Neue Wirkstoffe in der Hämophilie-Therapie: Keine Blutung auch ohne Spritzen von Faktor 8 und Faktor 9?

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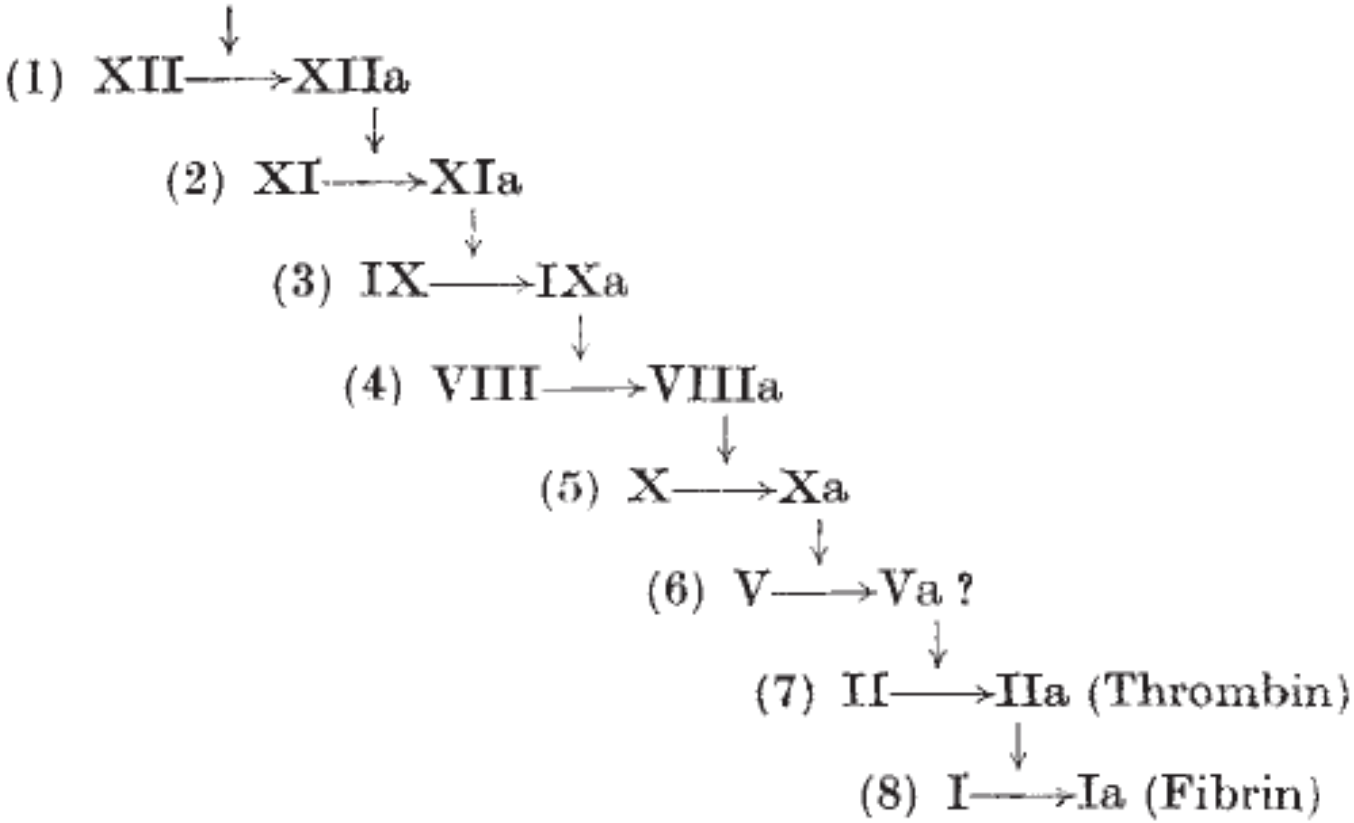
Institut für Klinische Hämostaseologie und Transfusionsmedizin

