

Relationship between factor VIII levels and bleeding for rFVIII-SingleChain in severe hemophilia A

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BACKGROUND & OBJECTIVES

- Publications on the exposure-effect relation of the available factor concentrates are limited, while such analyses give insight on the efficacy of treatment and the potential to reduce bleeding.
- Study aim: examine the relationship between the dose, FVIII levels and occurrence of bleeding for rFVIII-SingleChain (Afstyla®).

METHODS



Patients with severe hemophilia A on prophylaxis with rFVIII-SingleChain



Data from three rFVIII-SingleChain clinical trials were pooled [1-3]

- The predictive performance of the published rFVIII-SingleChain population PK model [4] was evaluated and expanded
- The probability of bleeding was described with a parametric repeated time-to-event (RTTE) model.
- The effect of FVIII levels was evaluated on the bleeding hazard using a Imax model.
- The models were developed by means of non-linear mixed effects modelling using NONMEM v7.4.1.

RESULTS

Population PK model

- The previously published population PK model showed adequate predictive performance, but was improved by inclusion of estimation of the residual FVIII level of a previous dose and inter-individual variability (IIV) on residual error (p<0.01).

Table 2: Final estimates of repeated time-to-event model

Parameter	Estimate	RSE (%) [Shrinkage]
Scale (year ⁻¹)	6.37	14.3
IC ₅₀ (IU/dL)	8.90	11.7
Shape (year ⁻¹)	0.777	2.2
Inter-individual variability hazard (CV%)	330.8	6.7 [10.6]

Repeated time-to-event (RTTE) model

- The probability of bleeding decreased during the study observation time and was best described by a Weibull hazard function (Figure 1 and Table 2).
- The model described the data adequately (Figure 2).
- No time-dependency between successive bleeds was identified with the Markov hazard function.
- Covariate analysis showed that subjects with a higher pre-study annual bleeding rate experienced a higher bleeding hazard during study.
- Simulations demonstrates that a median patient has 2 bleeds per year (90% PI: 0 – 17) when a trough FVIII level of 1 IU/dL is targeted during prophylaxis.

CONCLUSION

- The developed model described the relation between FVIII dose, FVIII levels and bleeds for rFVIII-SingleChain adequately.
- The obtained estimates were similar to those published in RTTE models for BAY 81-8973 and BAY 94-9027 FVIII concentrates[5,6], indicating similar efficacy and potential to reduce bleeding.

RESULTS

Table 1: Patient and data characteristics

	Median (range) or number (%)
Patients	241
Follow up time (day)	1090 (29 – 1910)
Age (years)	19 (1 – 58)
FVIII levels measured one-stage assay	3052
FVIII levels measured chromogenic assay	2545
Total number of bleeds	2080
Joint bleeds	1346 (65%)

