Integrated modelling of factor VIII activity kinetics, occurrence of bleeds and individual characteristics in haemophilia A patients using a full random effects modelling (FREM) approach

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PAGE meeting
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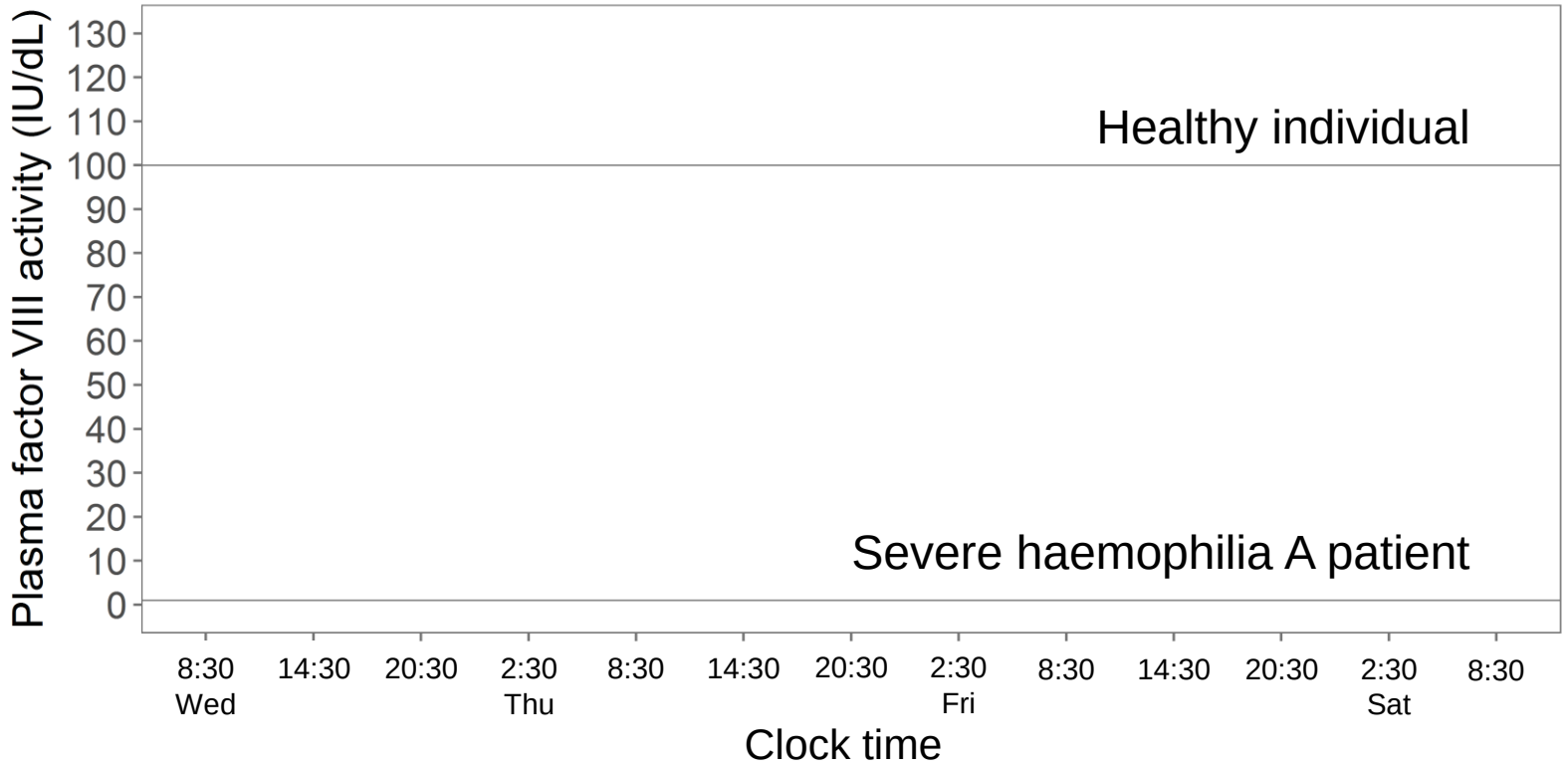
Haemophilia A

- Congenital X-linked bleeding disorder
- Deficiency of **coagulation factor VIII (FVIII)**
- Characteristic phenotype: bleeding events

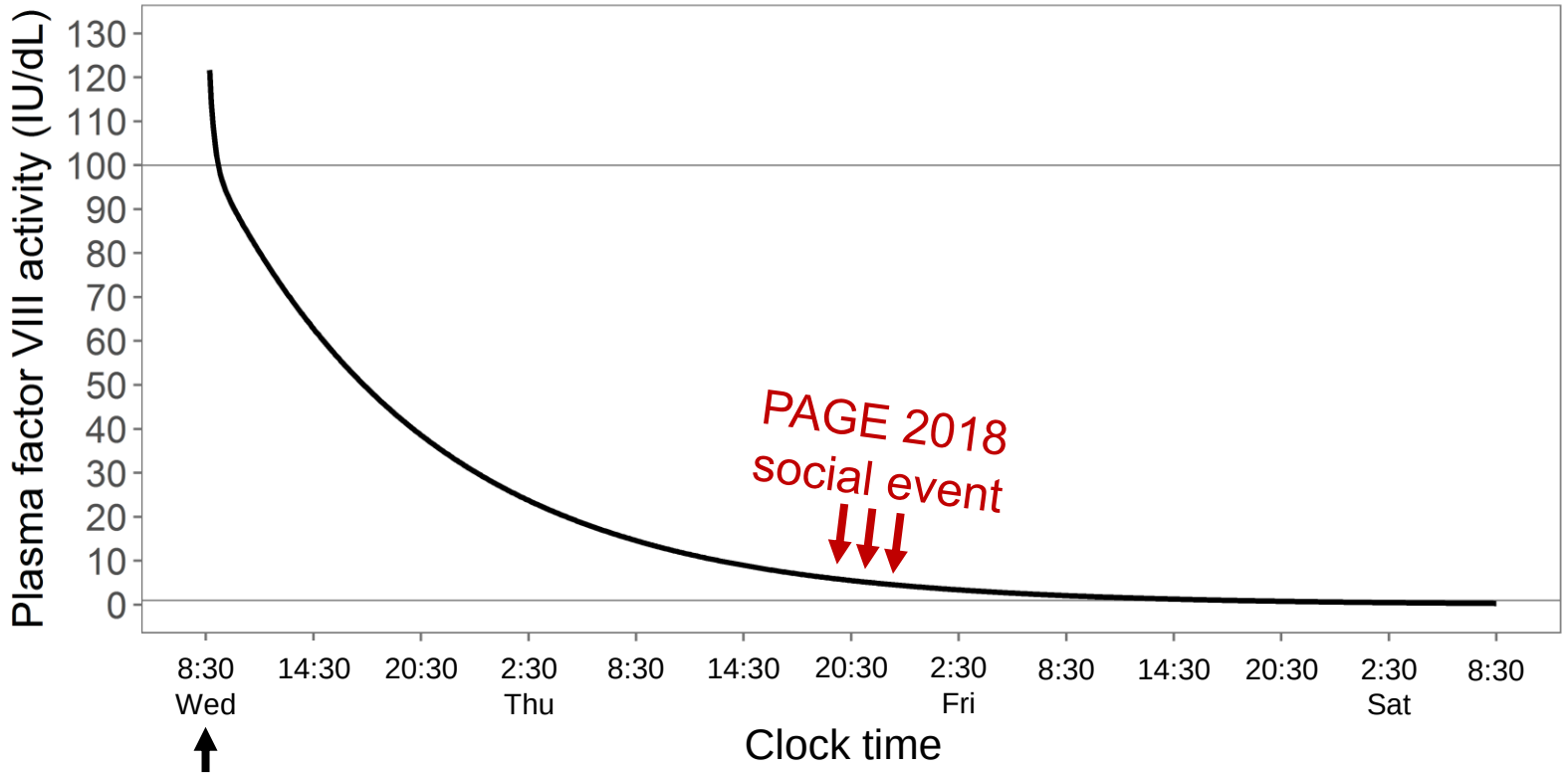
Severity[1]	Endogenous FVIII activity (IU/dL or % normal)	Bleeding events
Severe	< 1	Spontaneous bleeding
Moderate	1 – 5	Occasional spontaneous bleeding
Mild	5 – 40	Severe bleeding with major trauma

