Towards PK-guided dosing of prophylactic plasma-derived von Willebrand factor/factor VIII therapy in von Willebrand disease

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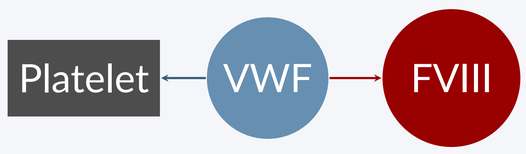
Take home messages

- Administration of plasma-derived **von Willebrand factor (VWF)/factor VIII (FVIII)** concentrate in a **1:1 activity ratio** does **not** necessarily result in **equal exposure** to both components within a patient.
- The **wide between-patient variability** in VWF and FVIII exposure combined with **heterogeneous bleeding responses** underscores the potential added value of **pharmacokinetic (PK)-guided dosing** in **von Willebrand disease** (VWD) patients on prophylaxis.

Background

- VWD is the most common **inherited bleeding disorder**, caused by a **quantitative or qualitative defect** of **VWF** [1].

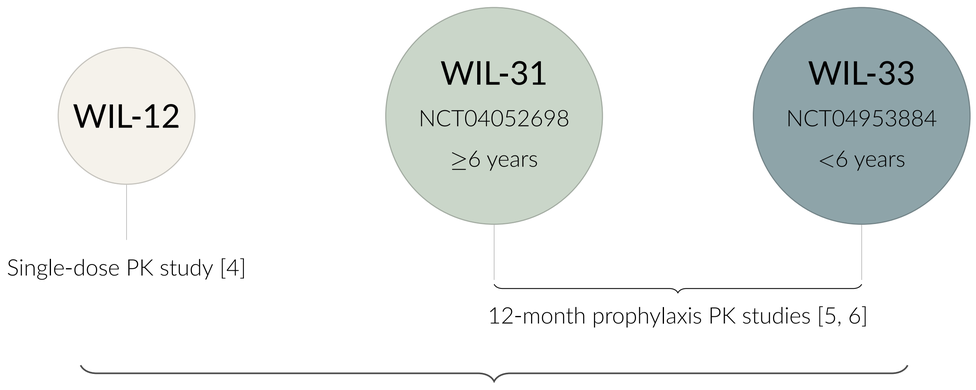


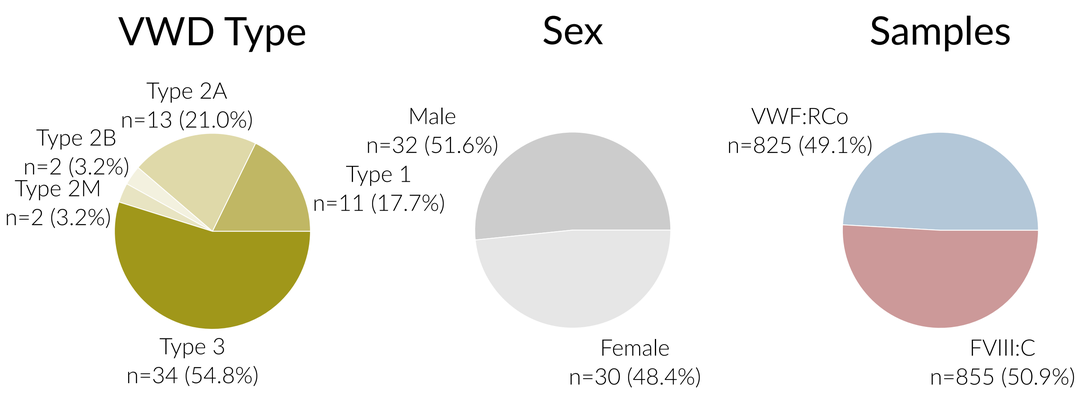
- VWD patients suffer from a **heterogeneous bleeding phenotype** including mucocutaneous, joint, muscle and heavy menstrual bleeding [2].
- Observed differences in breakthrough bleeding patterns in VWD patients on prophylaxis may be caused by **between-patient variability** in **PK** and **pharmacodynamics (PD)** [3].

Aim

- To describe the **PK** of VWF and FVIII following **prophylactic treatment with plasma-derived VWF/FVIII 1:1 concentrate** (Wilate®) in patients with **severe VWD**.
- To explore the **relationship between VWF/FVIII levels** and **bleeding events** during prophylaxis with plasma-derived VWF/FVIII 1:1 concentrate.