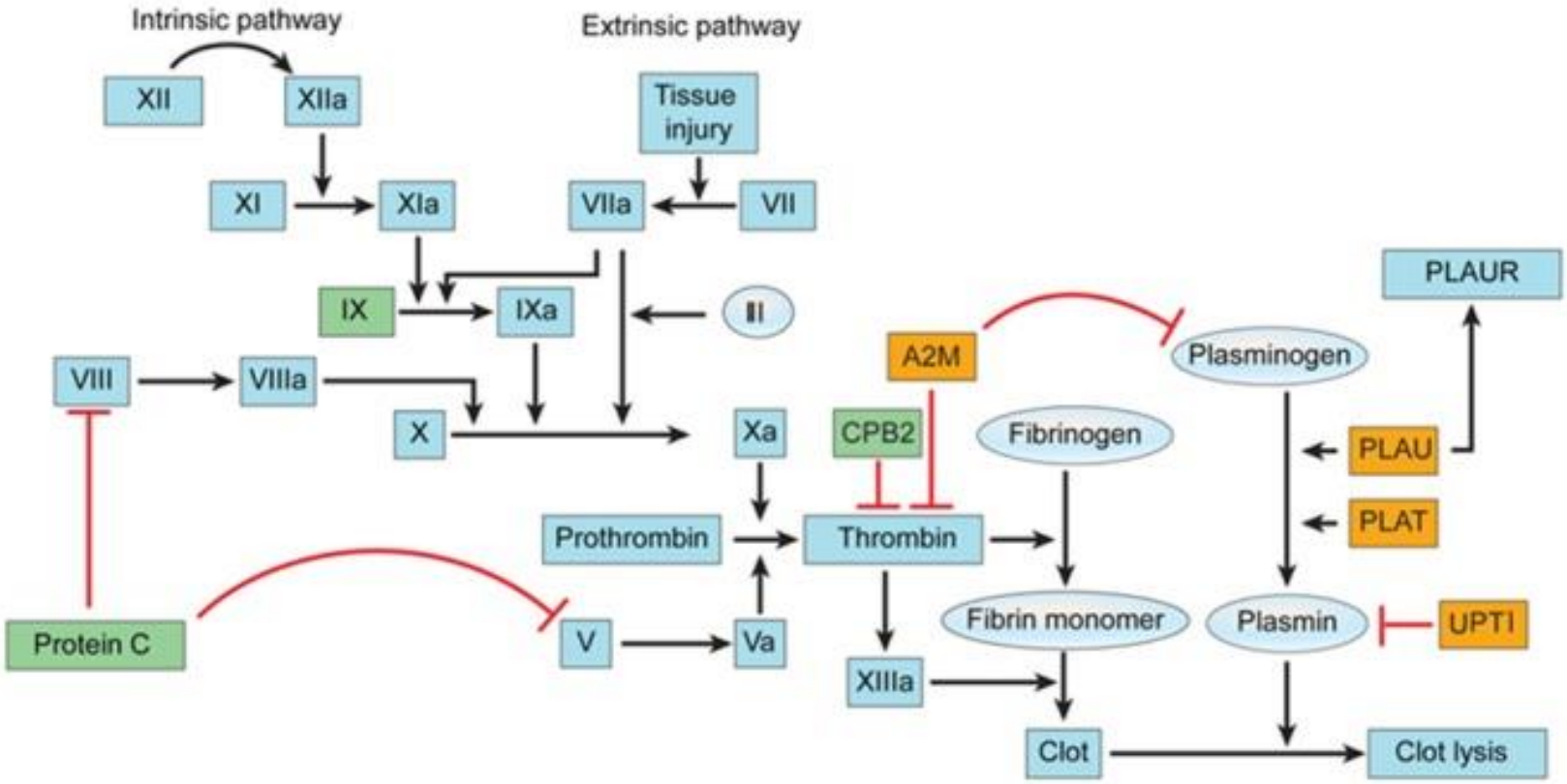
UKS
Universitätsklinikum
des Saarlandes

Kaskadenmodell der Gerinnung



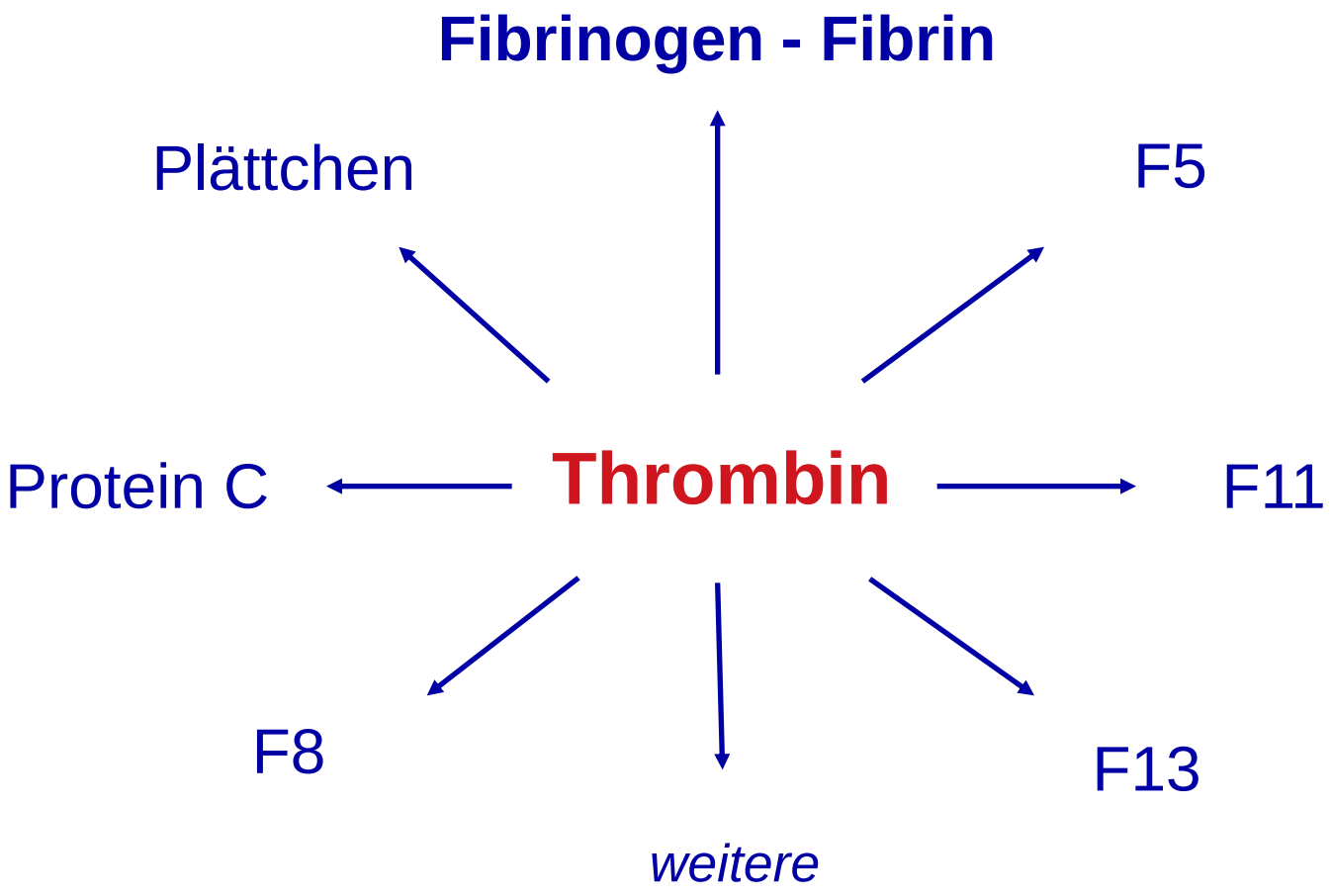
MacFarlane RG. Nature 1964

Kaskadenmodell der Gerinnung



Yoon YE, et al. PloS One 2015

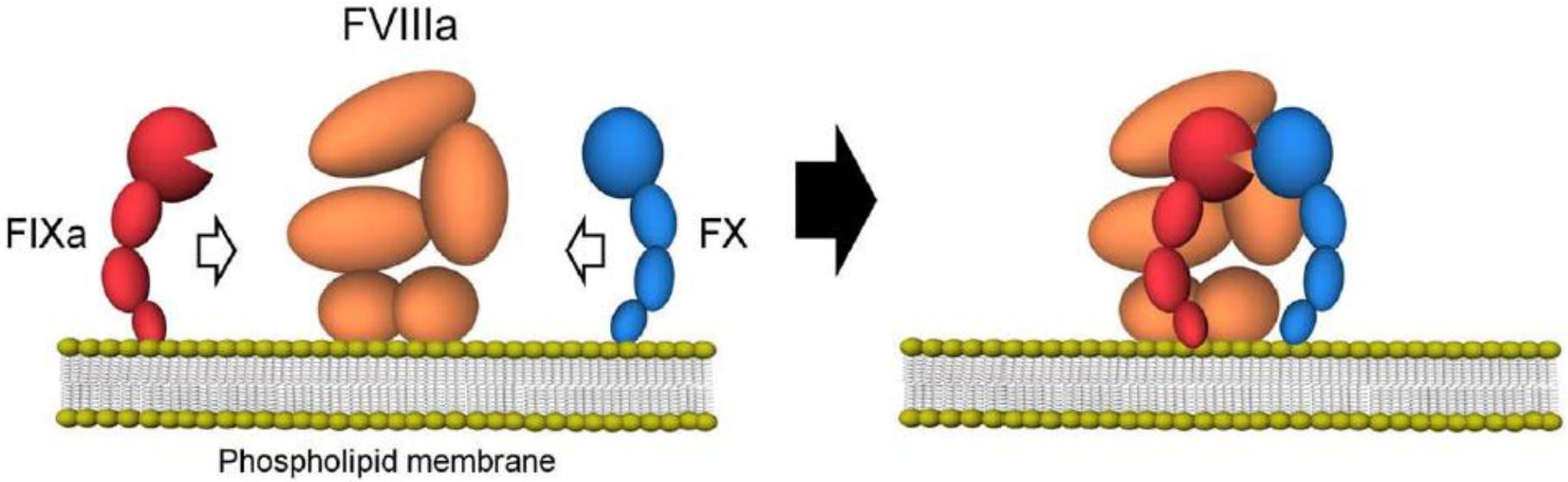
Zentrale Funktion von Thrombin



Einteilung der Hämophilie

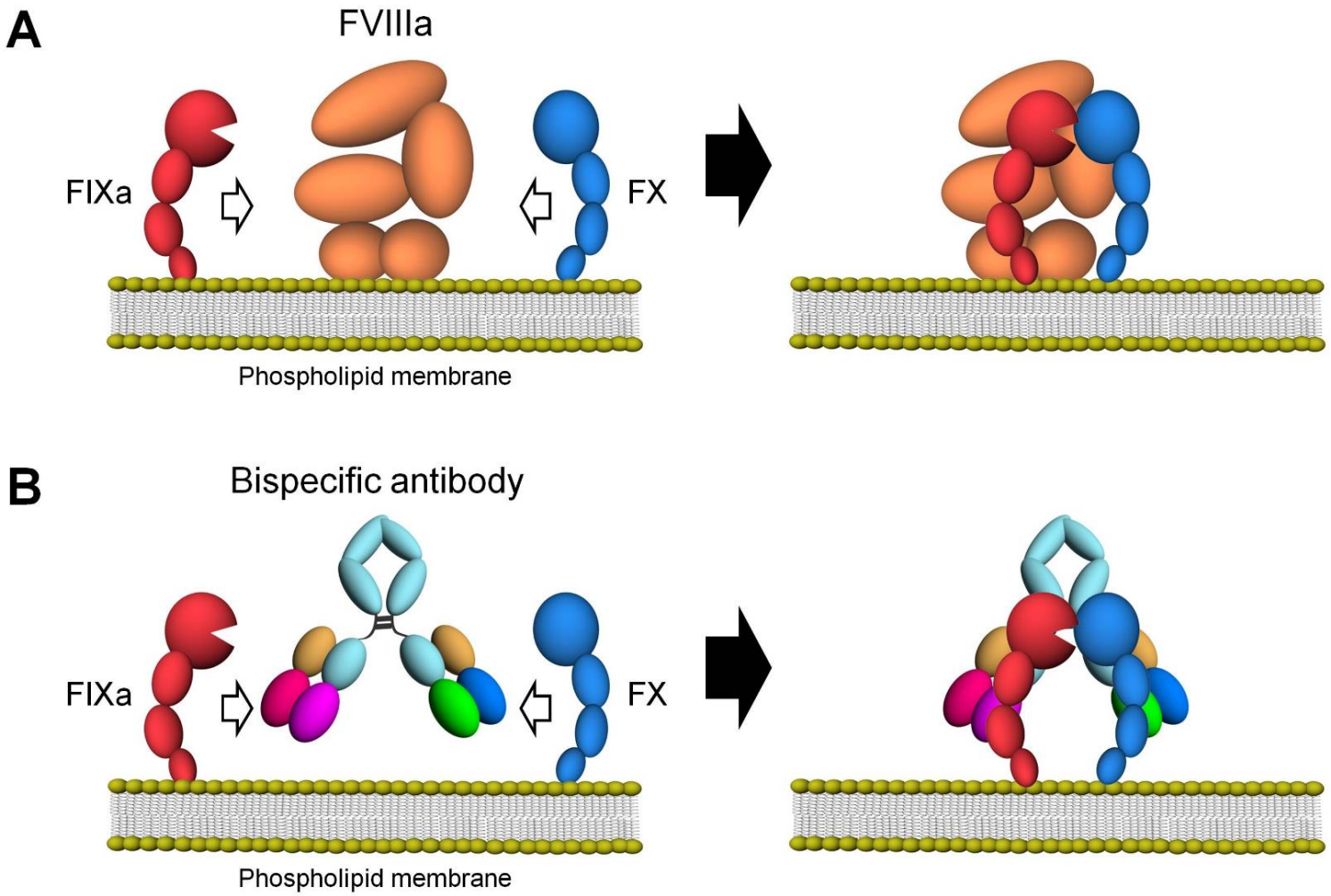
