Hemophilia: new developments in patient treatment

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10th ECAT participants' meeting, November 11, 2015

Current treatment

- Wild-type coagulation factor concentrate, discussion about inhibitor-genicity
- Modified concentrates (B domain deleted), issues with monitoring

- Safety and availability are a given
- Choices are limited to dosing schedules
  - Pharmacokinetics, optimal start of prophylaxis

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New developments

Alternative approaches

Gene therapy

Longer acting clotting factors

Optimize treatment with current concentrates, pharmacokinetics

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Longer acting

- Fusion, to interfere with clearance
  - Fc fusion (registered, FVIII and FIX)
  - Albumin fusion (registered, FIX)
  - PEGylation (phase III data)

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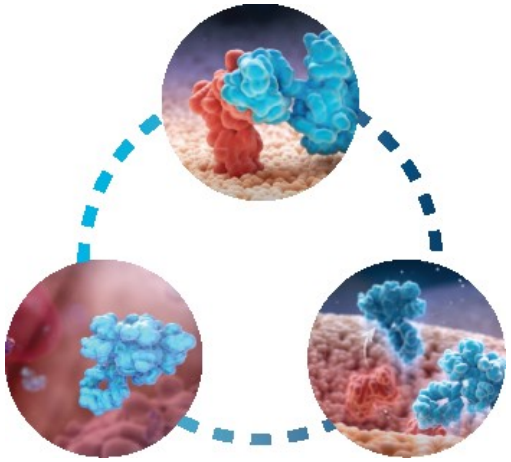
Longer acting clotting factors: Fc tail

- Fc part of IgG interacts with neonatal Fc recepter (FcRn), prolonging IgG halflife

Same happens if Fc is fused with other protein!



From Eloctate website

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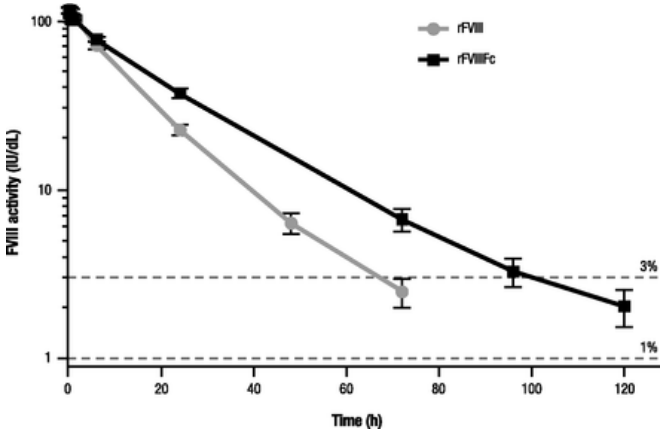
A-LONG study

- rFVIIIFc, T1/2 19h
- 165 PTPs, ≥ 12 jaar



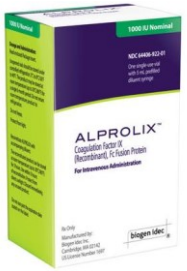
- Every 3-5 days ABR 1.6
  - 30% 2x/wk, 33% every 3d, 33% every 5d
- Every week ABR 3.6

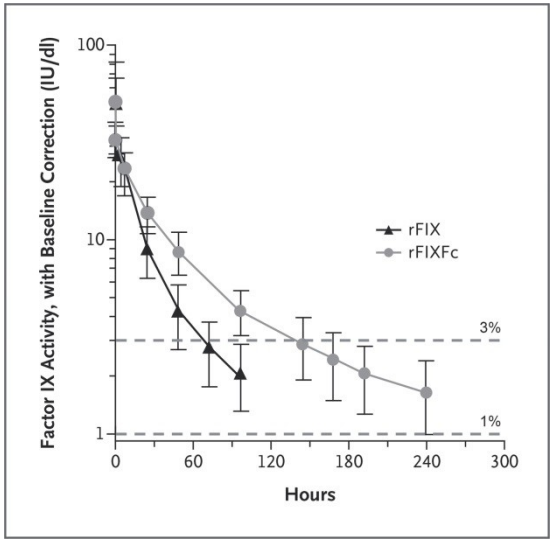
- No unexpected AEs, no inhibitors
  - 2014: FDA approval
  - 2016: available NL as Elocta

