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## ON HAEMOPHILIA, VWD AND RARE BLEEDING DISORDERS

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# Disclaimer

This conference is hosted by Haemophilia Foundation Australia.

Conference speakers include health professionals, researchers, government officials and bleeding disorders community members.

**Some of the treatments discussed may not be registered or funded currently in Australia and should not be considered as a promotion or recommendation. Please discuss this with your health professional.**

# Mild Haemophilia in Adults

## Focus on Medical Issues

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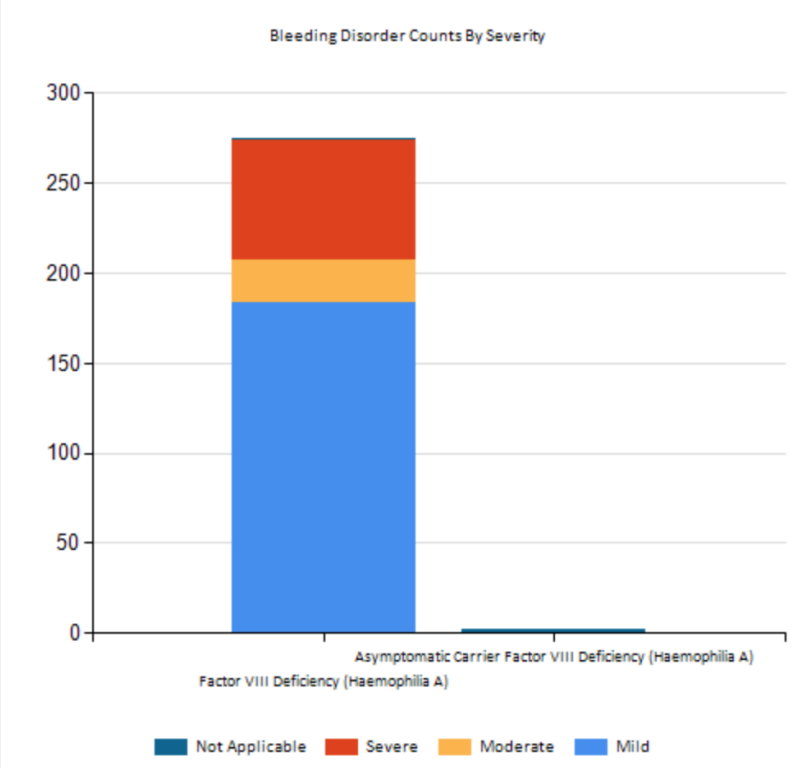
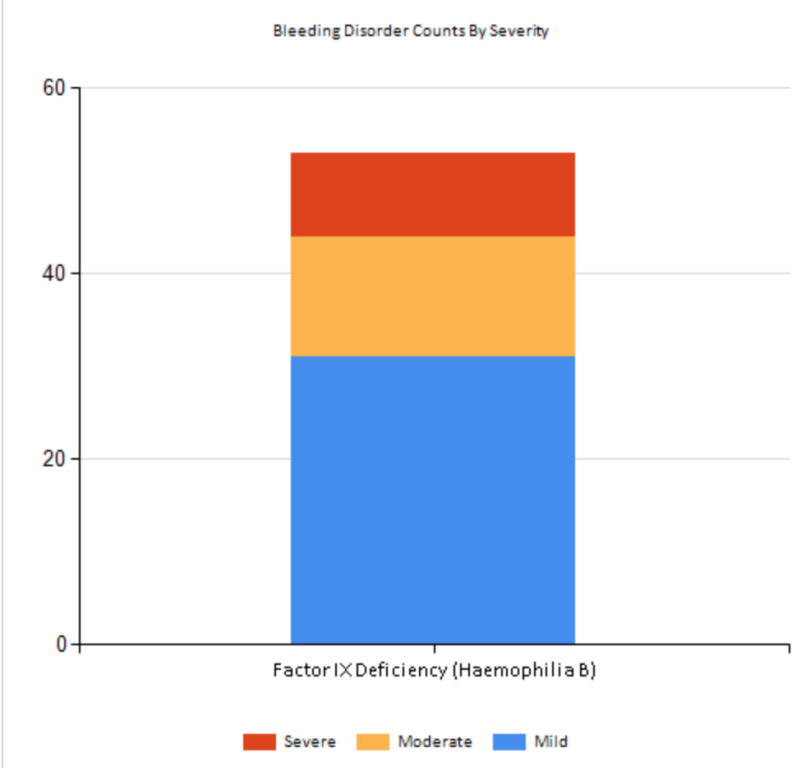
# Content

- Definition
- Epidemiology
- Clinical Manifestations
  - Overall Bleed Frequency
  - Joint bleeds, Joint Arthropathy,
  - Quality of Life
  - Inhibitor Development
- Treatment Options
- Managing medical issues that develop with aging
- Ongoing Challenges

# Epidemiology

- Mild Haemophilia: Factor Level 5-40%



# Clinical Manifestations

- Patients with mild HA often require and receive less intense therapy and medical attention
- Meta-analysis of 17 studies included data for 3213 mild HA patients aged 13 years and older out of a total of 20587 total HA patients.

