

Relationship between factor IX activity levels and bleeding in patients with haemophilia B: a Repeated Time-To-Event analysis

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Introduction

- Haemophilia B is a bleeding disorder caused by factor IX (FIX) deficiency.
- When left untreated, patients regularly experience bleeds, especially in joints and muscles.
- Bleeds were differentiated in damage-causing (defined as all bleeds not categorised as nuisance bleeds) and nuisance bleeds (defined as bruising, mucosal bleeds and bleeds of an unknown cause).
- rIX-FP (albutrepenonacog alfa, Idelvion[®]), an extended half-life (EHL) FIX concentrate, is given as prophylactic replacement therapy.

Complication

- The relationship between plasma FIX activity and its therapeutic effect is complex.
- Patients receiving rIX-FP experience unexpected breakthrough bleeds even with adequate plasma FIX activity¹.
- It is becoming increasingly evident that FIX activity in the extravascular space contributes to haemostatic efficacy².
- Bleeding events should be addressed in order to specify which FIX exposure needs to be targeted.

Aim

- To investigate the relationship between prophylactic dose, FIX activity levels and bleeding for rIX-FP.

Results

- An exponential hazard function best described the data (**Table 1, 2**), meaning a constant bleeding hazard was present.
- Without FIX activity in the plasma, an annual bleeding rate (ABR) of 7.3 year⁻¹ is found.
- A constant plasma FIX activity level of 12 IU/dL decreased the bleeding hazard by 50%.

Table 1: Baseline patient characteristics.

	Number (n, median)	% or range
Patient characteristics		
Participants	114	
Follow-up time (days)	416	(6 – 1233)
Age (years)	26	(1 – 61)
Weight (kg)	64.0	(11 – 130)
Height (cm)	172.0	(78 – 190)
BMI (kg/m ²)	21.6	(16 – 35)
Pharmacokinetic data		
rIX-FP dose per week (IU/kg)	38.0	(6.5 – 71.4)
FIX activity levels per patient	15	(2 – 60)
Bleeding data		
Total bleeds	514	
Patients without bleeding	31	(27)
No. of bleeds per patient	3	(0 – 33)
Pre-study ABR	3	(0 – 50)
During-study ABR	3	(0 – 52)
Severity		
Damage-causing	306	(60)
Nuisance	208	(40)

Table 2: Final estimates of the RTTE model.

Parameters	Estimate	RSE(%)	[Shr.]
All bleeds			
Scale, λ (year ⁻¹)	7.34	(24)	
IC ₅₀ (IU/dL)	12.0	(30)	
IIIV Hazard (CV%)	182	(10)	[20]
Damage-causing bleeds			
Scale, λ (year ⁻¹)	3.33	(28)	
IC ₅₀ (IU/dL)	12.2	(36)	
IIIV Hazard (CV%)	275	(11)	[23]
Nuisance bleeds			
Scale, λ (year ⁻¹)	2.36	(31)	
IC ₅₀ (IU/dL)	12.3	(41)	
IIIV Hazard (CV%)	175	(13)	[31]

Results (continued)

- The fit of the RTTE model to the data is adequate (**Figure 1**).
- Simulations suggest that damage-causing bleeds are harder to prevent (**Figure 2**).

