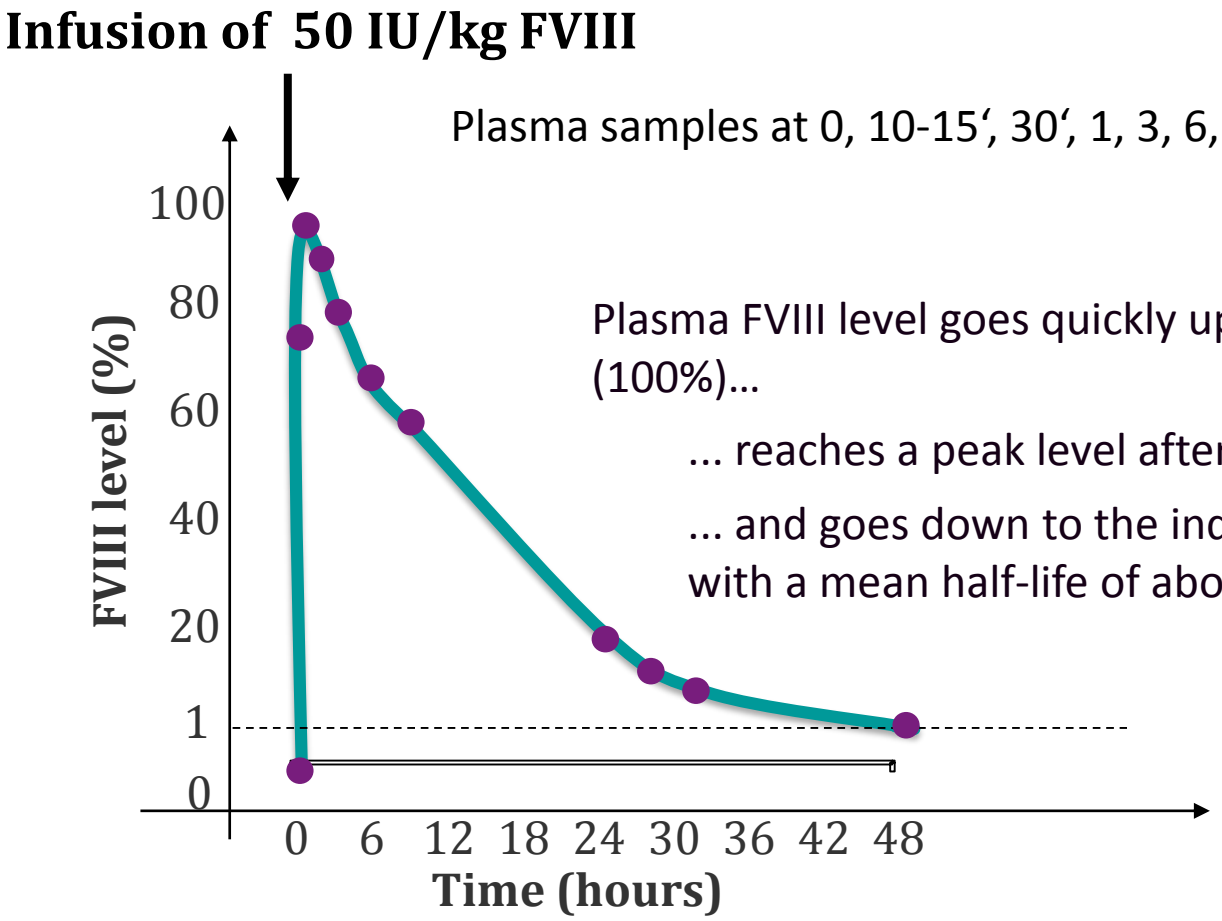
Why may PK-guided prophylaxis be important?

- Enables precise adjustment of dosing level and frequency to maintain adequate haemostatic levels and prevent bleeding

- Measuring PK parameters
  - **Individual PK profile**
    - Factor levels are measured at multiple time points (too many)
    - Ordeal for patients – particularly children.
  - **Population-based PK**
    - Model developed based on algorithm to estimate an individual's PK profile using only a few time points

Collins PW et al. *Heamophilia* 2011;17:2-10.

What do PK curves look like and which PK parameters are usually measured ?



Do you undertake pharmacokinetic assessment of patients on prophylaxis?

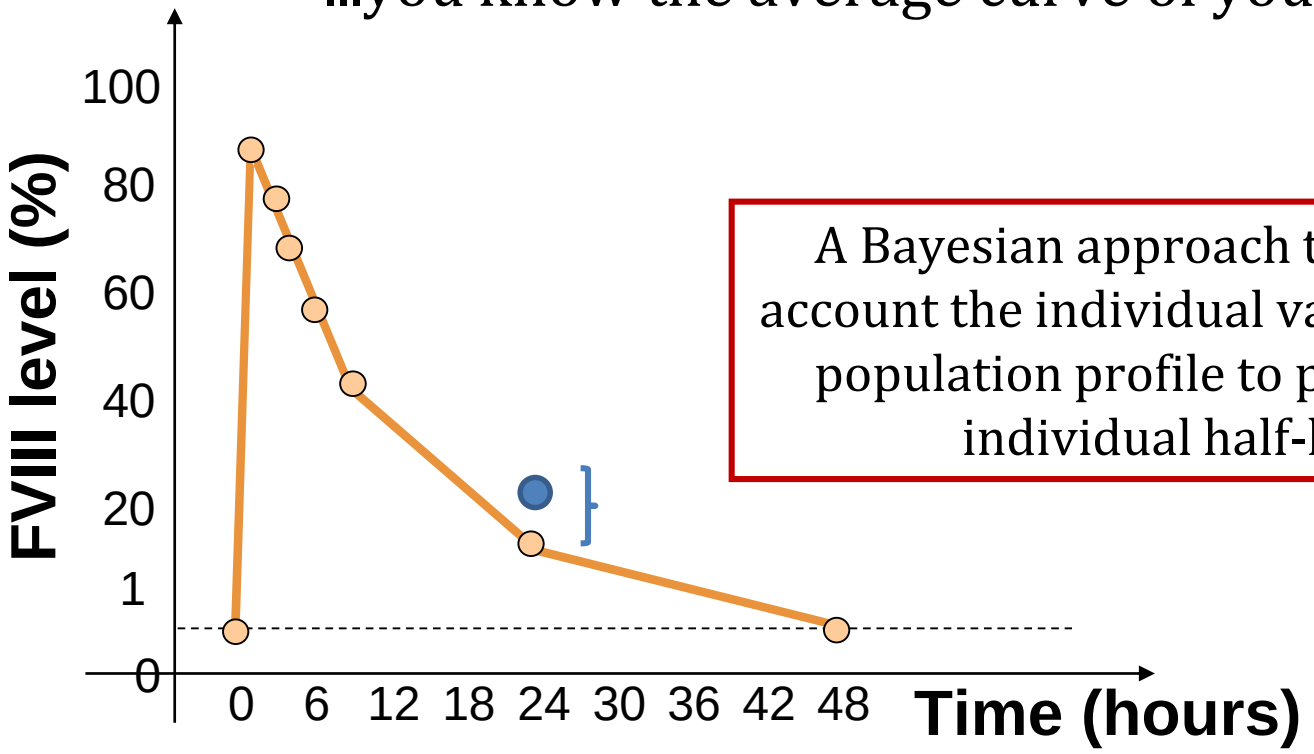
1. Trough levels
2. Formal PK assessment
3. Modified PK assessment
4. Clinical assessment only (bleeding)

What are the barriers to formal (full) PK assessment

1. Too difficult for the patient
2. Not necessary to know full PK profile
3. Better way of performing PK
4. All of the above
5. Other

Bayesian Pharmacokinetic evaluation

...you know the average curve of your population!