**TABLE 2** Bleeding episodes reported in mild HA patients

| Study | Population (FVIII level/ age) | Follow-up period | Bleeding events | |
|---|---|---|---|---|
| | | | % (n/N) of patients with bleeding | episodes/pt year (SD) |
| Prospective cohort (US, Canada)[12] | 6%-40% (median NR) Age NR | 5 y (2002-2006) | 36% (4/11) had bleeding score[a] >0, indicating at least one bleeding episode other than surgery, dental procedures and major accidents | NR |
| Cross-sectional survey (Finland)[22] | 5%-40% (median NR) Age ≥16 | 1 y (years NR; publication 1996) | 40% (8/20) had at least one episode of moderate bleeding[b]; none had severe bleeding | NR |
| Retrospective cohort (Italy)[8] | 0.6-0.33 IU/mL (median 0.15 IU/mL) Median age 35 (range 3-88)[c] | 10 y (range 1-39; 1985-2010) | 91% (68/75) had at least one bleed during follow-up[c]: 27% joint, 35% muscle, 73% muco-cutaneous, 13% postoperative, 21% after dental work | 0.56 (0.67) Includes all bleeds regardless of treatment |
| Retrospective cohort (Slovenia)[25] | 5%-40% (mean 8.5%) Age 13-54 | 6 y (2007-2014) | 57% (8/14) Includes surgery, trauma, dental procedures | 0.44[d] Includes all bleeds regardless of treatment |
| Retrospective cohort (Canada)[26 e] | 5%-40% (mean 0.15 IU/mL) Adults ≥18 (mean age 46) | 5 y (year NR; publication 2008) | 17% (8/46) with 2 or more bleeds requiring medical assessment or therapy in past 5 y | NR |
| Prospective cohort (Italy)[27] | NR (median NR) Adults ≥18 | Duration NR (2011-2013) | 5.5% (1/18) had evidence of cerebral microbleed[f] | NR |
| Prospective cohort (US)[3,20,28g] | 6%-30% (median NR) Adults ≥18 | 2 y (2005-2007) | NR (23 patients with data) | 4.5 (10.0) Definition of bleeding episodes not available |

Haemophilia, Volume: 25, Issue: 5, Pages: 755-763, First published: 11 July 2019, DOI: (10.1111/hae.13777)