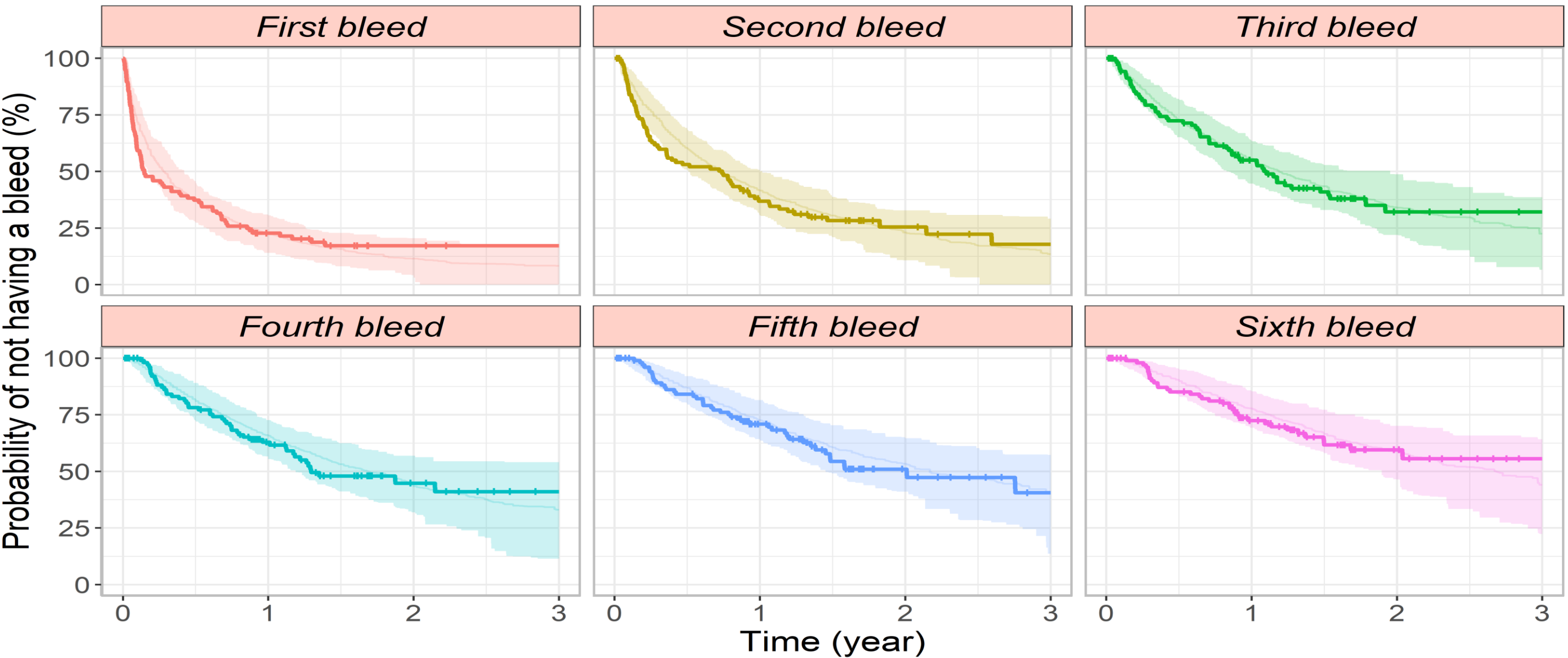


Figure 1: Observed and simulated Kaplan-Meier plots for the first six bleeding events during study duration. The solid thick line in each panel demonstrates the observed percentage of individuals not experiencing bleeding event n using the RTTE model. 90 patients had at least 1 bleed; 75 patients had at least 2 bleeds; 60 patients had at least 3 bleeds; 50 patients had at least 4 bleeds; 44 patients had at least 5 bleeds and 37 patients had at least 6 bleeds. Vertical lines in the solid line indicate censoring. The observed and simulated Kaplan-Meier curves overlap, indicating that the model describes the bleeding data adequately.