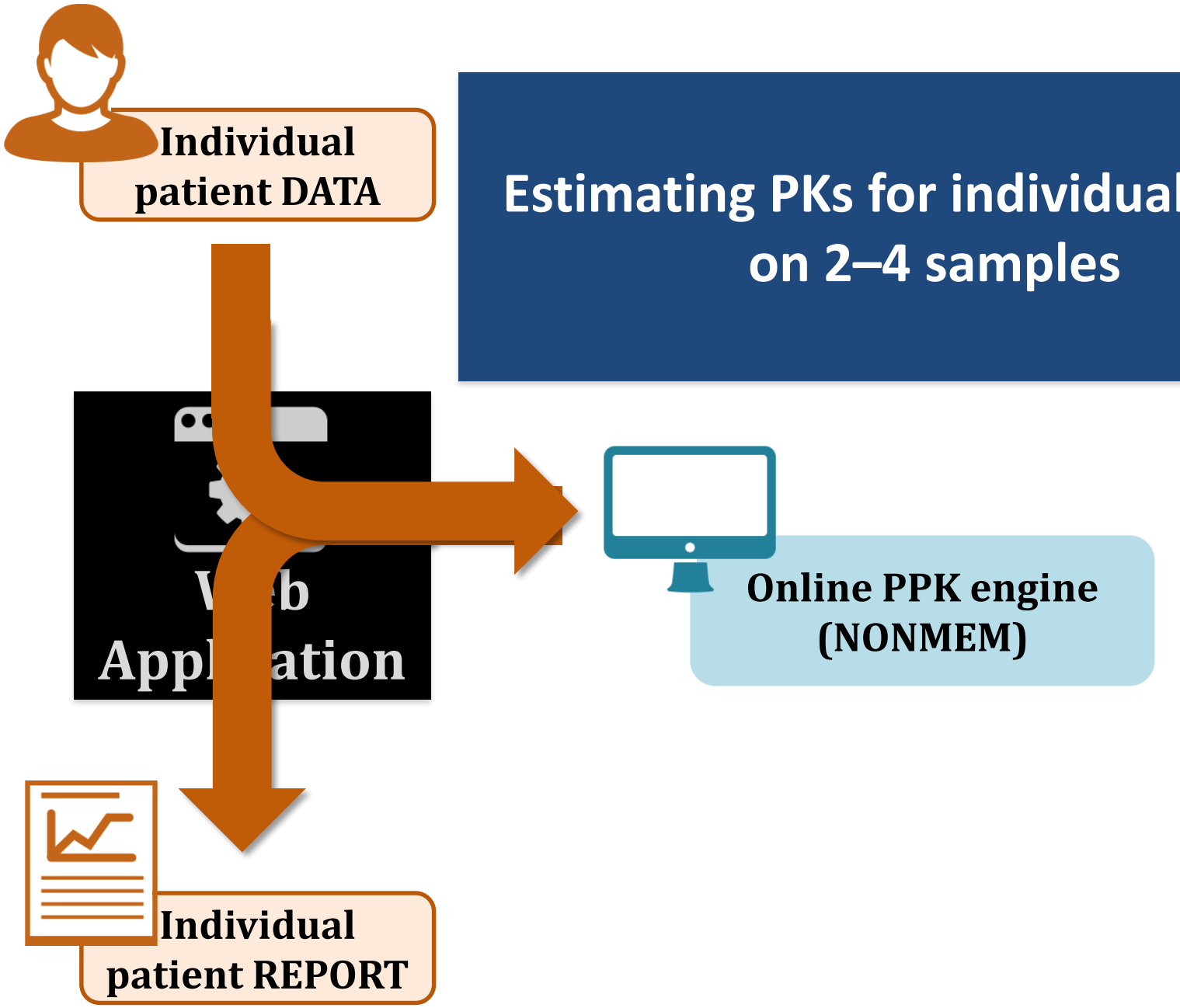
A Bayesian approach takes into account the individual value and the population profile to predict an individual half-life

Join the WAPPS network at:
www.wapps-hemo.org

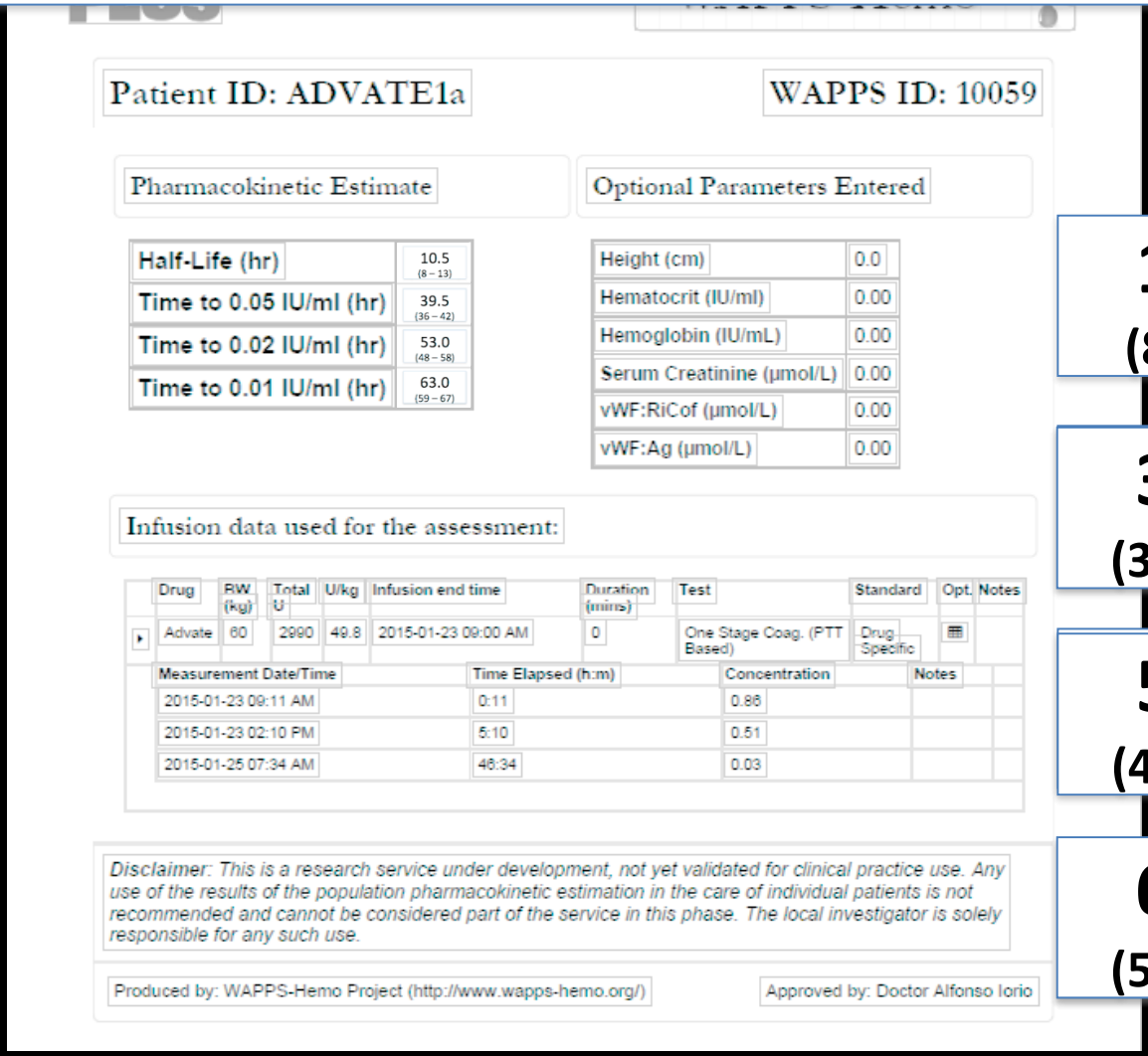
Using PK data

Need a user-friendly way of using Bayesian analysis

- Software programmes
- Input data – desired goals – doses and intervals


Individual patient DATA
Estimating PKs for individuals based on 2–4 samples
Web Application
Online PPK engine (NONMEM)
Individual patient REPORT

Pharmacokinetic Estimates



Patient ID: ADVATE1a

WAPPS ID: 10059

Pharmacokinetic Estimate

Half-Life (hr)	10.5 (8 – 13)
Time to 0.05 IU/ml (hr)	39.5 (36 – 42)
Time to 0.02 IU/ml (hr)	53.0 (48 – 58)
Time to 0.01 IU/ml (hr)	63.0 (59 – 67)

Optional Parameters Entered

Height (cm)	0.0
Hematocrit (IU/ml)	0.00
Hemoglobin (IU/mL)	0.00
Serum Creatinine (µmol/L)	0.00
vWF:RiCof (µmol/L)	0.00
vWF:Ag (µmol/L)	0.00

Infusion data used for the assessment:

Drug	BW (kg)	Total U	U/kg	Infusion end time	Duration (mins)	Test	Standard	Opt.	Notes
Advate	60	2990	49.8	2015-01-23 09:00 AM	0	One Stage Coag. (PTT Based)	Drug Specific		

Measurement Date/Time	Time Elapsed (h:m)	Concentration	Notes
2015-01-23 09:11 AM	0:11	0.86	
2015-01-23 02:10 PM	5:10	0.51	
2015-01-25 07:34 AM	48:34	0.03	

Disclaimer: This is a research service under development, not yet validated for clinical practice use. Any use of the results of the population pharmacokinetic estimation in the care of individual patients is not recommended and cannot be considered part of the service in this phase. The local investigator is solely responsible for any such use.