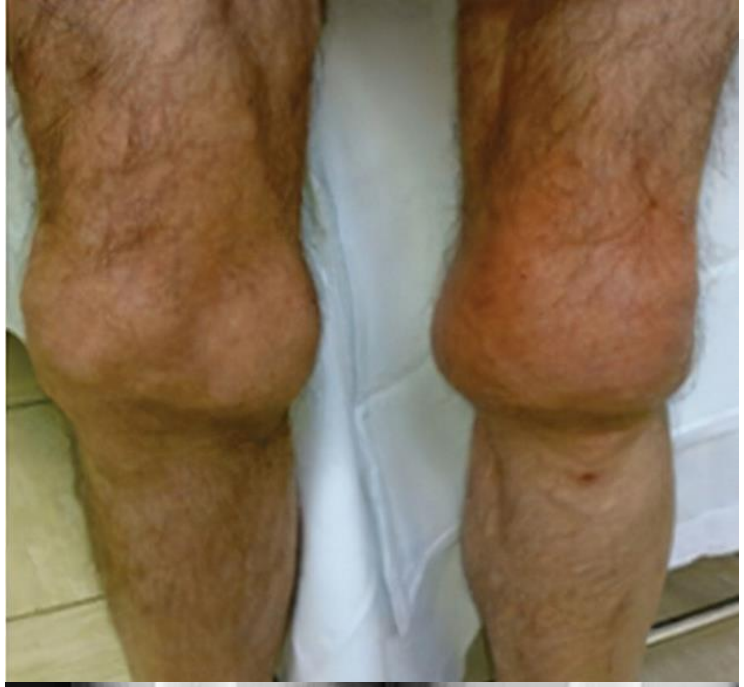
# Bleeding Episodes

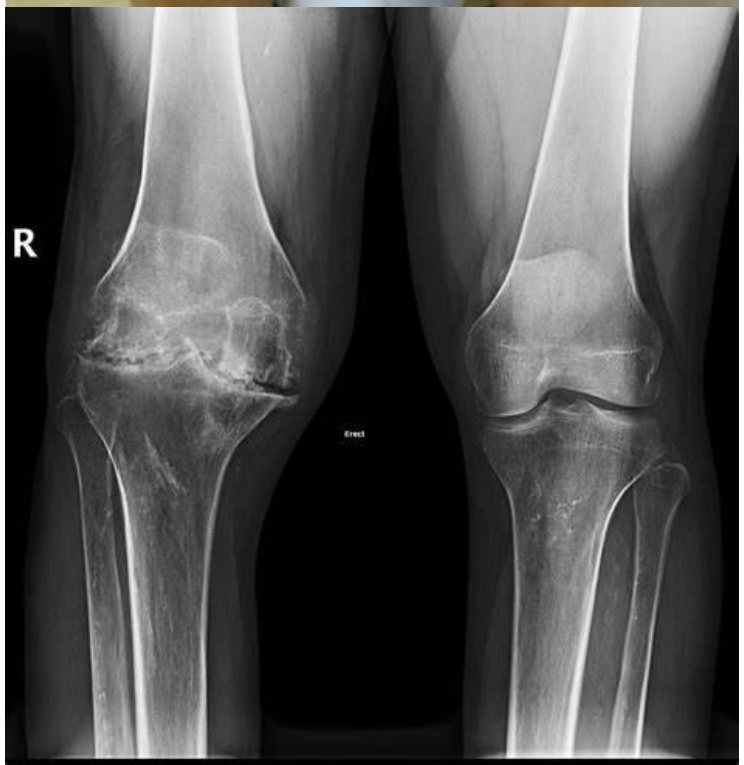
- Many patients do not frequently experience bleeding related issues and are not always able to recognise bleeding episodes
- Healthcare providers may not attribute symptoms to bleeding leading to a delay in diagnosis and a lack of treatment

- This maybe particularly so with women who experience heavy menstrual bleeding or post partum haemorrhage
  - Misconception that “carriers” do not bled