Mahlangu, Blood 2013

B-LONG study

- rFIXFc, T1/2 82h (≈ 3 days)
- 123 PTPs
- No inhibitors





- 2016: available in NL as Alprolix

Regimen	Start with	ABR
1x/wk, dose adjusted	50U/kg	3.0
100U/kg, interval adjusted	10 days	1.4
On demand	20-100U/dose	17.7

Powell, New Engl J Med 2013

Longer acting

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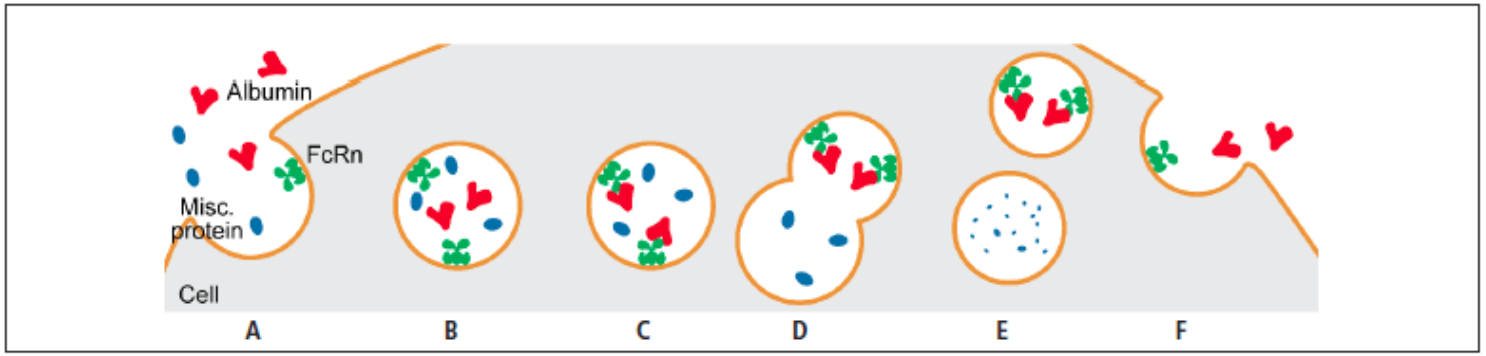
Longer acting clotting factors: albumin fusion

- Attractive option, naturally occurring protein
  - Levimir insulin
- Works like Fc fusion: interacts with FcRn, ‘recycles’ clotting factor



Metzner, T&H 2013

Clinical data rIXFP

- 63 PWH, factor IX < 2%, 12-61 yr
- Prophylaxis 1x/ 7, 10 or 14 days

- T ½ 102h
- Trough 20% while on 40E/kg/ 1 wk
  12% while on 75E/kg/ 2 wks
- ABR 0 in 1x/wk, 1.08 in 1x/2 wk

→ *what would happen if you lowered the dose..*

Santagostino, Blood 2016

Longer acting

- Fusion, to interfere with clearance
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Longer acting clotting factors: PEGylation

- Well known additive, no reported side effects: PEG interferon, laxative
  - But no data for long term, iv use
- Polyethylene glycol polymers bind to specific sites of factor VIII
  - random binding led to interference with VWF binding, and reduced activity