Klassifikation	Schwer	Mittelschwer	Mild
F8 / F9 Aktivität (% normal)	<1%	1%–5%	>5%–40%
Häufigkeit von Blutungen	24–48 pro Jahr	4–6 pro Jahr	ungewöhnlich
Ursache von Blutungen	spontan	kleinere Verletzung	Größere Verletzung, OP

Funktion F8 / F9



Sampei Z, et al. PLoS One 2013

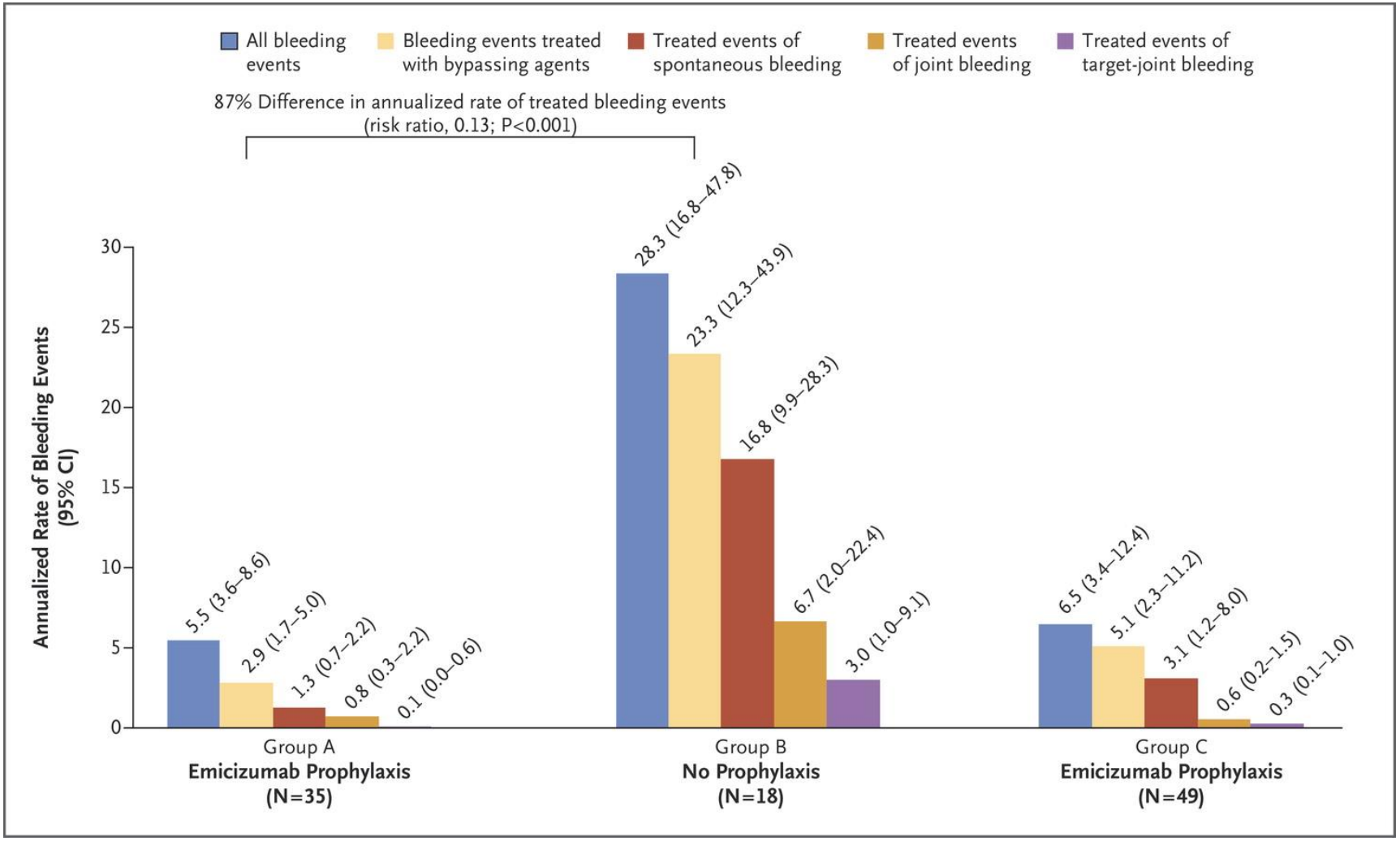
Emicizumab
bispezifischer Antikörper als Ersatz für F8



