# MOVE HAEMOPHILIA 2023

December 2023

# MOVE HAEMOPHILIA 2023

# 29TH & 30TH SEPTEMBER 2023
# BRUSSELS, BELGIUM

# PART 2

**This programme is supported through an independent educational grant from Sobi.**

**The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.**

# MOVE HAEMOPHILIA 2023 – EDUCATIONAL CONTENT

## Part 2

1. Management of comorbidities in persons with haemophilia
2. Physiotherapy management in haemophilia
3. Laboratory issues in the era of factor and non-factor therapies

# MANAGEMENT OF COMORBIDITIES IN PERSONS WITH HAEMOPHILIA

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# DISCLOSURES

**Please note:** The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions.

Expert Disclosures:

- **Prof. Boban** has received financial support/sponsorship for consultation, or speaker fees from the following companies: Bayer, CSL Behring, NovoNordisk, Octapharma, Roche, Pfizer, Sobi, Takeda

# PWH EXPERIENCE AGE-RELATED AND HAEMOPHILIA RELATED COMORBIDITIES

| |
|---|
| Haemophilic arthropathy and loss of BMD |
| Bleeds and risk of inhibitors |
| Hepatitis C, cirrhosis and hepatocellular carcinoma |
| HIV |
| Cardiovascular disease (hypertension, ischaemic heart disease, atrial fibrillation) |
| Malignancy |
| Renal disease |
| Sexual disfunction |
| Depression, dementia |
| Reduced mobility |
| Reduced access to health care, ability to self-treat |

BMD, bone mineral density; HIV, human immunodeficiency virus; PWH, people with haemophilia

Shapiro S, Makris M. Br J Haematol. 2019;184(5):712-720

# CARDIOVASCULAR DISEASES IN PWH

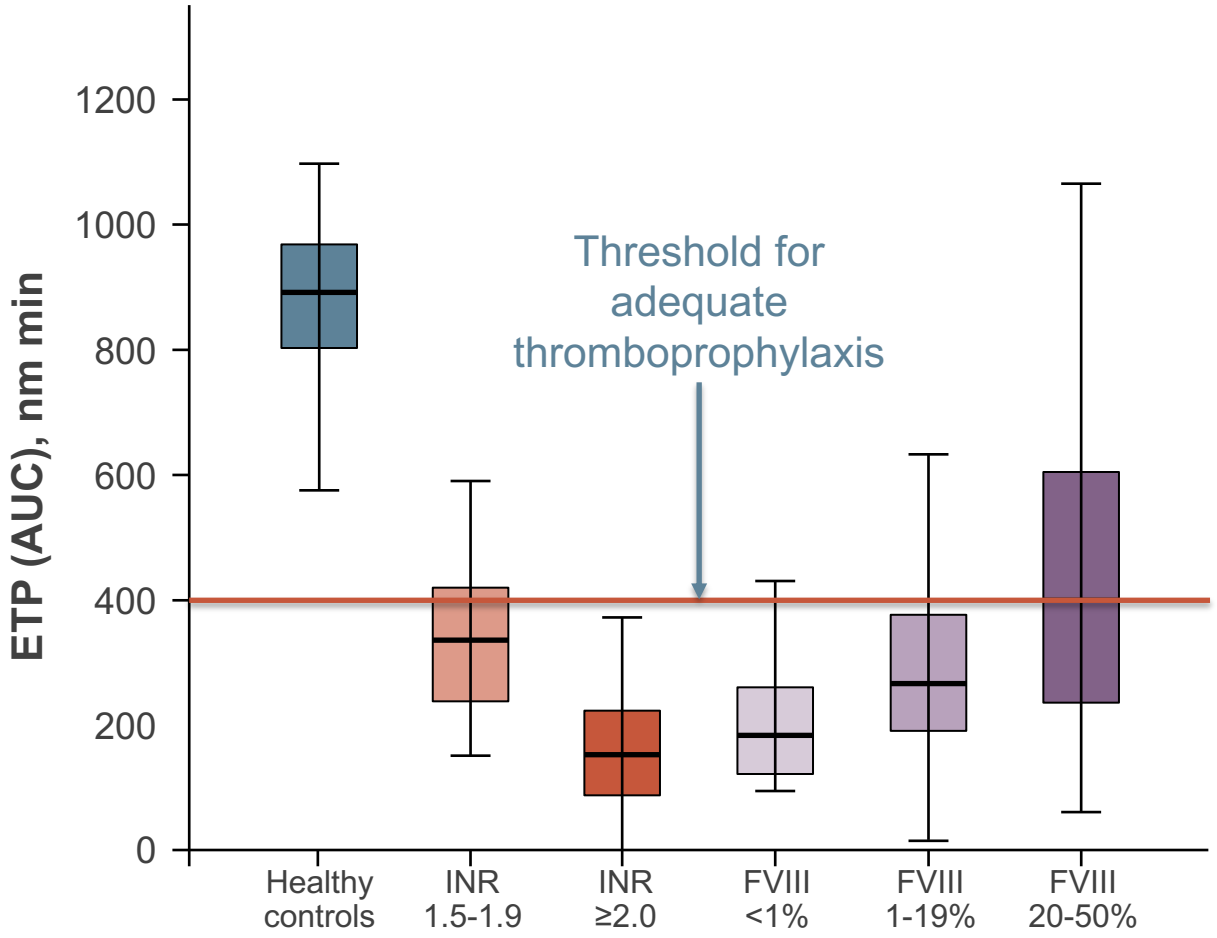
- PWH are not protected against the development of atherosclerosis[1,2]
- Atherothrombotic events in PWH might be lower when compared with the general population[3]
- Mortality of ischemic heart disease was lower than in general population (62% [95% CI: 51–76]) of general population rates)[4]

CI, confidence interval; PWH, people with haemophilia

1. Tuinenburg A, et al. Arterioscler Thromb Vasc Biol. 2012;32(3):799-804; 2. Biere-Rafi S, et al. J Thromb Haemost. 2012;10(1):30-7; 3. van Der Valk P, et al. Blood Adv. 2022;6(3):902-908; 4. Darby SC, et al. Blood. 2007;110(3):815-25

# ARE PWH NATURALLY ANTICOAGULATED?

## ENDOGENOUS THROMBIN POTENTIAL

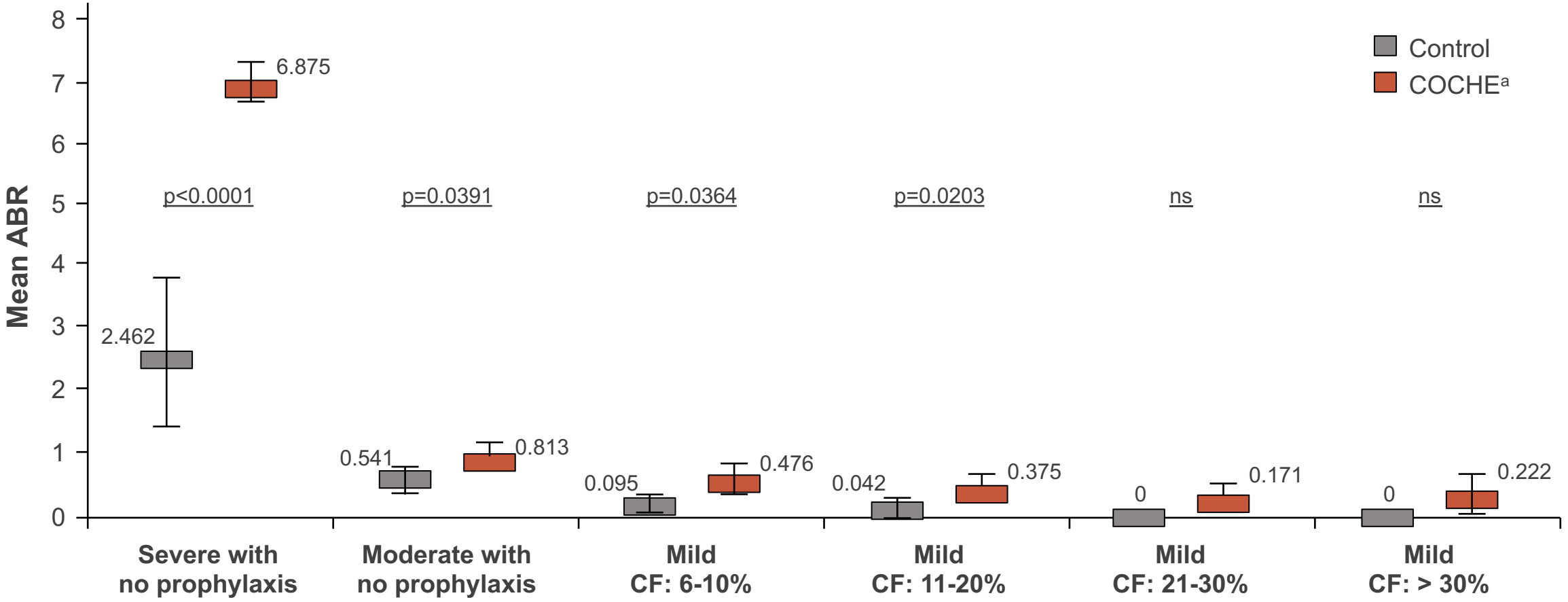



- Severe hemophilia patients had comparable ETP to therapeutic international normalized ratio (INR)
- In non-severe hemophilia, 33% had higher ETP than therapeutic INR