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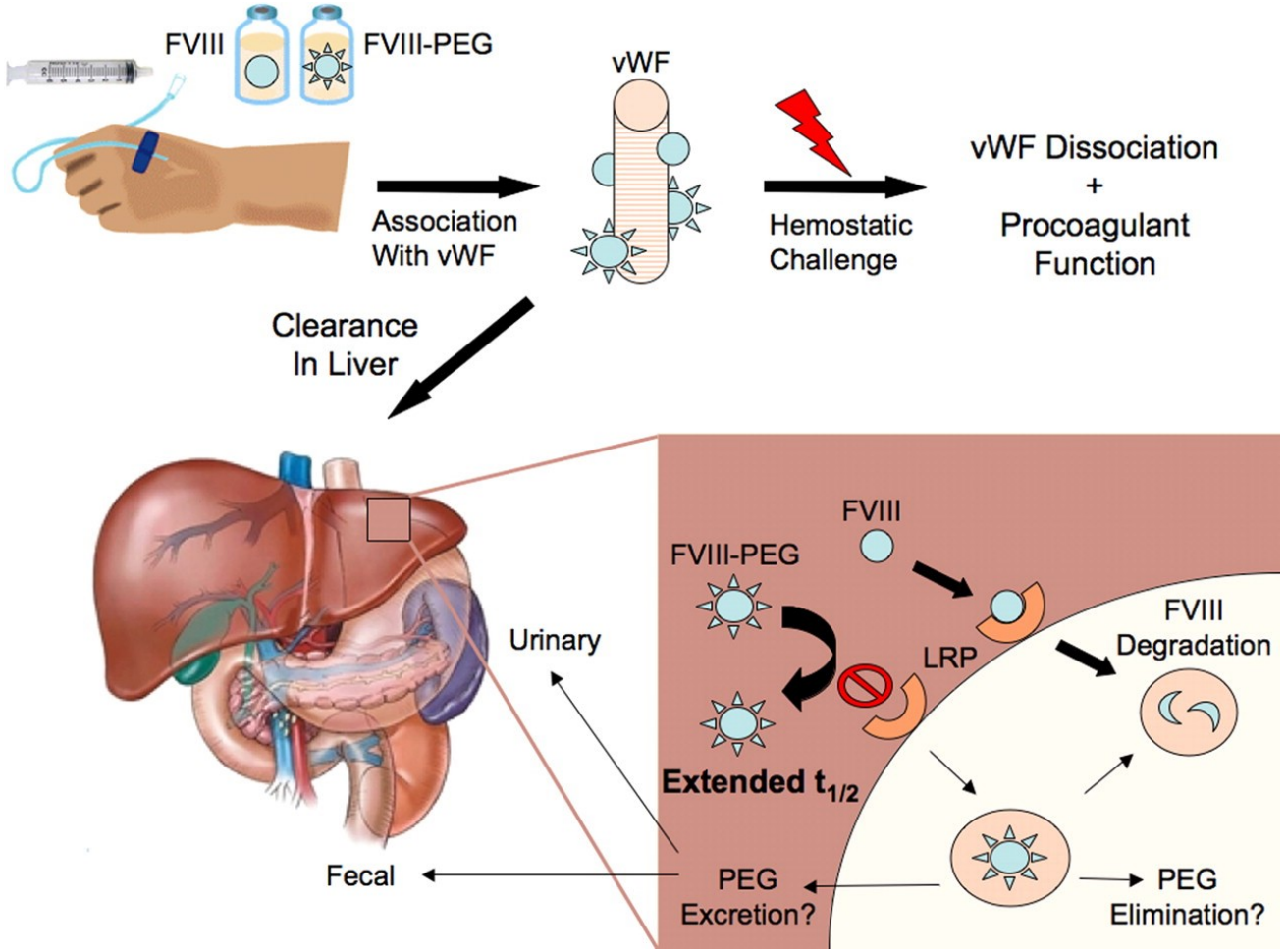
Longer acting clotting factors: PEGylation



Pipe, Blood 2010

Current status

- Three FVIII molecules in phase III studies
  - Two B domain deleted, one full length
  - Outcomes reported in abstract form
  - In general: t ½ appr 18 h
  - Effective with increased interval
  - But: high doses, compared to Dutch standard
- FIX phase III published
  - ABR 1.0 with 40^{E}/kg/w, 2.9 with 10^{E}/kg/wk

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Collins, Blood 2014

Why better results for factor IX than for factor VIII?

- Fusion proteins are still stabilized by VWF
- T ½ of longer acting VIII molecules = T ½ of VWF, appr. 18 h

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Gene therapy

- 2011 first published human results
  - 6 adult patients with severe haemophilia B
  - AAV8 vector, iv administration
  - Course over 6 months: 2-4% factor IX, no prophylaxis. Hepatitis requiring steroids.