Sampei Z, et al. PLoS One 2013

HAVEN 1

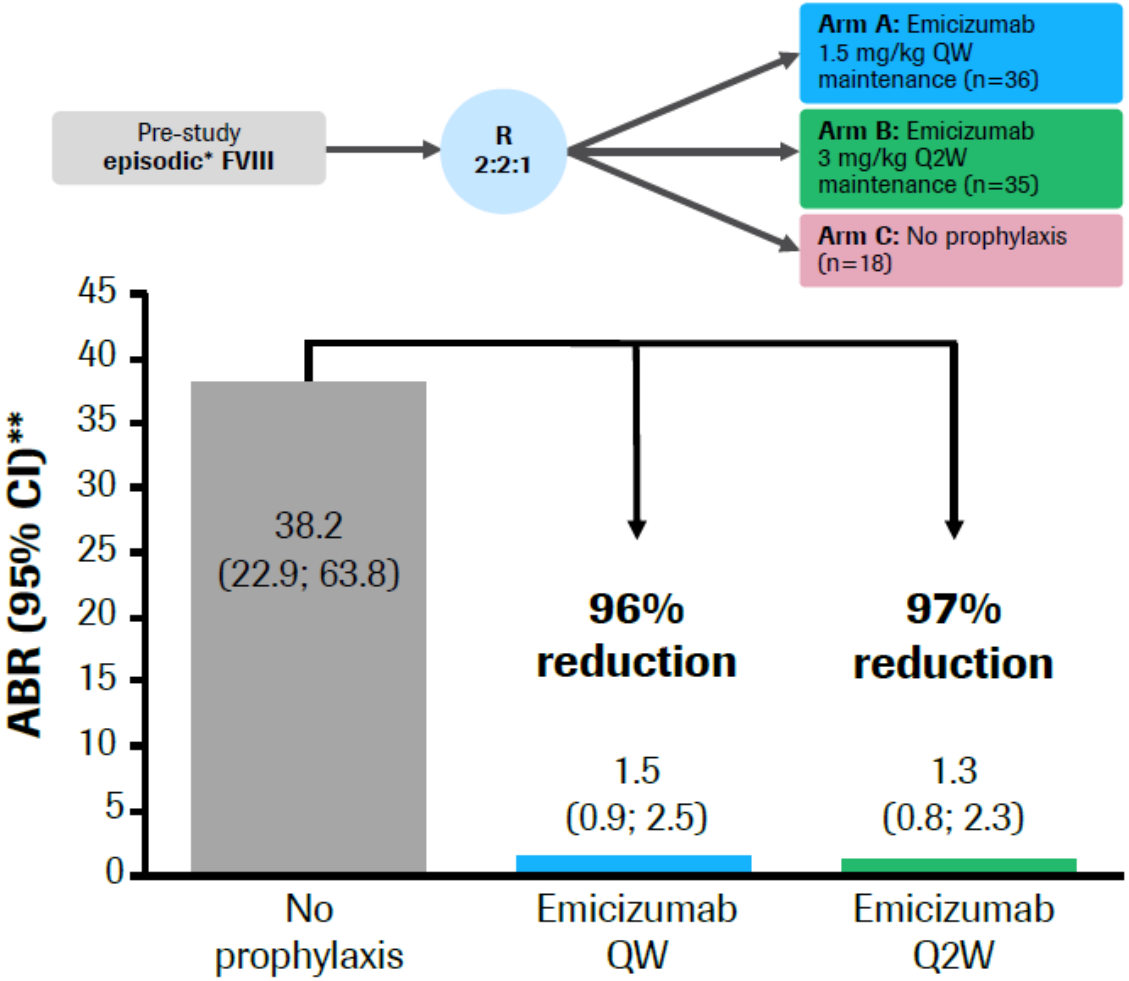
Emicizumab zur Prophylaxe (s. c.) bei Hämophilie A mit Hemmkörpern