Produced by: WAPPS-Hemo Project (http://www.wapps-hemo.org/)

Approved by: Doctor Alfonso Iorio

10.5
(8 – 13)

39.5
(36 – 42)

53.0
(48 – 58)

63.0
(59 – 67)

Pharmacokinetic Estimates

Half-Life (hr)	10.5 (8 – 13)
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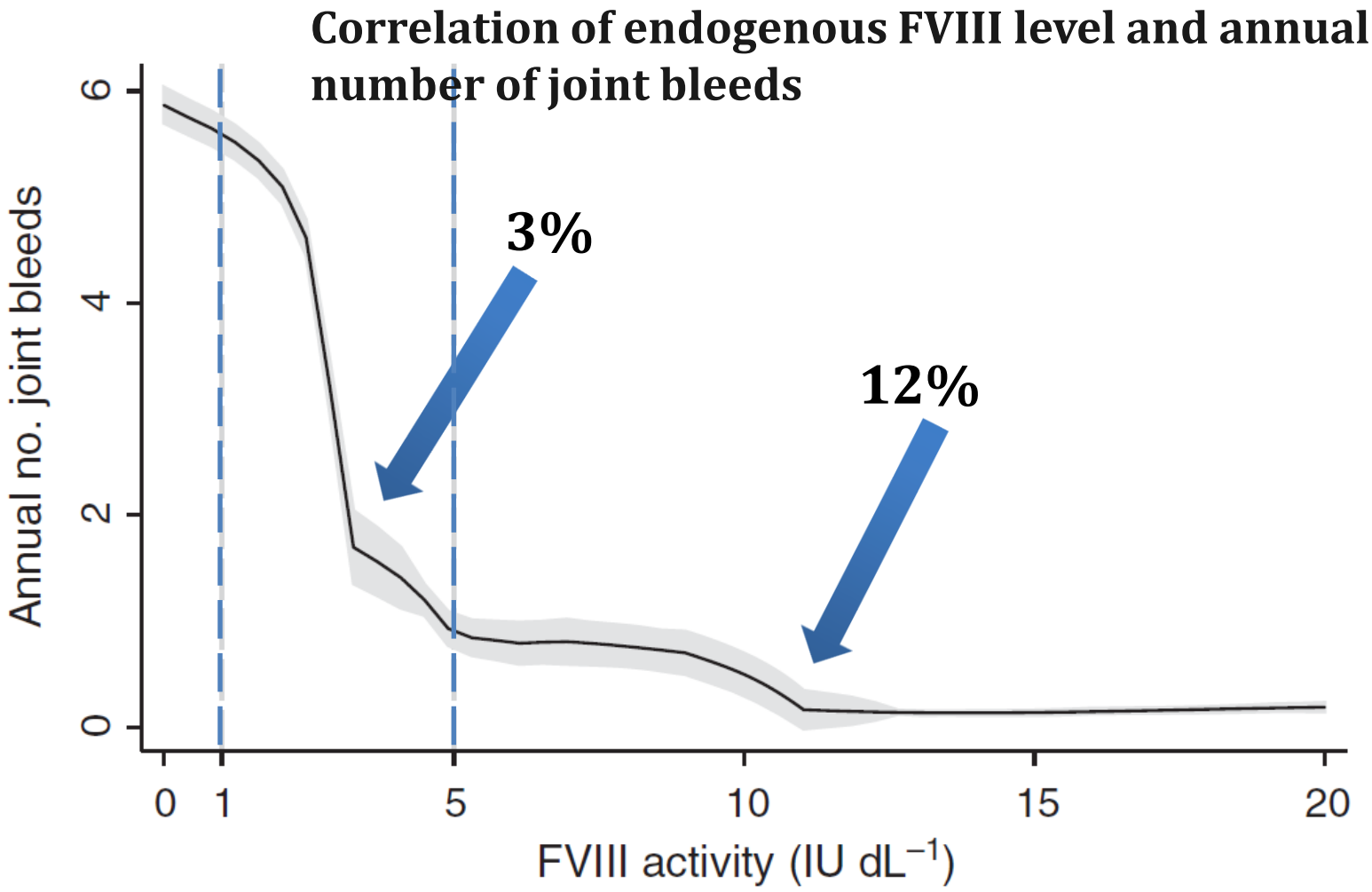
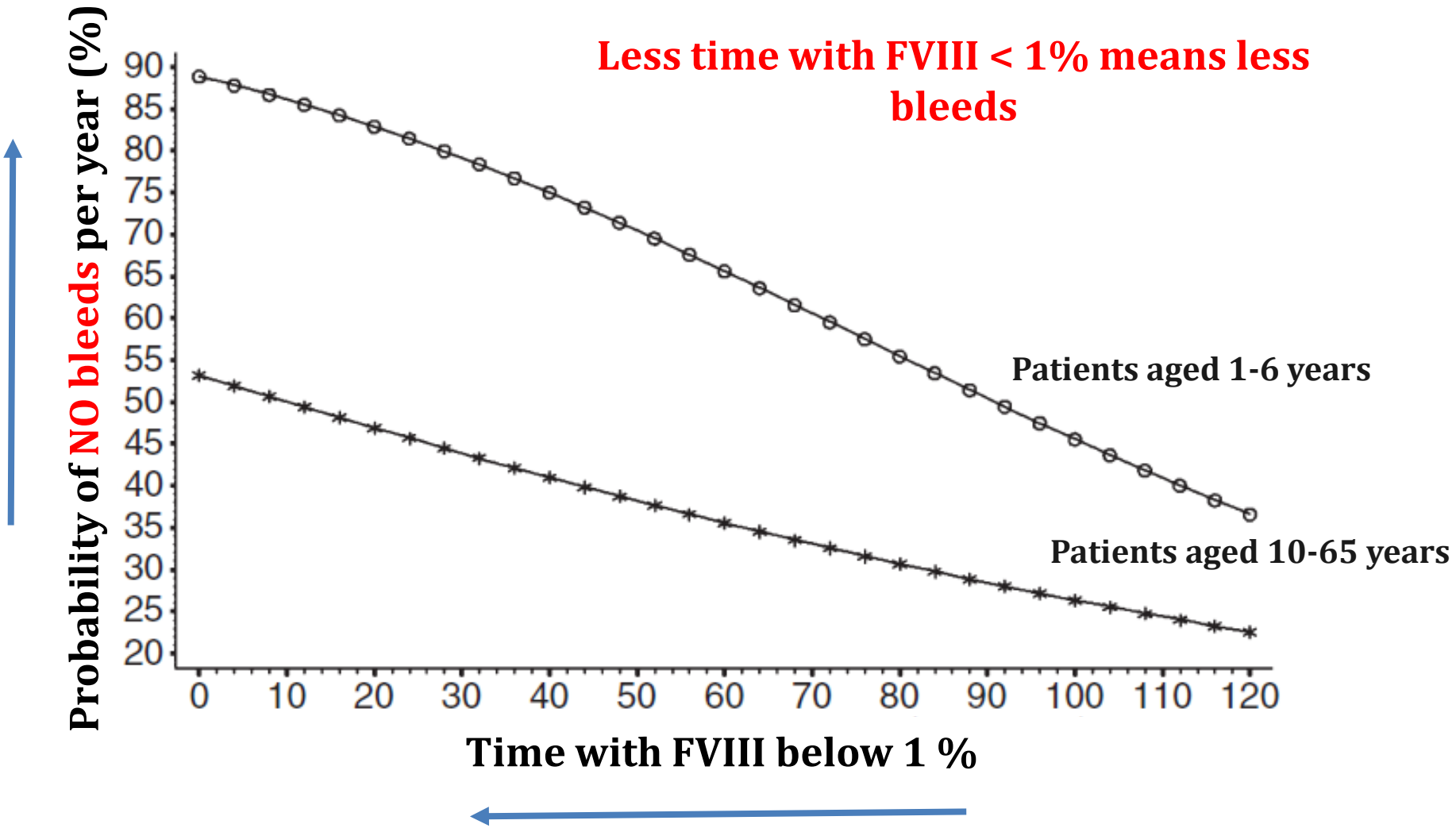
Time to 0.02 IU/ml (hr)	53.0 (48 – 58)
Time to 0.01 IU/ml (hr)	63.0 (59 – 67)

Which FVIII Trough Levels are needed to achieve Zero Joint Bleeds?



Den Uijl et al. *Haemophilia* 2011; 6: 849-53

Correlation of Time spent below 1% FVIII and Bleeding Risk in Severe Hemophilia A



