Bayesian forecasting utilizing bleeding information to support dose individualization of factor VIII

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(3) Bayer, Wuppertal, Germany

28th PAGE meeting
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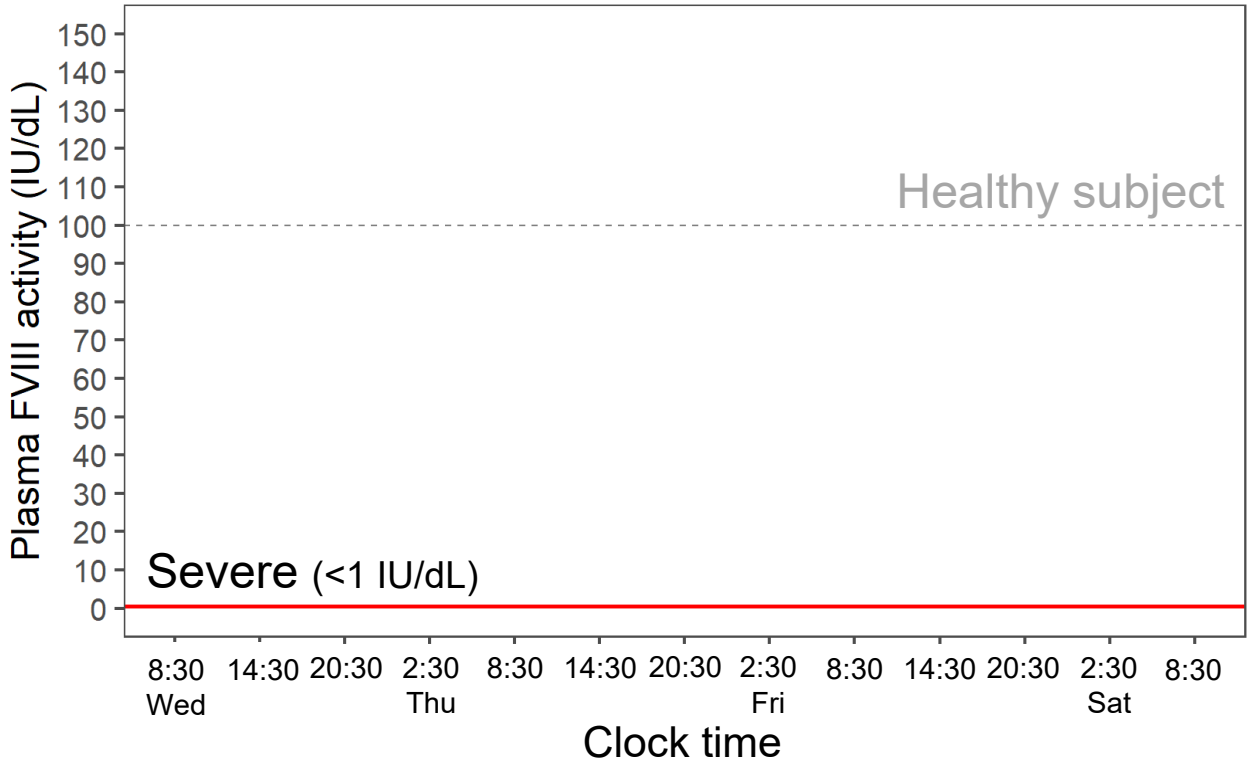
Haemophilia A