ETP, endogenous thrombin potential; INR, international normalised ratio; PWH, people with haemophilia

de Koning MLY, et al. J Thromb Haemost. 2017;15(5):868-875

# WHAT IS THE BLEEDING RISK IN PWH USING ANTIPLATELET OR ORAL ANTICOAGULANT THERAPY?




[a]COCHE is a prospective case–control study

ABR, annualised bleeding rate; CF, basal clotting factor; PWH, people with haemophilia

Guillet B, et al. Thromb Haemost. 2021;121(3):287-296

# THE FVIII/FIX THRESHOLD FOR ANTIPLATELET AND ANTICOAGULANT TREATMENT

## RECOMMENDATION

| Antithrombotic therapy | FVIII/FIX minimum trough level |
|---|---|
| **Single antiplatelet therapy (SAPT)**<br>**Aspirin, clopidogrel** | 1-5 IU/dL |
| **Dual antiplatelet therapy (DAPT)** | 20 IU/dL |
| **Oral anticoagulant therapy**<br>**VKA – INR 2.0-3.0**<br>**DOACs, full dose** | 20 IU/dL |

- Antithrombotic therapy in severe haemophilia – only with clotting factor prophylaxis
- **NO** antithrombotic therapy in patients with inhibitors not using emicizumab

DOAC, direct oral anticoagulant; FIX, factor IX; FVIII, factor VIII; INR, international normalised ratio; VKA, vitamin K antagonist

Schutgens REG, et al. Hemasphere. 2023;7(6):e900

# ATRIAL FIBRILLATION IN PWH

## RECOMMENDATION FOR ANTICOAGULATION THERAPY

**Assess risk with $CHADS_2$ score:[1,2]**
- CHF
- Arterial hypertension
- Diabetes mellitus
- Age ≥ 75 years
- Previous stroke/TIA

- DOACS over VKA
- Reduction of anticoagulant dose – same indications as in general population
- Do not use aspirin instead of anticoagulant treatment

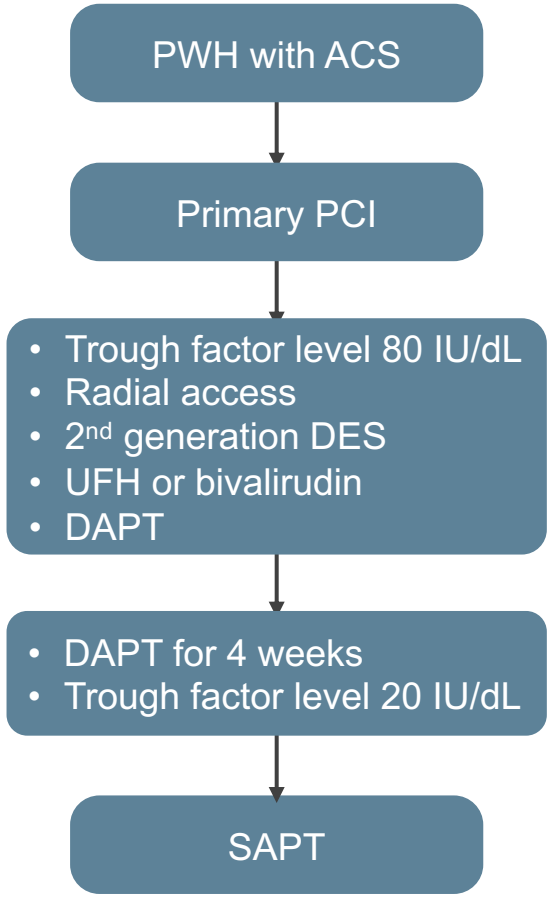
| Basal FVIII/FIX activity | Thrombotic risk | Anticoagulant treatment |
|---|---|---|
| **> 20%** | Low | None |
| | High | DOACs |
| **< 20%** | Low | None |
| | High | LAAO |

CHF, chronic heart failure; TIA, transient ischaemic attack; DOAC, direct oral anticoagulant; FIX, factor IX; FVIII, factor VIII; LAAO, left atrial appendix occlusion; PWH, people with haemophilia; VKA, vitamin K antagonist

Schutgens REG, et al. Hemasphere. 2023;7(6):e900; 2. Olesen JB, et al. BMJ. 2011;342:d124

