Extravascular distribution of factor IX: Evidence and relevance for hemophilia B replacement therapy

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CONCLUSIONS

- Experimental and clinical evidence suggests that factor IX (FIX) has a role to play beyond intravascular hemostasis.
- It is only possible to measure extravascular transfer indirectly based on pharmacokinetic data, and the clinical implications remain to be fully understood.
- Extravascular distribution of FIX should be considered when discussing the treatment of individuals with hemophilia B.

AIM

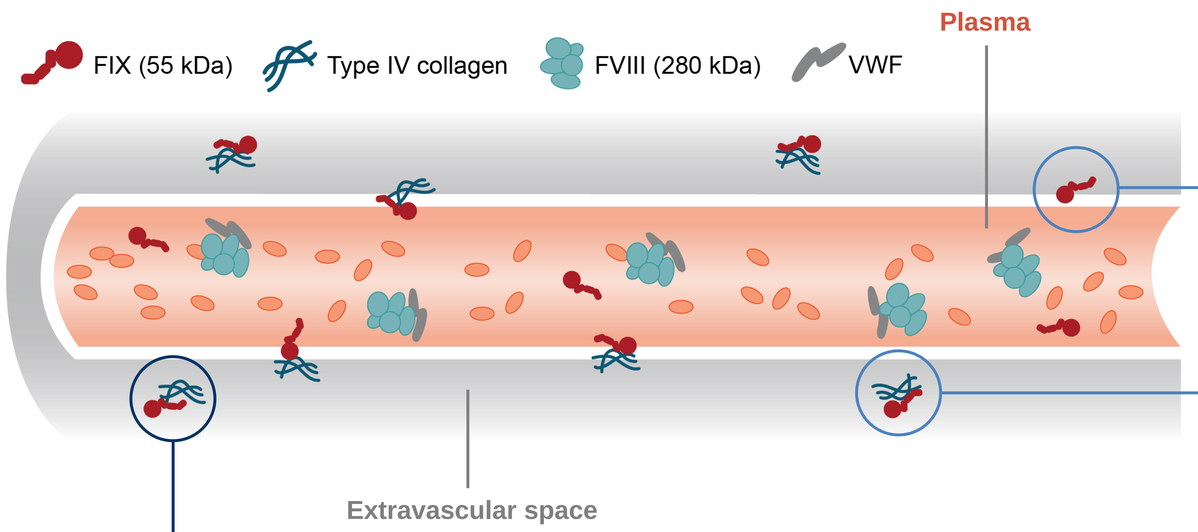
- Factor VIII (FVIII; 280 kDa) circulates in plasma bound to von Willebrand factor, while FIX (55 kDa) distributes between plasma and the extravascular space.[1–6] This may be relevant for hemophilia B replacement therapy.
- **With increasing numbers of publications over recent years, we aimed to critically review data relating to the extravascular distribution of FIX, both the native molecule and therapeutic products, summarizing current understanding and potential implications for hemophilia B management.**

METHODS

- Interrogating the MEDLINE and Embase databases using pre-agreed search terms retrieved 472 publications (1957 to October 2024).
- Screening titles and abstracts identified 96 papers/ abstracts potentially relevant to the extravascular distribution of FIX.
- Information from selected publications was collated and critically interpreted by seven reviewers from seven countries who had scientific/clinical expertise in hemophilia B. It was then summarized to describe the extravascular distribution of FIX and relevant clinical and therapeutic implications that may logically follow from the established facts but remain to be confirmed.

RESULTS

- Based on key evidence,[1–38] accumulated information about the extravascular distribution of FIX was summarized into nine key statements.



Scientific evidence

- **FIX**, unlike FVIII, **rapidly distributes** out from the plasma pool and into the **extravascular space**
- Endogenous FIX has a **high V_D** and is in **dynamic equilibrium** between plasma and the extravascular compartment
- FIX co-localizes and binds with **type IV collagen**
- Approximately two-thirds of total FIX exists **reversibly bound** to type IV collagen in the vessel wall and the extravascular space
- FIX binding to type IV collagen may produce **an extravascular reservoir** of FIX extending the plasma hemostatic role

Clinical implications

- Plasma FIX activity alone **may not be reflective** of the hemostatic potential of FIX prophylactic treatment
- EHL FIX products, when used as prophylactic treatment, achieve **similar bleed rates** but a **wide range of FIX plasma trough levels**
- FIX is present in **tissues outside the plasma** compartment, with functional FIX detected in **synovial fluid**
- Extravascular FIX could be relevant for **controlling and preventing** both clinical and subclinical bleeds

EHL, extended half-life; FVIII, factor VIII; FIX, factor IX; V_D, volume of distribution; VWF, von Willebrand factor.

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