[1] Srivastava *et al.* Haemophilia. 2013 Jan;19(1):e1-47.

Haemophilia A



Haemophilia A



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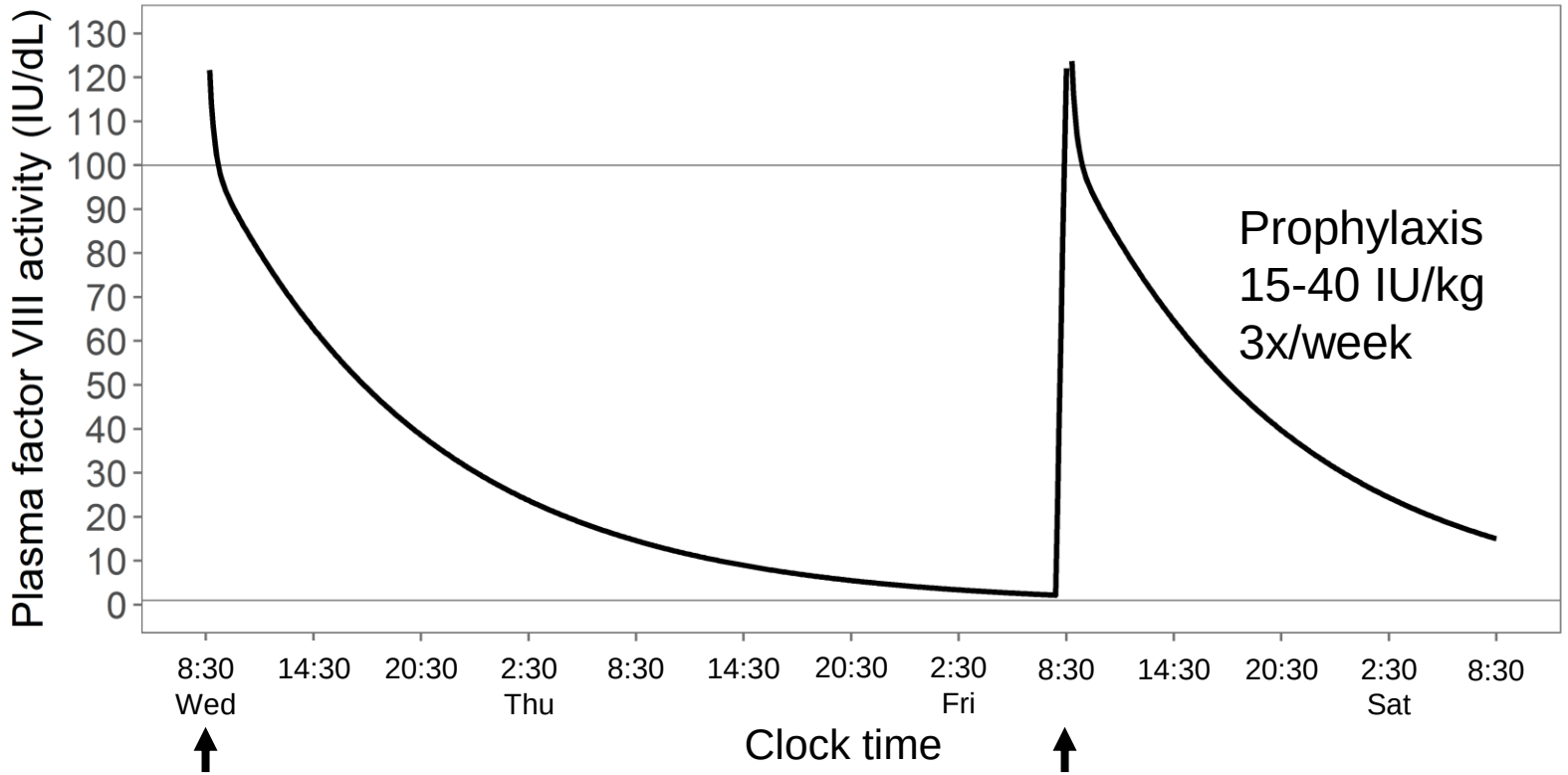
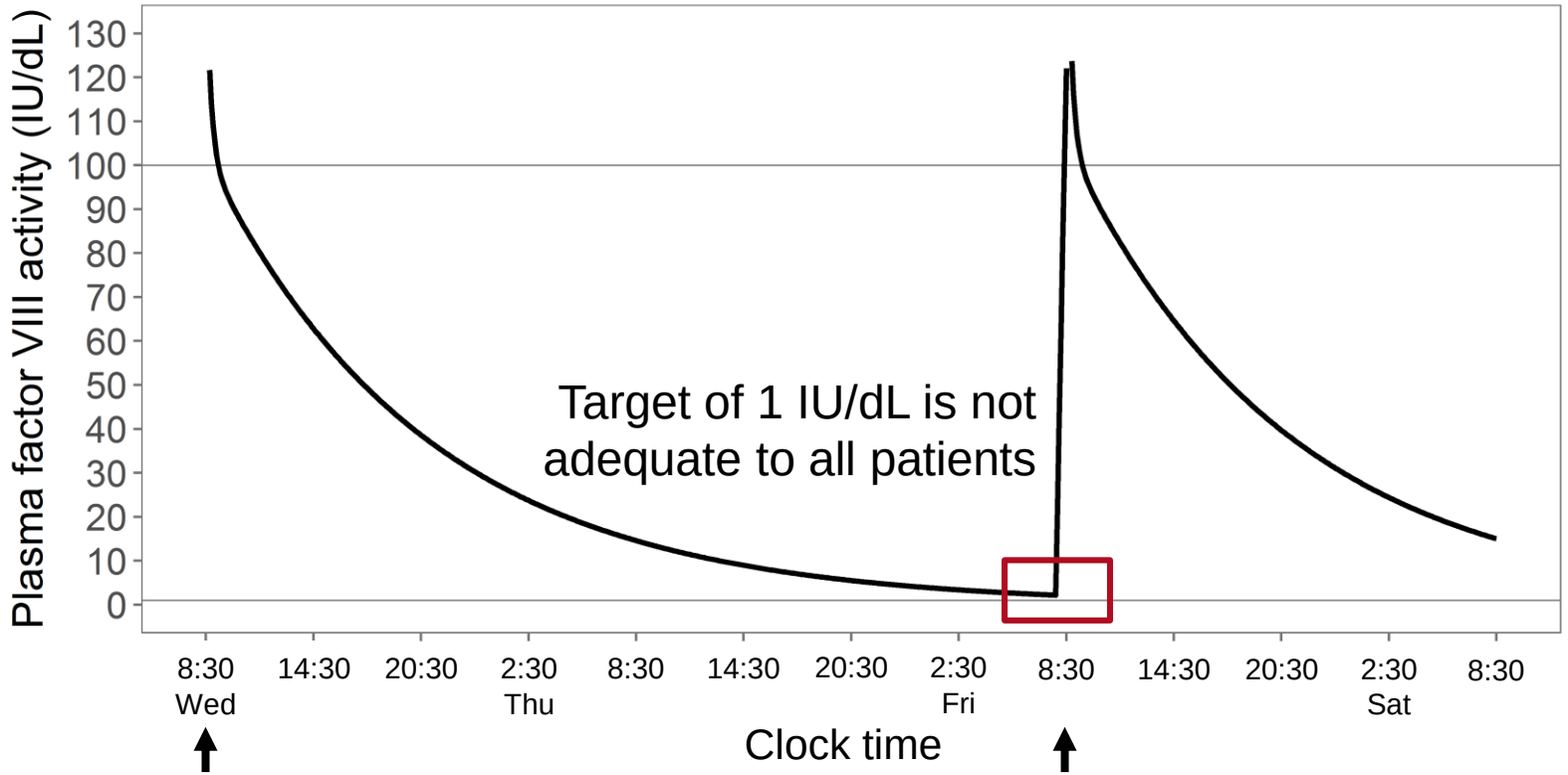
Haemophilia A