# ACUTE CORONARY SYNDROME IN PWH

## THERAPY

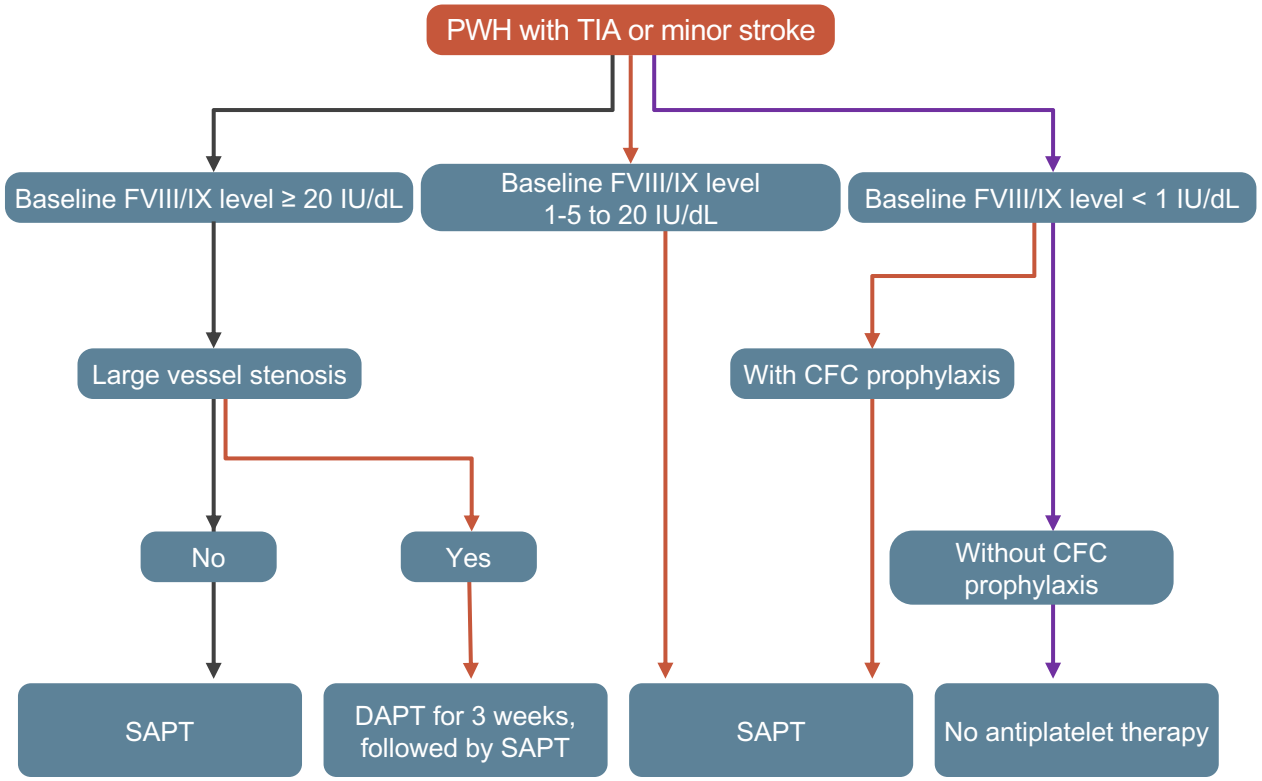


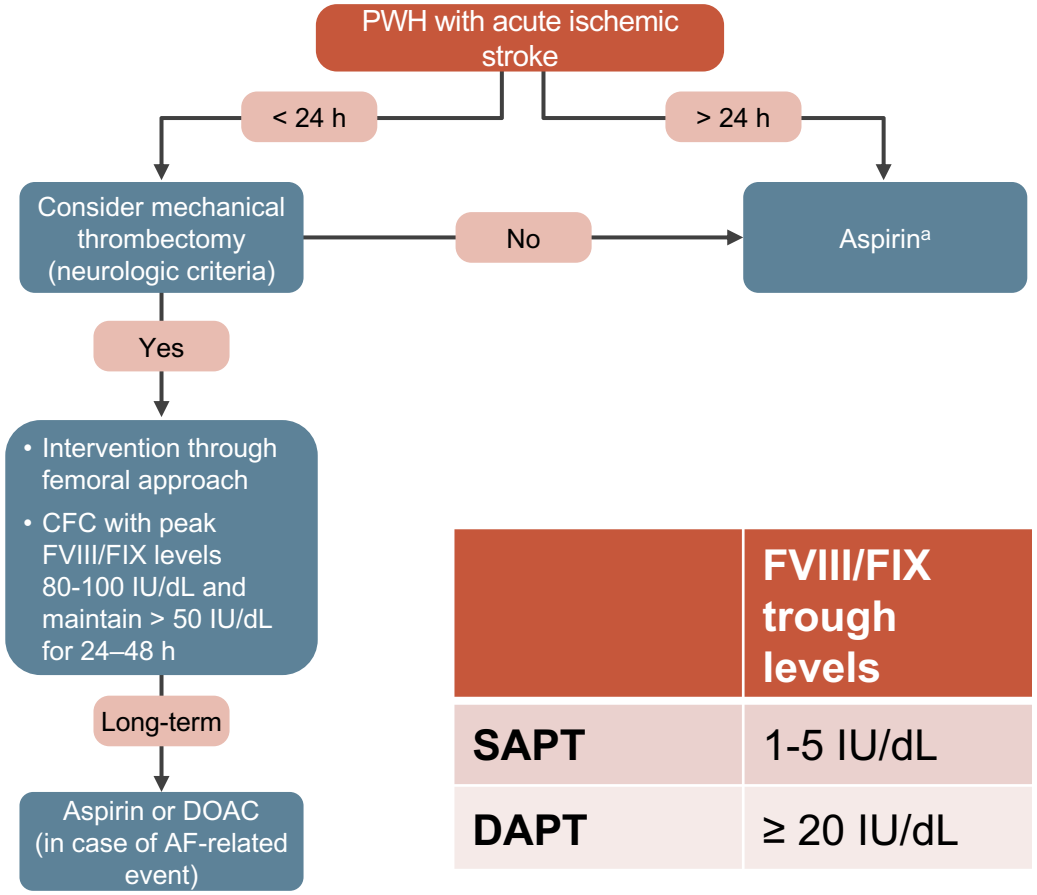

| Clotting factor concentrate trough FVIII/FIX levels | |
|---|---|
| **During PCI** | 80 IU/dL |
| **Anticoaguant treatment** | >20 IU/dL |
| **DAPT (4 weeks)** | >20 IU/dL |
| **SAPT, long-term Chronic coronary syndrome** | >1-5 IU/dL |

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; FIX, factor IX; FVIII, factor VIII; PCI, percutaneous cardiac intervention; PWH, people with haemophilia; SAPT, single antiplatelet therapy; UFH, unfractionated heparin

Schutgens REG, et al. Hemasphere. 2023;7(6):e900

# TIA AND ACUTE ISCHAEMIC STROKE IN PWH




| | FVIII/FIX trough levels |
|---|---|
| **SAPT** | 1-5 IU/dL |
| **DAPT** | ≥ 20 IU/dL |

[a]Typically, a loading dose of 300 mg, followed by daily 80–100 mg is used

AF, atrial fibrillation; CFC, clotting factor concentrate; DAPT, dual antiplatelet therapy; FIX, factor IX; FVIII, factor VIII; h, hours; PWH, people with haemophilia; SAPT, single antiplatelet therapy; TIA, transient ischaemic attack

Schutgens REG, et al. Hemasphere. 2023;7(6):e900

# VENOUS THROMBOEMBOLISM IN PWH

## THROMBOPROPHYLAXIS

- No use of routine pharmacological thromboprophylaxis in the perioperative period
- Individual approach in surgery with high VTE risk
- Extended duration of pharmacological thromboprophylaxis NOT needed
- NO routine pharmacological thromboprophylaxis in PWH that are medically ill
- Mechanical over pharmacological thromboprophylaxis, if indicated

PWH, people with haemophilia; VTE, venous thromobembolism.

Schutgens REG, et al. Hemasphere. 2023;7(6):e900

# VENOUS THROMBOEMBOLISM IN PWH

## TREATMENT

- Acute VTE in PWH is very rare event
- Treatment should be individualised
- Removal of the cause (removal of the catheter, cessation of the procoagulant therapy)
- Minimal duration of anticoagulant treatment (6 weeks)
- FVIII/FIX trough level >20 IU/dL
- In mild haemophilia, individually assess risk of thrombosis/bleeding

FIX, factor IX; FVIII, factor VIII; PWH, people with haemophilia

Schutgens REG, et al. Hemasphere. 2023;7(6):e900

# LIVER HEALTH IN PWH

- High prevalence of viral hepatitis (HBV, HCV) [1,2]
  - persons with severe inherited bleeding disorders before 1992[2]
  - infectivity of plasma depended on the plasma source[1,2]
  - 70-80% HCV infected persons developed chronic HCV infection[2]
- 13-17% develop end-stage liver disease[1]
- HIV co-infection accelerates liver fibrosis[1]
- HCC is the most common cancer in PWH[1]
- Liver disease is common cause of death in PWH[1,3]
- Liver transplant in PWH has increased risk of  bleeding complications (comapred to non-haemophiliacs)
  - no difference in in-hospital mortality between these groups[1]

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PWH, people with haemophilia

1. Isfordink CJ, et al. Br J Haematol. 2021;195(2):174-185; 2. Isfordink CJ, Haemophilia. 2023 Jan;29(1):106-114. 3. Arafat Ul Alam, et al. Blood 2020;136(Suppl. 1):30

# FOLLOW-UP OF SUSTAINED VIROLOGICAL RESPONSE AFTER HCV INFECTION

## RECOMMENDATION

1. Patients who at the time of SVR have compensated liver disease (compensated advanced chronic liver disease, cACLD - advanced fibrosis/cirrhosis)
   - 6-monthly screening for HCC
   - liver ultrasound and AFP
2. Patients who had already experienced complications due to portal hypertension (e.g. varices, ascites, variceal haemorrhage, hepatic encephalopathy)
   - close follow-up
   - risk for liver decompensation still exists
3. Patients with other risk factors of liver damage
   - alcohol intake, metabolic comorbidities

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response

La Mura V, et al. Blood Adv. 2023:bloodadvances.2023010723

# LIVER HEALTH

## GENE THERAPY

- A specific diagnostic work-up is mandatory for haemophilia gene therapy[1]
- Liver imaging by abdominal ultrasound and Fibroscan[2]
- Transaminase levels should be consistently within the normal range[2]

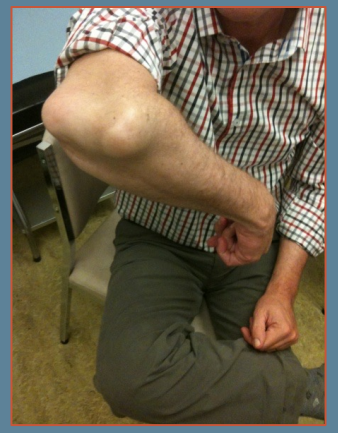
## RECOMMENDATIONS[2]

- Exclusion criteria for gene therapy:
  - pre-existing liver disease (cirrhosis/advanced fibrosis/malignancy)
  - active/chronic viral infections with hepatitis B or hepatitis C virus
  - hepatotoxic medication (e.g. HIV medication)
- After gene therapy
  - alcohol abstinence for at least 6 months
  - weight management
  - not taking hepatotoxic medications
  - no excessive physical activity
  - participation in follow-up examinations

HIV, human immunodeficiency virus

1. Miesbach W, et al. J Thromb Haemost. 2023;21(2):200-203; 2. Miesbach W, et al. J Hepatol. 2023;78(3):467-470

# PHYSIOTHERAPY MANAGEMENT IN HAEMOPHILIA

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Images provided by S. Lobet

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# THE MOST AFFECTED JOINTS IN HAEMOPHILIA

- 90% of **bleeding episodes** affect the musculoskeletal system
- Up to 80% of bleeds occur in **ankles, knees and elbows**
- Bleeding episodes often begin by **2 years of age**