Oldenburg J, et al. NEJM 2017

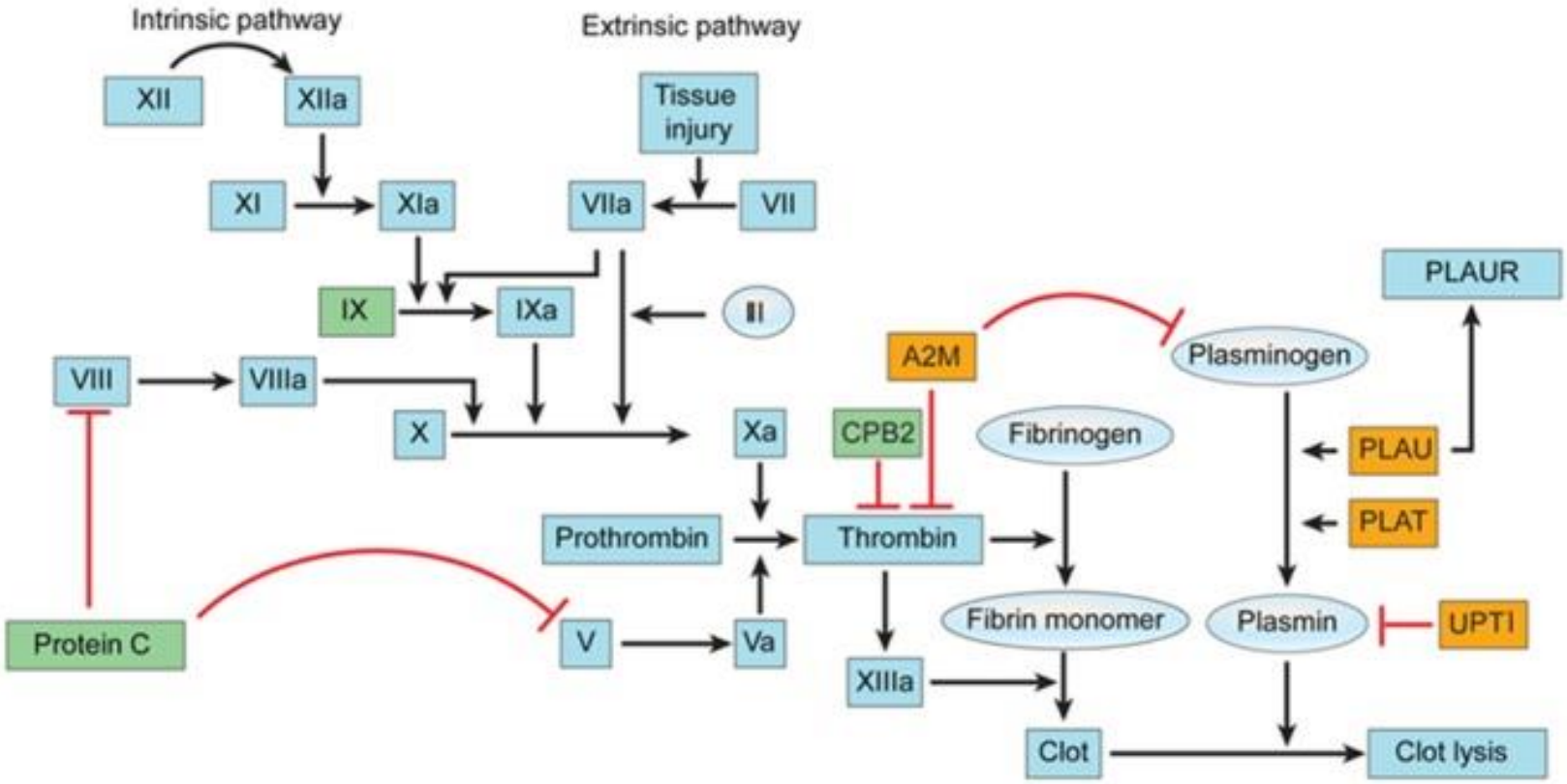
HAVEN 3 (Phase III)