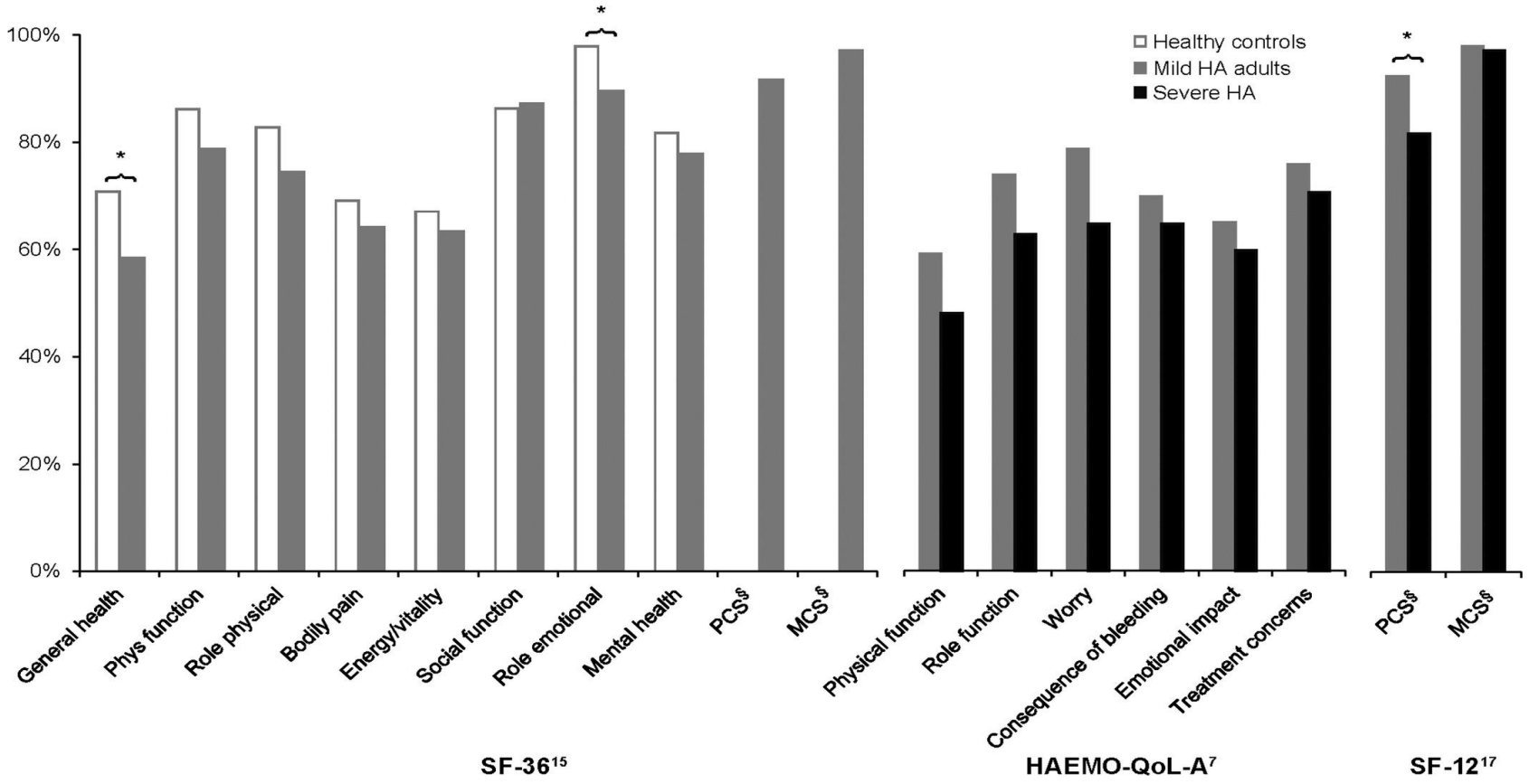
# Joint Bleeds leading to Arthropathy

- Fewer than 1% of patients had prophylactic use of FVIII
- A Canadian study comparing mild HA adults with age-matched controls found the maximum joint score to be significantly higher (worse) in mild HA.





# Quality of Life



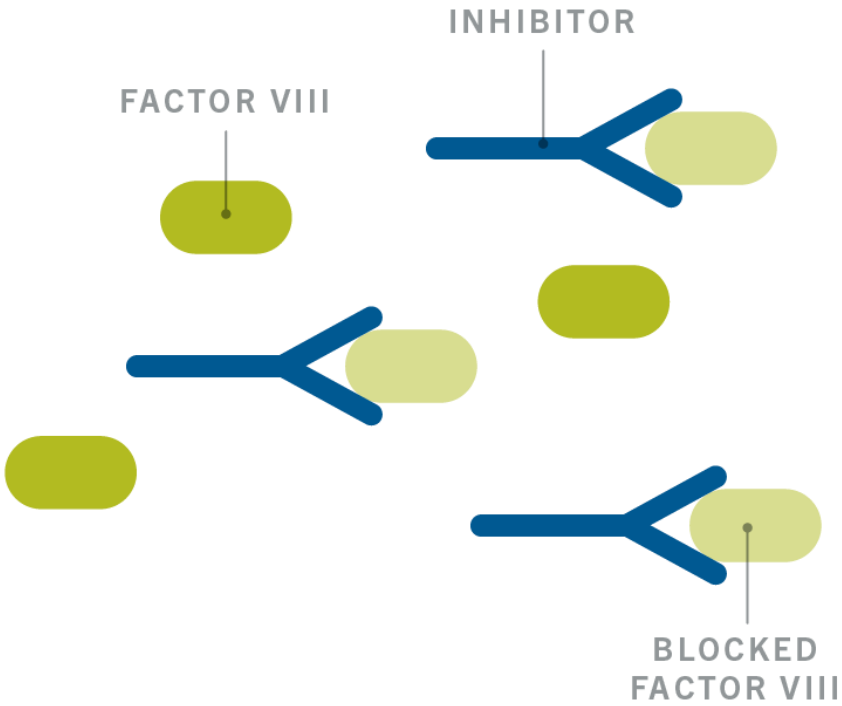

Walsh M, Macgregor D, Stuckless S, Barrett B, Kawaja M, Scully MF. Health-related quality of life in a cohort of adult patients with mild hemophilia A. *J Thromb Haemost*. 2008; 6: 755-761.

# Joint Arthropathy/ QOL

- Few studies put mild HA outcomes in the context of population norms
- Therefore, the clinical impact of mild HA may be under-represented and unmet needs may not be identified and addressed
- Hard to know whether the medical community fully understands the disease burden of patients with mild haemophilia and its limitations on patients daily activities and QOL.

# Inhibitor Development

- Development of inhibitors to FVIII in mild HA: 4.0%-7.8% over 10 years
- Generally inhibitors were detected:
  - median age of 33 years
  - after a median of 5.5 bleeding episodes
  - usually following intensive replacement therapy
  - Can result in spontaneous bleeding, bleeding similar to acquired haemophilia patients and rarely fatal bleeding
  - Can persist



# Risk Factors for Inhibitor Development

- Family History
- Age
- Mutation Type
  - Unlike Inhibitor development in severe haemophilia A patients, inhibitor formation in patients with mild/moderate hemophilia A is associated with missense mutations
  - These mutations lead to the formation of a dysfunctional protein that stimulates inhibitor formation

