Mild Haemophilia – not so mild

? The new frontier

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Definitions

- Haemophilia A and B are inherited bleeding disorders characterised by deficiency of Factors VIII or IX.
- Mild haemophilia is defined by factor levels of >5 to 40%
  - Female carriers can fall into this range
  - Broad range of possible factor levels and possible bleeding phenotypes
- But 3 different assays with different reagents even within one type of assay
- Sometimes discrepant results
- Inter laboratory variability is high

Definitions

- Factor levels may be influenced by physiologic changes such as intercurrent infection/inflammation/pregnancy/age
- Value of genetic testing – can provide information about the risk of inhibitor development and is an area of opportunity for precision medicine to impact
  - Data available on international registries/databases
- Family history
- What is the bleeding phenotype? Not known at the outset. Other modifying genes that may influence bleeding phenotype

Diagnosis

Haemophilia A	2020-21	
	National Total	**Percentage**
Severe	725	30.92%
Moderate	234	9.98%
Mild	1386	59.10%
Total	2345	

Haemophilia B	2020-21	
	National Total	**Percentage**
Severe	111	20.44%
Moderate	129	23.76%
Mild	303	55.80%
Total	543	

- Diagnosis is often delayed
  - French study of 599 PWH (1980 – 1994) median age at diagnosis for those with mild was 28.6 months versus 5.8 months for severe and 9 months for moderate
- May be underdiagnosed
  - WFH reports 37% incidence of mild HA in high income countries vs 9% in lower income countries. Sweden 54%. Australia 55.8 – 59.1%
- If no family history often diagnosed with unexpected bleeding following injury or procedure

Presentation/engagement

- Less engagement with HTN as “mild” – so seen as not needing to be reviewed as frequently or needing as much education
- Infrequent spontaneous bleeds so less experienced at recognising and managing bleeds
- No “at home” treatment* or experience with venous access
- Often present late with potential for more severe consequences than if managed early.

*except DDAVP

Presentation/engagement with health services

- Canadian qualitative study of PwMH “why don’t they recognise bleeds and access treatment and healthcare in a more timely manner” published in Haemophilia in 2012 by Nilson et al
  - 18 PwMH aged 17-31 years FVIII n=14 FIX n=4
  - Age at diagnosis median 5.5 yrs (0-16)
  - Factor levels 5-10% n=4 11-15% n=2 16-22% n=4 with 9 not knowing their factor level
  - Reason for last reported bleed mostly sports/musculoskeletal injury/surgery/nose bleeds/dental extraction – 62%

Presentation/engagement

- Missed work/school days in last year due to some injury
  - 0 n=12
  - 1-2 days n=3
  - 5 days n = 1
  - 12-20 days n = 2
- What subjects told the researchers
  - They tended to resist or ignore their condition/diagnosis
  - They felt normal so often participated in not recommended sports
  - Many felt that the education and recommendations provided by the HTN did not apply to them
  - Most did not have a good understanding of the signs and symptoms of bleeding and often managed with ice and wait and see if it gets better on its own/don’t have time to get it checked right now

Presentation/engagement

- Following this study they developed an “app” called the HIRT App (Haemophilia Injury Recognition Tool) which is an injury self management tool with plans to incorporate it into the Canadian Bleeding Disorder Registry
- App launched in 2014.

HIRT?

Announcing *HIRT?*

(**H**emophilia **I**njury **R**ecognition **T**ool)

This is an innovative INJURY self-management App developed specifically for young men with mild hemophilia.