Emicizumab zur Prophylaxe (s. c.) bei Hämophilie A <u>ohne</u> Hemmkörper



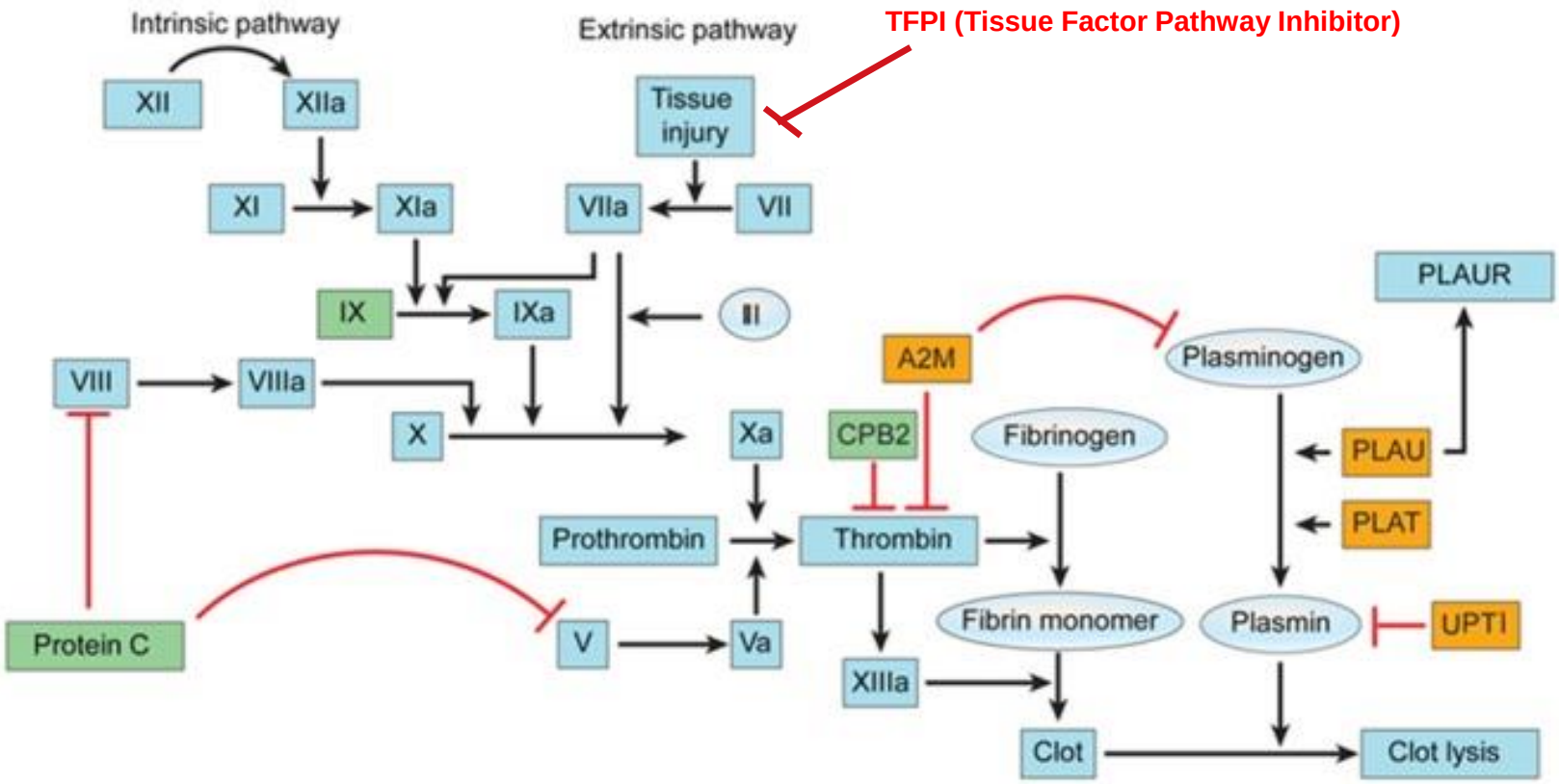
Mahlangu J, et al., NEJM 2018

Kaskadenmodell der Gerinnung



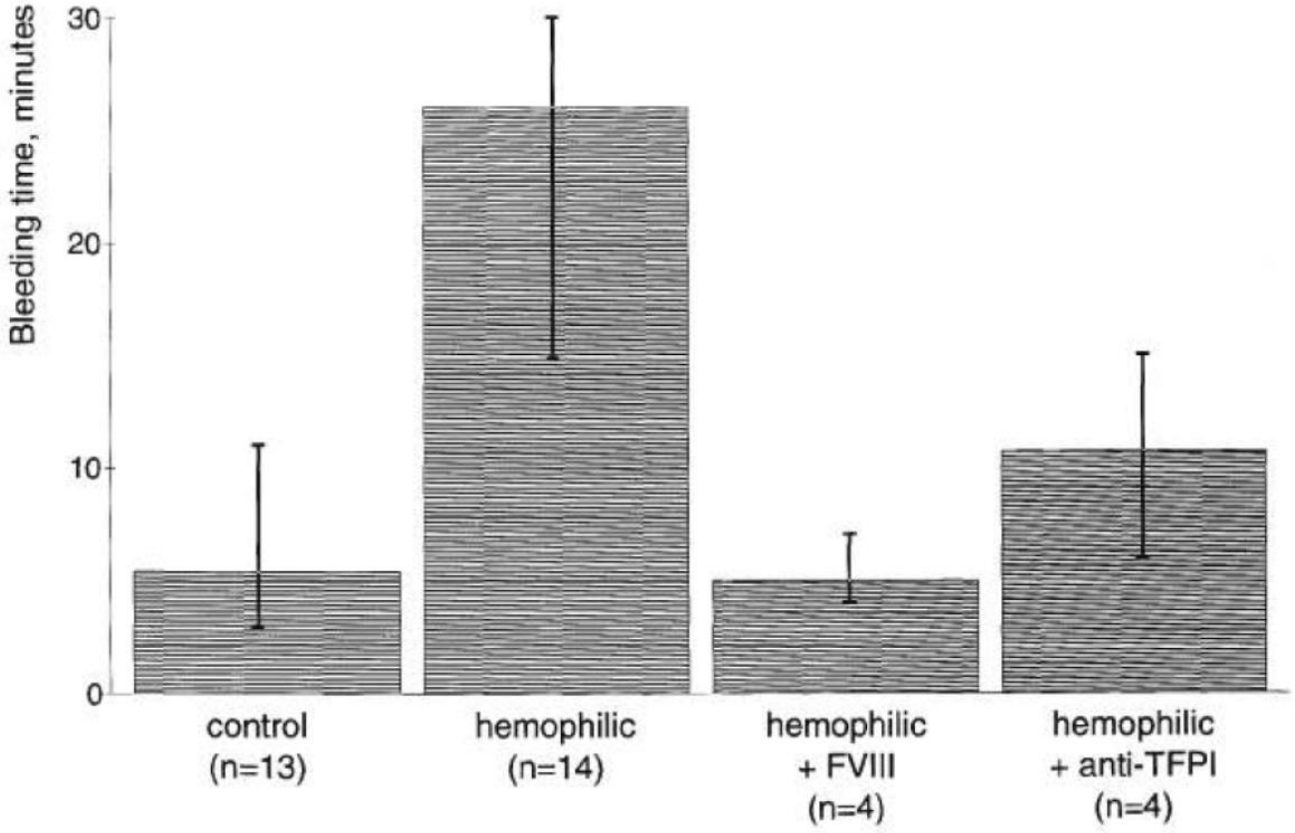
Yoon YE, et al. PloS One 2015

Kaskadenmodell der Gerinnung



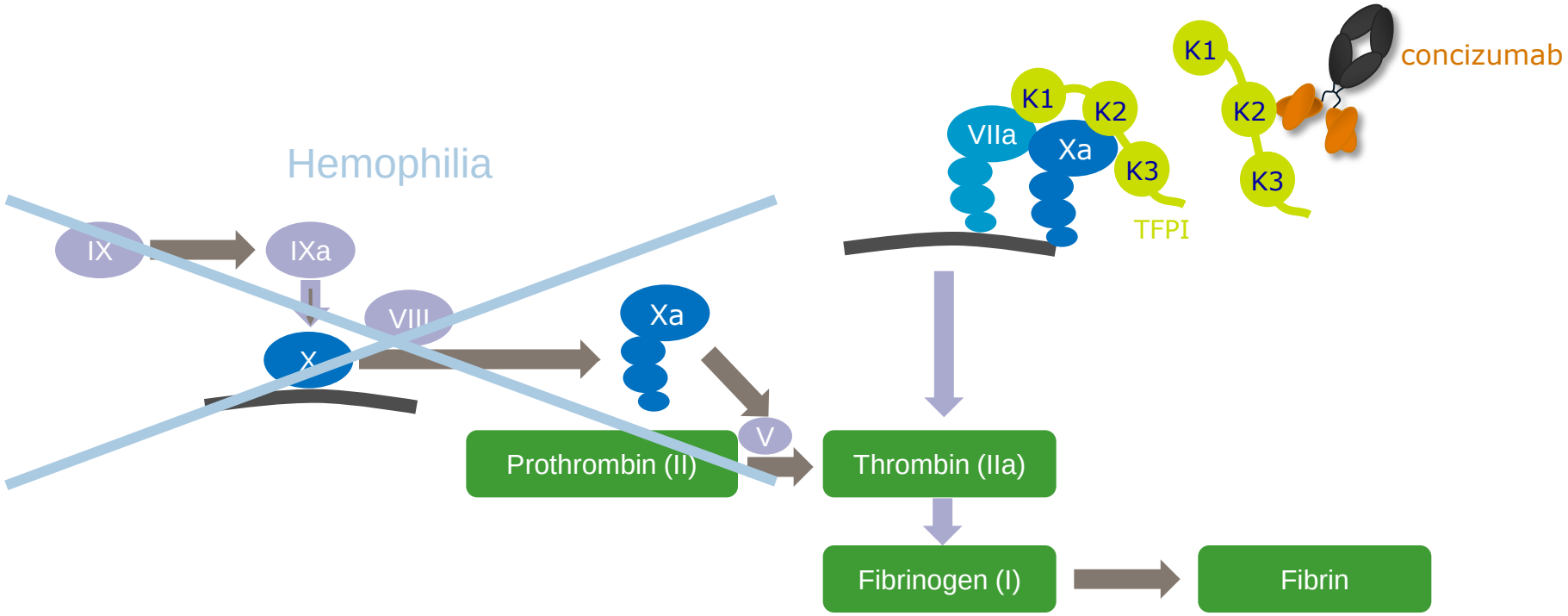
Yoon YE, et al. PloS One 2015

Hemmung von TFPI erhöht das Gerinnungspotential bei Hämophilie



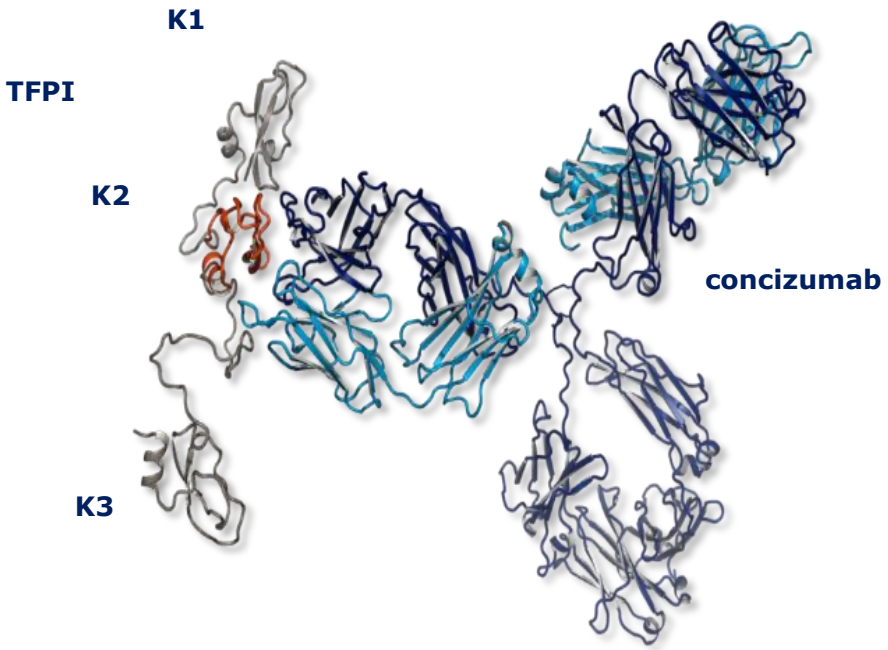
Erhardtsen E, et al. Blood Coagul Fibrinol 1995; Hilden I, et al. Blood 2012
Gu JM, et al. AAPS J 2017; Parng C, et al. J Pharm Sci 2018