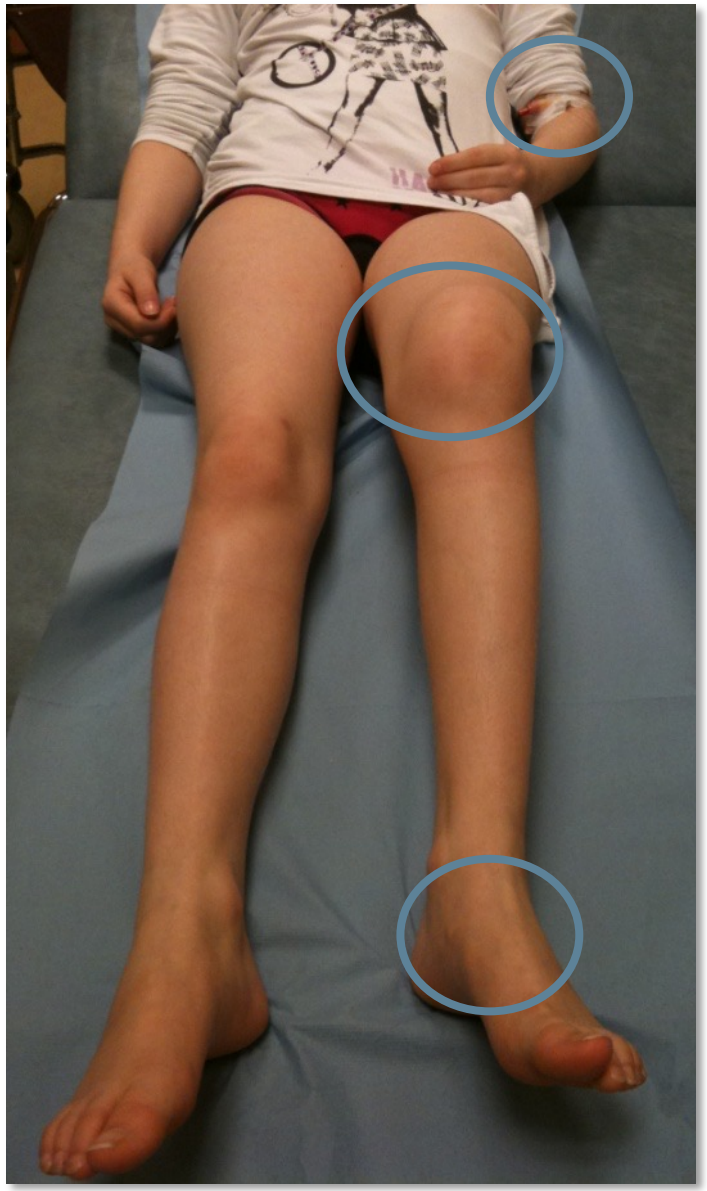


Image provided by S. Lobet

Lobet S, et al. J Blood Med. 2014;5:207-18

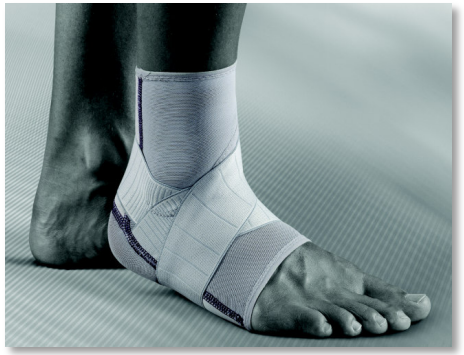
# TREATMENT OF ACUTE PHASE: RRICE (FIRST 72 HOURS)

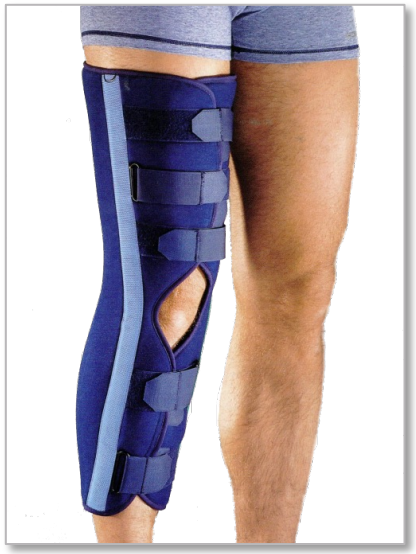
- **R**eplacement of clotting factors
- **R**est (immobilization)
- **I**ce
- **C**ompression (except psoas)
- **E**levation
- Any modality that applies energy **is not indicated during acute bleeding**


Image designed and provided by S. Lobet and C. Lambert

# REST (IMMOBILISATION): CLINICAL MINIMUM !!!

- **Ortheses / braces**
- **Open cast (compartment syndrome!)**





**Prolonged rest**
- Reduced muscle strength
- Impaired joint control

**Early mobilization**
- Promote blood resorption
- Maintain strength and proprioception
- Risk of re-bleed!

Images provided by S. Lobet

# PREVENT WEIGHT-BEARING SITUATION FOR 5–7 DAYS AFTER AN ACUTE BLEED

- **Forced loading** with intra-articular blood promotes the inhibition of **metabolic activity** of **chondrocytes**
  (*in vivo* study)

Beagle dogs: Utrecht

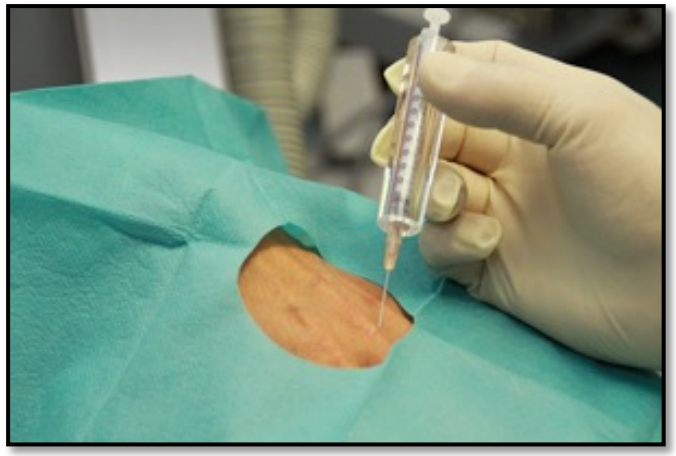
Murine model: Chicago

Images provided by S. Lobet

Hakobyan N, et al. Haemophilia. 2005;11:227-32; Hooiveld MJJ, et al. Arthritis Rheum. 2004;50:2024-31

# INDICATIONS OF SYNOVECTOMY

- The gold standard for any physiotherapy intervention in PWH is to be done with adequate factor replacement cover



However situations arise when factor is not available

- No treatment (under-resourced countries)
- Factor is not working (presence of an inhibitor, impigement,…)
- In these cases, synovectomy (chemical, radioisotope, surgical) is a good indication

Images provided by S. Lobet

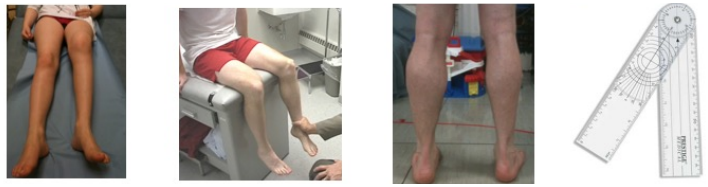
# INDICATIONS OF SYNOVECTOMY

- Reduces bleeding ? Yes[1]
- Reduces pain ? Probably Yes[1] but:
  - Articular degeneration already present cannot be improved with synovectomy[2]
  - For radiosynoviorthesis, response takes place at 1-2 weeks after but maybe delayed for 4 weeks[3]
- Increases range of motion ? NO![1]
- If no change in bleeding frequency after 6 weeks: failure[3]

1. Sabet A, et al. Eur J Nucl Med Mol Imaging. 2016;44:461-67; 2. Chojnowski MM, et al. Reumatologia. 2016;54(3):108-16;
3. EANM Procedure Guidelines for Radiosynovectomy. Eur J Nucl Med (2003) 30:BP12–BP16

# RESULTS OF CLINICAL AND FUNCTIONAL TESTS AFTER 4 MONTHS IN A COMMUNITY REHABILITATION PROGRAM

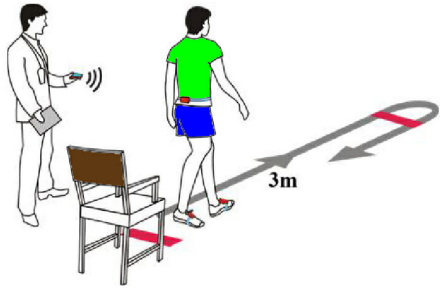
## Haemophilia Joint HealthScore 2.1 (HJHS)

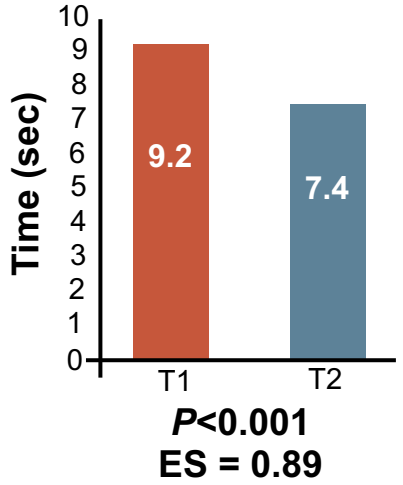





*P*<0.001
ES = 0.23

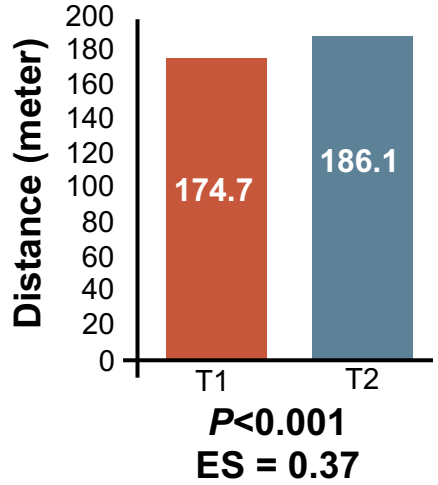
## Timed Up and Go (TUG)




*P*<0.001
ES = 0.89

## 2-Minute Walking Test (2MWT)




*P*<0.001
ES = 0.37

T1 =September 2018 (baseline)

