WEBINAR SERIES | SESSION 4

PRACTICAL EDUCATION ON BLEEDING DISORDERS

Knowledge for All

Medical educational webinar series on global topics surrounding bleeding disorders.

THURSDAY, DECEMBER 16, 2021, 8–10 A.M. EST

English with simultaneous translation into Arabic, French, Russian and Spanish.

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

WELCOME

GLENN PIERCE, MD PhD

WFH VICE PRESIDENT, MEDICAL

AGENDA

1. Opening & welcoming remarks
2. Update from ASH Congress
3. Dental considerations
4. Liver health
5. Q&A
6. Obesity
7. Pain
8. Mental health
9. Q&A
10. Closing remarks

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SPEAKERS

Glenn Pierce, MD PhD
WFH Vice President, Medical

Lochana Nanayakkara, BDS, MSc
WFH Dental Committee Chair

Kate Khair, PhD
Director of Research, Haemnet

Cedric Hermans, MD, PhD
WFH Medical board member
Belgium

Nathalie Roussel, PhD
Associate Professor, University of Antwerp

Bruce Luxon, MD, PhD
Chair, Department of Medicine, Georgetown University

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American Society of Hematology, Atlanta, Georgia, USA
Some Interesting Talks

Glenn Pierce, MD PhD
Vice President, Medical, WFH
La Jolla, California, USA

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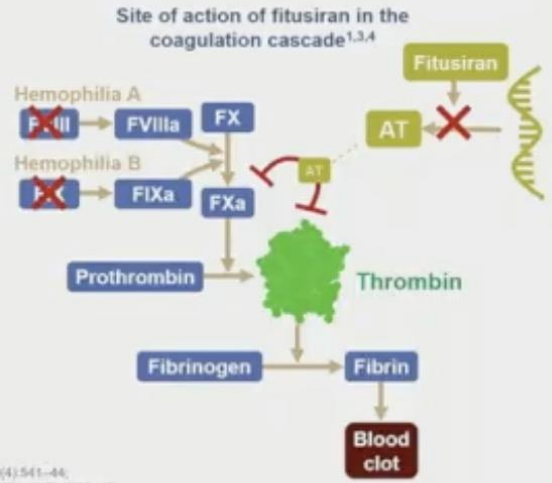
Fitusiran: A Novel Investigational Prophylaxis siRNA Therapeutic for Hemophilia

- Fitusiran is a subcutaneous siRNA therapeutic designed to **lower antithrombin (AT)** with the goal of promoting sufficient potential to generate thrombin to **rebalance hemostasis in people with hemophilia A or B, with or without inhibitors**[1]
  - Case reports of hemophilia co-inherited with thrombophilia suggest this may be an effective strategy[2]
  - Previous study data demonstrate that subcutaneous administration of fitusiran lowered AT, resulting in **increased thrombin generation** and an improved bleeding phenotype[1,3,4]

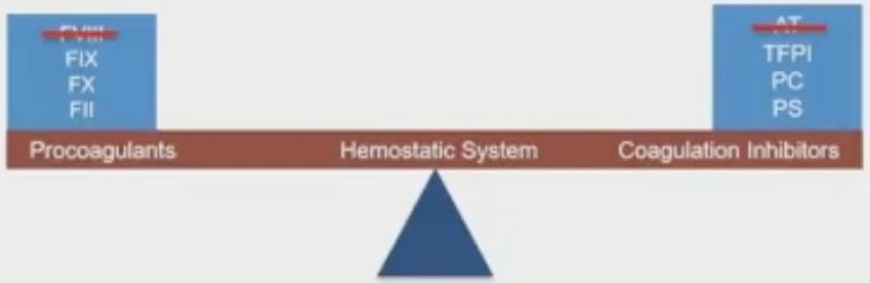


AT, antithrombin; OLE, open-label extension
1. Pasi KJ, *et al. N Engl J Med.* 2017;377:819–828; 2. Shetty S, *et al. Br J Haematol.* 2007;138(4):541–44;
3. Machin N and Ragni M. *J Blood Med.* 2018;9:135–40; 4. Pasi KJ, *et al. J Thromb Haemost.* 2021;19(6):1436–46.