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

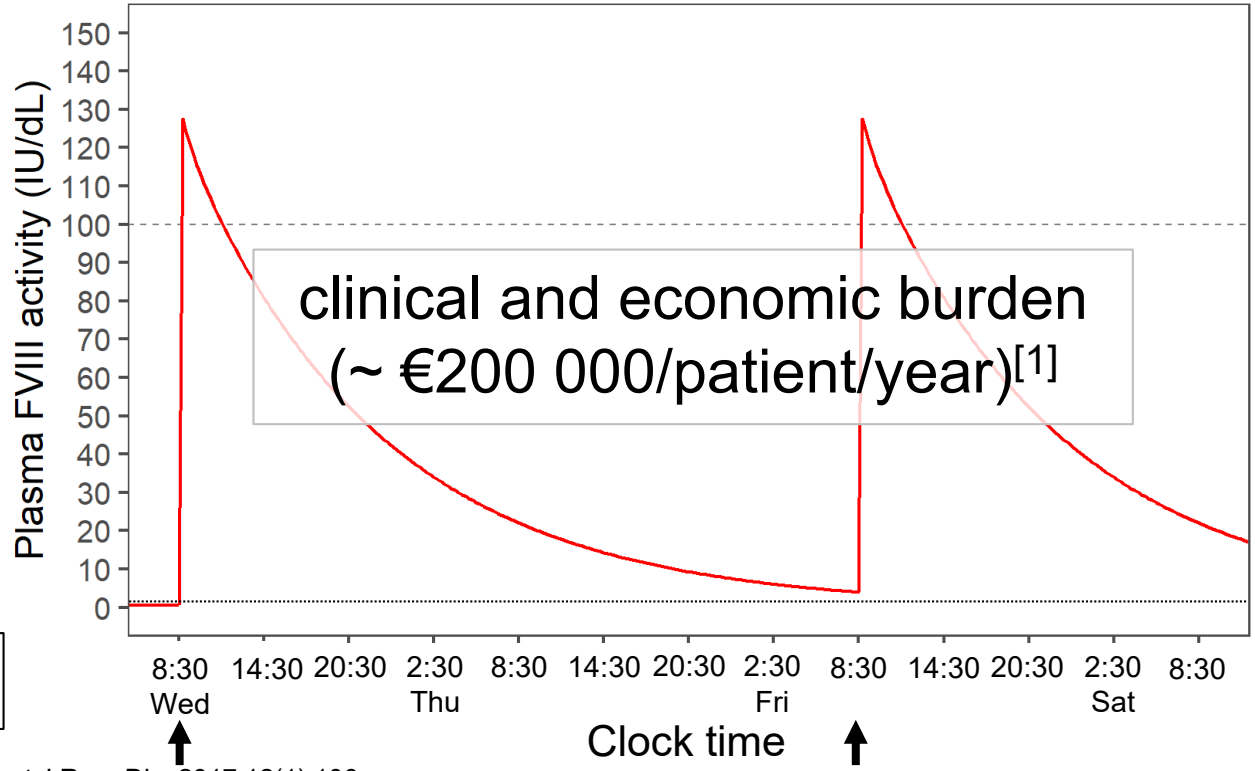
Severe haemophilia A

Endogenous plasma factor VIII activity <1 IU/dL



FVIII replacement therapy

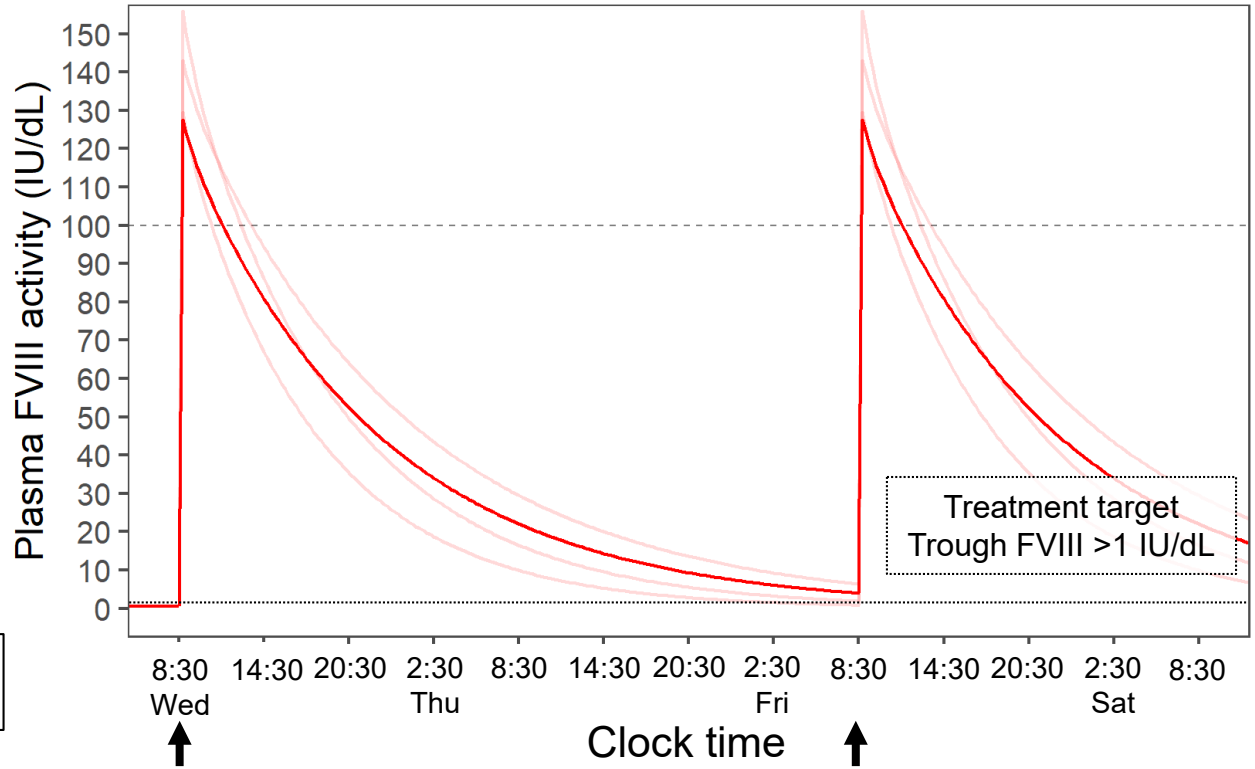
Prophylactic administration of 15-40 IU/kg 3x week



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

FVIII replacement therapy

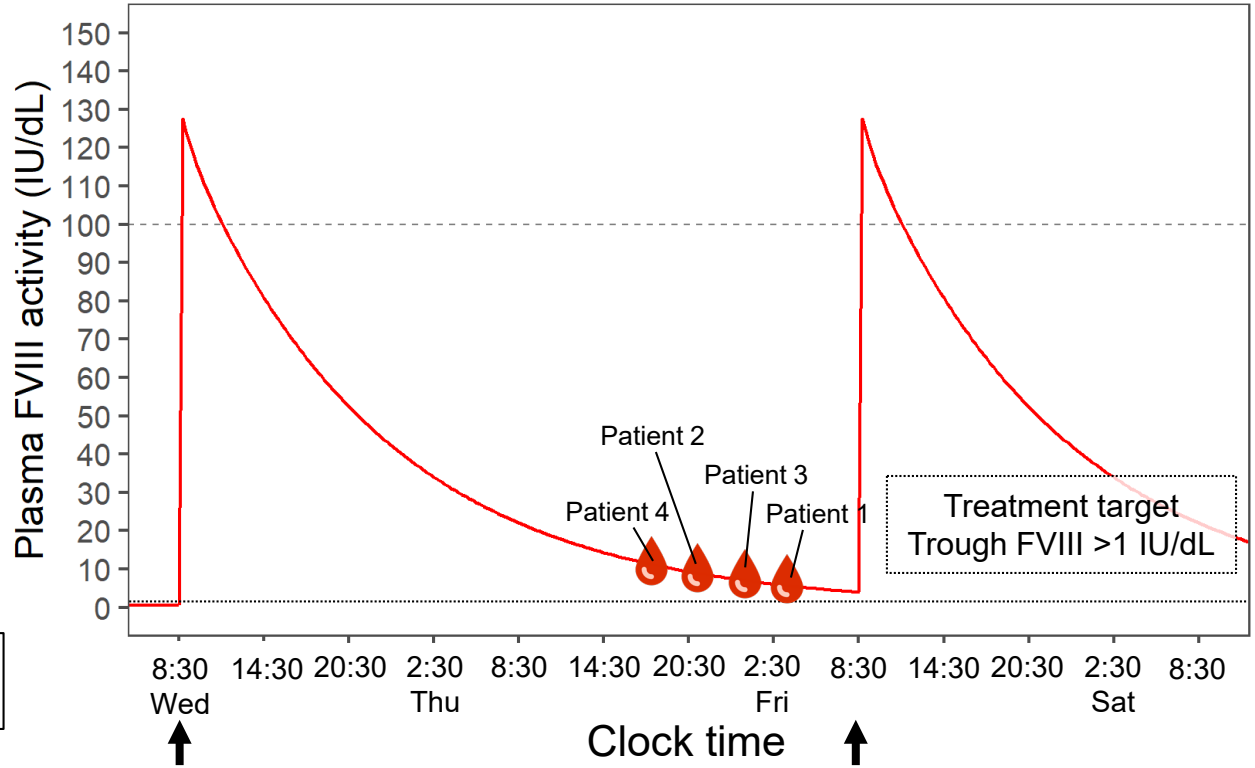
PK-guided model-based dose individualization increasingly encouraged [1,2]