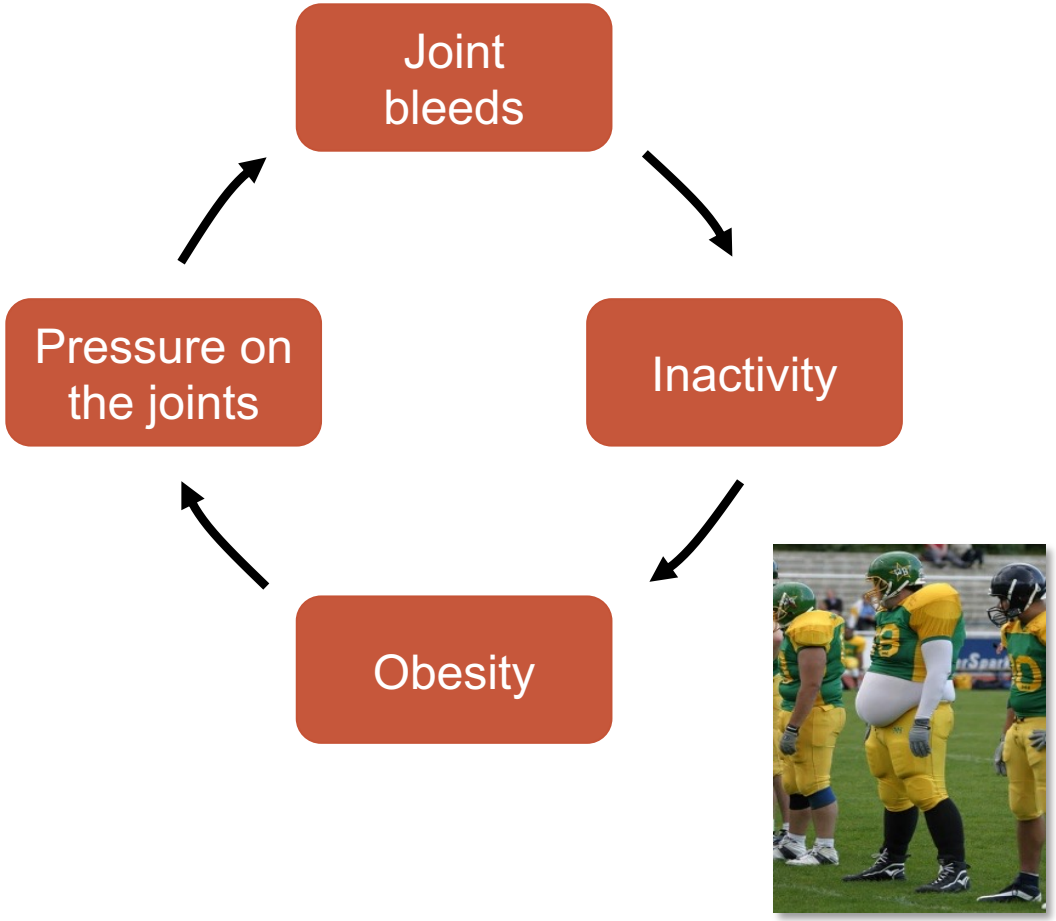
T2 = January 2019 (at 4 months)

2MWT, 2-minute walking test; ES, effect size; HJHS, haemophilia joint health score; TUG, timed up and go

Images reproduced with permission from S Lobet; figure generated based on Lobet S, et al.

1. Lobet S, et al. Haemophilia. 2019;25:859-66

# JOINT DISEASE: A MAJOR CONSEQUENCE OF OVERWEIGHT AND OBESITY IN PEOPLE WITH HAEMOPHILIA



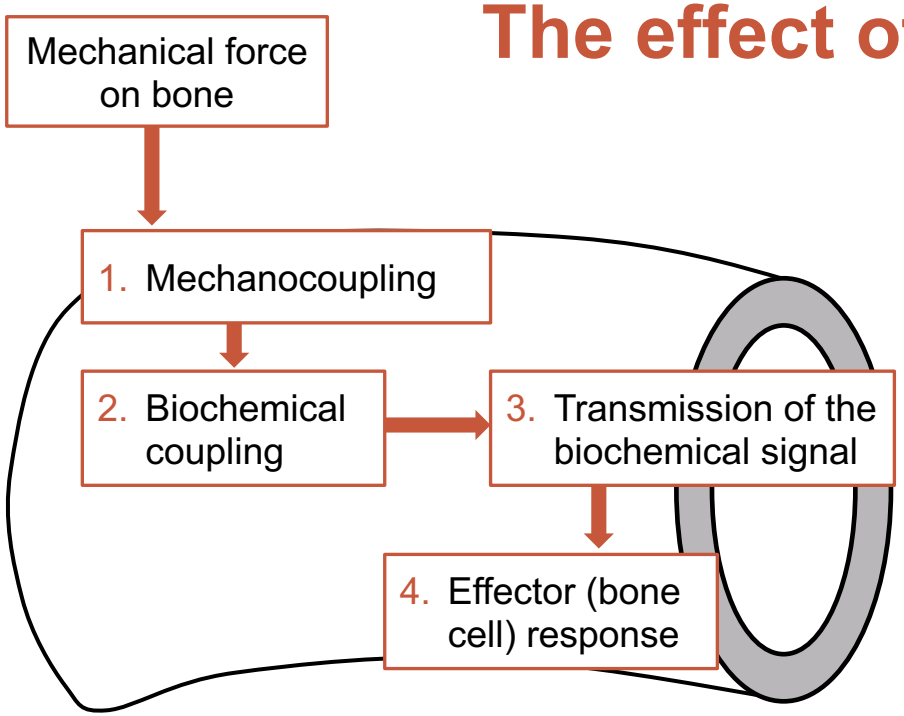

- **General population**: knee osteoarthritis increased 5× in men with BMI 30–35 vs BMI <25[1]
- **Obesity** is also a **risk factor** for non-bearing joints[2]
- **Moderate weight loss** significantly reduces several markers of systemic inflammation (TNFα, IL-6, CRP)[3]

BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; TNFα, tumour necrosis factor alpha

Images provided by speaker

1. Zheng H, et al. BMJ Open. 2015;5(12):e007568; 2. Yusuf E, et al. Ann Rheum Dis. 2010;69:761-5; 3. Nicklas BJ, et al. CMAJ. 2005;172(9):1199-1209

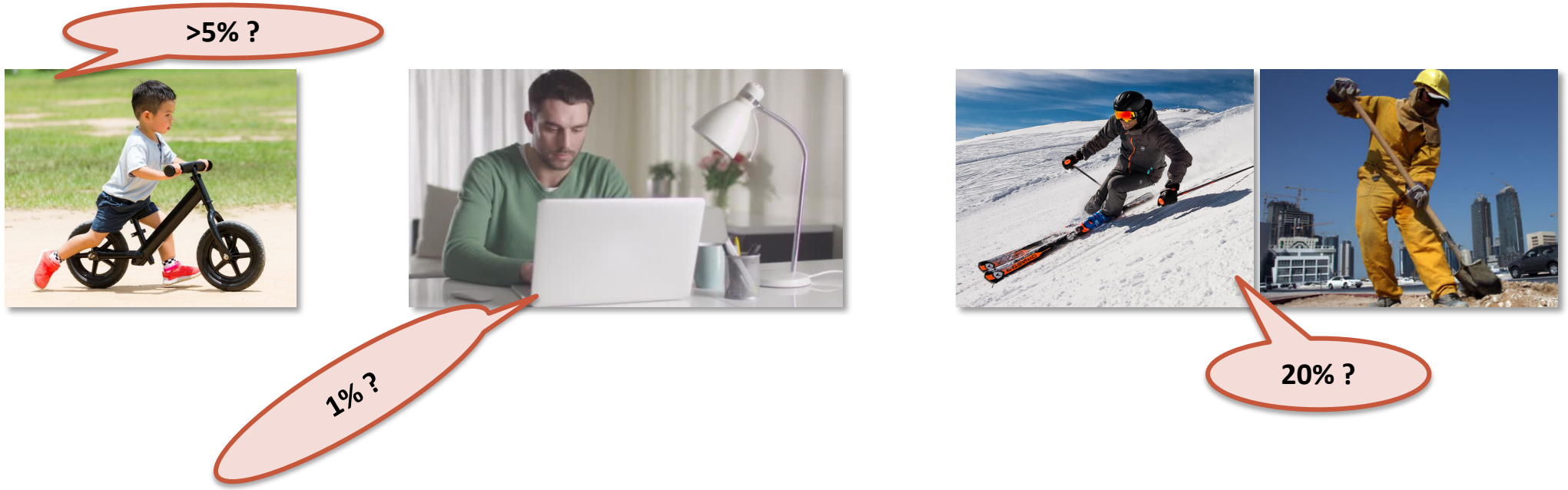
# EFFECT OF EXERCISE ON BONE MINERAL DENSITY