# Treatment Options

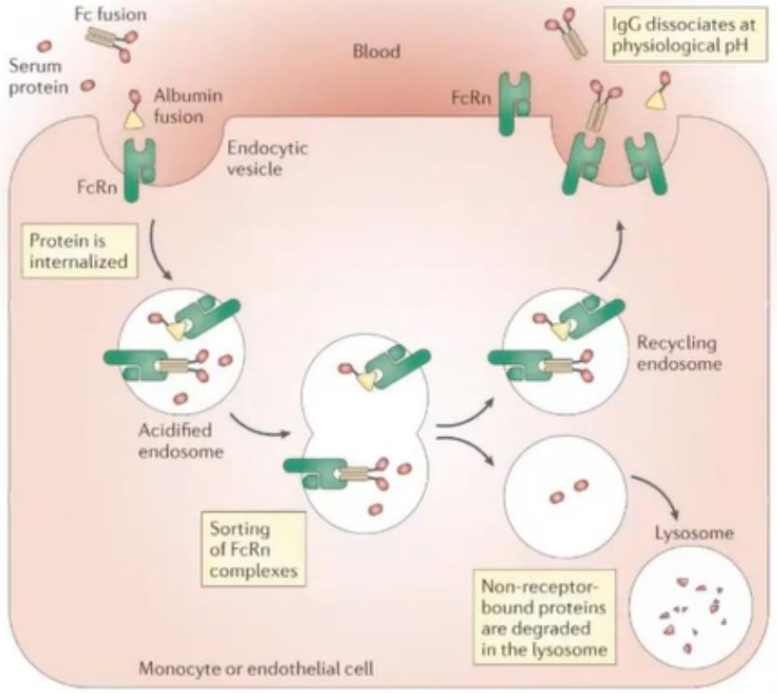
- Factor Replacement Therapy
  - Standard half life products
    - Recombinant factor replacement
    - Plasma derived products
  - Extended Half Life products
    - Pegelation for Factor 8 and 9
    - Fc fusion for Factor 8 and 9
    - Albumin fusion for Factor 9
    - Von Willebrand Factor for Factor 8
- Emicizumab
- DDAVP – releases stored Factor 8 and VWF from Endothelial cells
- Adjuvant Therapy
  - Tranexamic acid – inhibits fibrinolysis and thus stabilises clots

| Both Treatment of Bleeding & Prophylaxis | Treatment of Bleeding* | Prophylaxis |
|---|---|---|
| Factor replacement<br>Bypassing agents | DDAVP<br>Anti-fibrinolytic | Emicizumab<br>Gene Therapy (investigational)<br>Fitusiran (investigational)<br>TFPI inhibitors (investigational) |

# Extended Half Life (EHL) Products

## Neonatal Fc-receptor

- FC-fused
  - Factor VIII (BDD)-FC (Eloctate):
    - 1.5x longer half-life
  - Factor IX-FC (Alprolix):
    - 2.5-3.0x longer half-life
- Albumin-fused
  - Factor IX-albumin (Idelvion):
    - >5x longer half-life



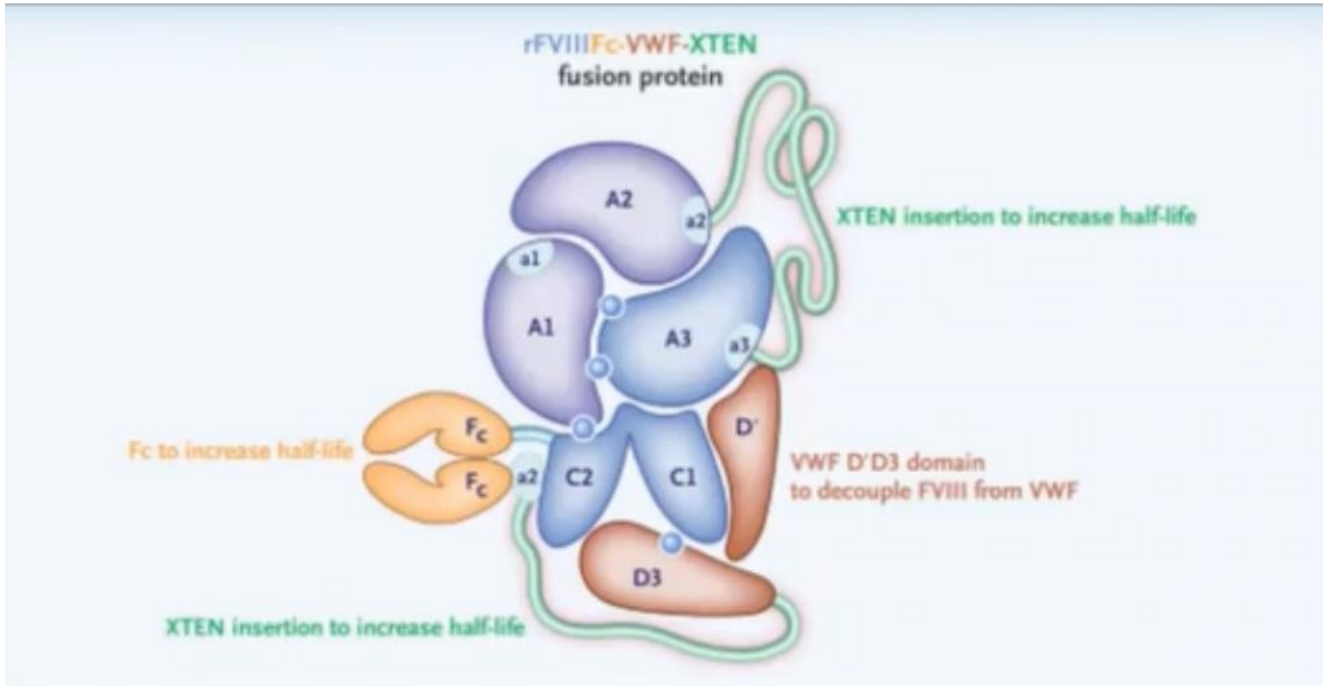

Mitragotri S. et al. *Nature Reviews Drug Discovery* 2014; 655-672
Coyle et al. *J Thromb Haemost* 2014; 12(4): 488-496