[1] Berntorp E. J Thromb Haemost. 2017;15(6):1103-5 [2] Iorio A *et al*. J Thromb Haemost. 2017;15(12):2461-5

FVIII replacement therapy

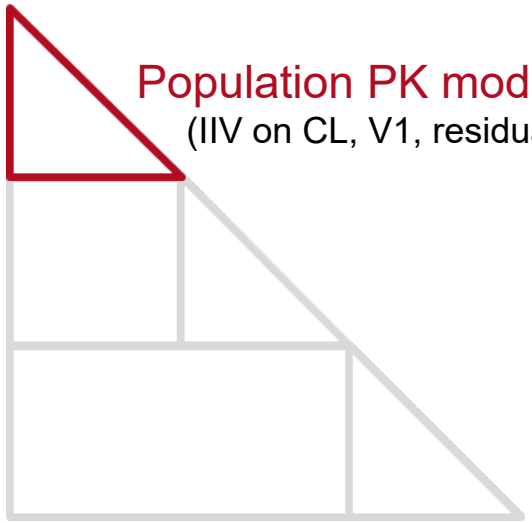
PK-guided model-based dose individualization increasingly encouraged [1,2]



[1] Berntorp E. J Thromb Haemost. 2017;15(6):1103-5 [2] Iorio A *et al*. J Thromb Haemost. 2017;15(12):2461-5

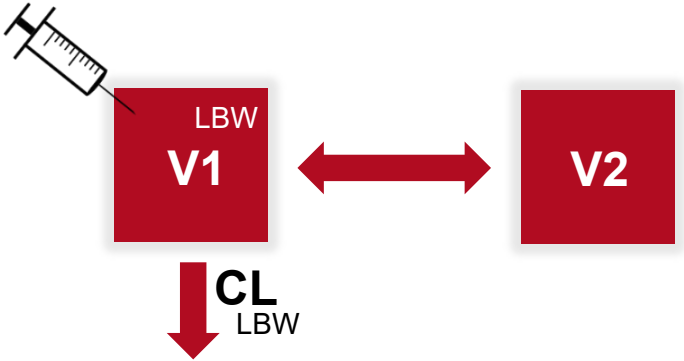
PK-bleed-covariate model

Dose-exposure-response relationship



Population PK model

2-compartment model



CL: clearance; IIV: inter-individual variability; LBW: lean body weight; V1 and V2: central and peripheral volumes of distribution

Abrantes *et al.* PAGE 27 (2018) Abstr 8646 [www.page-meeting.org/?abstract=8646]

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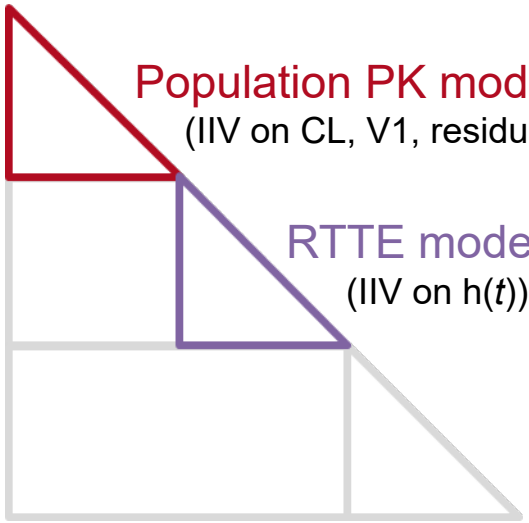

Bleed model

Repeated time-to-event model

$$h(t) = 3.0 \cdot e^{-0.57 \cdot (t - 1)} \cdot \left(1 - \frac{FVIII}{FVIII + IF50}\right) \cdot e^{\eta}$$

CL: clearance; IIV: inter-individual variability; V1: central volume of distribution

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PK-bleed-covariate model

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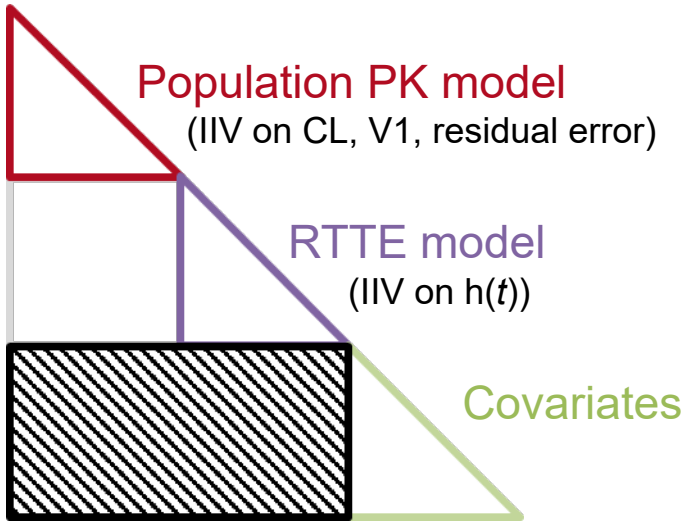


Covariates

Full random effects modeling

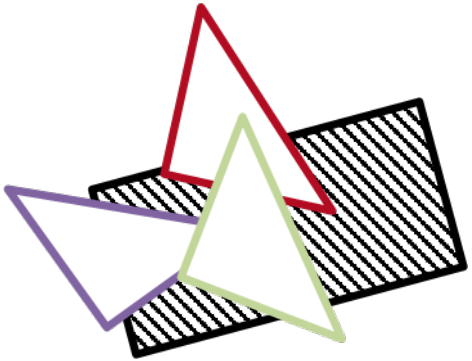
- Age
- Body weight, LBW, BMI
- Race
- von Willebrand factor levels
- Number of spontaneous bleeds within 12 months pre-study
- Pre-study treatment (prophylaxis/on-demand)
- Number of target joints at study start
- Study

BMI: body mass index; CL: clearance; IIV: inter-individual variability; LBW: lean body weight; V1: central volume of distribution

Abrantes *et al.* PAGE 27 (2018) Abstr 8646 [www.page-meeting.org/?abstract=8646]

Aim

Use the PK-bleed-covariate model to contrast different sources of patient information in their ability to predict future occurrence of bleeds



Wait…
but why?