## The effect of mechanical stress!

Images provided by S. Lobet

# PATIENTS WITH DIFFERENT LIFESTYLE AND ACTIVITY LEVELS MAY NEED DIFFERENT LEVELS OF PROTECTION



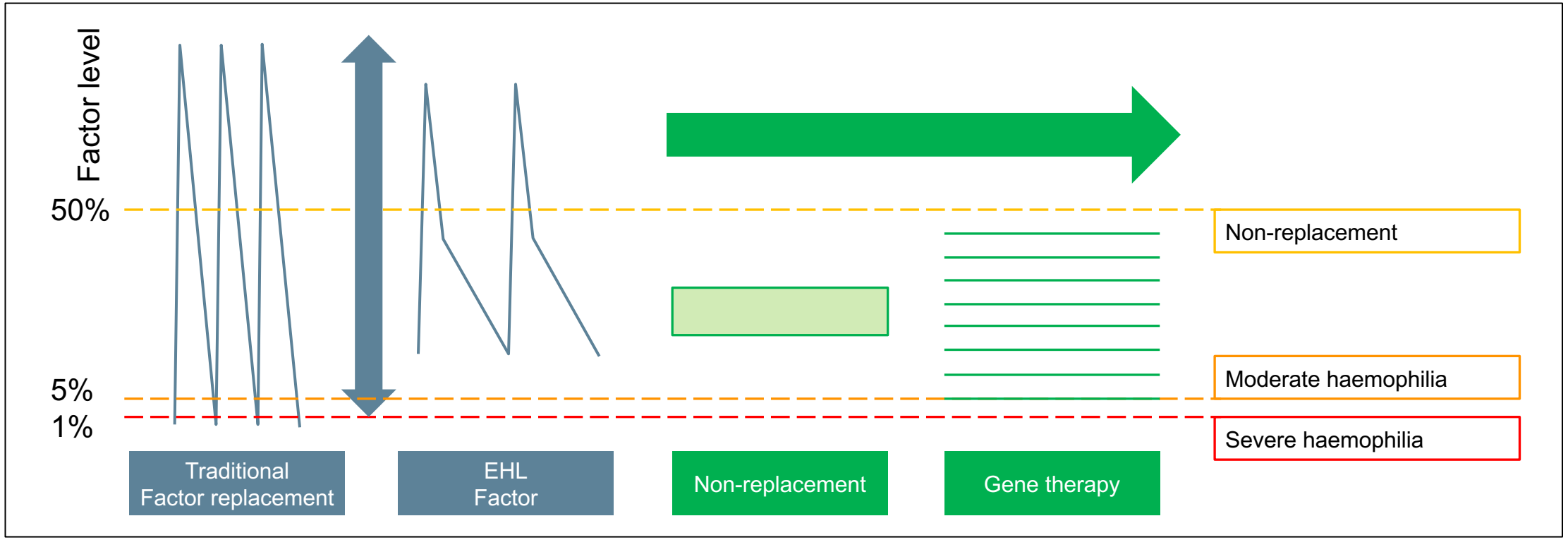

**Optimal prophylaxis regimens for people with haemophilia with an active lifestyle are still not well defined!**

Images provided by S. Lobet

Wang M, et al. Blood Coagul Fibrinolysis. 2016;27:737-44

# KEY DIFFERENCES IN HAEMOSTATIC COVERAGE WITH DIFFERENT PHARMACOLOGICAL APPROACHES FOR HAEMOPHILIA

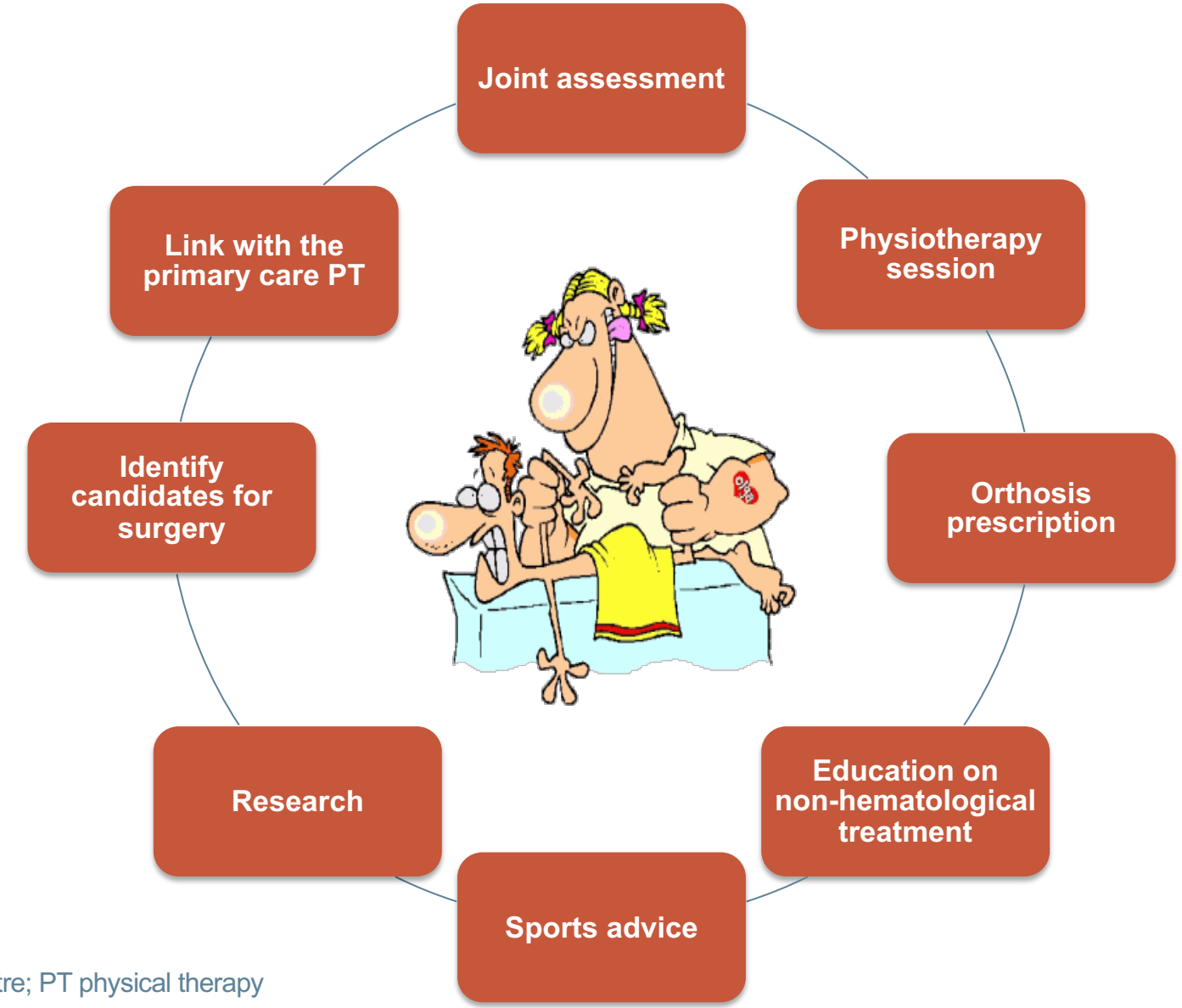
- **Replacement therapy** can be adapted to suit different needs such as **bouts** of intense **physical activity**!




EHL, extended half-life

Lobet S. et al. J Clin Med. 2021;10(13):2822

# INVOLVEMENT OF THE PHYSIOTHERAPIST IN THE HTC




HTC, haemophilia treatment centre; PT physical therapy

Images provided by S. Lobet

# LABORATORY ISSUES IN THE ERA OF FACTOR AND NON-FACTOR THERAPIES

**Dr. Steve Kitchen**

**Sheffield Haemophilia and Thrombosis Centre, UK**

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# LABORATORY MONITORING AFTER CONCENTRATE INFUSIONS

- Assay differences reported for some extended half-life (EHL) products
- How big a difference is important?
  - +/- 25-30% increasingly used in assay studies
- Clinically relevant assay = assay used for potency assignment (used in clinical trials to establish dosing/efficacy)
- FVIII – chromogenic or one stage for potency
- FIX products labelled by one stage assay (different reagent sets)