# Pegylation Reduces Clearance

| | Factor VIII | Size | Random/Site specific | Method | Relative half-life |
|---|---|---|---|---|---|
| Bax855 (Adynovate®) | Full-length | 20 kDa | Random | Covalently attached to accessible amine groups | ~1.4 |
| BAY94-9027 (Jivi®) | B-domain truncated | 60 kDa | Site-specific | Covalently attached to modified cysteine residue K1804C | ~1.5 |
| N8-GP (Esperoct®) | B-domain truncated | 40 kDa | Site-specific | Enzyme transfer to unique O-linked glycan | ~1.6 |
| | **Factor IX** | **Size** | **Random/Site specific** | **Method** | **Relative half-life** |
| N9-GP (Rebinyn) | Full-length | 40 kDa | Site-directed | Attached to N-linked glycans | 5x |

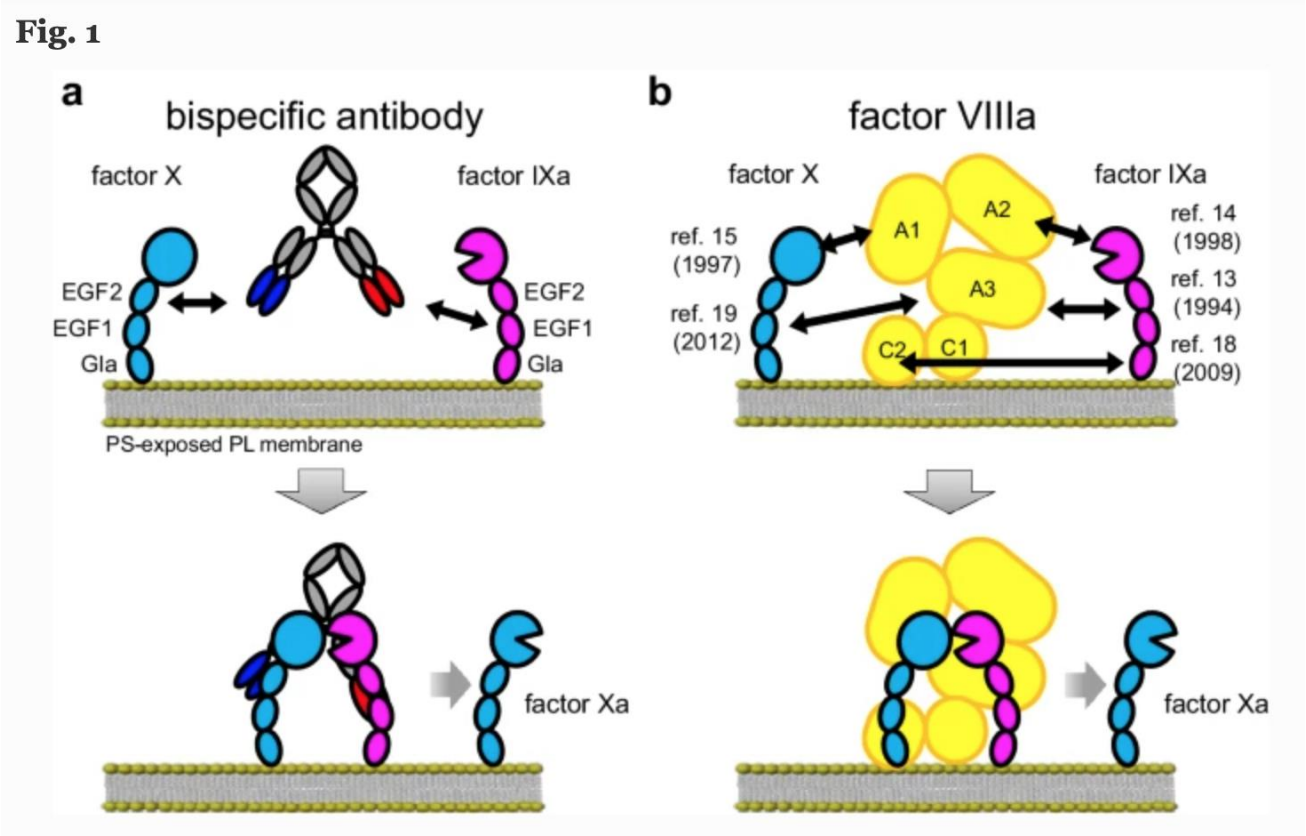
# BIVV001 Phase 1 Results

| | BIVV001 65 IU/kg (n=6) | rFVIII (n=7) | BIVV001 50 IU/kg (n=8) | rFVIII (n=9) |
|---|---|---|---|---|
| T ½ (hours) | 37.6 | 9.1 | 42.5 | 13.2 |
| IR (IU/dl per IU/kg) | 2.72 | 2.00 | 2.48 | 2.11 |