Concizumab – Anti-TFPI



Eichler H, et al. ISTH 2017

Concizumab – Anti-TFPI



- Therapeutisches Anti-TFPI (concizumab, BAY1093884, PF-06741086)

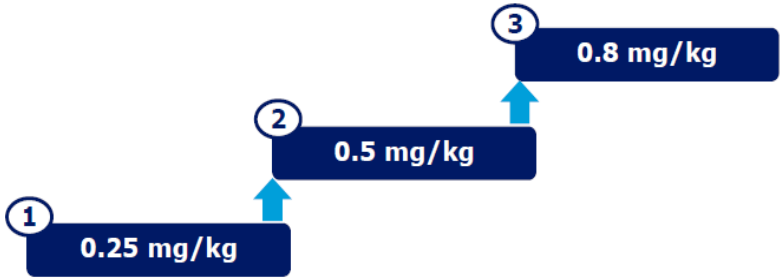
Hilden I, et al. Blood 2012

explorer™3 trial design

A multi-centre, randomised, placebo-controlled, double-blinded, multiple-dose trial investigating safety, pharmacokinetics and pharmacodynamics of concizumab administered subcutaneously to haemophilia A subjects

Planned dose

Dose escalation decision



Design

- Cohorts: each with 8 subjects dosed 12 times every 4th day to placebo or concizumab 2:6 randomisation scheme

Trial objectives

- assess the safety
- assess pharmacokinetics, pharmacodynamics and immunogenicity