- 2015 first trial open for Dutch subject
- 2016 WFH: avalanche of new data

Nathwani, New Engl J Med 2011

Hemophilia B, WFH

- All studies use in vivo approach with AAV virus (coagulation factor cassette in virus, iv administration)
- All have issues with immune respons

- Uniqure: n= 5, 1 nonresp, rest 3.1-6.7%
  - AAV5, wild type hFIX
- Spark: n = 4, all resp, 21-42% FIX
  - rAAV SPK 100, FIX-Padua

Hemophilia A, WFH

- Unexpected very good results from Biomarin trial

  AAV5, B-domain deleted factor VIII

  N=2, low dose, FVIII < 5%

  N=7, high dose, FVIII > 15% (4/7 > 50%)

- Immune response in first high dose patient, subsequently prophylactic steroids

Future directions

- Ex vivo transvection of autologous stem cells (phase 1 planned 2017/18)
- Gene editing: ZFN, talen,

  CRISPR-Cas9

ARTICLE

doi:10.1038/nature20134

CRISPR/Cas9 β-globin gene targeting in human haematopoietic stem cells

Daniel P. Dever[1]*, Rasmus O. Bak[1]*, Andreas Reinisch[2], Joab Camarena[1], Gabriel Washington[1], Carmencita E. Nicolas[1], Mara Pavel-Dinu[1], Nivi Saxena[1], Alec B. Wilkens[1], Sruthi Mantri[1], Nobuko Uchida[3]†, Ayal Hendel[1], Anupama Narla[4], Ravindra Majeti[2], Kenneth I. Weinberg[1] & Matthew H. Porteus[1]

Non-clotting factor based approaches

- Inhibition of TFPI
- Mimicry of cofactor function of VIII
- Reduction of antitrombin

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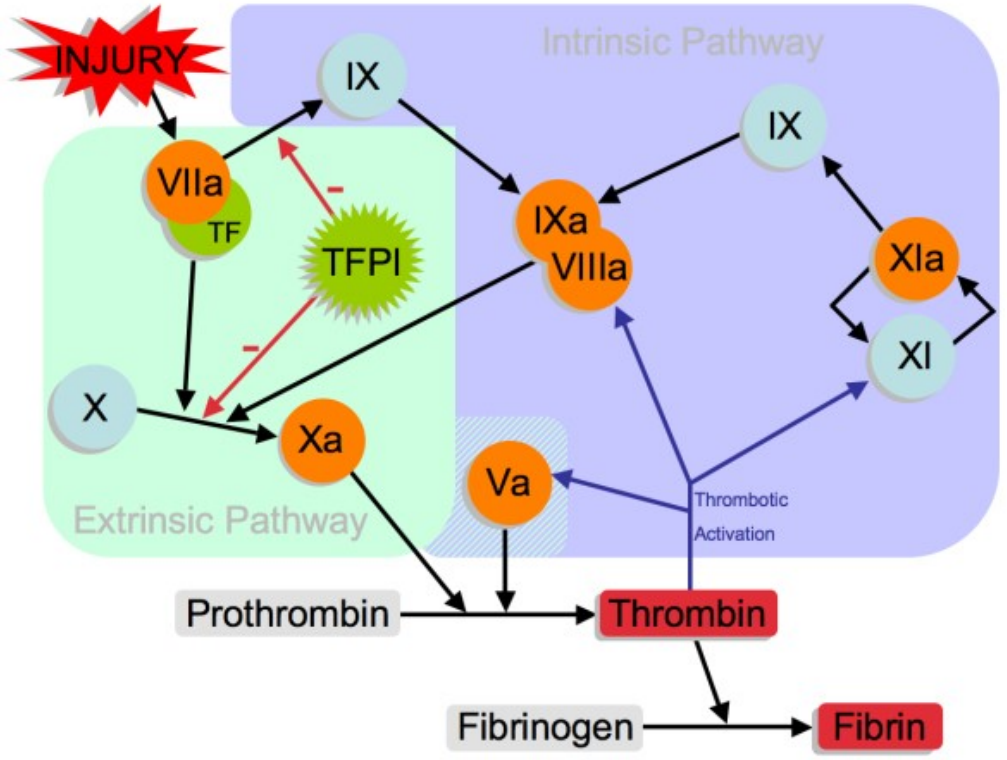
Inhibition of TFPI

- TF/factor VII initiates coagulation, forms small amount of Xa. Negative feedback by TFPI
- Subsequent large amount of Xa is formed through IX/VIII
- Compensate absence of IX/VIII by inhibition of TFPI?