Current model-based dose individualization methods are mainly PK-guided

Considering other sources of patients' information may ↑ accuracy in predictions and cost-effectiveness

Clinical data

Evaluations based on observed data

***LEOPOLD I and II* clinical trials**[1-3]

- 121 patients with severe haemophilia A (≥12 years)
- Prophylactic treatment with octocog alfa
- 12 months
  - 798 sparse FVIII activity observations
  - 530 bleeding events (~1% of all observed days)
  - 11 covariates

  (*subset of data used to develop the PK-bleed-covariate model*)

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

Bleeding forecasting workflow

Bayesian forecasting + calculation of P_i(bleeding)

June						
M	T	W	T	F	S	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	1	2	3	4	5

EBEs patient *i*

- [x] Day 1
- [ ] Day 1, 2
- [ ] Day 1 … *n-1*

P_i(bleeding) patient *i*

- [ ] Day 2
- [ ] Day 3
- [ ] Day *n*

n: last day of patient *i* in the study

P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

EBEs: empirical Bayes estimates (*individual parameters*, eg. individual clearance or individual bleeding hazard)

$P_i(\text{bleeding}) = 1 - e^{-\int_t^{t+24} h_i(t)\,dt}$, where *t* is the end of the Bayesian forecasting observation period

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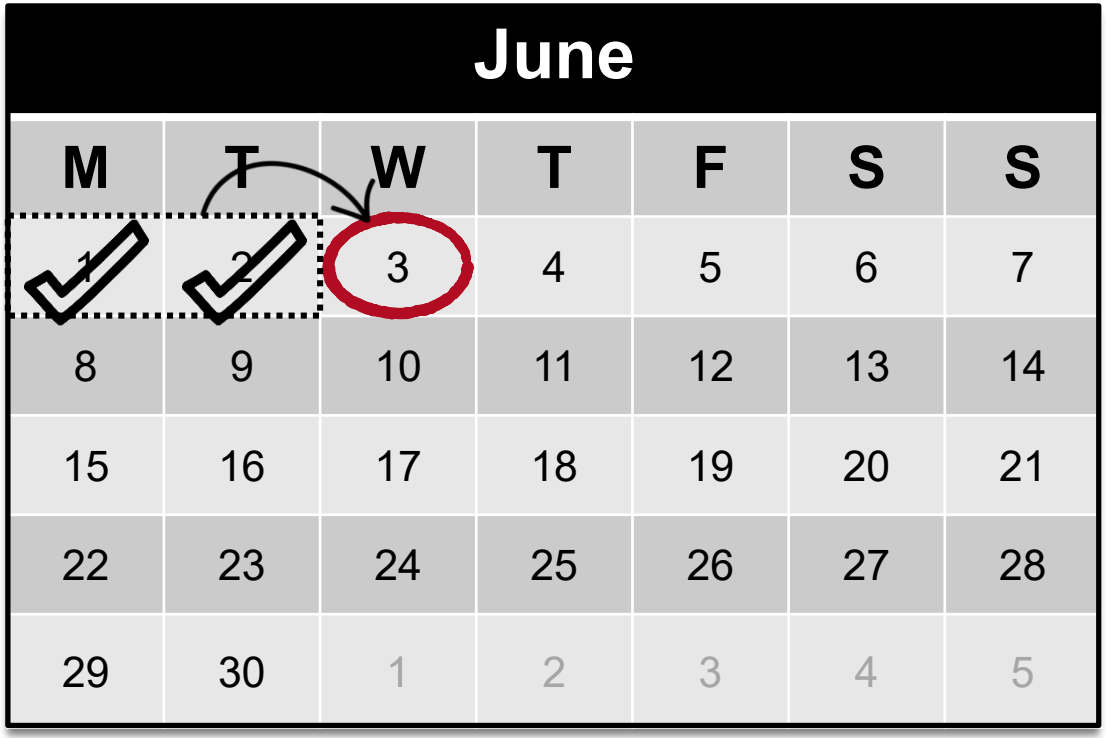
Bayesian forecasting + calculation of P_i(bleeding)



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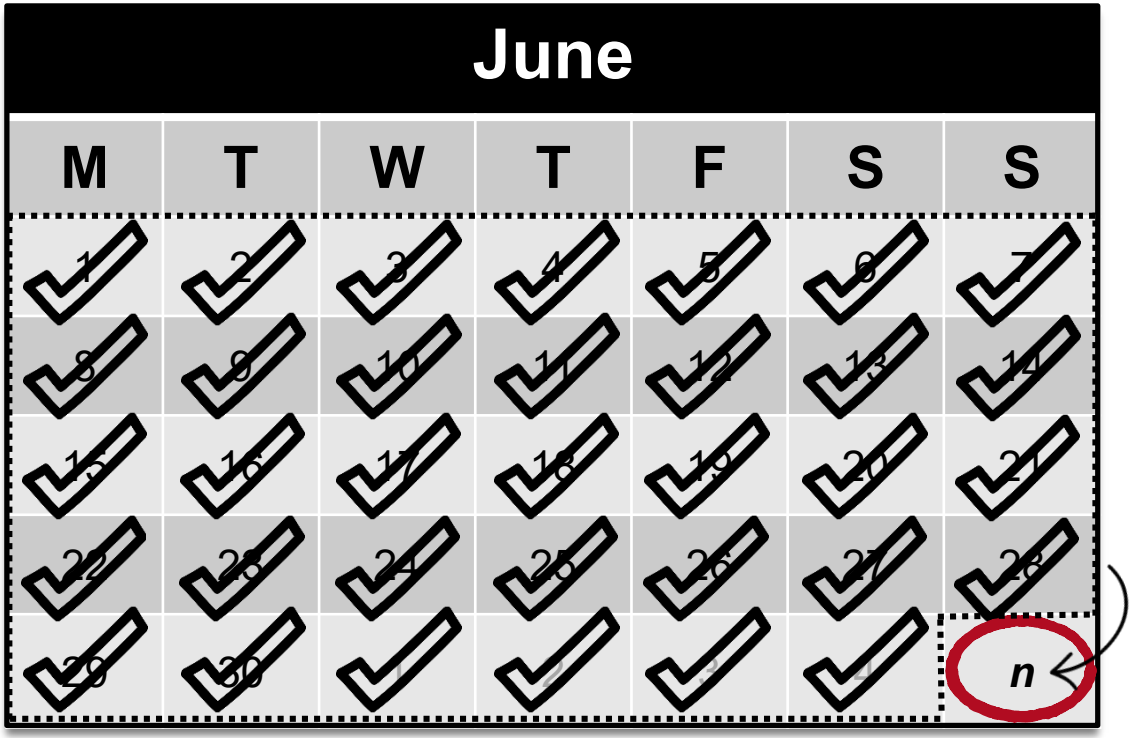