Adapted from Collins PW et al. *J Thromb Haemost.* 2009; 7(3): 413-

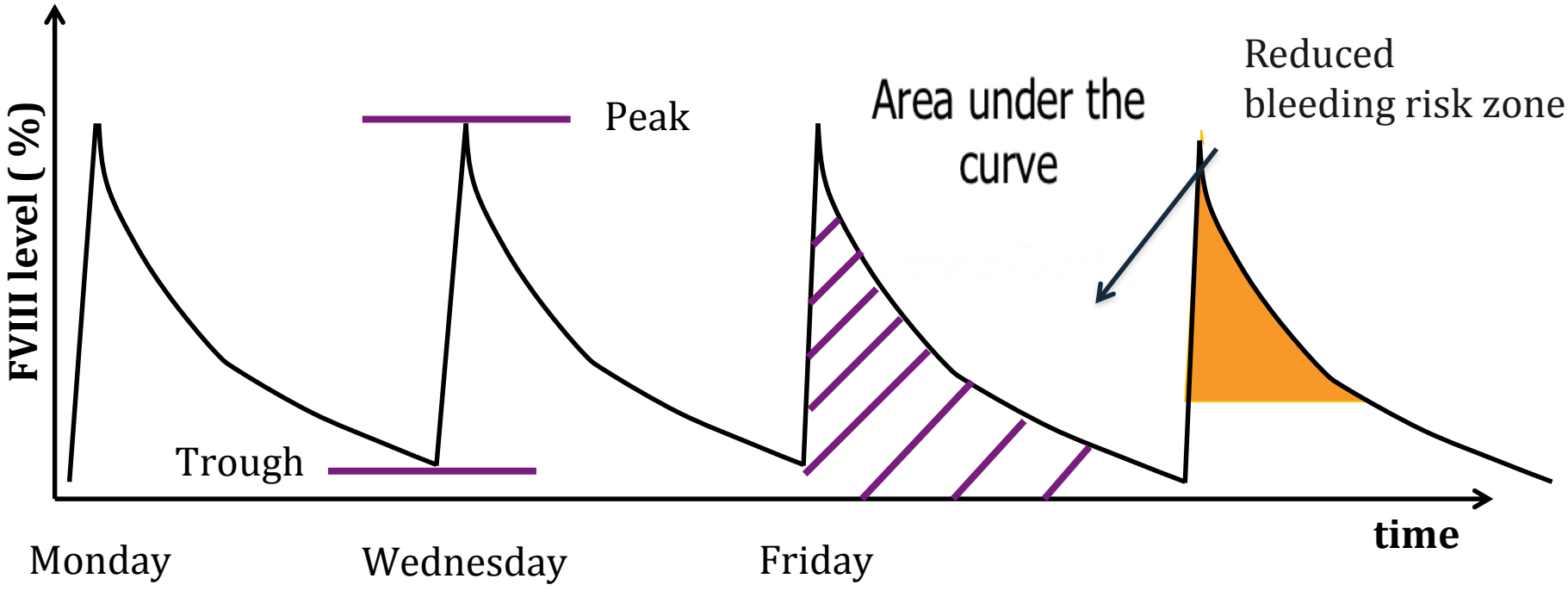
Patients with Different Lifestyle and Activity Level may need Different FVIII Trough Levels

>3% ?

10% ?

1% ?

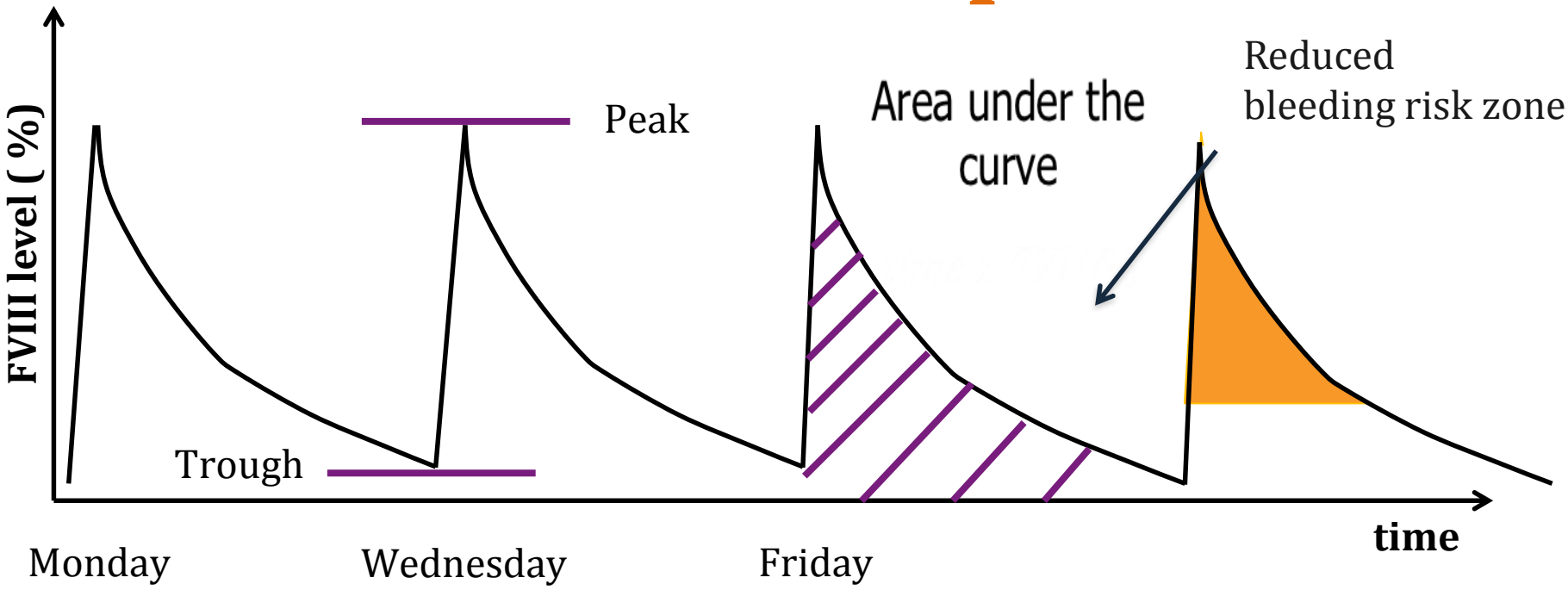
Which factors are important?



Under which circumstances might these parameters be useful?

Collins PW: Plenary lecture „Personalized Prophylaxis“ WFH congress July, 10 2012

Which factors are important?

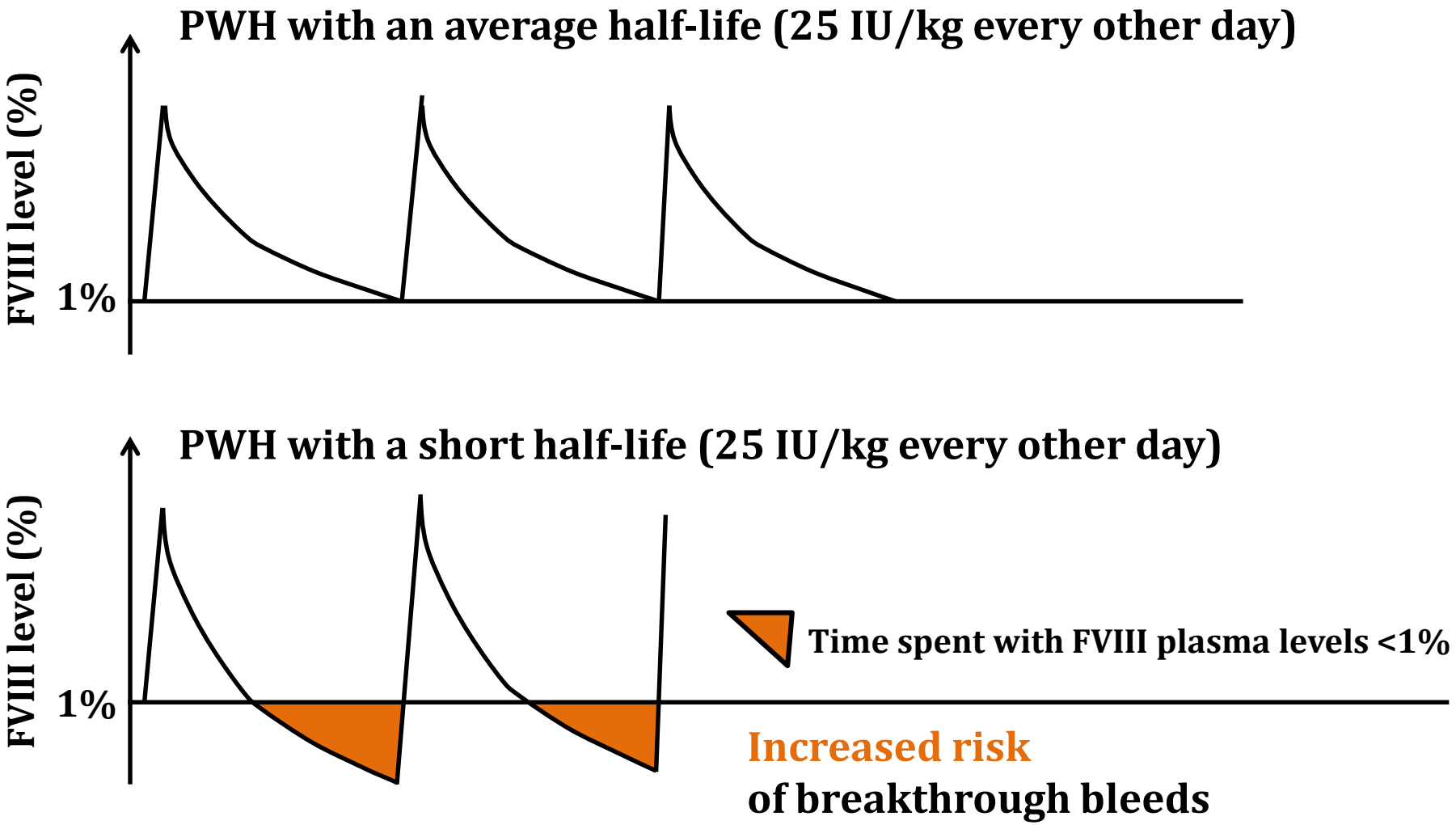


Peak / time spent in reduced bleeding risk zone:	Important to prevent activity related and traumatic bleeds
Trough	Important to prevent spontaneous break through bleeds
AUC	Important to prevent subclinical bleeds, maximizing the window of protection

Collins PW: Plenary lecture „Personalized Prophylaxis“ WFH congress July, 10 2012

Tailoring Treatment

Standard prophylaxis not optimal for everybody



What other parameters are important in determining regime?