Rebalancing Agents

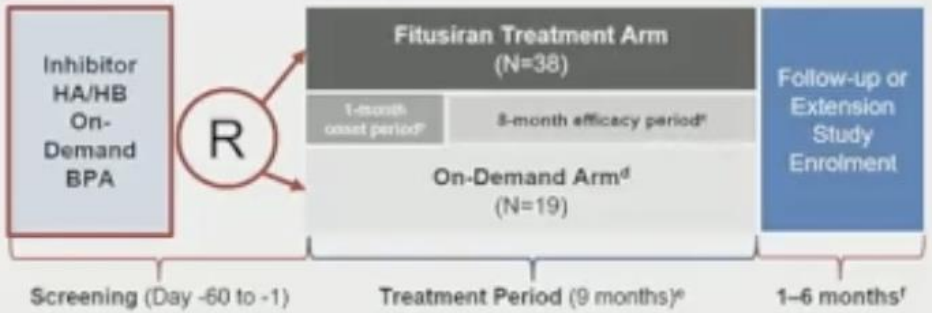
Bleeding Disorder

Balance Restored—No bleeding/No Clotting



Fitusiran Phase 3 ATLAS-INH: Study Design

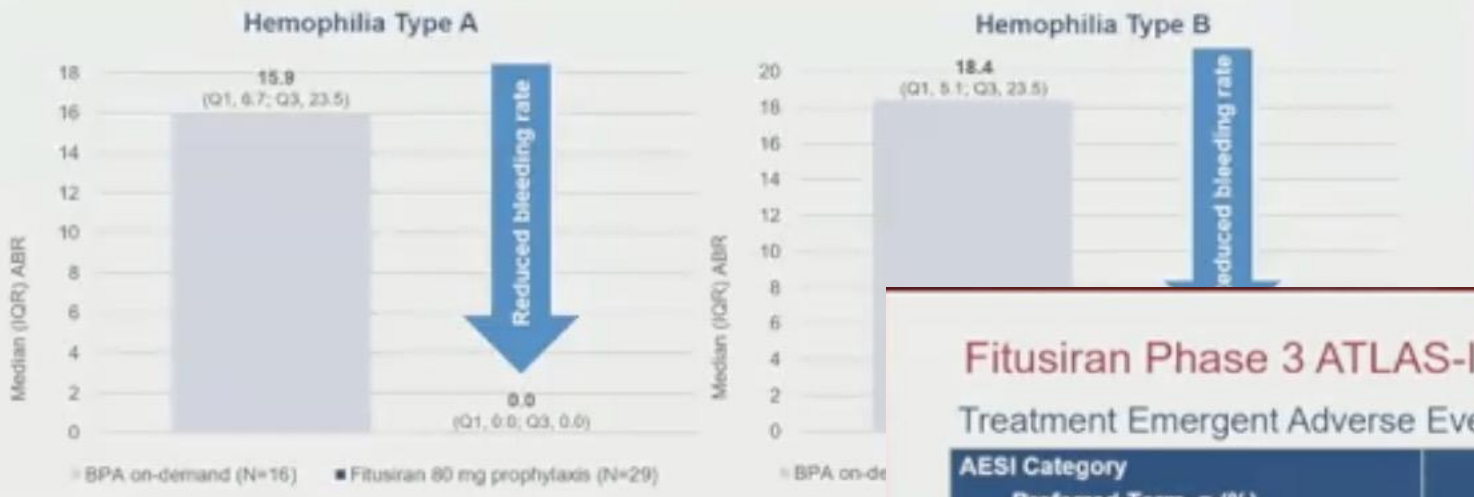
- The study included eligible male patients (≥12 years), with hemophilia A or B, with inhibitors receiving on-demand treatment with bypassing agents (BPA)[a]
  - Patients were randomized 2:1 to receive **monthly 80 mg subcutaneous fitusiran prophylaxis**, with use of on-demand BPAs for treatment of breakthrough bleeds, or to continue with on-demand BPA



The Phase 3 ATLAS-INH study (NCT03417102) was designed to evaluate the efficacy and safety of fitusiran in people with hemophilia A or B, with inhibitors

Fitusiran Phase 3 ATLAS-INH: Analysis of Bleeding Events by Hemophilia Subgroup

Observed median ABR by hemophilia subtype for treated bleeds and duration of follow-up in the efficacy period[a]
(statistically significant reduction in bleeding using negative binomial model, p<0.0001)



[a]Efficacy period was during which bleeds were counted for the purpose of ABR calculation for primary efficacy analysis: fitusiran treatment up to Day 246.

Fitusiran Phase 3 ATLAS-INH Results: Safety and Tolerability

Treatment Emergent Adverse Events of Special Interest

AESI Category Preferred Term, n (%)	BPA On-demand (N=19)	Fitusiran 80 mg Prophylaxis (N=41)
ALT or AST elevations >3 x ULN		
Increased transaminases	0 (0%)	5 (12.2%)
Increased alanine aminotransferase	0 (0%)	4 (9.8%)
Increased hepatic enzyme	0 (0%)	1 (2.4%)
Cholestasis	0 (0%)	1 (2.4%)
Suspected or confirmed thromboembolic events		
Deep vein thrombosis[a]	0 (0%)	1 (2.4%)
Subclavian vein thrombosis[a]	0 (0%)	1 (2.4%)
Thrombophlebitis superficial[a]	0 (0%)	1 (2.4%)
Thrombosis[b]	0 (0%)	1 (2.4%)