Today 8:30



Haemophilia A



Haemophilia A

Major economic burden

- Cost of €200 000/year across the five most populated EU countries[1]
  - 34-87 times higher than the mean per capita health expenditure

[1] O'Hara J, et al. Orphanet J Rare Dis. 2017;12(1):106.

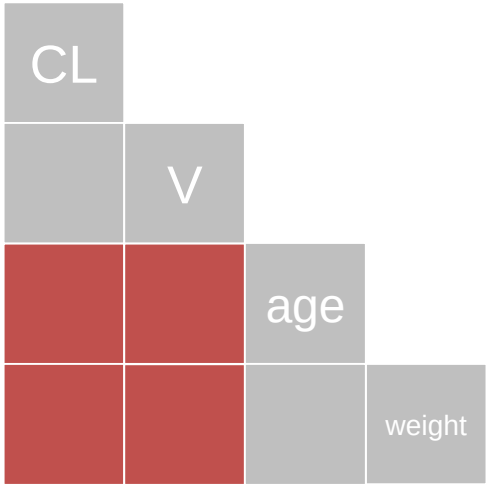
Full random effect modelling (FREM)

- Single-step simultaneous covariate model building technique [1,2]

- Covariates treated as observations and their distributions modelled as random effects

$$COV = \theta_{cov} + \eta_{cov}$$

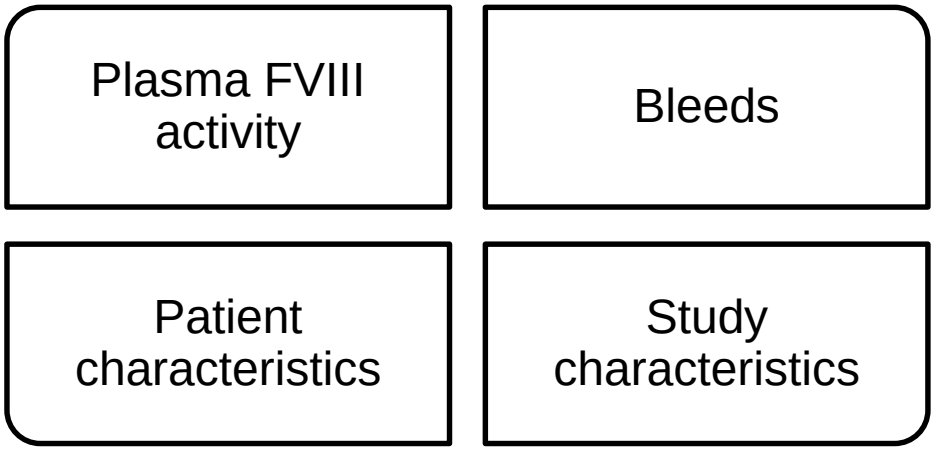
Covariance matrix



[1] Karlsson MO. PAGE 21 (2012) Abstr 2455 [www.page-meeting.org/?abstract=2455]
[2] Yngman et al. PAGE 26 (2017) Abstr 7365 [www.page-meeting.org/?abstract=7365]