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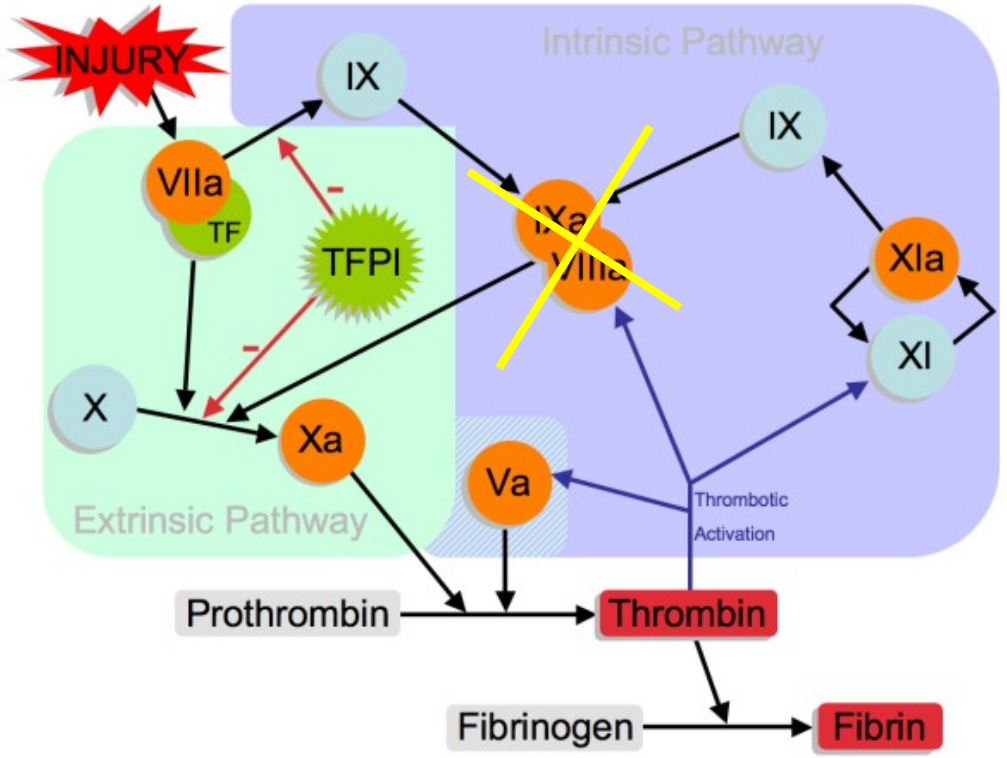

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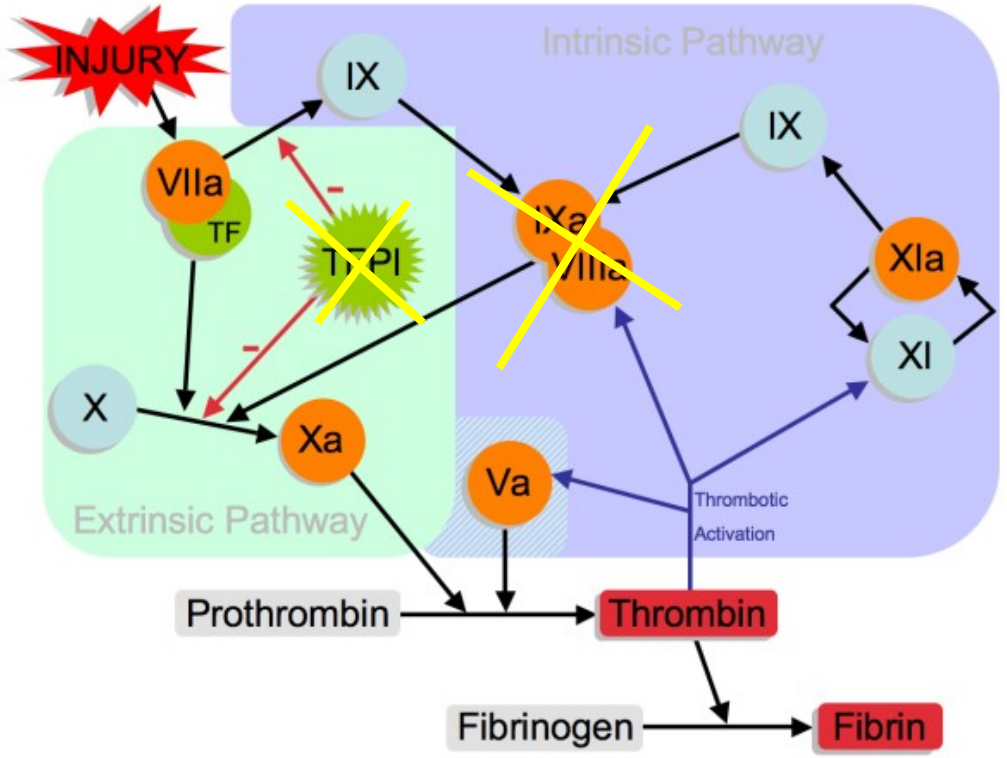