Should trough levels be targeted and if so what should the target trough level be?

Bleeding is the key endpoint

To prevent bleeding, different patients very likely need different treatment schedules, depending on

- Physical activity (trauma)
- Target joints
- The rest of their haemostatic system

Prophylaxis strategy today

- **Weight-based standard dosing**
  - Expensive
  - Not flexible
  - May not be suitable for all patients
  - May not be necessary for all patients

Haemophilia

Haemophilia (2012), 18 (Suppl. 4), 1–12 DOI: 10.1111/j.1365-2516.2012.02822.x

ORIGINAL ARTICLE

WFH: Closing the global gap – achieving optimal care

MARK W. SKINNER
World Federation of Hemophilia, Washington, DC, USA

"...it may be time to consider whether a 1% target is sufficient to prevent bleeding or if it is simply conveniently based on existing economics and treatment protocol burdens (frequency of dosing and venous access).

Although it may seem impossible to imagine, based on currently available therapies, the paradigm may shift to a point were treatment goals could more closely mimic a normal state."

Personalised prophylaxis

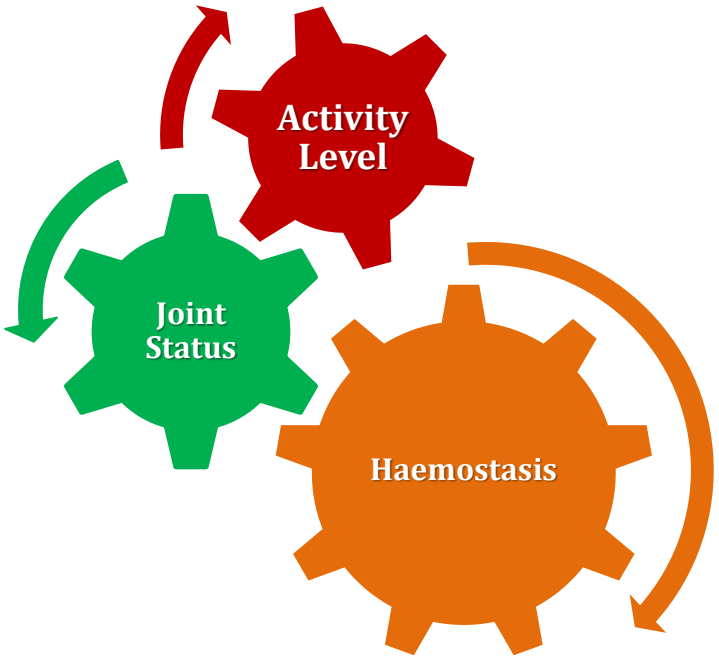
Tailor to breakthrough bleeds

- Take into account:
  - Target joints
  - Physical activity (and timing of sport)
  - The (predicted) trough level achieved (which depends primarily on the individual's t½)

- Is it necessary to use strict PK analysis?

Individualised prophylaxis: Should be …

- Based on FVIII PK parameters
- Based on bleed pattern (presence of target joints/joint damage)
- Tailored to activity level (sports)
- Tailored to personal circumstances
- Based on all available information
- Efficient

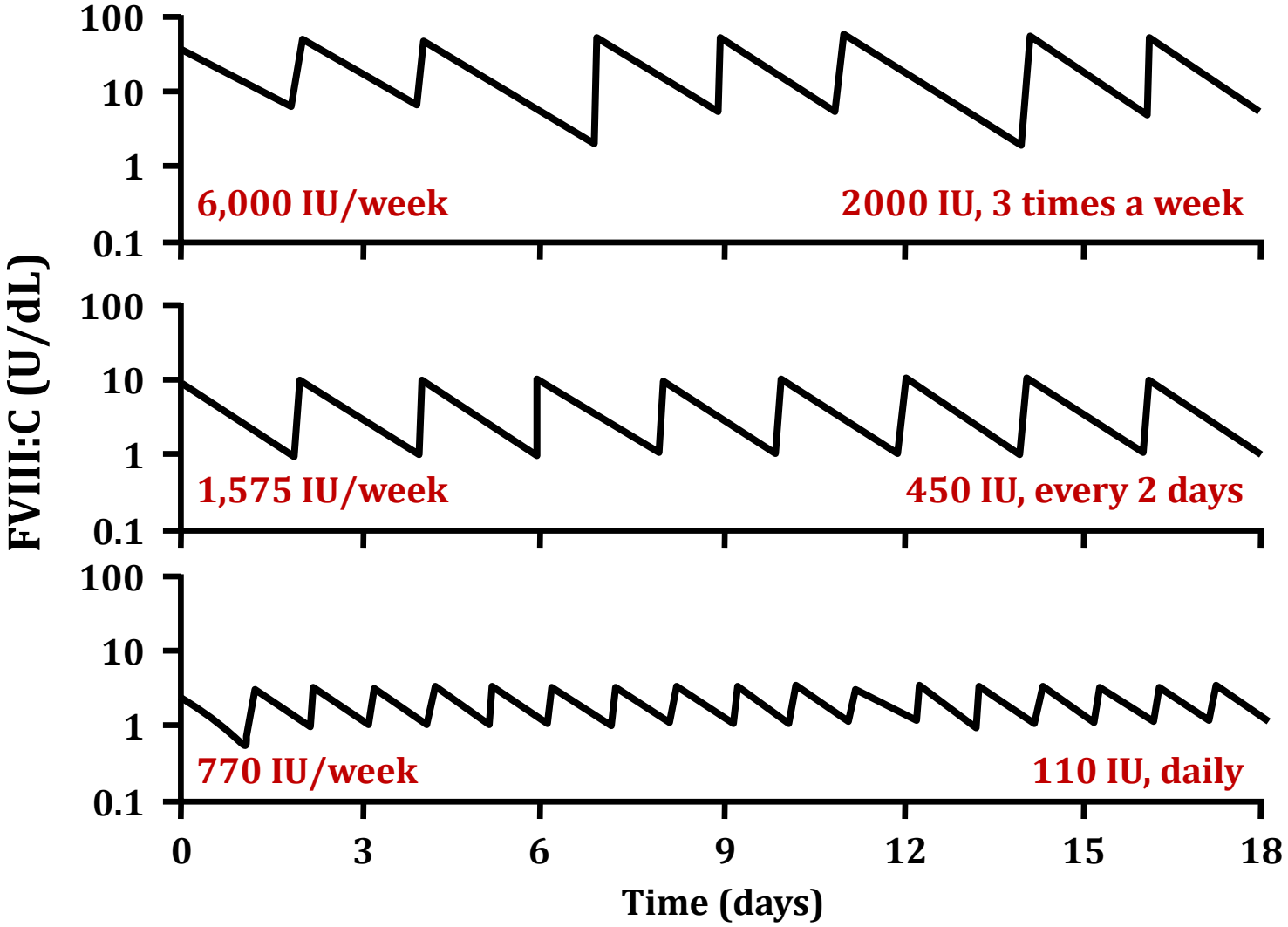


Valentino LA. *Haemophilia* 2014;20:607-15.

Strategies to Optimise Haemophilia Therapy by Individualising the Prophylactic Regimen to the Needs of Each Patient

Strategy	Parameter(s)
Clinical approach	Clinical bleeding pattern Clinical response to treatment
Pharmacokinetic approach	Individual PK data Number of infusions per week to maintain residual plasma FVIII > 1 %
Laboratory markers such as global haemostasis assays	Thrombin generation measurement may be useful for determining individually tailored prophylactic regimens

Pharmacokinetic dosing



Carlsson et al. *Eur J Haematol* 1993;51:247–52.

What about the new longer half-life products?

New "longer half-life" products

Bioengineering Strategy	Choice of Cell line	Products*	$T_{1/2}$ (h)	$T_{1/2}$ vs FVIII
Fc-Fusion protein (BDDrFVIII)	HEK	ELOCTA®[1]	~19	×1.6
Single site-specific PEGylation (40 KDa PEG) of a BDDrFVIII	CHO	N8-GP[2]	19	×1.6
Site-specific PEGylation (60 Kda PEG) of a BDDrFVIII	BHK	BAY-94[3]	19	×1.4
Controlled PEGylation (2 X 20 kDa branched-chain PEG) of FLrFVIII	CHO	BAX 855[4]	NA	×1.5

BHK: Baby Hamster Kidney; CHO: Chinese Hamster Ovary; HEK: Human Embryonic Kidney.

*Not all products are available / licensed in all markets. Please refer to your local summary of product characteristics for more information.

1. www.eloctate.com/about/half-life (Accessed October 2014). 2. Tiede A, et al. *J Thromb Haemost* 2013;11:670–678. 3. Coyle TE. *J Thromb Haemost.* 2014;12(4):488-96. 4. www.baxter.com/press_room/press_releases/2014/08_21_14_bax855.html (Accessed October 2014).