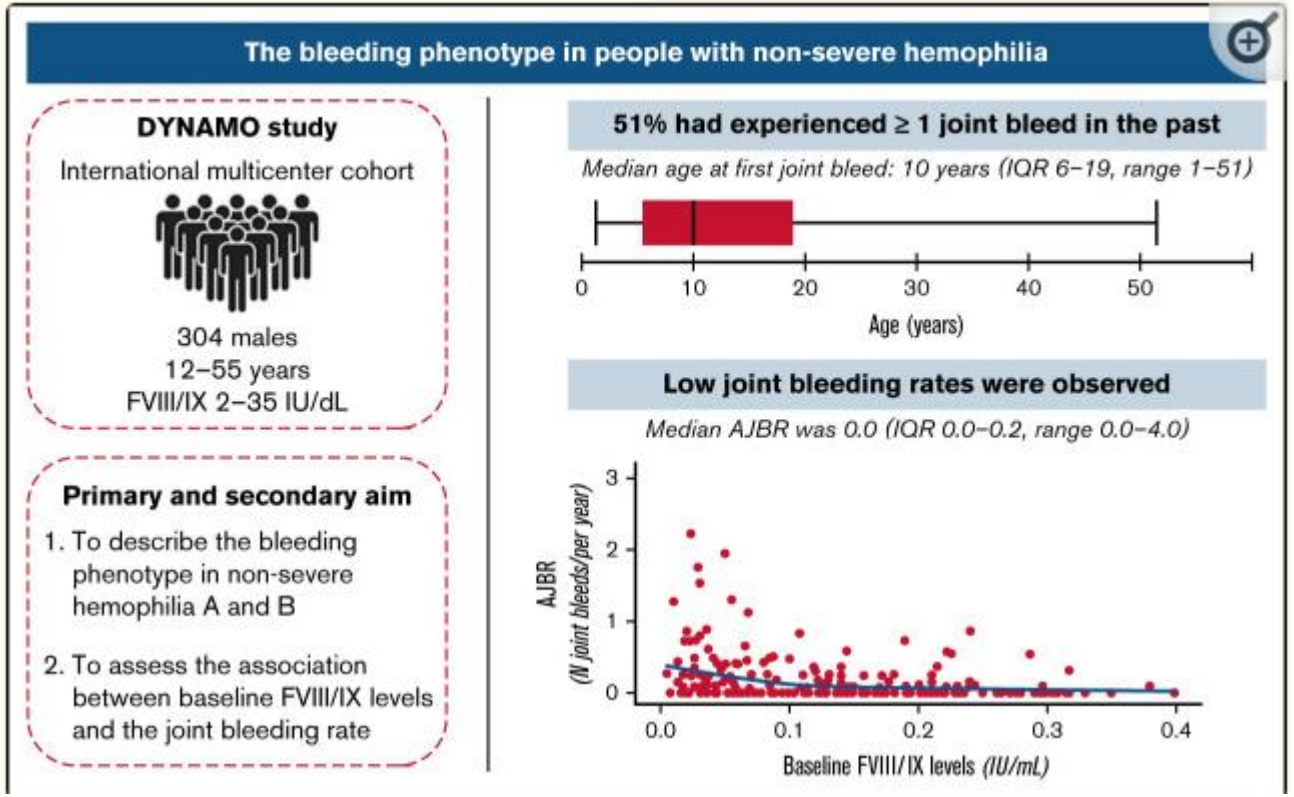
This App will assist the young men with mild hemophilia in injury self-management by:

- Helping to identify signs and symptoms of a bleed;
- Encouraging the use of first aid;
- Reminding them to reassess the injury (1 hour, 24 hours and 2 days) until the risk of rebleed has passed;
- Providing hemophilia centre telephone contact information in case the injury worsens and they require medical attention;
- Making the booklet "*Identifying Common Joint & Muscle Bleeds*" available within the App to assist with assessment.

Dynamo study group

- International multicentre study assessing males with non severe haemophilia aged 12-55yrs
  - Moderate n=70 Mild n=234
  - 81% had experienced 1 bleed
    51% had experienced 1 joint bleed

Blood Advances 2022 July26 6(14):4256-65



	Moderate	Mild
Age at Dx	1 (0-5)	5 (0-15)
Age at first bleed	3 (1-10)	11 (4-20)
Age at first joint bleed	7 (4-15)	13 (7-20)