Popular concept

- Antibody to Kunitz 2 domain
  - Concizumab →
- Oligonucleotide aptamer
  - Phase 1 unsuccessfull: increased bleeding, by interfering with clearance of TFPI
- Number of clinical studies starting to recruit

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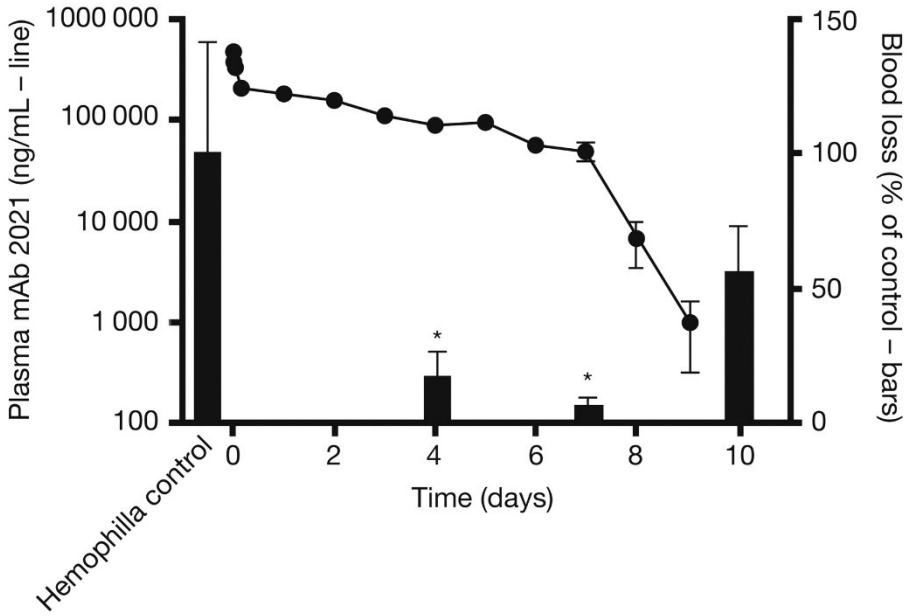
Concizumab



- Phase 1 data (incl 24 PWH): safe, allows for sc administration, indication of procoagulant effect

Hilden, Blood 2012; Chowdary JTH 2015

Non-clotting factor based approaches

- Inhibition of TFPI
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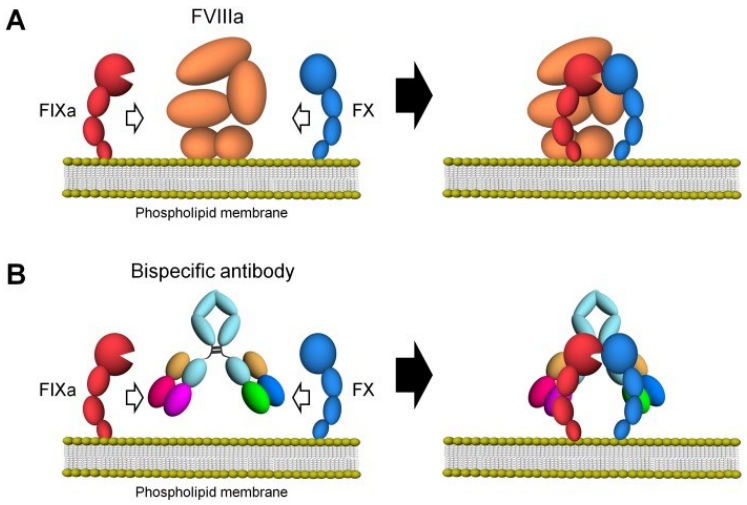
Mimicry of cofactor function of VIII