Headline 'Mean' Half-Life Extension Masks a Wide Variation in response

Variation in half-life with EHLs is greater than for 'standard' FVIII

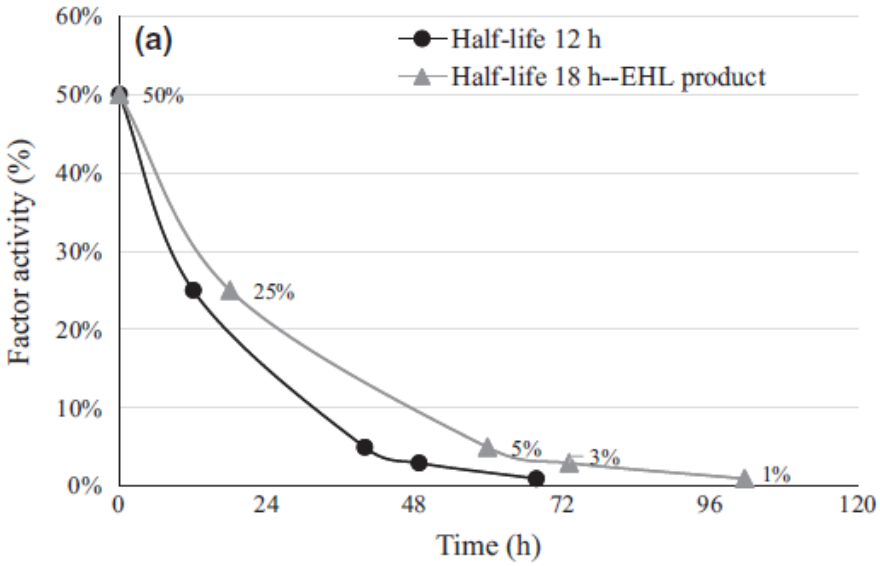
Those with a short half-life with standard FVIII will have a short half-life with an EHL

Croteau SE. *Haemophilia* 2015;21:285–288.

Comparative simulation of PK profiles of standard vs EHL FVIII products

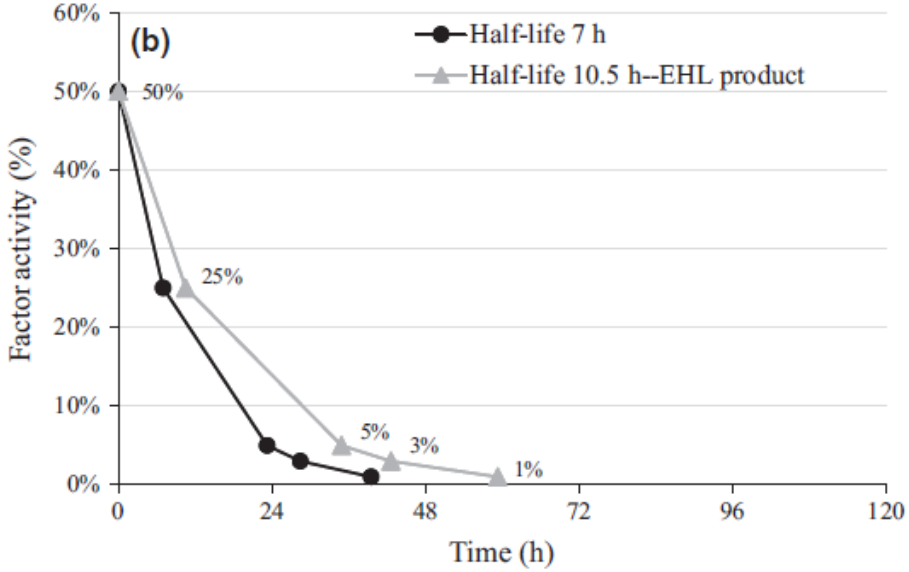
Anticipated half-life extension on EHL product of 1.5-times baseline PK profile

(A) Patient with average half-life of 12 h



(B) Patient with short half-life of 7 h

Not a rare situation, typical in paediatric patients



Croteau SE. *Haemophilia* 2015;21:285–288.

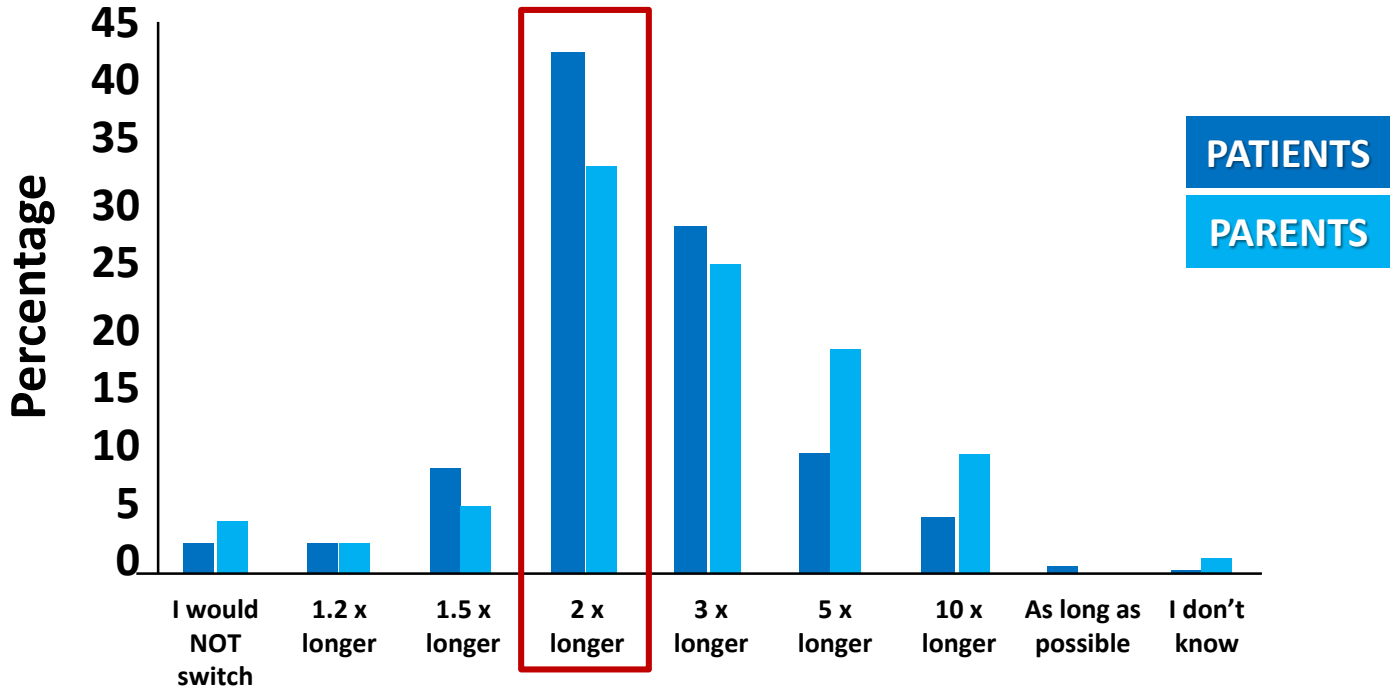
Children

- Shorter half-life than adolescents and adults
- Some children will not achieve significant extension of half-life with EHL-FVIII products
- May not be able to reduce the frequency of injections.

Young G, et al. *J Thromb Haemost* 2015;13:967–977.

Patient expectations of half-life extension

EHC Survey: Half-life prolongation time that would prompt switching to new EHL products among patients and parents



EHC Newsletter December 2015. http://static.ehc.eu/wp-content/uploads/EHC-Newsletter-December-2015-For-publication.pdf (Accessed September 2016).