FIX, factor IX; FVIII, factor VIII

Kitchen S, et al Semin Thromb Hemost. 2017;43(3):331-337

# ONE STAGE CLOTTING (APTT BASED) AND CHROMOGENIC FIX ASSAYS

**One stage**

Analyser dilutes sample

+

Add FVIII deficient plasma

+

Add APTT reagent and incubate

+

Add calcium

↓

Time clot

**Chromogenic**

Analyser dilutes sample

+

Add some FX

+

Add some FVIII, thrombin, phospholipid and calcium

Add a substrate that FXa cleaves

↓

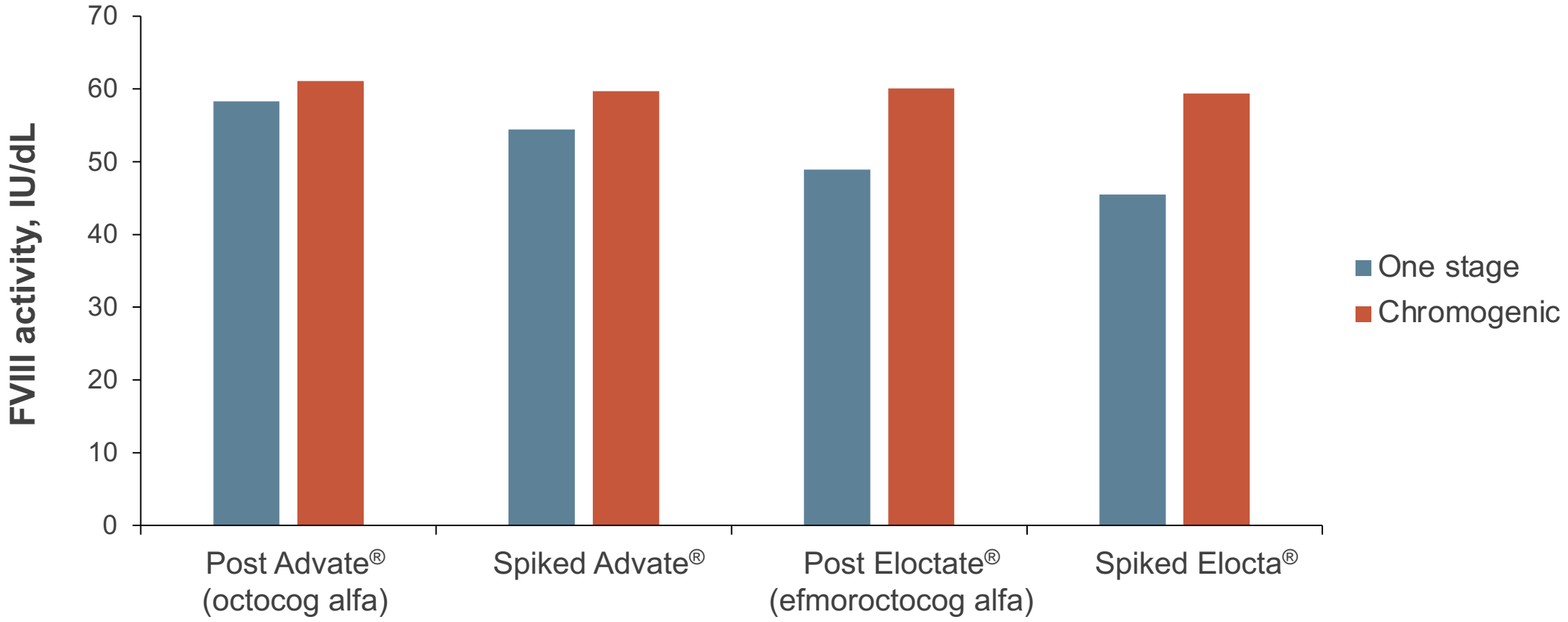
Endpoint -Colour

**In both cases, readings are converted to activity from a calibration curve**

APTT, activated partial thromboplastin time; FIX, factor IX; FVIII, factor VIII; FX, factor X; FXa, factor Xa

Marlar RA, et al. Eur J Haematol. 2020;104(1):3-14

# ONE STAGE AND CHROMOGENIC ASSAY IN SAMPLES CONTAINING ADVATE OR ELOCTATE (LOCALLY USED PLASMA STANDARDS)




FVIII, factor VIII

Kitchen S, et al. Int J Lab Hematol. 2019;41(2):176-183

# MONITORING MODIFIED FVIII

| | Modification | Chromogenic FVIII |
|---|---|---|
| Adynovate | PEGylated (20kd) | Yes |
| Afstyla | Single chain | Yes |
| Jivi | PEGylated (60kd) | Yes |
| Elocta/Eloctate | Fc Fusion | Yes |
| Esperoct | PEGylated (40kd) | Yes |
| Obizur | BDD porcine FVIII | No |

**Yes** means within 25–30% of expected value from labelled potency
**No** means bigger differences.

BDD, B-domain deleted; FVIII, factor VIII; PEG, polyethylene glycol
Kitchen S, et al Semin Thromb Hemost. 2017;43(3):331-337

# ONE STAGE ASSAYS WHICH OVER-ESTIMATE REBINYN/REFIXIA

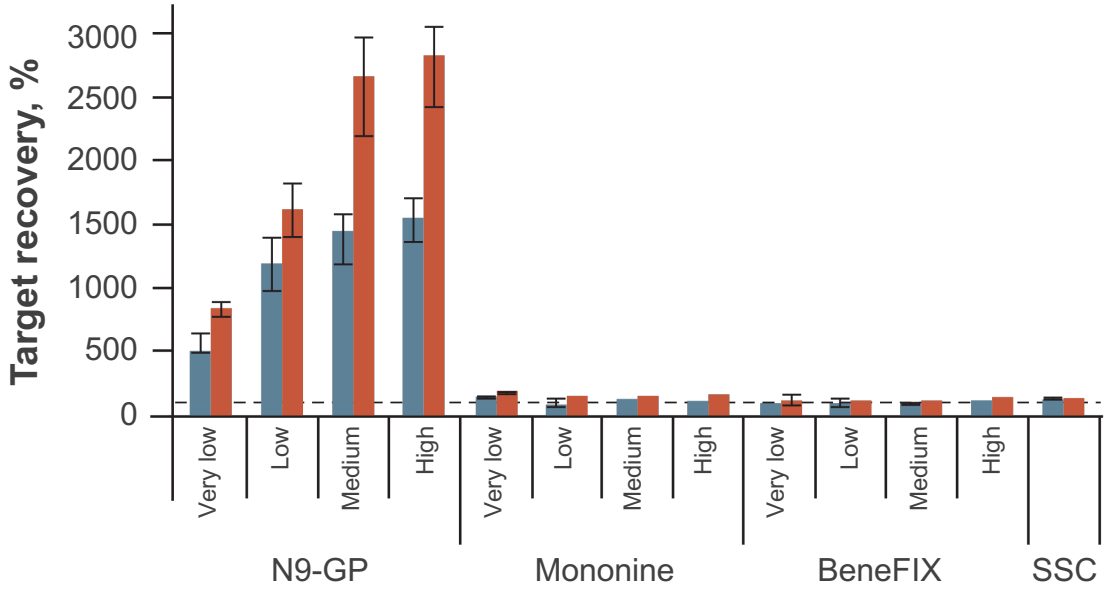
*Journal of Thrombosis and Haemostasis*, 14: 1–8 DOI: 10.1111/jth.13348

ORIGINAL ARTICLE

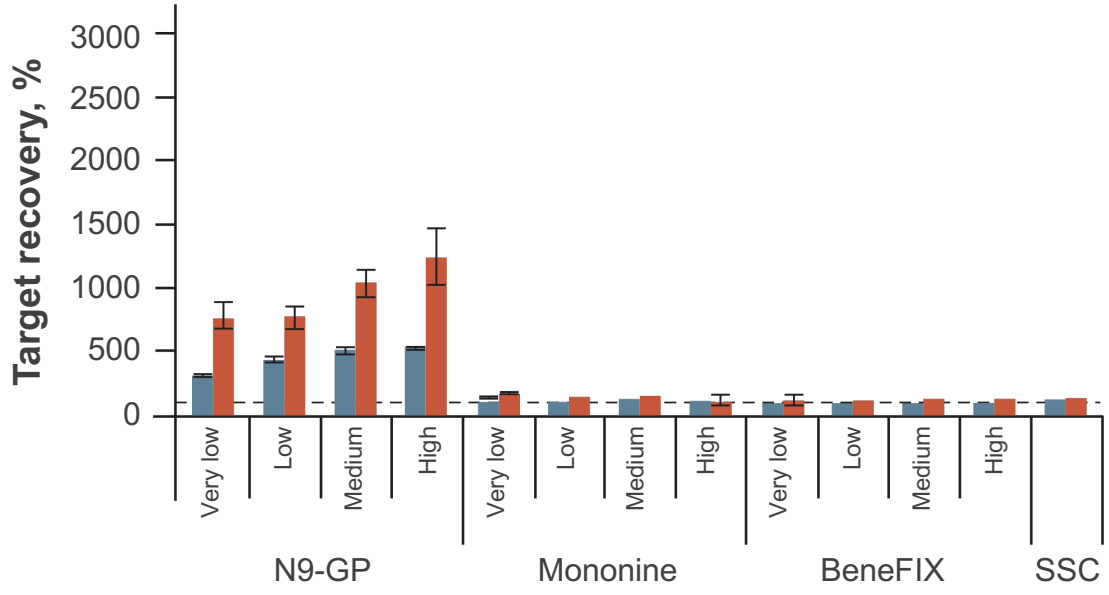
## Measuring factor IX activity of nonacog beta pegol with commercially available one-stage clotting and chromogenic assay kits: a two-center study

A. E. BOWYER,* A. HILLARP,† M. EZBAN,‡ P. PERSSON§ and S. KITCHEN*

**Pathromtin® SL**




**APTT SP**




N9-GP = rebinyn/refixia. Very low, 3 IU/dL; Low, 20 IU/dL; 60 IU/dL, Medium; High, 90 IU/dL
APTT, activated partial thromboplastin time; SSC, Scientific and Standardisation Committee
Bowyer AE, et al. J Thromb Haemost. 2016;14(7):1428-35