- Anti-factor IXa/X bispecific antibody acts as factor VIII



- ACE910, sc administration, long T ½
- Potentially effective in inhibitor patients

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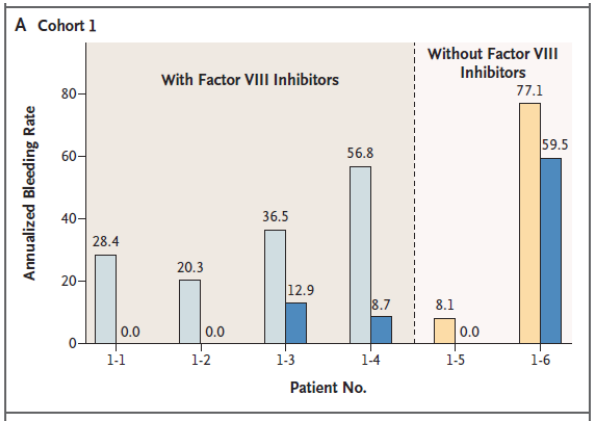
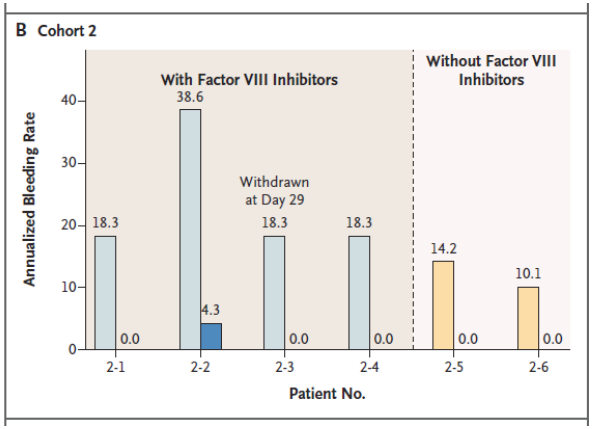
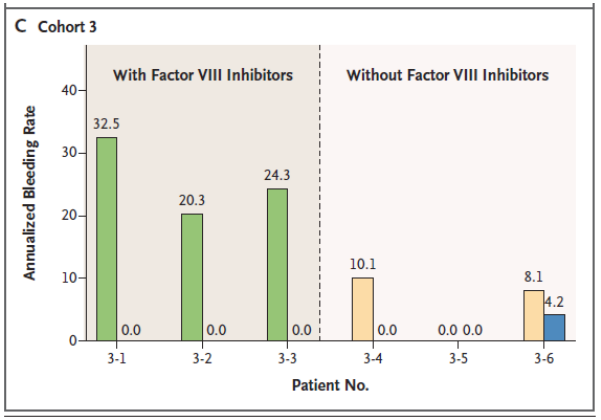
Sampei, PLoS One 2013

Clinical data for emicizumab

- 18 PWH, with or without inhibitors
- Sc administration, 1x/wk
- No safety issues
- Impressive ↓ ABR in higher doses:







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Shima, NEjM 2016

Non-clotting factor based approaches

- (Inhibition of fibrinolysis)

- Inhibition of TFPI
- Mimicry of cofactor function of VIII
- Reduction of antitrombin

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ALN-AT3

- Small interference RNA, with modification to target hepatocytes
- Decreases expression of antitrombin gene

- Potentially applicable in all bleeding disorders, including inhibitors
- Phase 1 data: ↓ AT, ABR 2-4 in inhibitor patients, no signs of DIC

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Sehgal, Nature Med 2015 and oral presentation ISTH 2015


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED

Clinical perspective, horizon of 3 years

- Routine clinical use of long-acting factor IX and intermediate-acting factor VIII
- TFPI inhibition accessible through clinical trials
- Gene therapy accessible for adult severe haemophilia B patients
- Rest of exciting new stuff will take longer

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