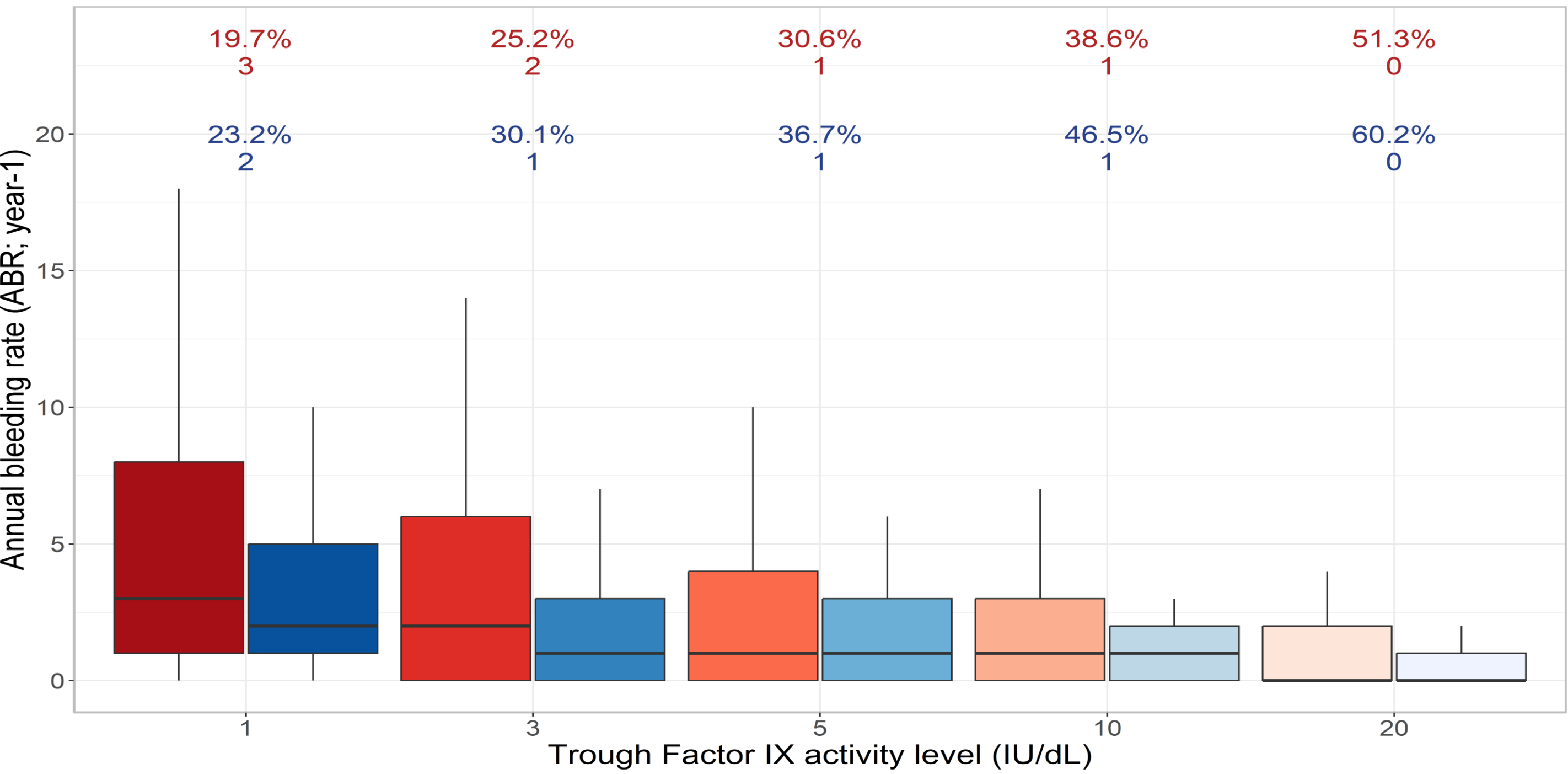


Figure 2: Simulation of ABR when varying trough FIX activity levels are maintained during a prophylactic regime. Virtual patients ($n=1000$) were assumed to have typical PK parameters. Administration of weekly prophylactic doses of 70, 560, 1120, 2590 and 5530 IU resulting in trough FIX activity levels of 1, 3, 5, 10 and 20 IU/dL, respectively, are visualized. Whiskers of the boxplot range represent the 80% prediction interval. For both damage-causing (red) and nuisance bleeds (blue), the percentage of persons with zero bleeds (top row) and median ABR (bottom rows) are displayed. The percentage of persons with zero bleeds increases in the presence of higher targeted trough FIX activity levels. Furthermore, lower FIX activity levels suffice for nuisance bleeds as opposed to damage-causing bleeds.

Discussion

- FIX activity levels in the plasma are a crucial biomarker, but may not solely be indicative of the haemostatic effect³.
- Characterisation of bleeding events remains a challenge due to varying bleeding rates at similar FIX activity levels in individuals⁴.
- Nevertheless, tailoring of dose on both individual PK and bleeding risk is of additional value in reaching sufficient FIX activity levels in patients.

References

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[4] Kloosterman FR, Zwagemaker AF, Bagot CN, et al. The bleeding phenotype in people with nonsevere hemophilia. *Blood Adv*. 2022;6(14):4256-4265.