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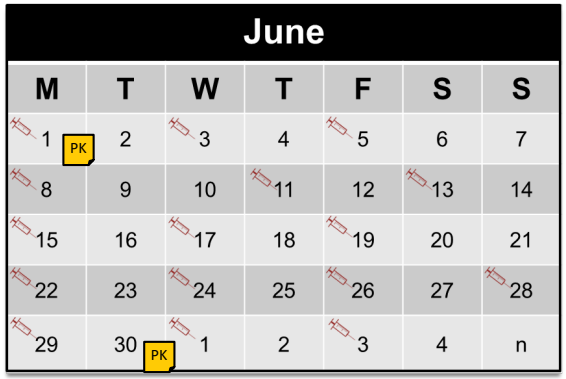
Information scenarios

"PK", "Bleed", and "All"

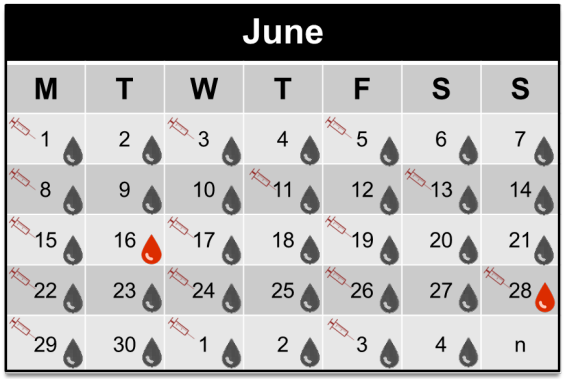
PK

PK observations



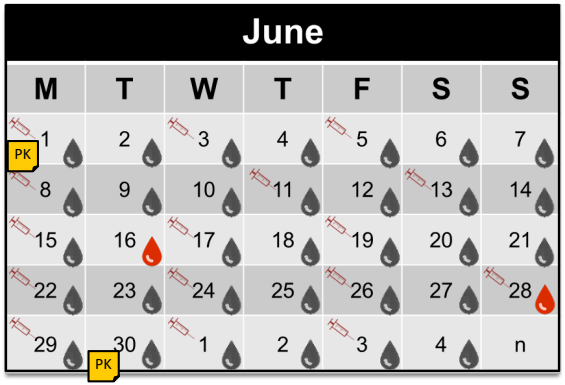
Bleed

Bleeding observations



All

PK, bleeding observations and covariates

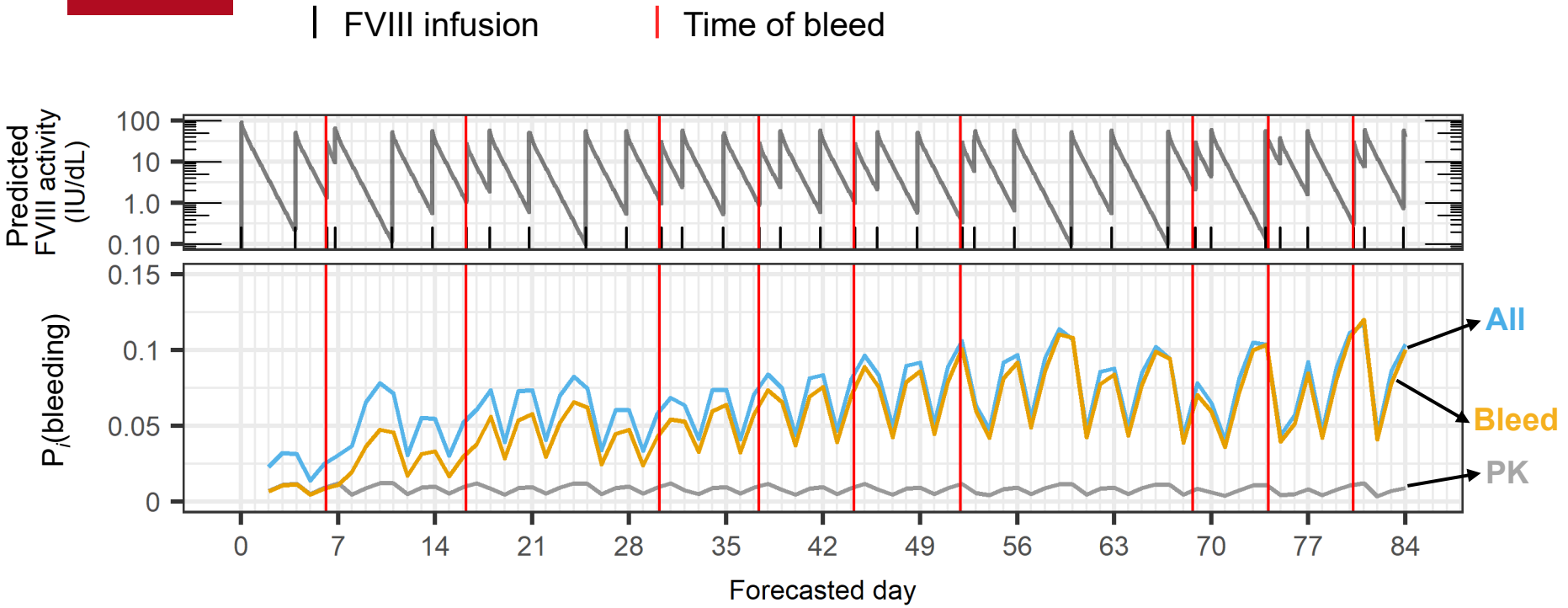


+ covariates

Infusion | PK PK sampling | No bleed | Bleed

Time-varying bleeding probabilistic forecast

Illustrative patient



P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

Predictive performance assessment

Three techniques were used

- P_i(bleeding) was compared with the actual occurrence or non-occurrence of a bleed on the forecasted day
  - Separation plots[1]
  - Receiver operating characteristic (ROC) analyses[2]
  - Precision-recall analyses[3]

P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

[1] Greenhill B *et al.* American Journal of Political Science. 2011; 55 991-1002. [2] Fawcett T. Pattern recognition letters. 2006; 861-874.
[3] Saito T, Rehmsmeier M. PLoS One. 2015;10(3):e0118432

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Separation plots

Merged P_i(bleeding) data for all days for all patients

Patient	Forecasted day	P_i(bleeding)	Bleed
1	2	0.020	0
1	3	0.075	0
1	4	0.051	0
1	*n*	0.037	0
2	2	0.056	0
2	3	0.012	0
2	4	0.094	1
2	*n*	0.031	0
3	2	0.252	1
3	3	0.181	0
3	4	0.138	0
3	*n*	0.121	0

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Separation plots

Rows ordered according to the ascending order of P_i(bleeding)