# Emicizumab: HAVEN Studies

- Previous HAVEN studies have shown with long-term emicizumab prophylaxis in people with severe haemophilia A with or without FVIII inhibitors
  - low annualised bleed rates
  - decreased bleeding into joints
  - favourable safety profile



# HAVEN 6

- HAVEN 6 is a multicentre, open-label, single-arm phase 3 study taking place in 22 specialty clinics and hospitals in Europe, North America, and South Africa.

- Eligible participants were people of all ages weighing at least 3 kg with a diagnosis of moderate (FVIII activity ≥1%–≤5%) or mild (FVIII >5%–<40%) haemophilia A without FVIII inhibitors requiring prophylaxis as assessed by the treating physician.

# Results

| | Participants (n=72) |
|---|---|
| Haemophilia severity | |
| Moderate | 51 (71%) |
| Mild | 21 (29%) |
| Sex | |
| Male | 69 (96%) |
| Female | 3 (4%) |
| Age, years | |
| Median (IQR) | 23·5 (12·0–36·0) |
| Range | 2–71 |
| Current treatment | |
| Prophylactic* | 37 (51%) |
| Episodic† | 35 (49%) |
| Past history of FVIII inhibitors‡ | 2 (3%) |
| Pre-treatment bleeds | |
| Mean number of bleeds in past 24 weeks | 4·7 (SD 13·2) |
| Median number of bleeds in past 24 weeks | 2·0 (IQR 0·0–4·5) [range 0–96] |
| Calculated ABR, median§ | 4·3 (IQR 0·00–9·78) |
| Model-based ABR | 10·1 (95% CI 6·93–14·76) |
| Participants with target joints | 24 (33%) |
| Number of target joints | |
| Mean (SD) | 0·6 (1·2) |
| Median (range) | 0·0 (0–8) |

# Results

| | Treated bleeds | Treated joint bleeds | Treated spontaneous bleeds | Treated target joint bleeds | All bleeds |
|---|---|---|---|---|---|
| Model-based ABR (95% CI) | 0·9 (0·55–1·52) | 0·2 (0·09–0·57) | 0·2 (0·11–0·33) | 0·1 (0·03–0·40) | 2·3 (1·67–3·12) |
| Calculated mean ABR (95% CI)† | 0·9 (0·02–5·48) | 0·2 (0·00–4·15) | 0·3 (0·00–4·23) | 0·1 (0·00–3·92) | 2·3 (0·35–7·75) |
| Calculated median ABR (IQR)† | 0·0 (0·00–0·98) | 0·0 (0·00–0·00) | 0·0 (0·00–0·00) | 0·0 (0·00–0·00) | 1·0 (0·00–3·11) |
| Calculated ABR range† | 0·00–7·05 | 0·00–3·63 | 0·00–6·09 | 0·00–3·21 | 0·00–21·04 |
| Participants with zero bleeds, n (%)‡ | 48 (67%) | 64 (89%) | 59 (82%) | 68 (94%) | 24 (33%)§ |

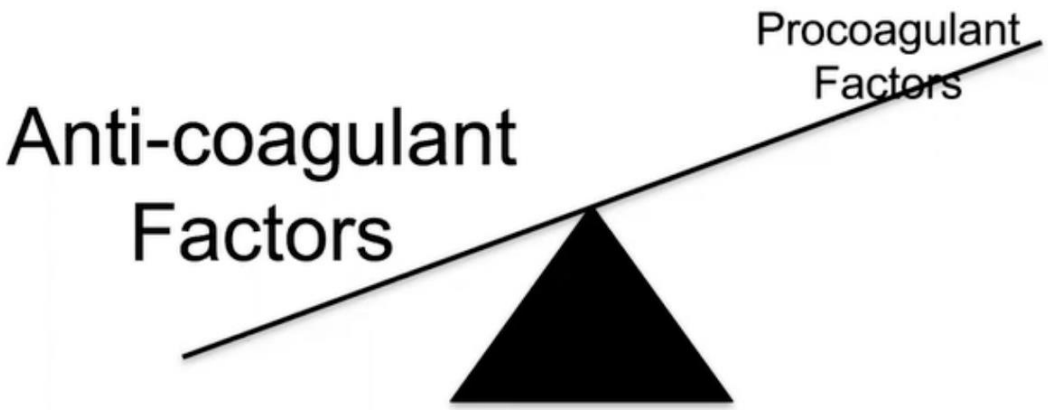
Median (range) follow-up time: 55·6 weeks (8·7–89·9). Compliance with bleed reporting on-study via the BMQ was >90%. ABR=annualised bleed rate. BMQ=bleed and medication questionnaire. *One participant (1%) had <24 weeks of follow-up, and 57 (79%) of 72 participants had ≥52 weeks of follow-up. †Calculated as: (number of bleeds/total number of days during the efficacy period) × 365·25. ‡At interim analysis (median follow-up time of 27·5 weeks), participants with zero bleeds were: 57 (80%) treated bleeds; 33 (47%) all bleeds; 64 (90%) treated joint bleeds; 68 (96%) treated spontaneous bleeds; 67 (94%) treated target joint bleeds.[28] §The pre-study bleed model-based ABR for all bleeds in the 33% of patients (n=24) who had no bleeds on study was 5·4 (95% CI 3·25–9·08).