Aim

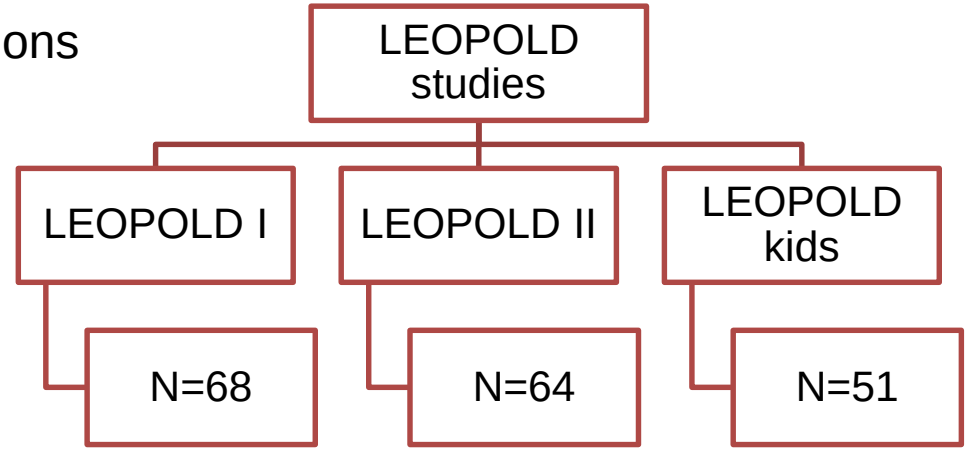
Develop an integrated pharmacometric model



Data

LEOPOLD clinical trials[1-3]

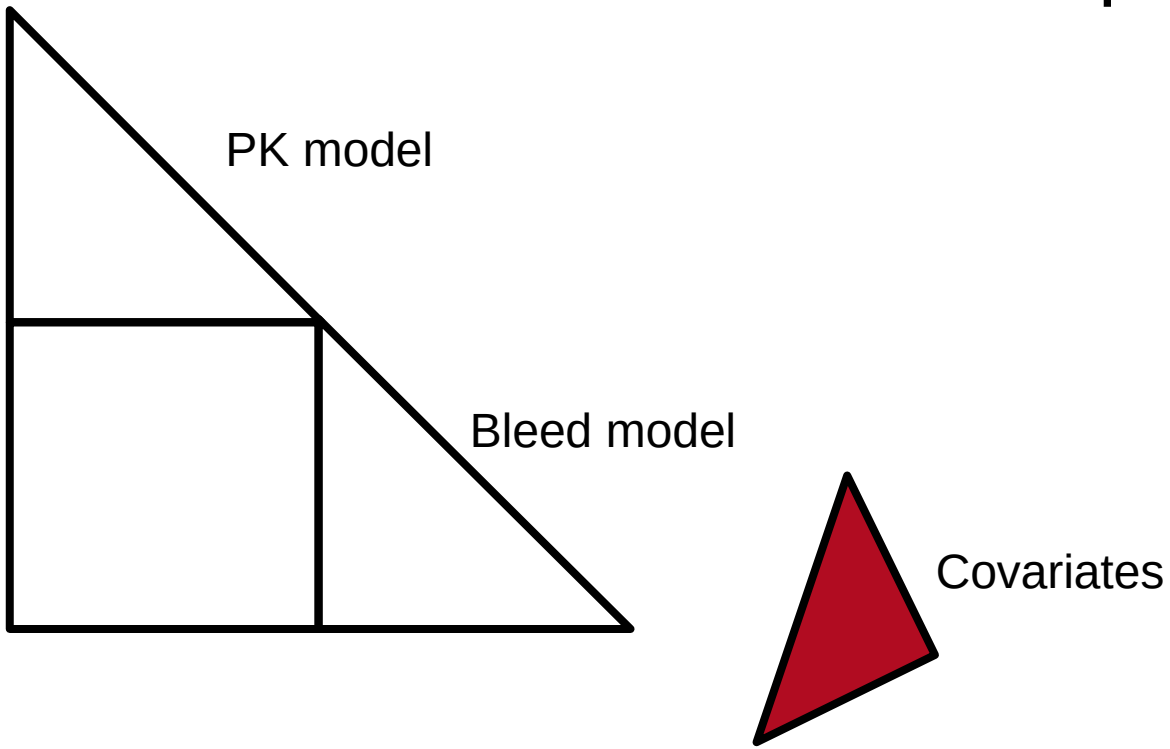
- Evaluated PK, efficacy and safety of BAY 81-8973 (octocog alfa, Kovaltry®)
  - 183 severe haemophilia A patients
  - 1535 FVIII activity observations
  - 633 bleeds



LEOPOLD: Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease

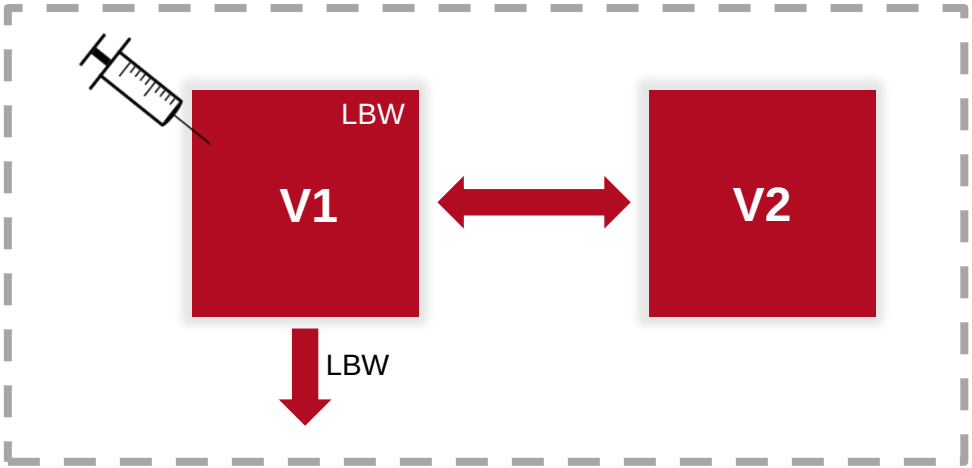
[1] Saxena K, et al. Haemophilia. 2016;22(5):706-12.
[2] Kavakli K, et al. J Thromb Haemost. 2015;13(3):360-9.
[3] Ljung R, et al. Haemophilia. 2016;22(3):354-60.