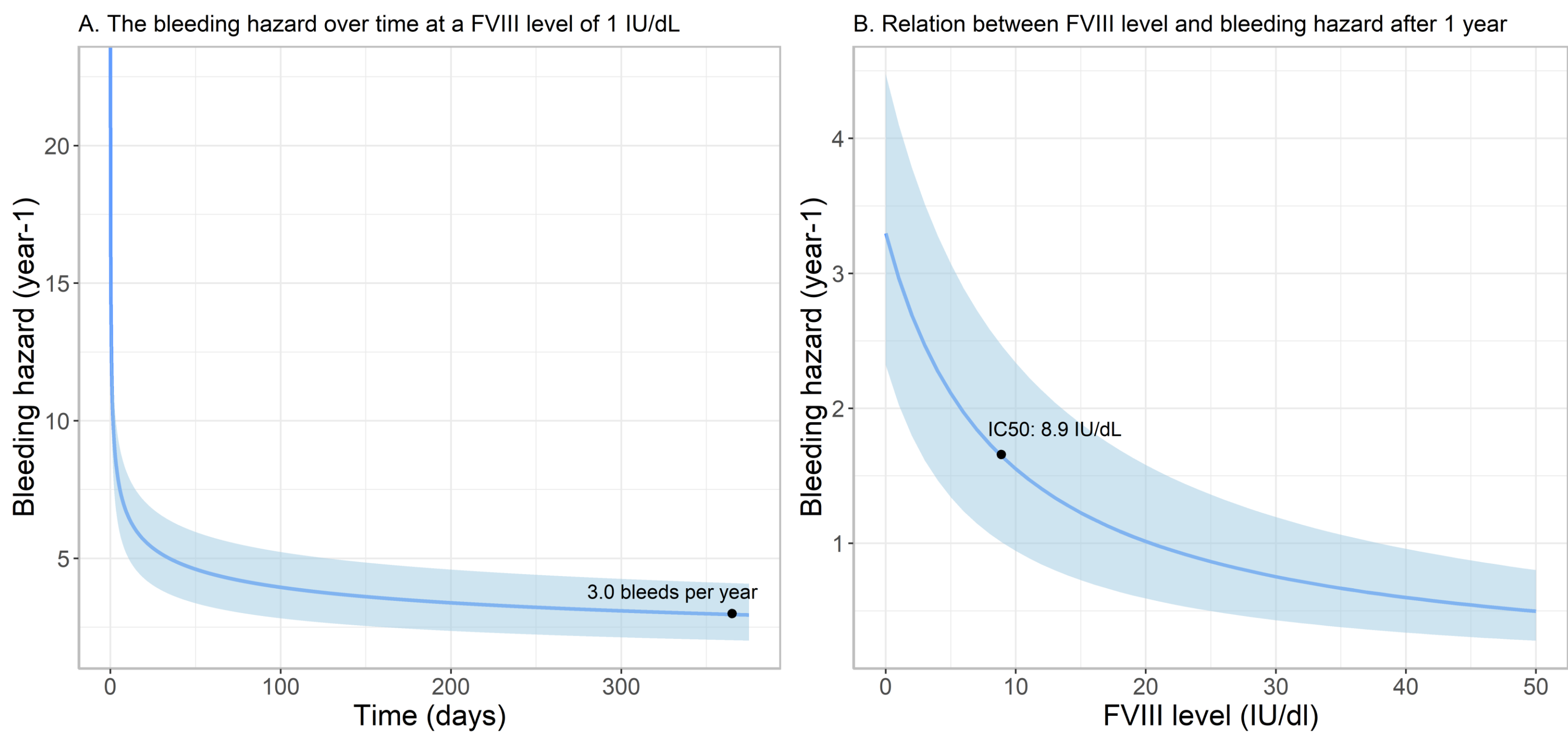


Figure 1: Visual representation of the final estimates of the repeated-time to event model. (A) The bleeding hazard over time is presented, in which the solid line depicts the estimated bleeding hazard over time for a constant FVIII level of 1 IU/dL, and the shaded area the 95%CI. After 1 year follow-up, the estimated bleeding hazard is 3.0 bleeds per year. (B) The relation between FVIII levels and bleeding hazard after 1 year follow-up in the study. A constant FVIII level of 8.9 IU/dL lowers the bleeding hazard by 50% compared to when no FVIII is present.

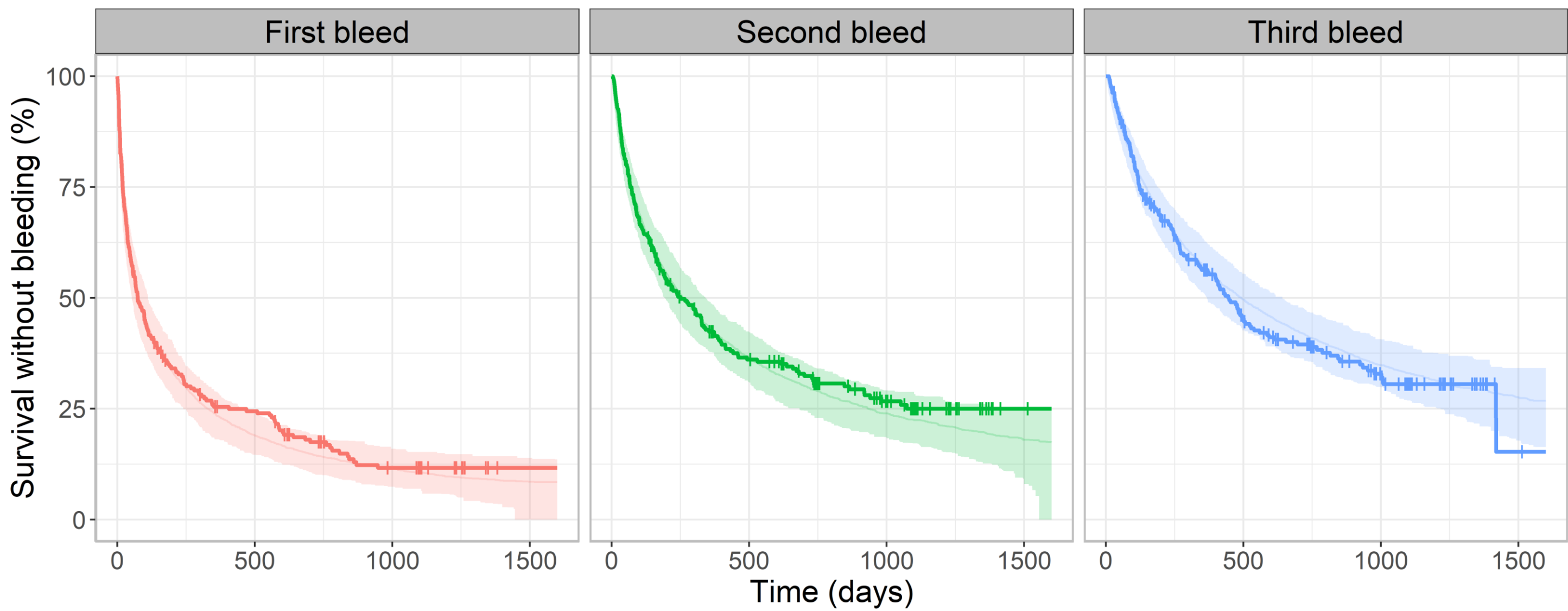


Figure 2: Observed and simulated Kaplan Meier curves for the first, second and third bleed during study. The solid thick line demonstrates the observed percentage of subjects that survive without bleeding, while the shaded area demonstrates the simulated percentage of subjects that survive without bleeding using the repeated time-to-event model (n=200). Vertical stripes indicate censoring.

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