Patient	Forecasted day	P_i(bleeding)	Bleed
2	3	0.012	0
1	2	0.020	0
2	*n*	0.031	0
1	*n*	0.037	0
1	4	0.051	0
2	2	0.056	0
1	3	0.075	0
2	4	0.094	1
3	*n*	0.121	0
3	4	0.138	0
3	3	0.181	0
3	2	0.252	1

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Separation plots

Highlighted rows corresponding to days when bleeds actually occurred

Patient	Forecasted day	P_i(bleeding)	Bleed
2	3	0.012	0
1	2	0.020	0
2	*n*	0.031	0
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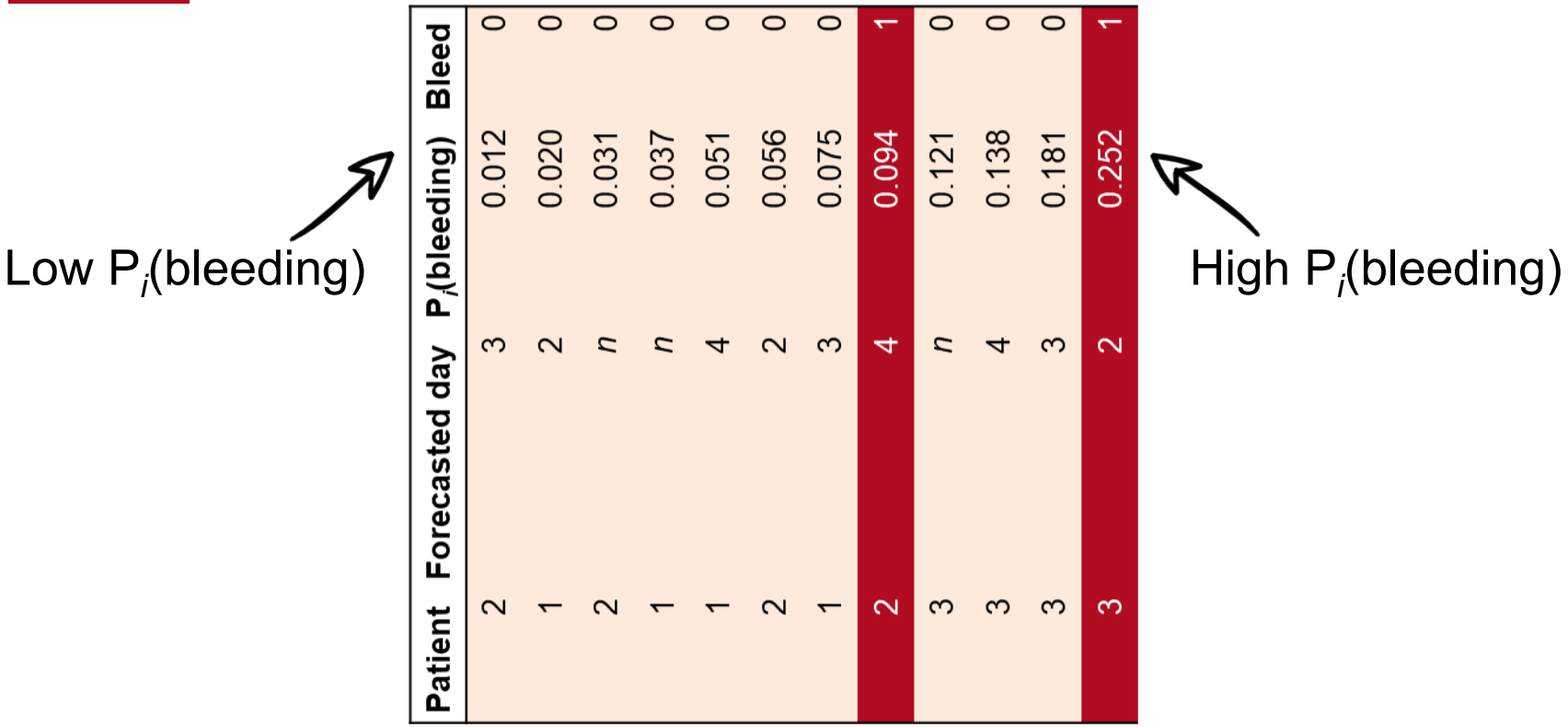