# MONITORING FVIII OR FIX CONCENTRATES

**Recommendation 3.2.18:**

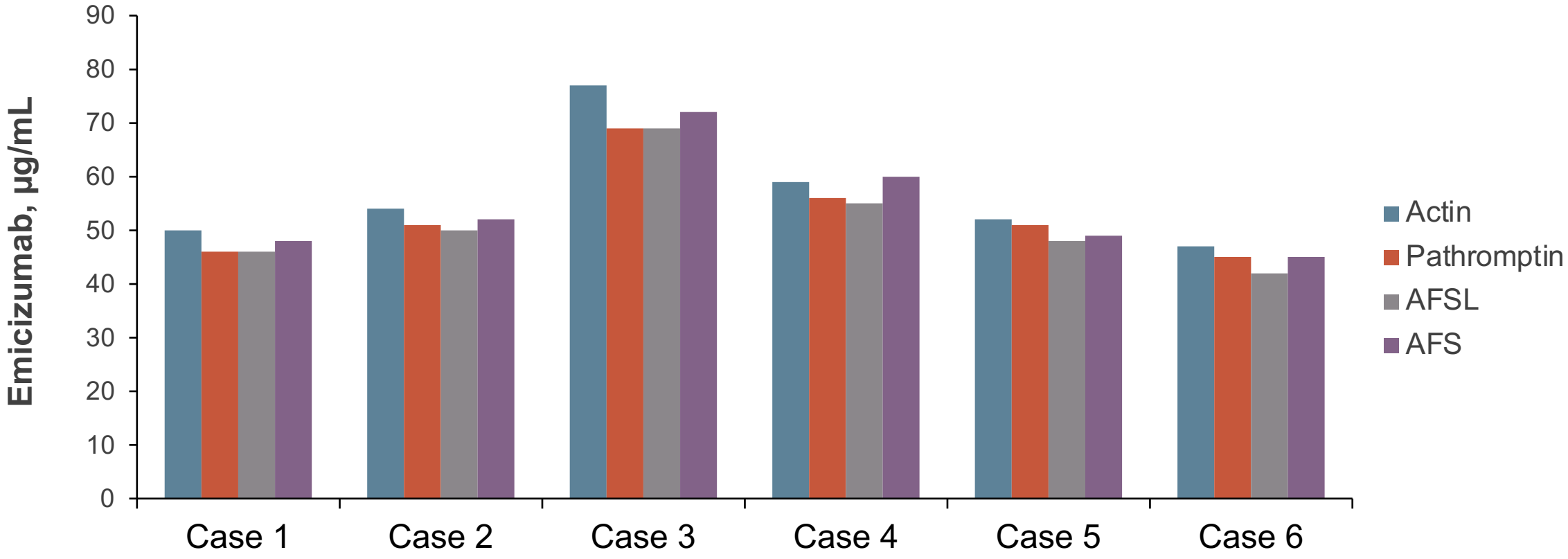
- For monitoring replacement therapy with FVIII or FIX concentrates, the WFH recommends that laboratories use a FVIII/FIX assay that has been validated for use with the specific concentrate used for treatment
- Remark:
  - This recommendation is particularly important for modified molecular forms of FVIII and FIX (CB)

CB, consensus based; FIX, factor IX; FVIII, factor VIII; WFH, World Federation of Hemophilia

Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1-158. Available from: https://elearning.wfh.org/resource/treatment-guidelines/ (accessed September 2023)

# EMICIZUMAB CALIBRATORS ALLOW USE OF DIFFERENT APTT REAGENTS

## SIX CASES AFTER >6 WEEKS OF MAINTENANCE DOSE




AFS, actin FS; AFSL, actin FSL; APTT, activated partial thromboplastin time

Unpublished Sheffield data

# MEASURING FVIII IN PRESENCE OF EMICIZUMAB

**Recommendation 3.2.32:**

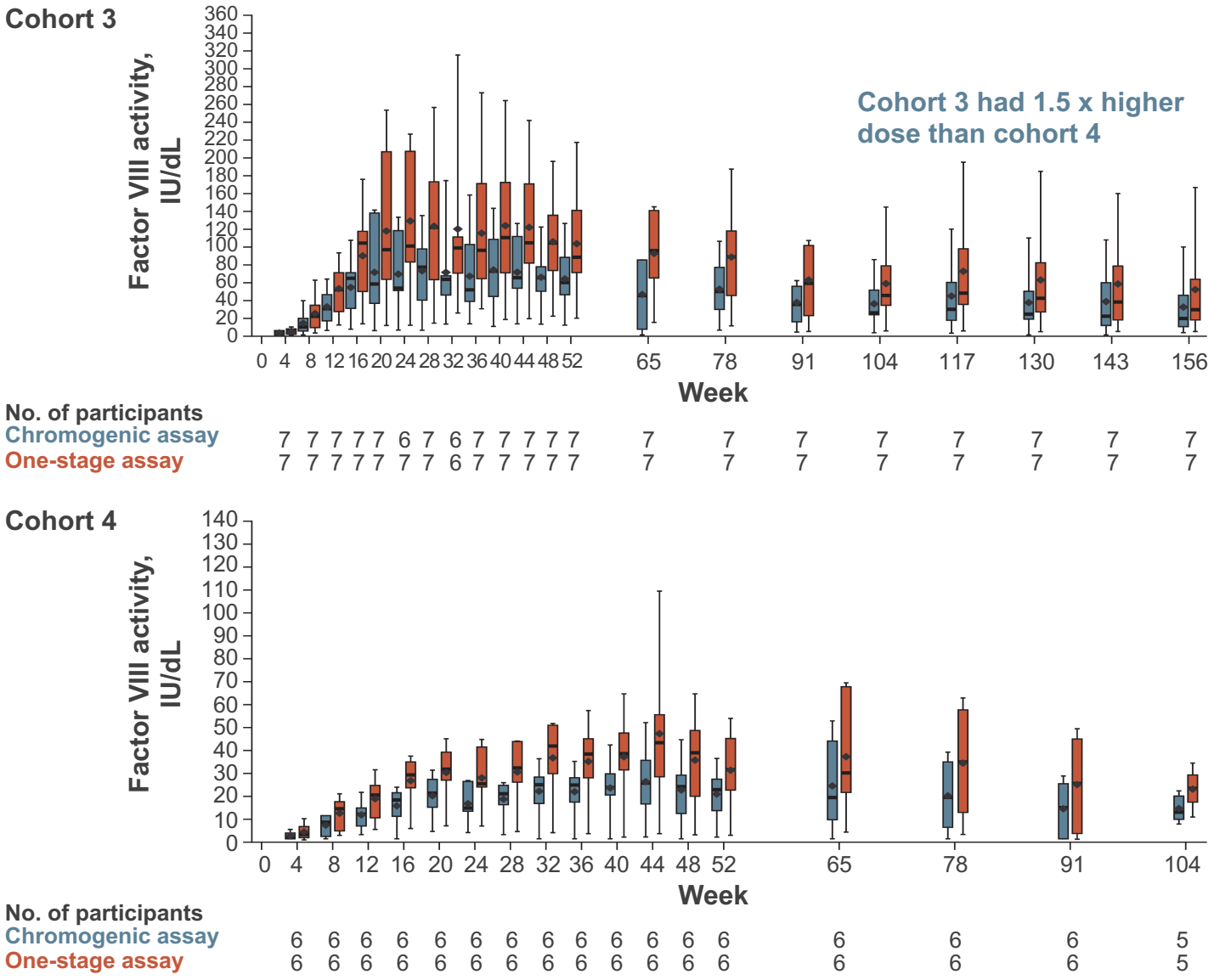
- For determination of FVIII activity in patients with haemophilia A receiving emicizumab, the WFH recommends use of a chromogenic FVIII assay containing bovine FX
- Remark:
  - At therapeutic levels, emicizumab affects any chromogenic FVIII assay containing FX of human origin. Emicizumab may also affect chromogenic FVIII assays containing FIXa of human and FX of bovine origin but only at emicizumab levels higher than those expected in patients receiving recommended doses (CB)

CB, consensus based; FIXa, activated FIX; FVIII, factor VIII; FX, factor X; WFH, World Federation of Hemophilia

Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1-158. https://elearning.wfh.org/resource/treatment-guidelines/

# GENE THERAPY FVII

## ONE STAGE FACTOR VIII ASSAYS CONSISTENTLY HIGHER THAN CHROMOGENIC




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A

K. John Pasi, M.B., Ch.B., Ph.D., Savita Rangarajan, M.B., B.S., Nina Mitchell, M.B., B.Chir., Will Lester, M.B., Ch.B., Ph.D., Emily Symington, M.B., B.S., Bella Madan, M.D., Michael Laffan, D.M., Chris B. Russell, Ph.D., Mingjin Li, M.Sc., Glenn F. Pierce, M.D., Ph.D., and Wing Y. Wong, M.D.

Assay relationship consistent with earlier data, i.e. One stage 1.65 x higher than chromogenic

One stage – AFSL/Siemens deficient/Precision calibrator/ BCS

Chromo – Coatest/Precision calibrator/BCS

AFSL, actin FSL. Pasi KJ, et al. N Engl J Med. 2020;382(1):29-40

# WHICH METHOD TO USE FOR FVIII GENE THERAPY?

- Clinical outcomes are needed to show which correlates best with efficacy/bleeding risk
- Correlation with joint bleeds – either assay “ clinically meaningful to distinguish haemophilic from non-haemophilic activity levels”
- Chromogenic chosen by BioMarin as “surrogate endpoint to conservatively assess haemostatic efficacy”
- Chromogenic FVIII preferred

FVIII, factor VIII

Rosen S, et al. Blood. 2020;136(22):2524-2534

# FIX PADUA GENE THERAPY
# WHICH FIX ASSAY TO USE?

- Clinical outcomes needed to show which correlates best with efficacy/bleeding risk
- Some laboratory data suggest the level of FX in chromogenic FIX kits may be an underestimation
- Higher one stage activity was thrombophilic in original Padua cases
- One Stage FIX preferred?? Which?

- **Interpretation of assay results after gene therapy can be affected by the assay method used**
- **Findings for FVIII are different to FIX**

FX, factor X

# CLINICAL TAKEAWAYS – PART 2

- Co-morbidities in people with hemophilia (PWH) are increasingly reported, predominantly in older PWH. Clinical practice guidance providing recommendations on antithrombotic therapy is available

- Physiotherapy remains crucial in PWH, both in those treated with evolving therapies and in those not receiving adequate treatment

- Laboratory testing of factor concentrates can vary between different methodologies. WFH recommends that laboratories use a FVIII/FIX assay that has been validated for use with the specific concentrates used for treatment.