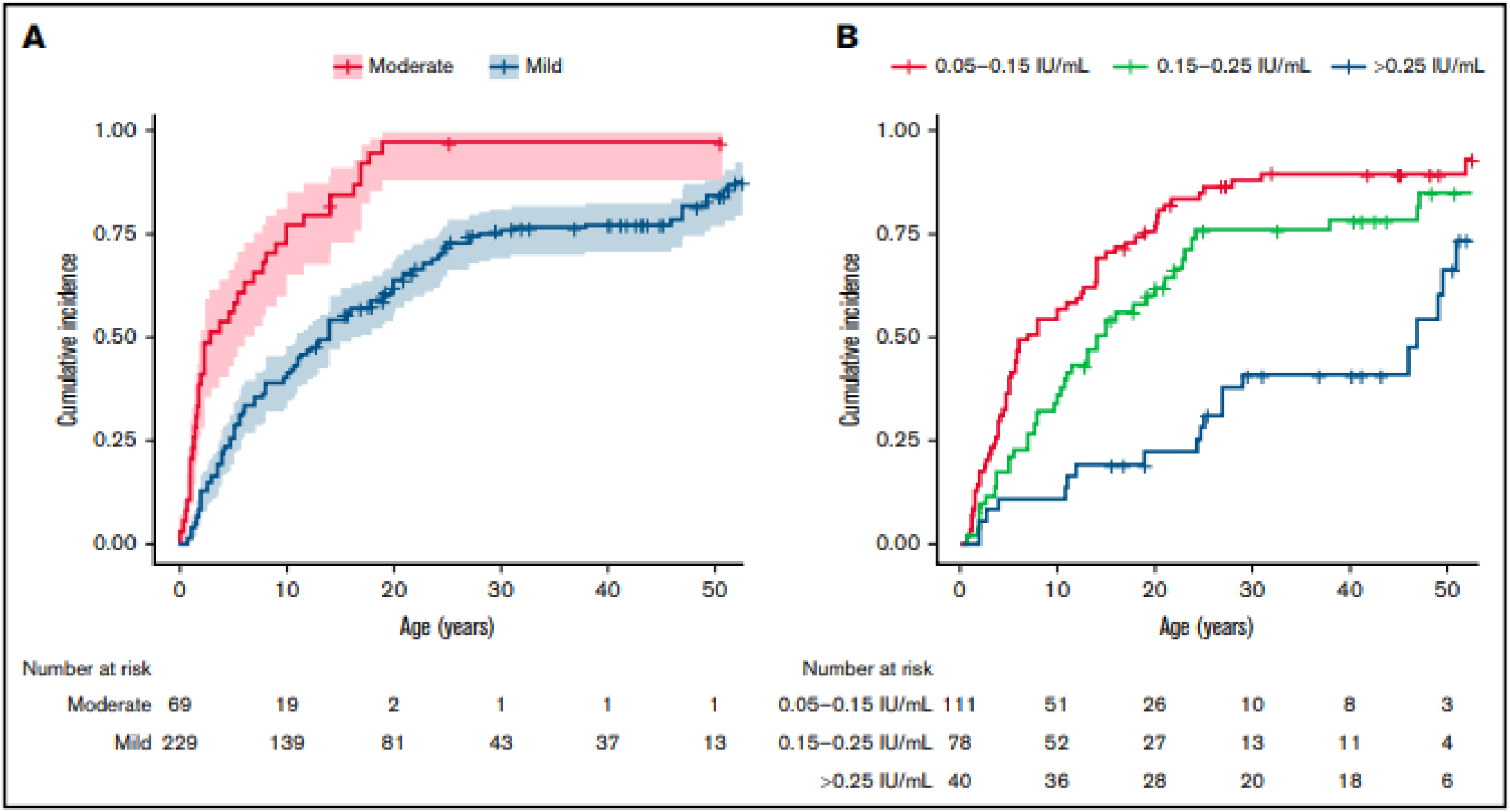


Figure 1. Kaplan-Meier analysis: age at first bleed. Analysis was conducted according to hemophilia severity (A) and categories within mild hemophilia (B). The line represents the cumulative incidence. The shaded area in panel A represents the 95% CI. Crosses represent right-censored patients.