Model development



NONMEM 7.3 using LAPLACE/IMPMAP+IMP methods, assisted by PsN

PK model



$$CL\ (dL/h) = 1.88 \times \left(\frac{LBW}{51.1}\right)^{0.61}$$

$$V1\ (dL) = 30.0 \times \left(\frac{LBW}{51.1}\right)^{0.95}$$

$$Q\ (dL/h) = 1.90$$

$$V2\ (dL) = 6.36$$

IIV_{CL} = 29.7 % CV

IIV_{V1} = 11.1 % CV

IIV_{RUV} = 48 % CV

RUV_{add} = 1.45 IU/dL

RUV_{prop} = 21.1 % CV

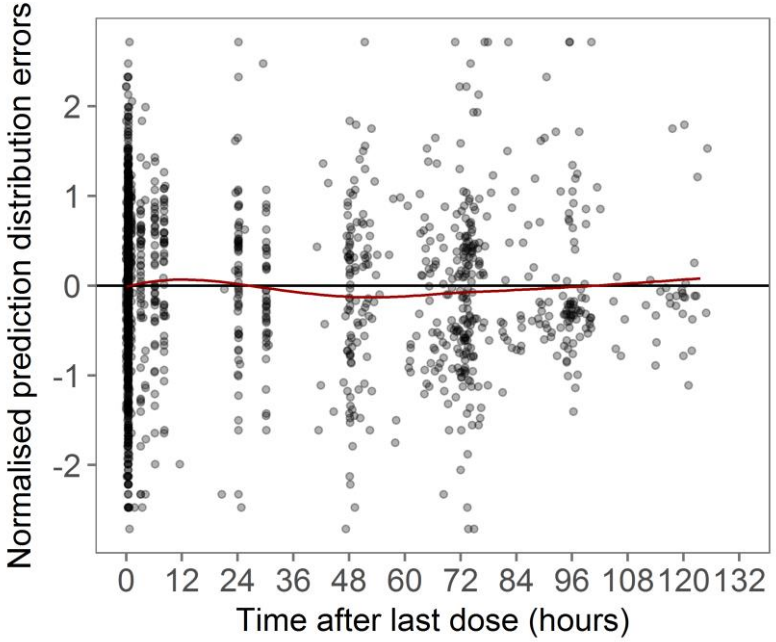
IIV: inter-individual variability

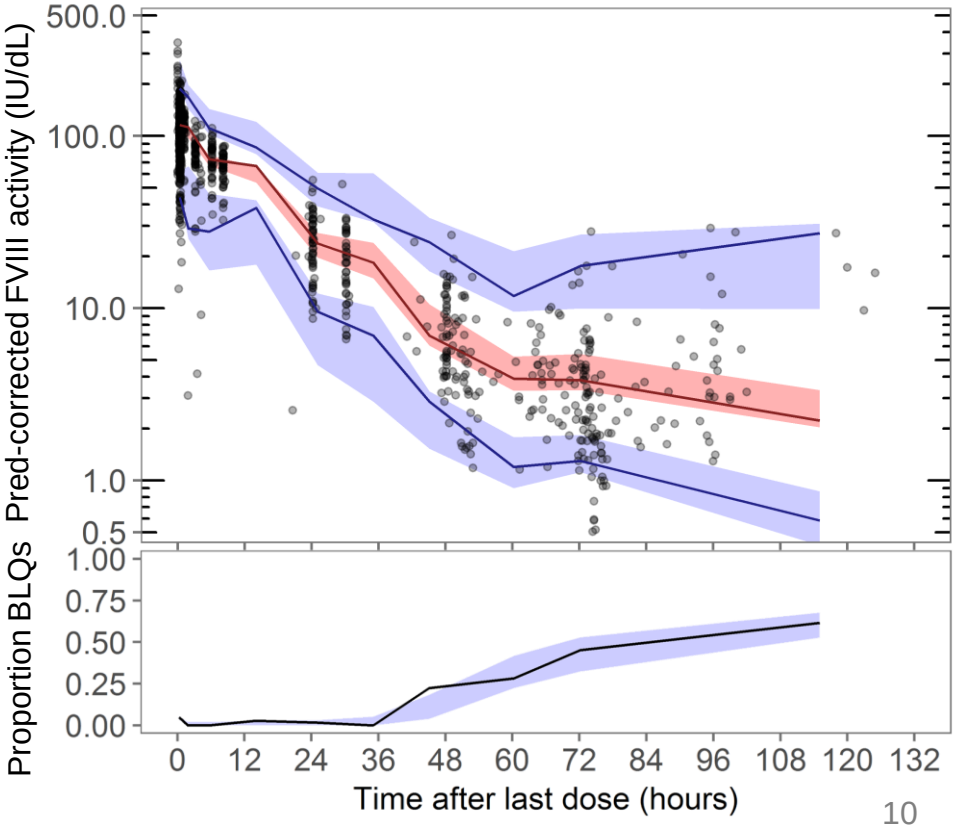
LBW: lean body weight

RUV: residual unexplained variability

Base model from Garmann *et al.* Haemophilia 2017 Jul;23(4):528-537

Model qualification: PK model



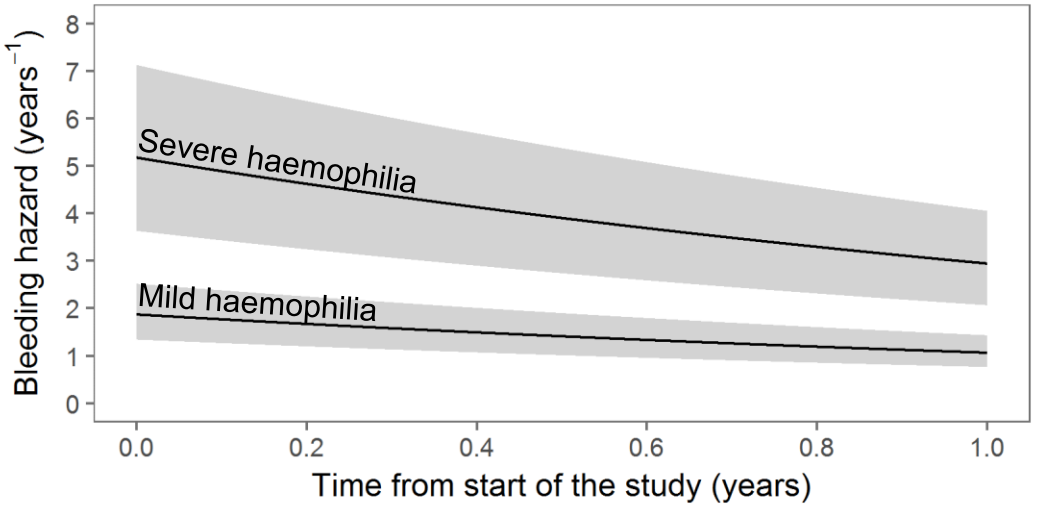


Repeated time-to-event (RTTE) model

$$h(t) = \lambda \cdot e^{\gamma \cdot (t - 1)} \cdot \left(1 - \frac{FVIII}{FVIII + IF50}\right)$$