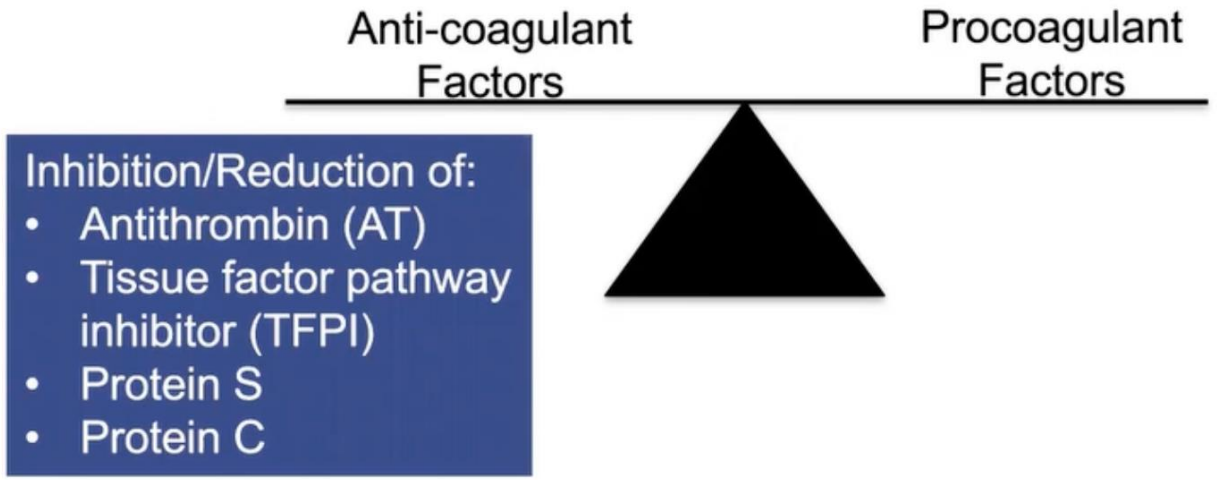
***Table 3:*** **Efficacy summary***

No New safety signals.
Main adverse reactions was injection site reactions, headache, joint aches
No deaths or microangiopathy occurred
1 thrombosed haemorrhoid deemed not related to emicizumab but rather related to constipation
2 patients developed anti-drug antibodies that had no effect
No patient developed inhibitors

# Non-Factor Replacement Therapy

- Rebalancing haemostasis
  - Futisiran (decreases anti thrombin), TFPI Inhibitors



# Managing medical issues that develop with Aging

- Major challenges that develop with aging in a bleeding population include
  - Increasing Surgical procedures
    - Surgery on Benign conditions such as Benign prostatic hypertrophy, Breast lesions, colonoscopy, hernia repairs
    - Joint surgery including joint replacement surgery
    - Cancer related surgery
    - Dental procedures and surgery
    - Increase in cardiovascular risk and stroke risk with need for antiplatelet agents

# Issues

- Venous Access
  - Most procedures will need factor replacement therapy to facilitate the operation and the healing period
  - Duration of factor replacement therapy varies with procedure
    - Pre-operation for colonoscopy through to 2-4 weeks for a joint replacement surgery or prostate operation
    - Often need peripheral inserted cannulas (PICC) to facilitate the delivery of the replacement therapy
- Inhibitor Development
- Semi emergent/ Emergency Surgery
  - Patients often lost to follow up in the HTC

# Ongoing Challenges

- Improving Haemophilia Knowledge in Patients and Healthcare Providers
  - Understanding Genetics/ Inheritance patterns
  - Risk behaviour is not discussed and following on, related bleeding episodes are not managed appropriately
  - Minimising Haemophilia in women can lead to mismanagement of heavy menstrual bleeding and pregnancy related bleed
  - How to manage age related illnesses in the setting of an underlying bleeding disorder
- Engagement with the Haemophilia community
  - Many patients with mild haemophilia often are less involved in the haemophilia community so may lack a support system to help them manage their disease
- Treatment and Access Issues
- Lack of data on mild Haemophilia
  - Impact on School/ Work/ Activities/ QOL

Thank you