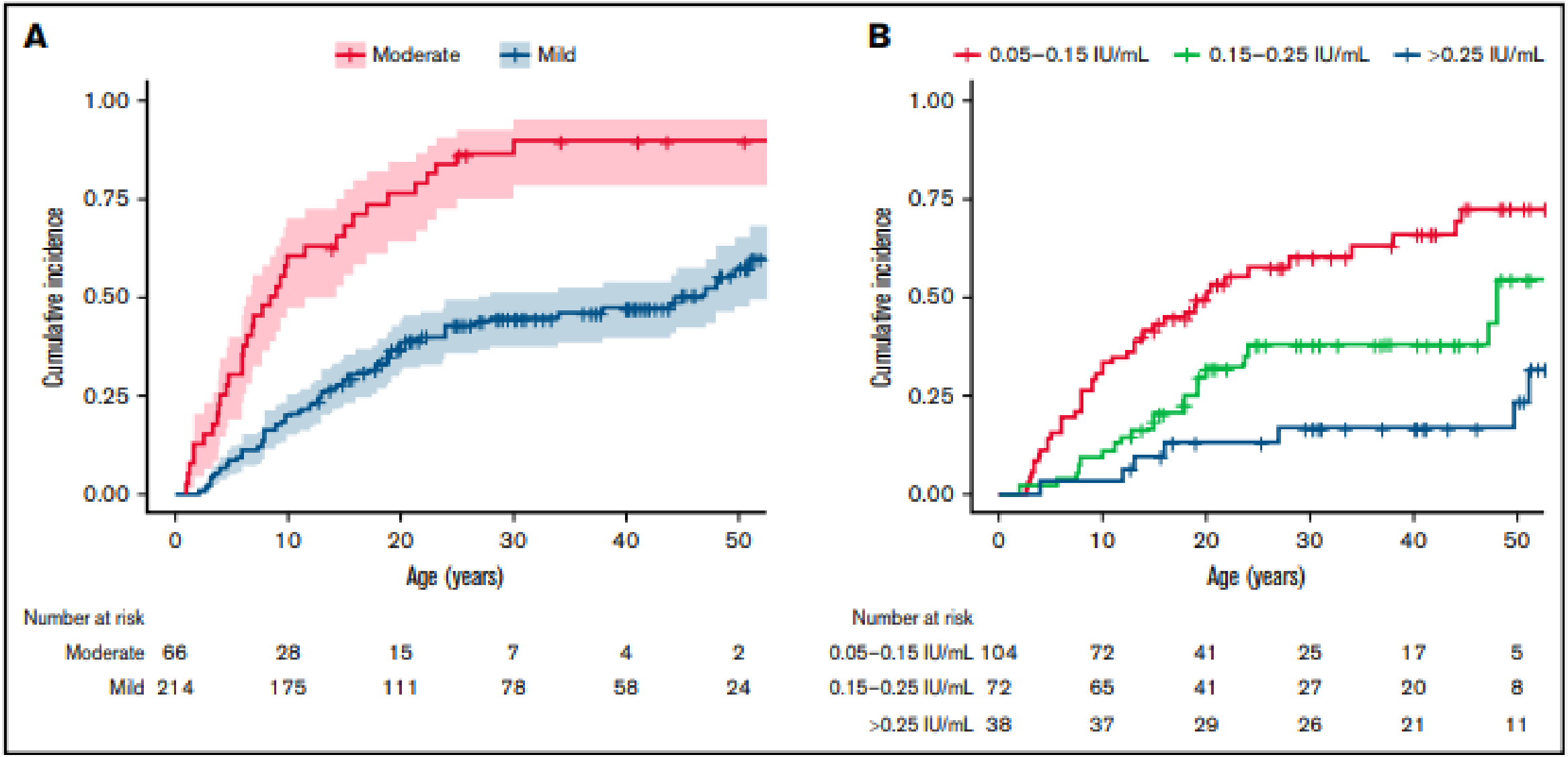


Figure 2. **Kaplan-Meier analysis: age at first joint bleed.** Analysis was conducted according to hemophilia severity (A) and categories within mild hemophilia (B). The ine represents the cumulative incidence. The shaded area in panel A represents the 95% CI. Crosses represent right-censored patients.

Joint status in Pw non severe HA

Zwagermaker et al J Thromb Haemost 2022;20:1126-37

- Joint status assessed in 51 subjects – moderate HA n=19 and mild n=32 aged 24-55 years (median 43 yrs) by MRI IPSG scores
- Despite the low frequency of joint bleeds reported in this group (median AJBR of 0) a substantial number had joint changes on MRI – the ankles being the most affected.
- In 14% of bleed free joints there was haemosiderin deposition observed.