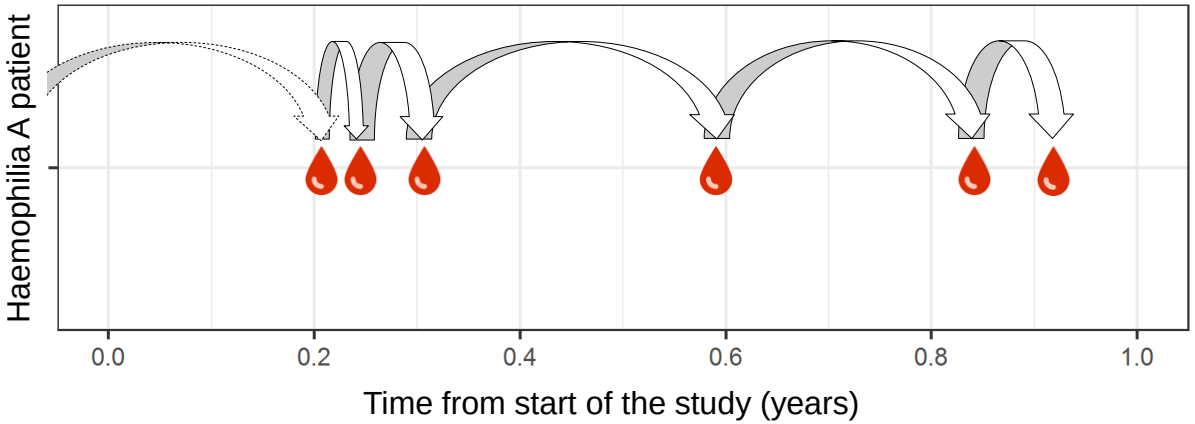
$\lambda_{0.5\ IU/dL}$ = 2.94 year^{-1}
$\lambda_{20\ IU/dL}$ = 1.06 year^{-1}
γ = -0.56 year^{-1}
IIV_{λ} = 129.5 %CV

Derived parameters
$\lambda_{(0\ IU/dL,\ 1\ year)}$ = 3.08 year^{-1}
IF50 = 11 IU/dL



95%CI obtained using sampling importance resampling
Base model from Garmann *et al*. PAGE 24 (2015) Abstr 3683 [www.page-meeting.org/?abstract=3683]

Time-dependency between consecutive bleeds?

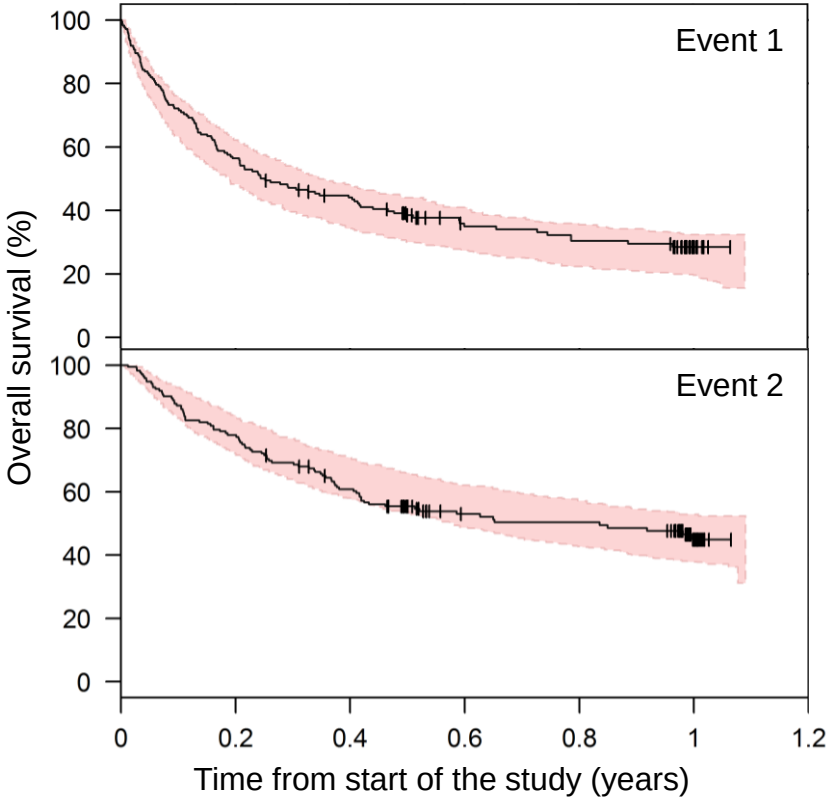


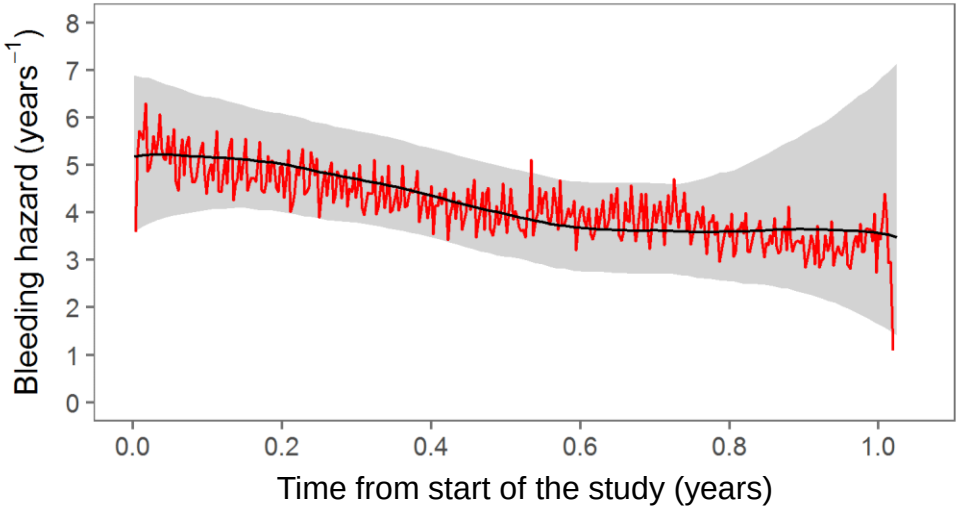
$$h(t) = \lambda \cdot e^{\gamma \cdot (t - 1)} \cdot \left(1 - \frac{FVIII}{FVIII + IF50}\right) + \lambda_{markov} \cdot e^{-\gamma_{markov} \cdot TSE}$$