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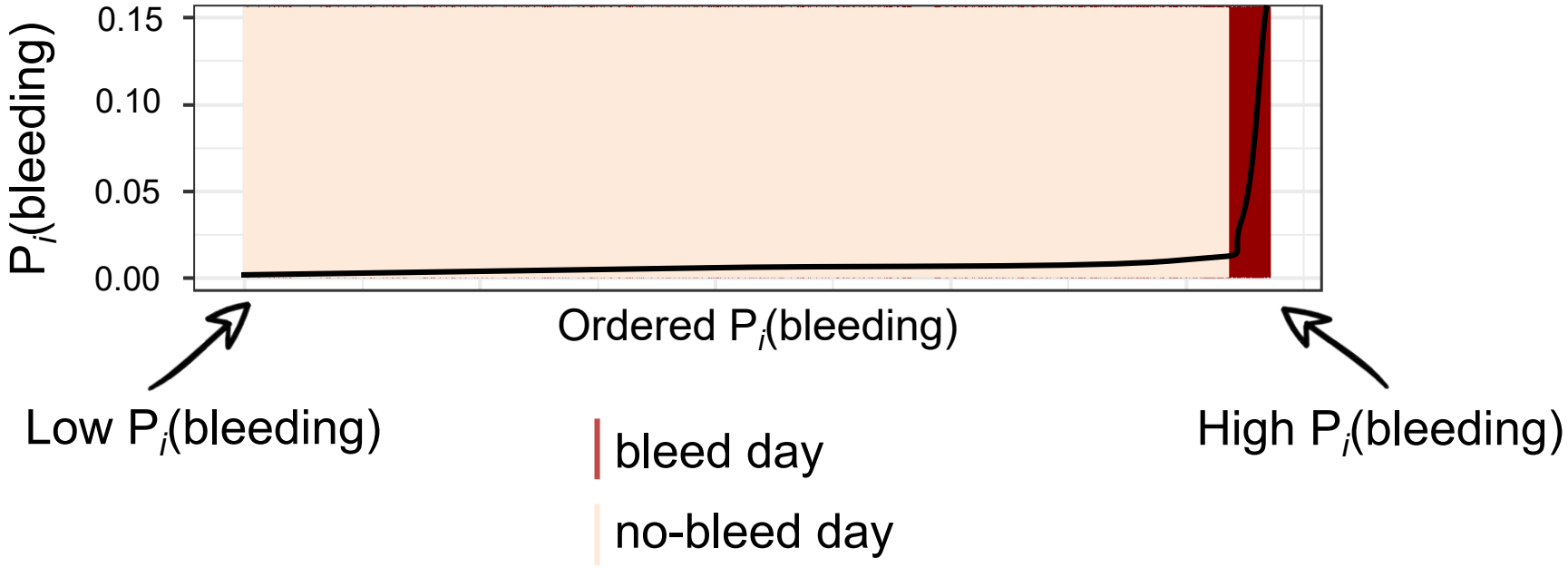
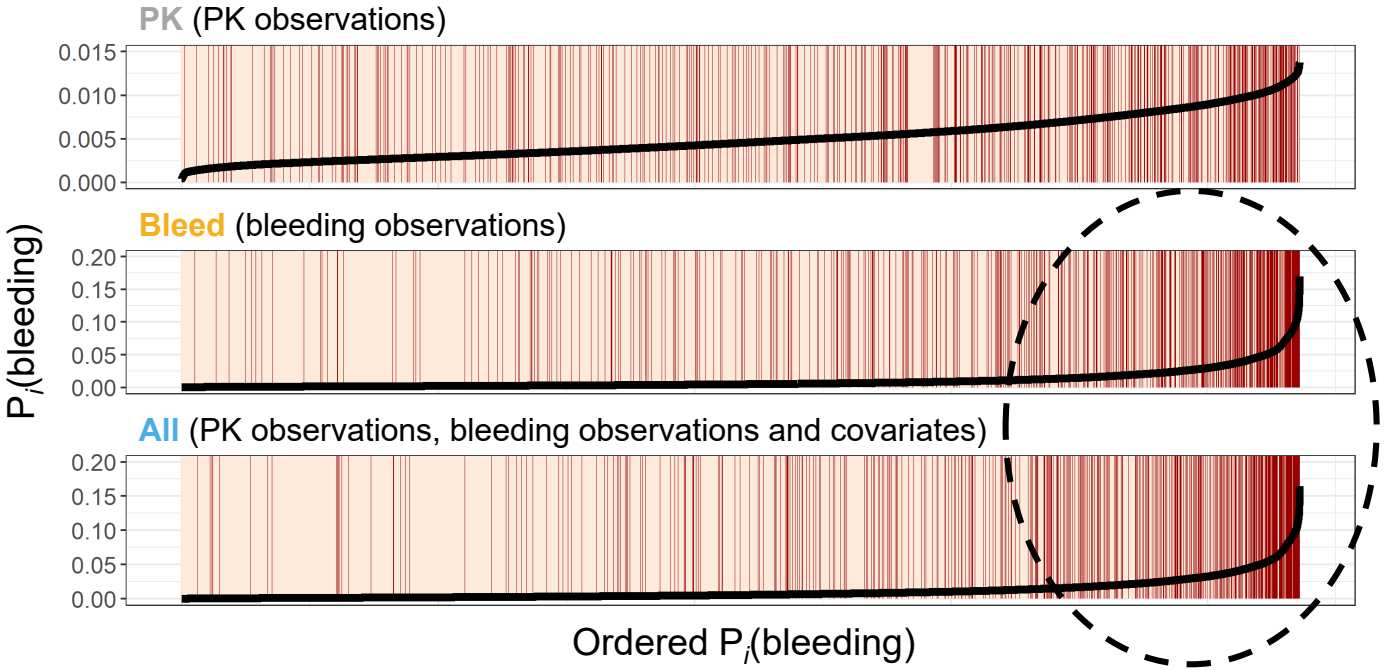


P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

Separation plots

***Bleed** and **All** associated with higher relative P_i(bleeding)*



bleed day

no-bleed day

P_i(bleeding)

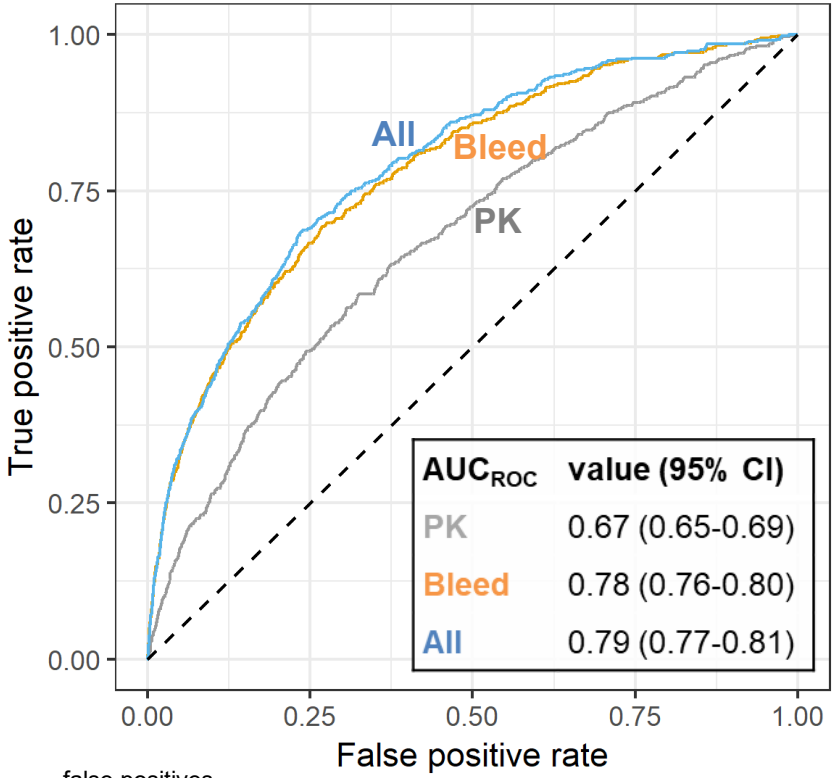
- Bleed days more often associated with higher P_i(bleeding) in **Bleed** and **All** than in **PK**
- PK information and covariates did not substantially improve the predictive performance

P_i(bleeding): individual forecasted probability of having a bleed in the upcoming 24 h

Separation plots showing all predicted days for all patients. Since the occurrence of bleeds was rare (~1.2% of forecasted days), vertical bars corresponding to bleed days were emphasized.