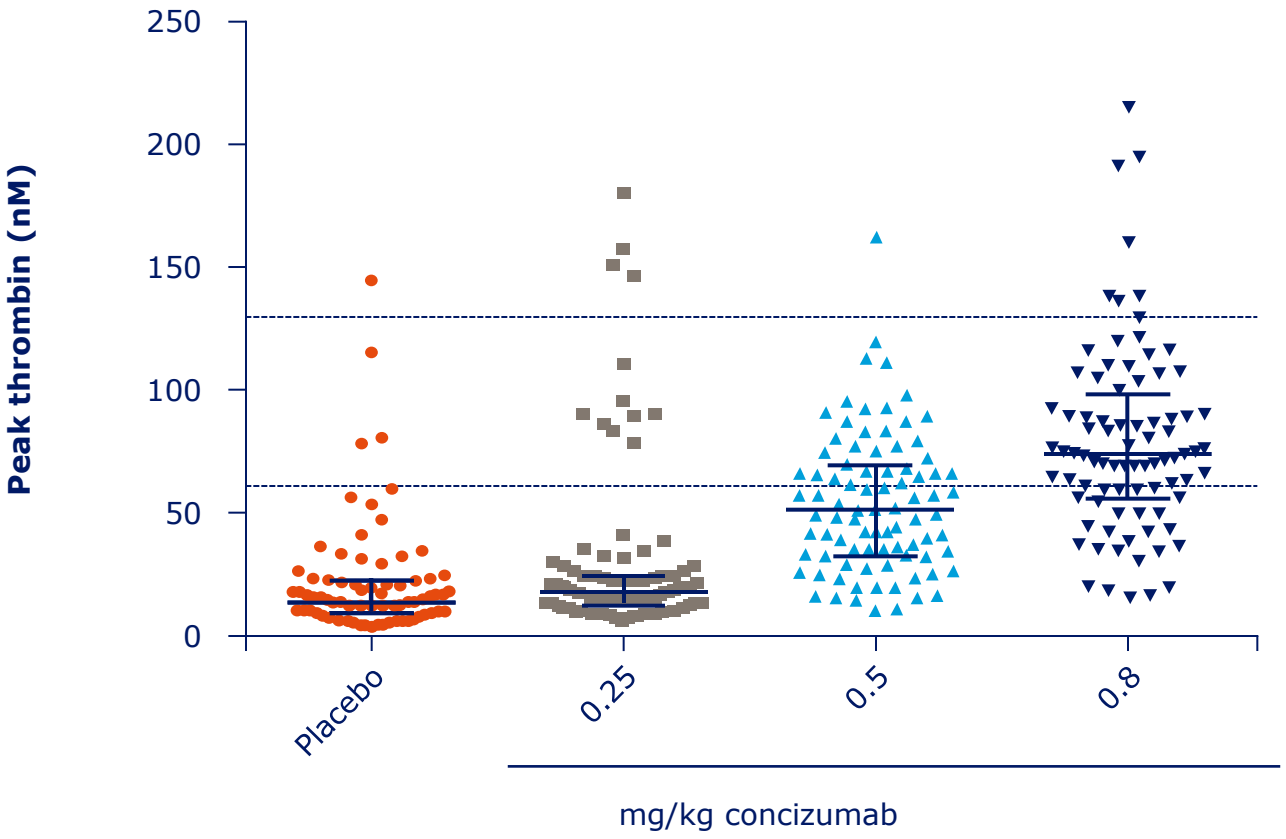
Primary endpoint

- number of adverse events

Eichler H, et al. J Thromb Haemost 2018

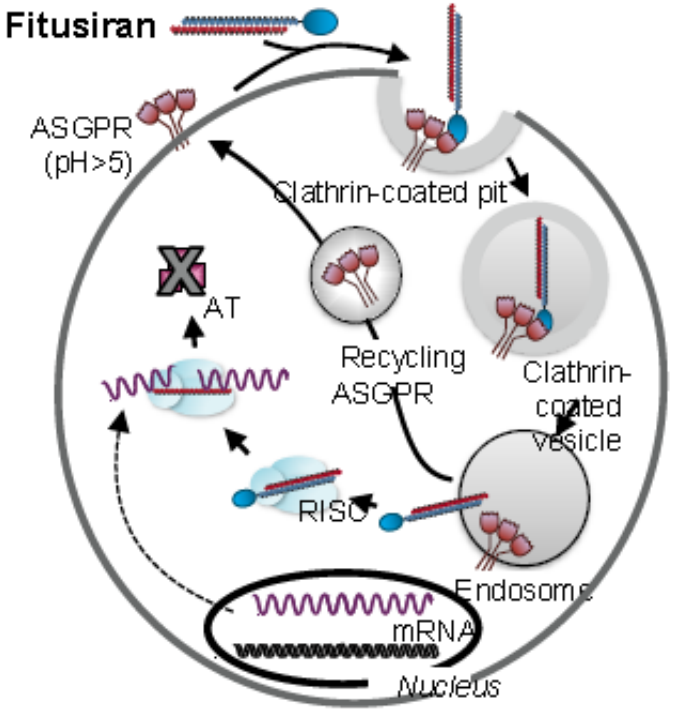
Concizumab – explorer3

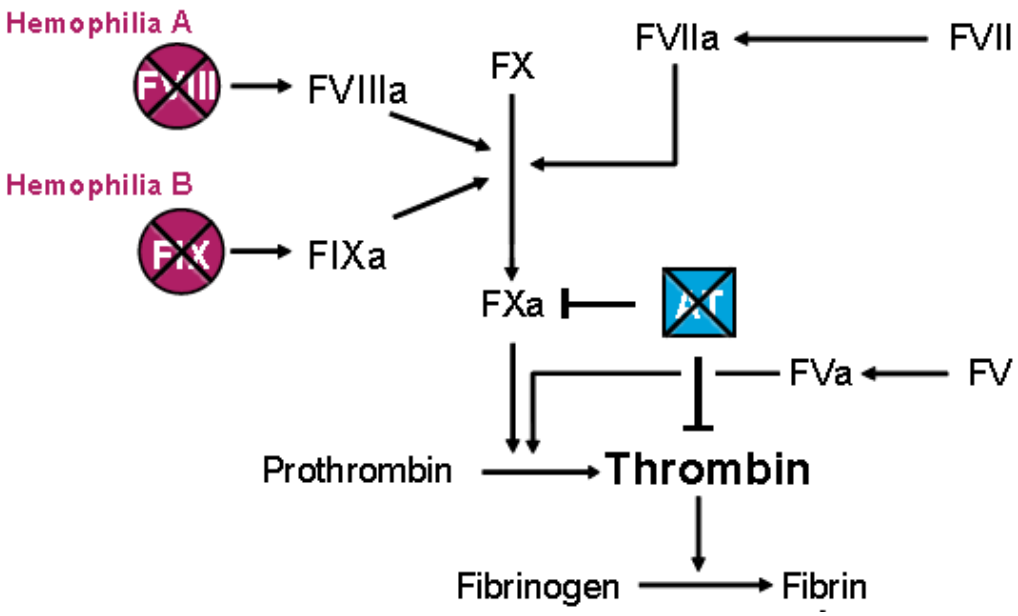
Zusammenhang Thrombin-Spiegel und Dosis von concizumab



Eichler H, et al. J Thromb Haemost 2018

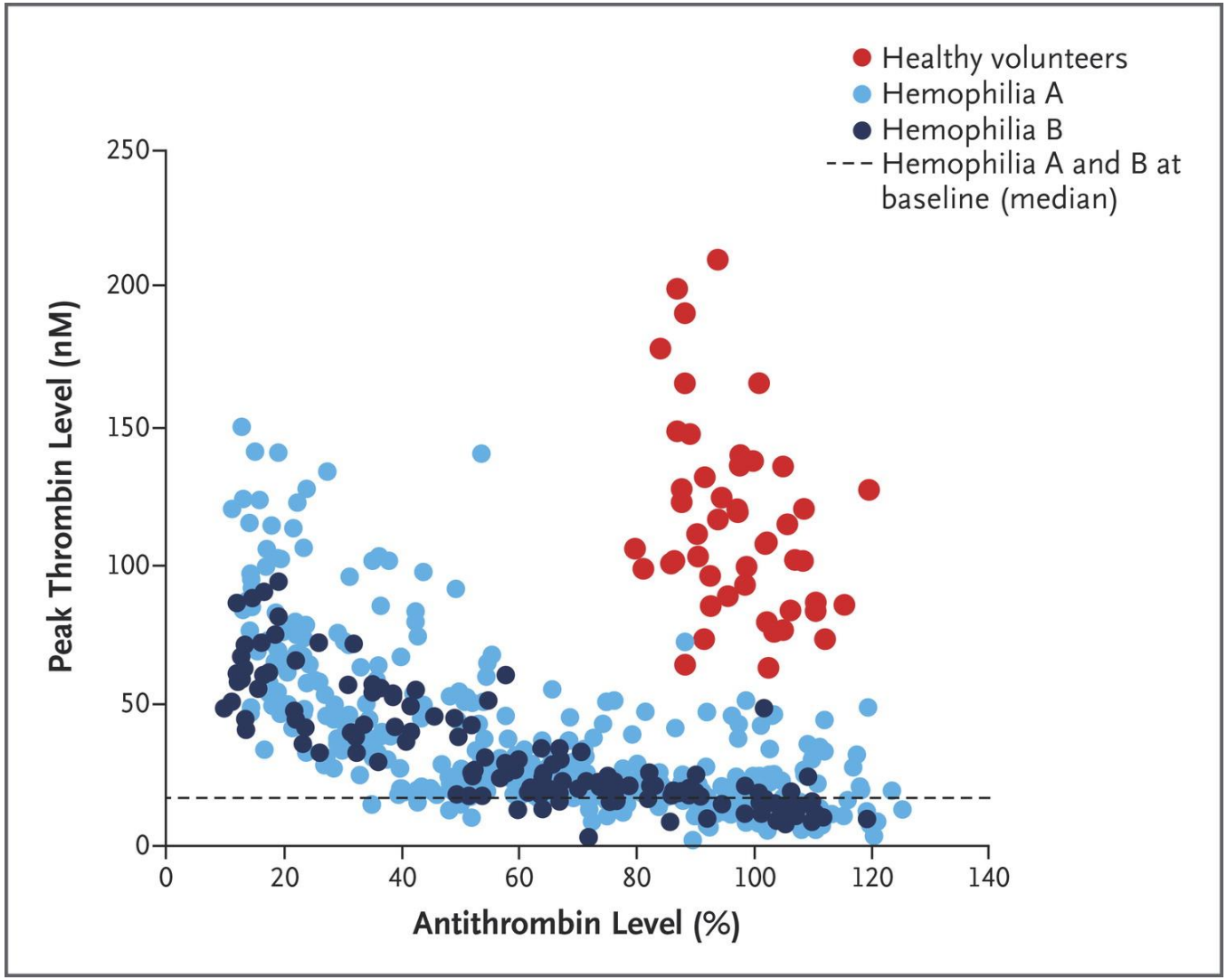
Fitusiran (ALN-AT3) – RNAi Antithrombin





Sehgal A, et al. Nat Med 2015

Fitusiran (ALN-AT3) – RNAi Antithrombin



Pasi KJ, et al. NEJM 2017

Neue Wirkstoffe in der Hämophilie-Therapie

- **(mögliche) Vorteile:**
- Subkutane Injektion
- Annäherung an normale Thrombin-Spiegel?
- Langfristige Vorteile für Blutungshäufigkeit und Gelenkgesundheit?

- **(mögliche) Nachteile:**
- Schwieriges Labormonitoring
- komplexere Therapiesteuerung – wie behandele ich Durchbruchsblutungen? Fehlbehandlungen möglich…
- Bindung an erfahrene Hämophilie-Zentren