At time=0, TSE derived from the mean inter-event time in the previous year

TSE: time since (last) event

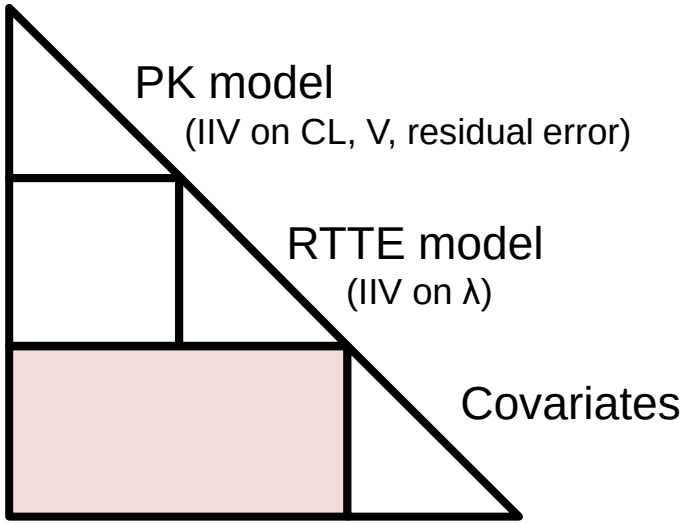
Model qualification: RTTE model





Kernel-based visual hazard comparison
Goulooze *et al.* AAPS J (2017) Nov 27;20(1):5

Covariate analysis

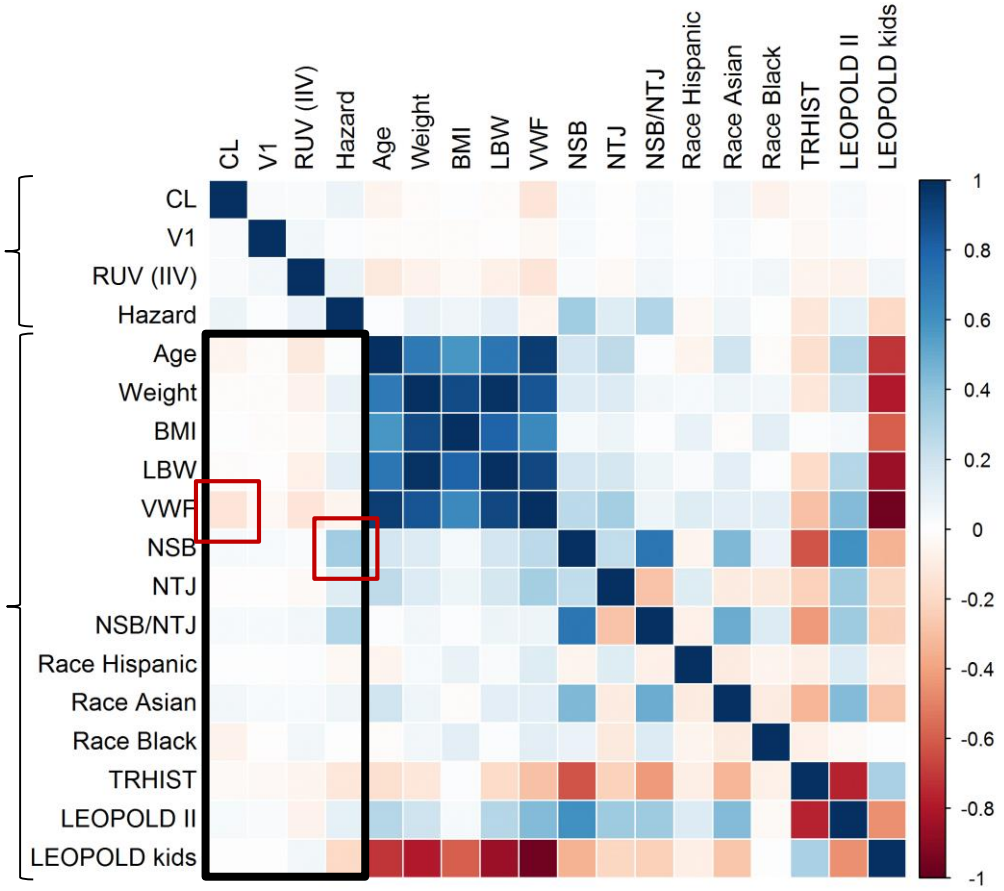


- Age
- Weight
- Body mass index
- Lean body weight
- Race
- Von Willebrand factor
- Number of spontaneous bleeds within 12 months pre-study
- Previous therapy history (on-demand/prophylaxis)
- Number of target joints at study start
- Study

FREM: correlation matrix

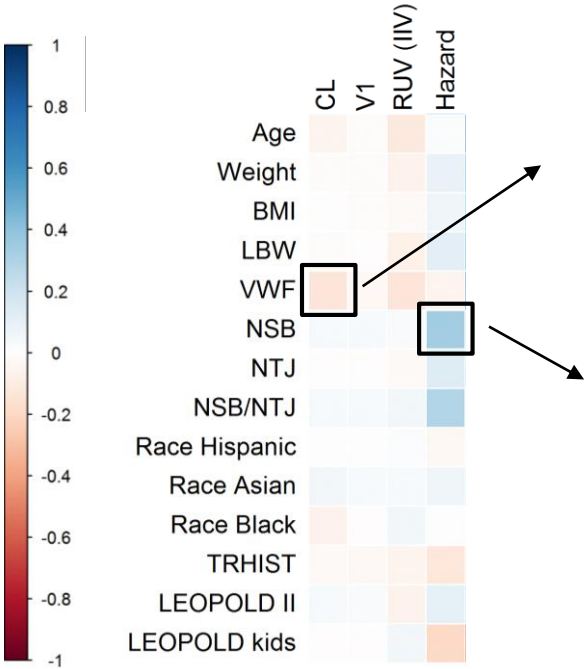
Model parameters

Covariates



BMI: body mass index
CL: clearance
LBW: lean body weight
NSB: number of spontaneous bleeds within 12 months pre-study
NTJ: number of target joints
RUV: residual unexplained variability
TRHIST: treatment history
V1: central volume of distribution
VWF: Von Willebrand factor