Summary

Minimal improvements in FVIII half-life are not sufficient to warrant a switch

- **MUST** do PK assessment on potential patients

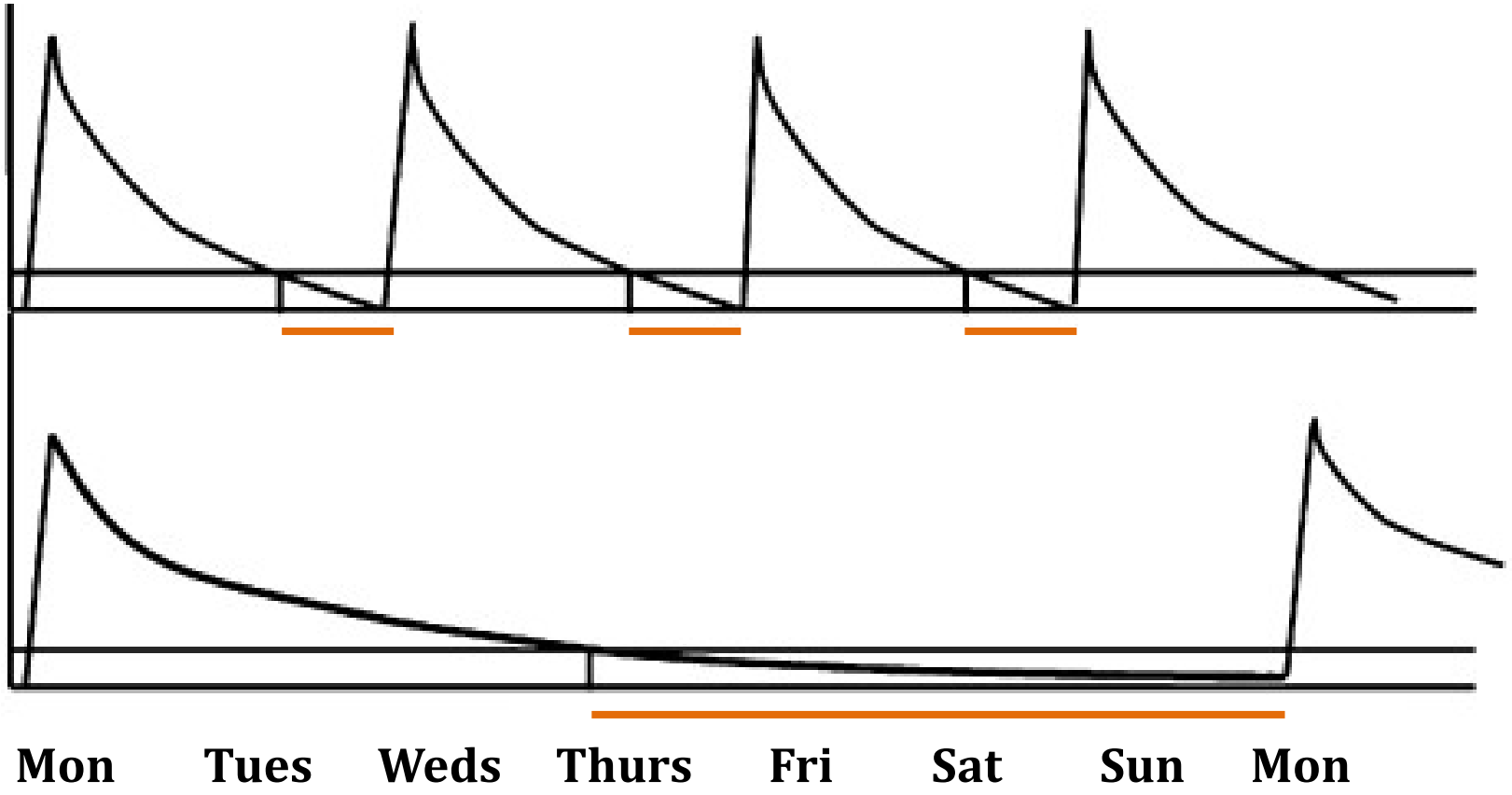
- Many children will not experience a significant increase in PK and so would not have a reduction in injection frequency

- For others – reducing dose frequency may not be cost effective

Summary (Contd)

- Detailed assessment to determine optimal treatment schedules for patients.
- Re-evaluate their whole prophylaxis and treatment regimes.
- How do you know what you are measuring?

When is the trough?



Collins P, et al. *Haemophilia* 2012;18:131-135

Trough level considerations related to longer-acting factors in clinical practice

Possible strategies

1. **Aim** for a **SIMILAR** trough level: Reduce dosing frequency

1. **Maintain** a **HIGHER** trough level: Reduce dosing frequency increase dose.

1. **Achieve** a **HIGHER** trough level: Maintain dosing frequency maintain dose.

Mahdi AJ, et al. *Br J Haematol* 2015; 169:768-76.

Some considerations

- Time spent at low levels needs to be considered since this is the main risk factor for breakthrough bleeds[1]
- Once-weekly prophylaxis may be achievable for some patients based on their individual PK and bleeding phenotype[2]
  - Individualisation may result in better outcomes
- People with a history of inhibitors may have a shorter individual half-life[1,2]
  - Fixed dosing regimens without individual PK assessment may not properly protect these patients from bleeding

1. Mahdi AJ, et al. *Br J Haematol* 2015; 169:768-76. **2.** Tiede A. *J Thromb Haemost* 2015; 13 Suppl 1:S176-9.

Further considerations regarding PK assessment

- In those patients who develop an inhibitor and who have undergone ITI

- What assessement do you use to judge success?

Agreed Definitions: Success, Failure, and Partial Success

As agreed at the ISTH VIII and IX SSC, Montepellier 2016

- **Success: Restoration of normal PK**
  - Recovery >66% and ½-life ≥7 hrs[1,2]
  - Or measurable FVIII trough 48 hrs after 50 IU/kg[4]

- **Partial response**
  - Stable clinical response to factor VIII, without an anamnestic rise in inhibitor with abnormal PK[1,4]

- **Failure**
  - Failure to achieve tolerance or partial response, with no specified time-limit

1. Hay CRM, DiMichele DM. *Blood*. 2012;119:1335-1344. **2.** Blanchette V et al. *J Thromb Haemost*. 2008,6:1319-1326.
3. Bjorkman S et al. *Blood*. 2012;119:612-618. **4.** Collins P et al. *Br J Haematol*. 2013;160:153-170.

Conclusions

- Renewed interest in exploring individual PK may help determine the best prophylaxis regime for an individual with haemophilia A
- Using Bayesian analysis, multiple sampling may not be required for determining PK
- For all patients, giving FVIII more often will be more cost-effective

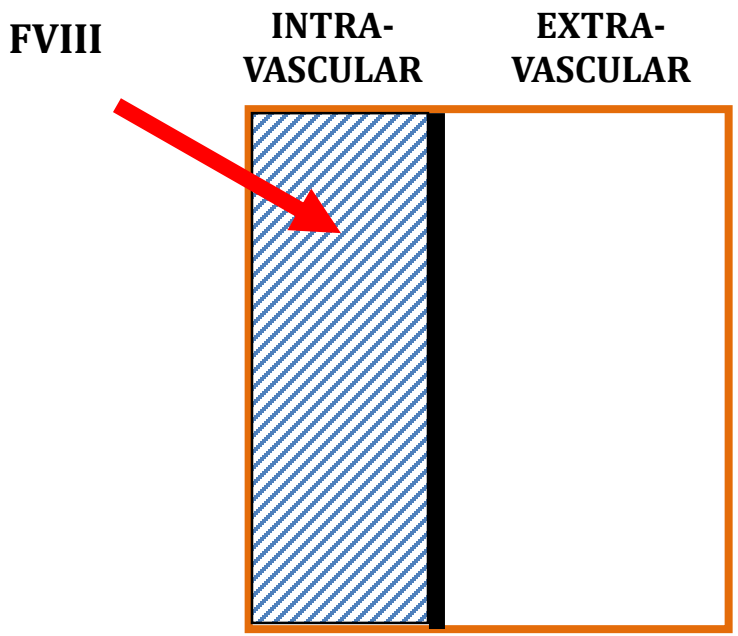
Conclusions (Contd)

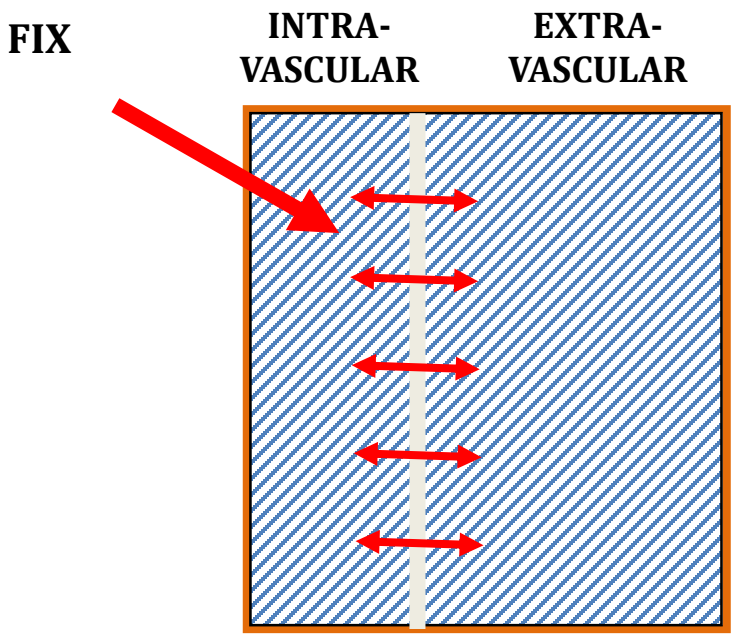
- Adherence is a major determinant of the effectiveness of prophylaxis and any regime will have be consensual
- Regimes limited by vial size and timing
- Assessment of joint bleeds (all manifestations) are the main determinants of clinical efficacy

Pharmacokinetics of FIX are more complex.