Receiver operating characteristic (ROC) analysis

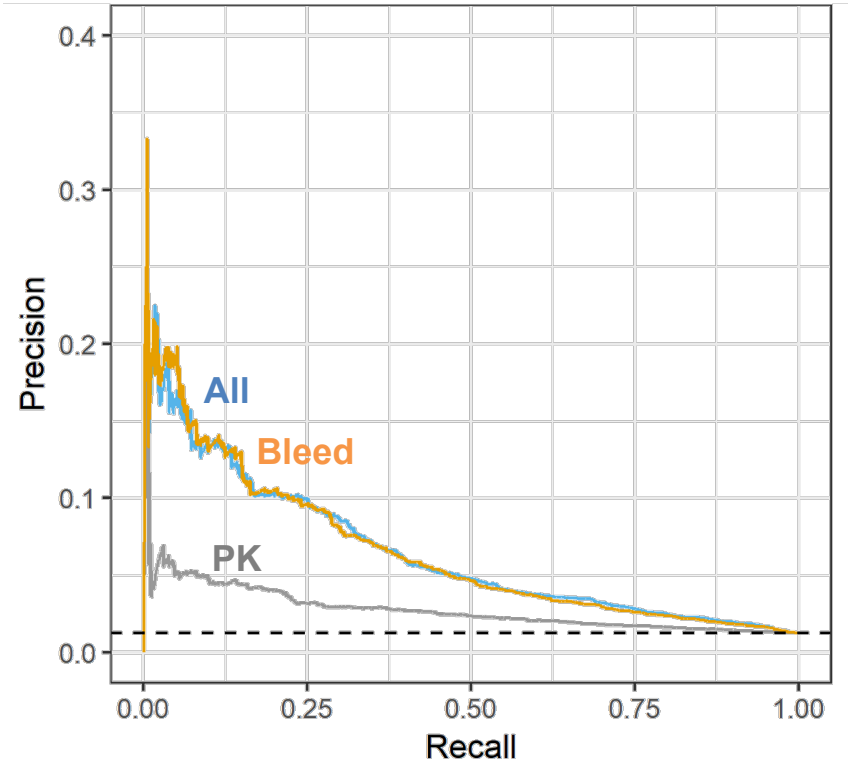
Bleeds were a main component driving the forecast of future bleeds



True positive rate = $\frac{\text{true positives}}{\text{positives}}$, false positive rate = $\frac{\text{false positives}}{\text{negatives}}$

Precision-recall analysis

Bleeds were a main component driving the forecast of future bleeds



Precision = $\frac{\text{true positives}}{\text{true positives + false positives}}$ (low precision observed for all information scenarios as expected); recall = true positive rate = $\frac{\text{true positives}}{\text{positives}}$

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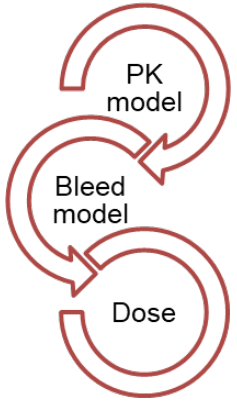
Some limitations

- Evaluation based on a subset of data used to develop the model
- Study design, for instance:
  - PK sampling times
  - Patients well protected against bleeds

What have we learnt?

- An **integrated PK-bleed-covariate model approach** can be used to forecast the occurrence of bleeds under prophylactic treatment
- Three techniques confirmed that **past bleeding information** is a main component driving the forecast of future bleeds
- Further steps to optimize **the proposed tool for FVIII dose adaptation** are required



Acknowledgements

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Uppsala Pharmacometrics Research Group

BAYER

Apotekarsocieteten

Vi gör Sverige kunnigare om läkemedel

Apotekare Gunnar Hylténs stiftelse

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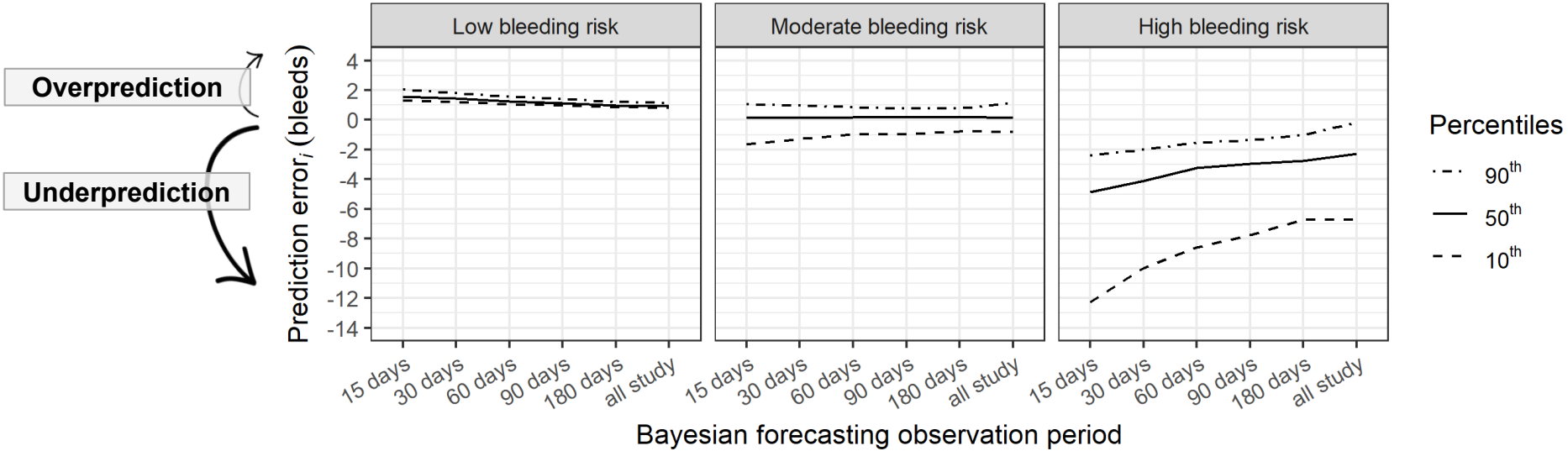
(2) Bayer, Berlin, Germany
(3) Bayer, Wuppertal, Germany

28th PAGE meeting
Stockholm, Sweden, 12 June 2019

Varying the observation period length

The longer the observation period for EBEs estimation the better

Information scenario: **Bleed**



Prediction error$_i$= Bleed$_{forecast}$ – Bleed$_{observed}$ where Bleed$_{forecast}$ and Bleed$_{observed}$ are the number of forecasted and observed bleeds during the whole individual study period. Bleeding risk was categorized as: **low risk**, if patients did not bleed during the study (N=33); **moderate risk**, 1-4 bleeds (N=49); and **high risk**, ≥5 bleeds (N=39)