	Elbows L/R	Knees L/R	Ankles L/R
Soft tissue changes	8%/23%	56%/66%	58%/50%
Osteochondral changes	0%/0%	17%/20%	31%/25%

PROBE – patient reported outcomes, burdens and experiences - study

- International study designed to take a 360 view of what it means to live with and age with haemophilia
- Questionnaire with assessment of pain, independence, education, employment, family life, mobility and current health issues
- Comparison with age and sex matched controls without a bleeding disorder
- Highlighted particular problems of men with Mild haemophilia
- Study reported outcomes for men > 45 yrs

	Mobility	ADL	Pain medication	Chronic pain
Mild haemophilia	29%	32%	71%	64%
Controls	0%	6%	61%	42%

Access to novel therapies

- Paucity of qualitative data, literature and research for this group
- Usually not eligible for clinical trials
- Management strategies comprise DDAVP (IV or subcut) for HA patients only, Factor replacement therapy otherwise.
- No current indication for novel therapies – but many in this group are experiencing significant morbidity and consequences of unrecognised bleeds
  - Emicizumab (HAVEN 6), Concizumab and other TFPI's, Fitusiran (small molecule ATIII inhibitor), Gene therapy

Unmet needs for PwMH

- Education and support for the management of haemophilia
- Engagement with HTC's and with the haemophilia community
- Recognition and prompt treatment of bleeds
- Recognition of the potential negative impact on mobility, the activities of daily life – including sexual health and intimacy – and chronic pain for PwMH. This includes loss of work or school days.
- Consideration for access to the pipeline of novel therapies that may help normalise their life

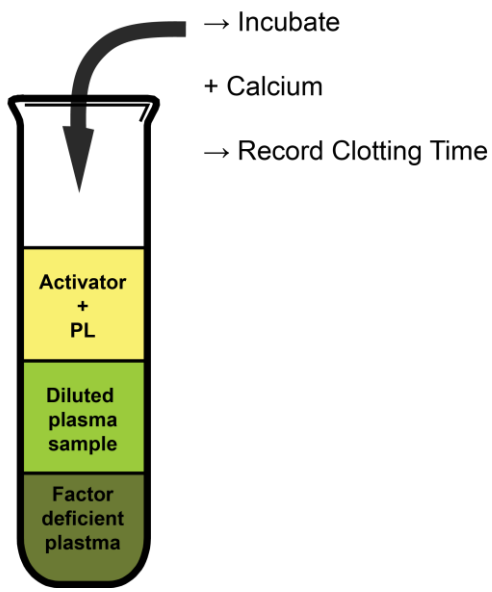
The future

- With access to novel therapies ALL patients will have the potential to convert to a MILD form of haemophilia. However, that seems to mean factor levels > 15%
- Opportunity to be aware that mild haemophilia has its own set of challenges and may not be “mild”.
- How to best define what we should be aiming for to achieve bleed protection? Should we re define mild haemophilia??

Can we hope for cure of mild haemophilia – the “haemophilia free mind”

The assay of a clotting factor relies upon measuring the degree of correction of the APTT when plasma is added to a plasma sample specifically deficient in the factor to be measured. An outline of the principles of a 1-stage Factor VIII assay is shown below:

1-stage Assay

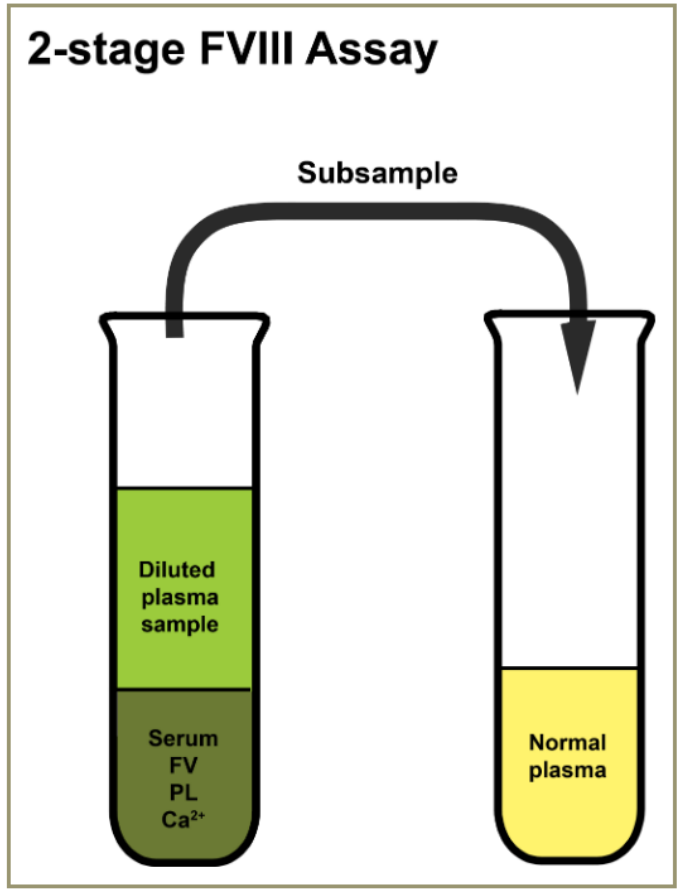


Reagents	
APTT Reagents	See APTT
Standard Reference Plasma	The reference plasma is used to derive the concentration of the test plasma by comparing the clotting times. Commercial reference standards in which the levels of the clotting clotting factors, are calibrated against international standards and their levels are reported in IU/dl or IU/ml and not %.
Factor deficient plasma (substrate plasma)	A plasma deficient in the clotting factor to be assayed - most commonly VIII, IX, or XI. The factor deficient plasma should have a level of the factor being assayed of <0.01 IU/mL and normal levels of all the other clotting factors that affect the APTT test.
Patient Plasma	Platelet Poor Plasma [PPP]

Platelet poor plasma [PPP] is incubated at 37°C then phospholipid (cephalin) and a contact activator (e.g. Kaolin, micronized silica or ellagic acid) are added. This leads to the conversion of Factor XI [FXI] to FXIa but the remainder of the pathway is not activated as no calcium is present. The addition of calcium (pre-warmed to 37°C) initiates clotting and the timer is started. The APTT is the time taken from the addition of calcium to the formation of a fibrin clot.

Most laboratories use an automated method for the APTT in which clot formation is deemed to have occurred when the optical density of the mixture has exceeded a certain threshold (clot formation makes the mixture more opaque and less light passes through).

Factor VIII is a cofactor in the coagulation cascade but has no intrinsic enzymatic activity. Therefore, the concentration of Factor VIII is made the rate limiting step in a reaction that generates Factor Xa - the First Stage of the Two Stage Assay. The Second Stage determines the amount of FXa produced.



Component	Explanation
Activated serum	This provides factors IX, X and XIa. XIa initiates coagulation in the patient sample. Commercially available or prepared by incubating whole blood in glass, centrifuging and then removing the serum.
Factor V	Commercially available, usually bovine. Factor V is required as a cofactor for the initial coagulation reaction
Adsorbed patient plasma	Adsorption with $Al(OH)_3$ removes factors II, VII, IX and X - the vitamin K dependent clotting factors. This prevents progression of the first stage beyond assembly of the Prothrombinase complex
Normal plasma	To supply Prothrombin and Fibrinogen so that coagulation can proceed to clot formation
$CaCl_2$ and Phospholipid	The reaction is dependent on calcium ions for factor activity and phospholipid surfaces to facilitate factor interactions

The patient's plasma is adsorbed to remove Prothrombin [Factor II] and so prevents clot formation when the coagulation cascade is initiated.

Stage 1: Coagulation is initiated by the addition of Factor XIa whilst factor X and V are provided in excess. The Factor VIII concentration is, therefore, the rate limiting step in the formation of Factor Xa.

Stage 2: In the second stage, a sample of the first stage mixture is added to normal plasma and the time to clot formation recorded. Since the clotting time will be dependent on the Factor Xa level in the sample from the first stage and the Factor Xa level is proportional to the concentration of Factor VIII in the patient's plasma, the Factor VIII level may, therefore, be derived from the clotting time of the second stage.

b. Chromogenic Factor VIII Assay

The assay is similar to the Two-stage Factor VIII assay in that it involves an incubation step to generate Factor Xa and a second stage to determine the amount of Factor Xa produced. In this case the amount of Factor Xa is measured by its action on a specific chromogenic substrate and since the colour intensity produced is directly proportional to the amount of FXa, which in turn is directly proportional to the amount of FVIII, the FVIII levels may be calculated from the absorbance of the sample at a specific wavelength (the optimal absorbance wavelength for the chromophore produced by FXa cleavage of the chromogen usually 405nm.