FREM: most relevant effect sizes identified

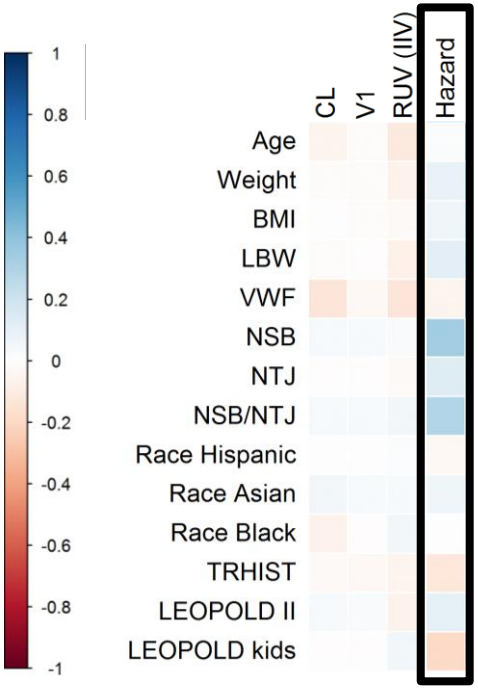


	VWF value (%)	CL (dL/h) [95%CI]	Effect size (%)
5th percentile	64	2.00 [1.93-2.18]	+6.28
Mean	116	1.88	reference
95th percentile	242	1.63 [1.32-1.77]	-13.5

	Number of bleeds within 12 months pre-study	Bleeding hazard (year^{-1}) [95%CI]	Effect size (%)
5th percentile	1	2.33 [1.99-2.69]	-24.5
Mean	21	3.08	reference
95th percentile	84	7.64 [4.80-12.7]	+148

BMI: body mass index; CL: clearance; LBW: lean body weight; NSB: number of spontaneous bleeds within 12 months pre-study; NTJ: number of target joints; RUV: residual unexplained variability; TRHIST: treatment history; V1: central volume of distribution; VWF: Von Willebrand factor

FREM: most relevant effect sizes identified



All covariates did not explain a major part of the variability on the bleeding hazard (total 132%)

BMI: body mass index; CL: clearance; LBW: lean body weight; NSB: number of spontaneous bleeds within 12 months pre-study; NTJ: number of target joints; RUV: residual unexplained variability; TRHIST: treatment history; V1: central volume of distribution; VWF: Von Willebrand factor

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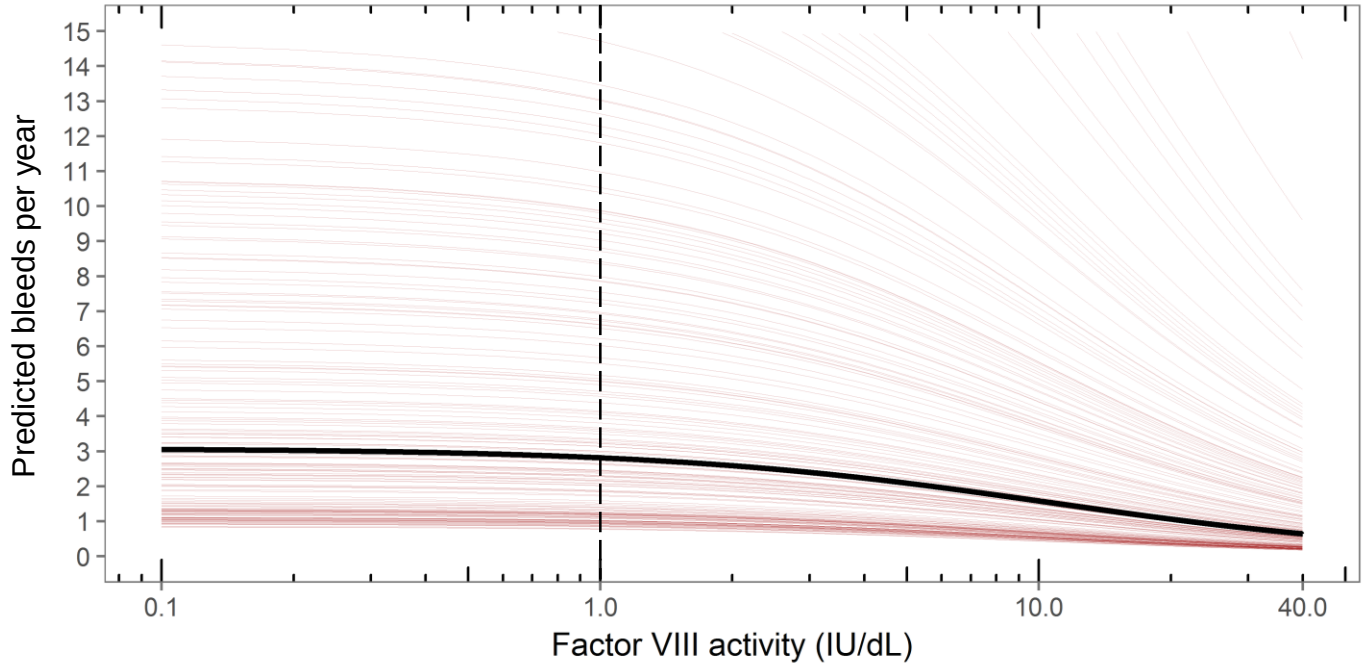
High (unexplained) bleeding variability under prophylaxis



What have we learnt?

- We characterized relationship between FVIII activity and occurrence of bleeds, accounting for all available individual and study characteristics
- Just a few predictors of bleeding risk identified: plasma FVIII activity and preceding bleeding frequency
- Individualization of treatment based on the underlying hazard may be the key to a more cost-effective prophylactic treatment of haemophilia A patients

Acknowledgements

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Uppsala Pharmacometrics Research Group

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