Study population





Age
Median: 18.5 y
Range: 1–68 y

Weight
Median: 59.5 kg
Range: 12.5–138.3 kg

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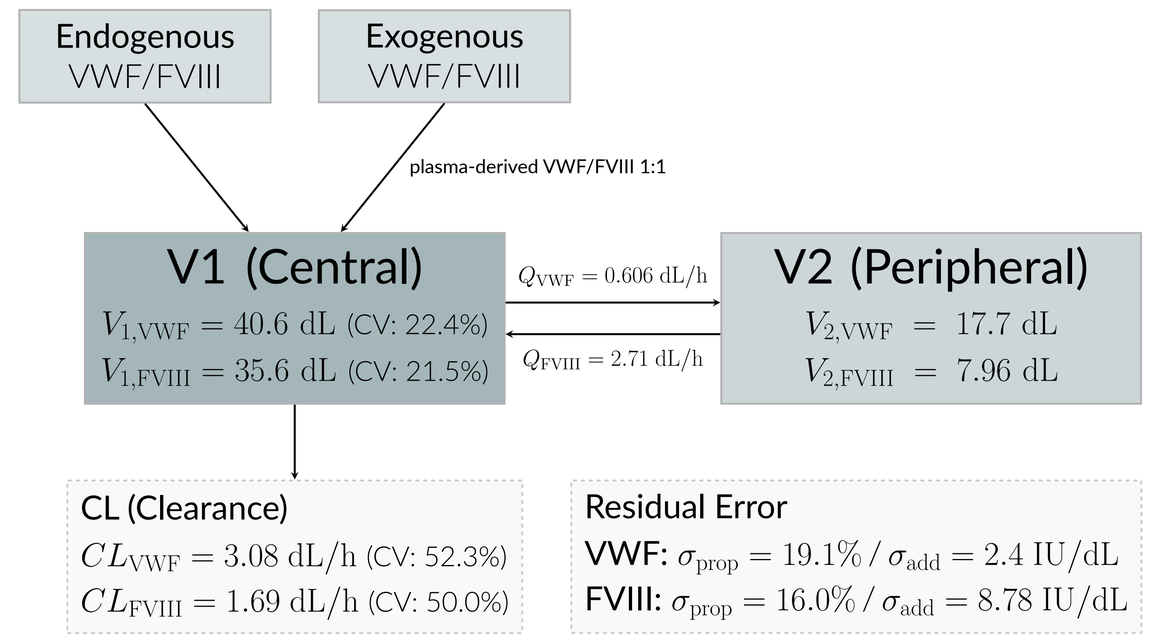
Final PopPK model

All PK parameters are allometrically scaled with fixed exponents referenced to a 70 kg individual



Exploratory pharmacodynamic analysis

- In total, **154 bleeding events** were recorded in **29/38** patients during WIL-31/33.
- Individual *post-hoc* VWF:RCo and FVIII:C levels at the time of each bleed were derived using the final PopPK model.

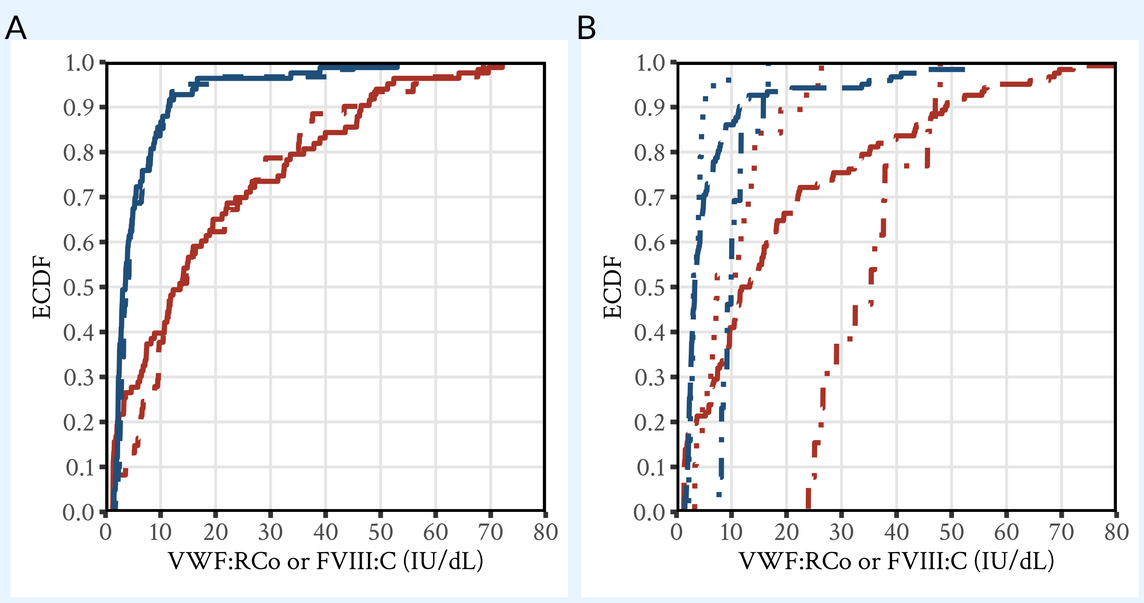


Figure 1. **Empirical cumulative distribution function of bleeding events versus individually predicted VWF:RCo (blue) and FVIII:C (red) at the time of bleed. (A)** Stratified by bleed type. Solid: spontaneous (n=83); dashed: traumatic (n=61). "Other" (n=10) not shown. **(B)** Stratified by VWD type. Dotted: type 1 (n=19); dash-dotted: type 2 (n=13); long-dashed: type 3 (n=122).

Conclusion and future perspective

- A **heterogeneous relative exposure** to VWF:RCo and FVIII:C was observed in VWD patients on plasma-derived VWF/FVIII 1:1 concentrate prophylaxis.
- **Wide between-patient variability** in clearance of plasma-derived VWF/FVIII 1:1 concentrate indicates that **body weight** is an **insufficient predictor** of factor exposure, leaving some patients potentially **underdosed** on standard body weight-based dosing regimens.
- While some patients remained **bleed-free** on prophylaxis, bleeding events in others occurred predominantly at **low VWF:RCo and FVIII:C levels**.
- Future work should **externally validate** our PopPK model, prospectively evaluate **PK-guided prophylaxis** in VWD, and investigate the **exposure–bleeding relationship** using a **repeated-time-to-event analysis** to define **evidence-based PK targets** for prophylactic therapy in VWD.