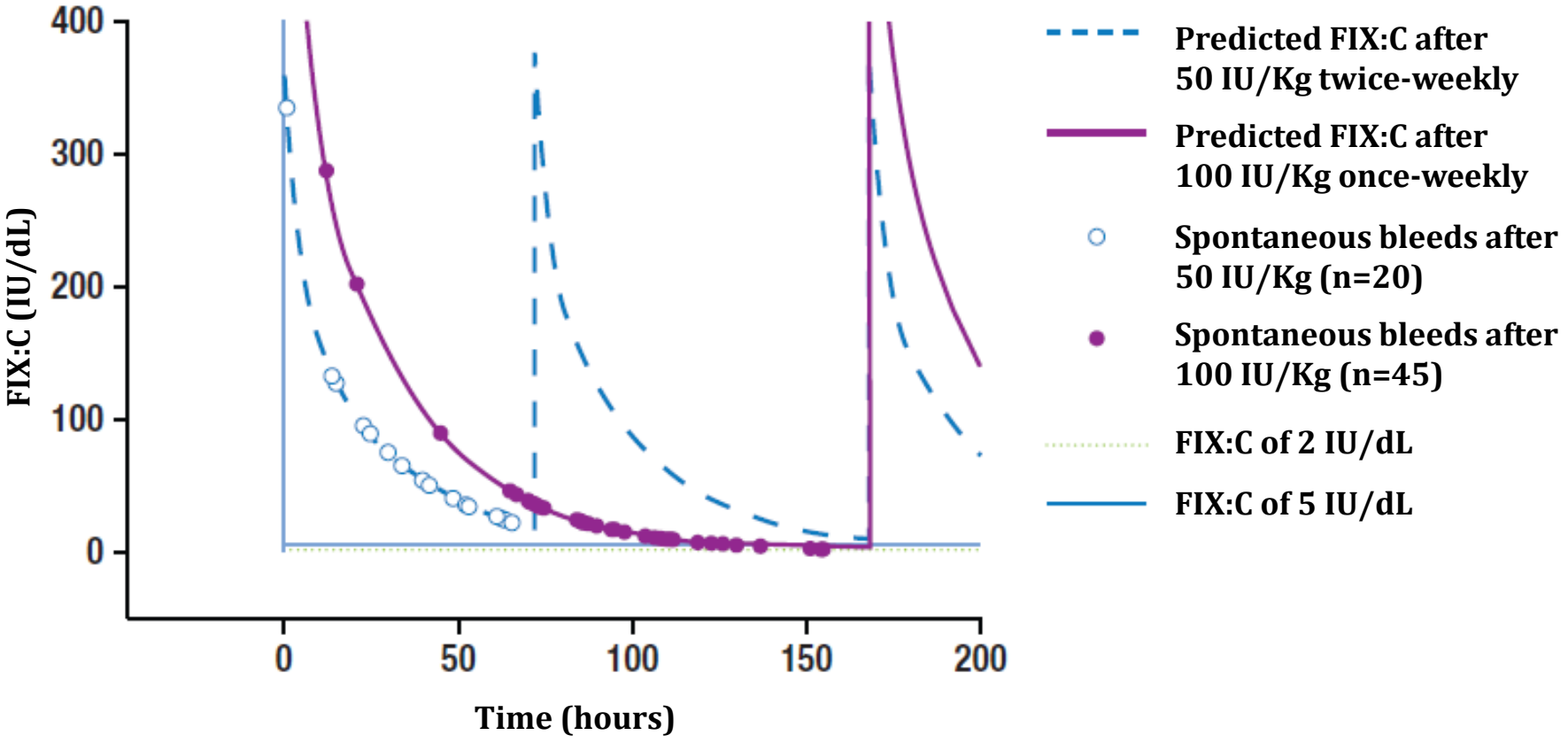
Influence of the molecular weight of FVIII and FIX on recovery

The distribution of FVIII and FIX between intra and extravascular spaces is influenced by their respective molecular weights



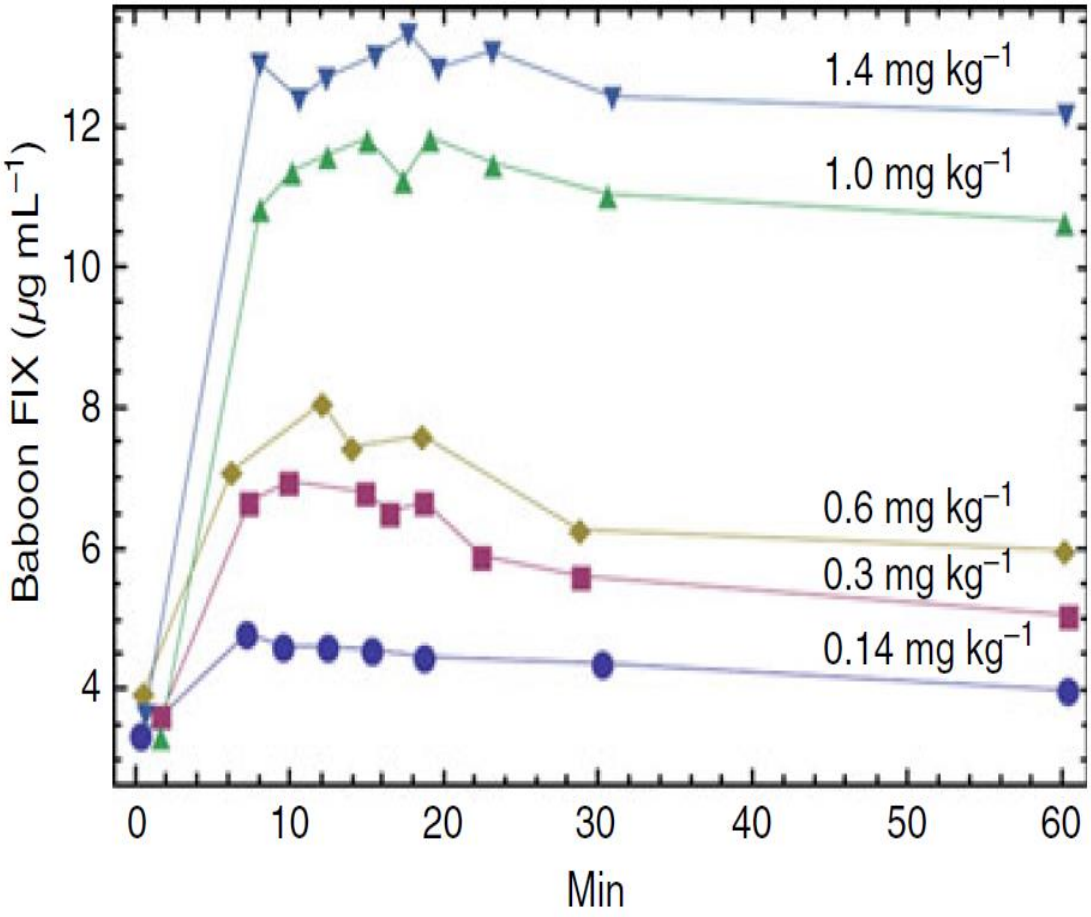


Time and Predicted FIX:C in Patients with Haemophilia B Having Spontaneous Bleeds During Prophylaxis



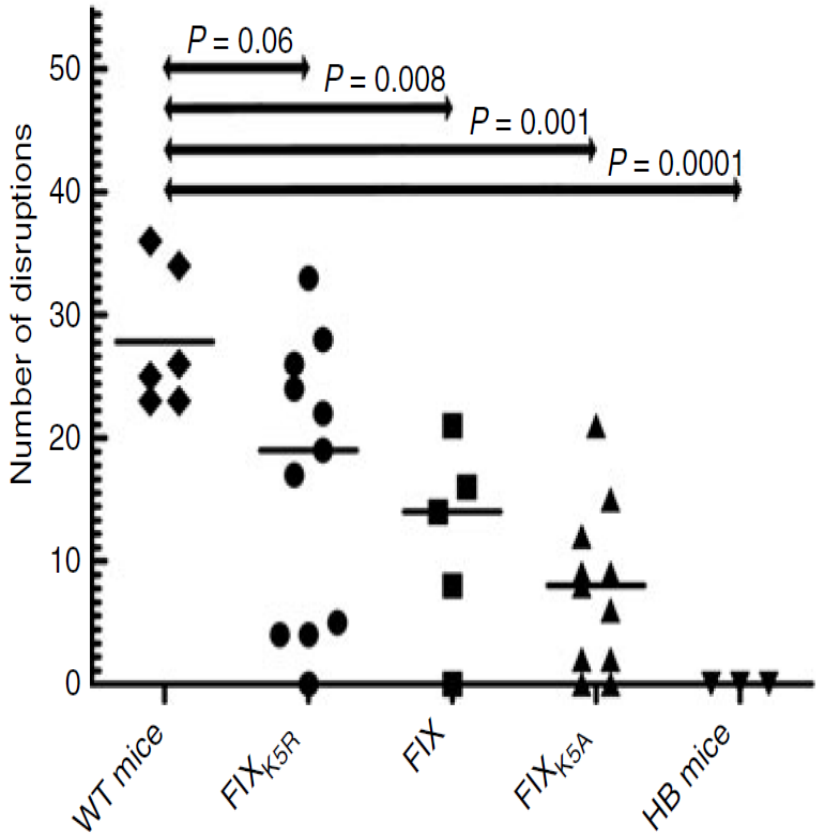
Poster Presented at the 53rd Annual Meeting of the American Society of Hematology, December 10–13, 2011, in San Diego, California.

Amount of baboon FIX released into the circulation following injection of bovine FIX at varying concentrations



Stern DM, et al. *Br J Haematol* 1987;66:227-232.

Ability to promote haemostasis 7 days after injection of different FIX molecules in mice



- FIX_{KFR} binds more tightly to collagen IV
- FIX_{K5A} binds less tightly to collagen IV

HB: Haemophilia B; WT: Wild-type

Feng D, Stafford KA, Broze GJ, Stafford DW. JTH 2013 11(12) 2176-2178.