Differences in reported TEAESIs between the fitusiran prophylaxis arm and BPA on-demand arm were consistent with previously identified risks of fitusiran

[a]TEAESIs occurred in a single subject in the setting of central venous access and infectious complications. All assessed by the investigator as unlikely related to fitusiran. [b]Verbatim: suspected spinal vessel thrombosis. Assessed by the investigator as possibly related to fitusiran and resulted in treatment discontinuation. For additional details on thrombotic events in the fitusiran clinical development program, please refer to the following presentations: Andersson S, *et al.* Oral Presentation at the European Association for Haemophilia and Allied Disorders (EAHAD) Congress, 2021; Negrier C, *et al.* Oral Presentation at the Society of Thrombosis and Haemostasis Research (GTH) Congress, 2021

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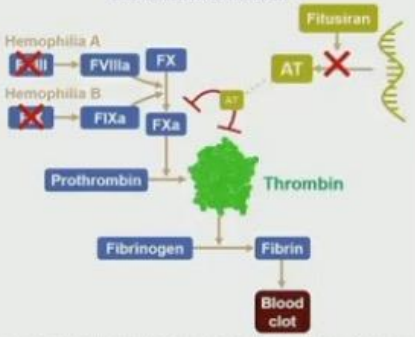
Fitusiran, an Investigational siRNA Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: First Results from a Phase 3 Study to Evaluate Efficacy and Safety in People with Hemophilia A or B *Without* Inhibitors (ATLAS-A/B)

Alok Srivastava, MD[1]; Savita Rangarajan, MD[2]; Kaan Kavakli, MD[3]; Robert Klamroth, MD[4]; Gili Kenet, MD[5]; Liana Khoo, MD[6]; Chur-Woo You, MD[7]; Weiqun Xu, MD, PhD[8]; Nivi Malan, MD[9]; Laurent Frenzel, MD, PhD[10]; Catherine N. Bagot, MD[11]; Oleksandra Sirenko, MD, PhD[12]; Chia-Yau Chang, MD[13]; Stacey Poloskey, MD[14]; Shauna Anderson, MD, PhD[15]; Zhiying Qiu, PhD[16]; Baisong Mei, MD, PhD[16]; Steven W. Pipe, MD[17]

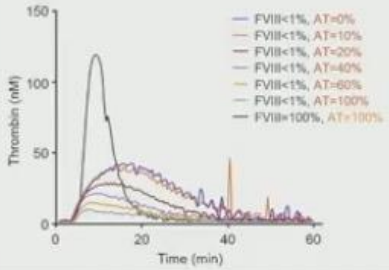
December 14, 2021

Thrombin Generation Matters

Site of action of fitusiran[1–3]

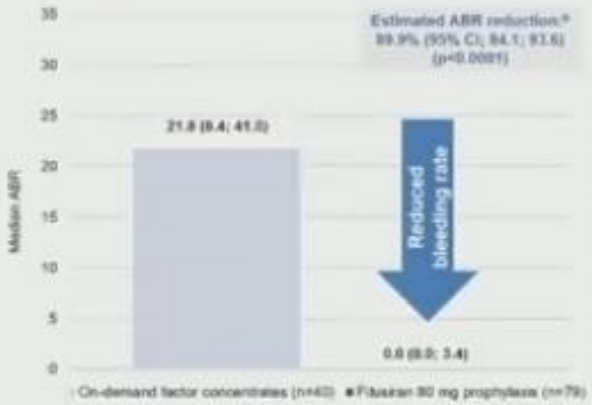


Ex vivo thrombin generation in human hemophilia A plasma depleted of AT[4]

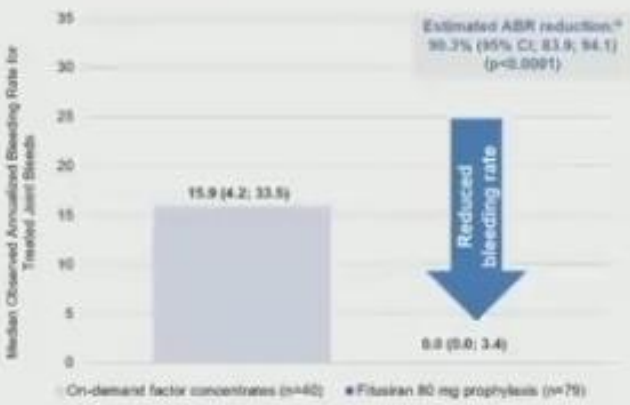


Fitusiran Phase 3 ATLAS-A/B: Treated Bleeds During Efficacy Period[a]

Observed median ABR for all treated bleeds (IQR)



Observed median ABR for treated joint bleeds (IQR)



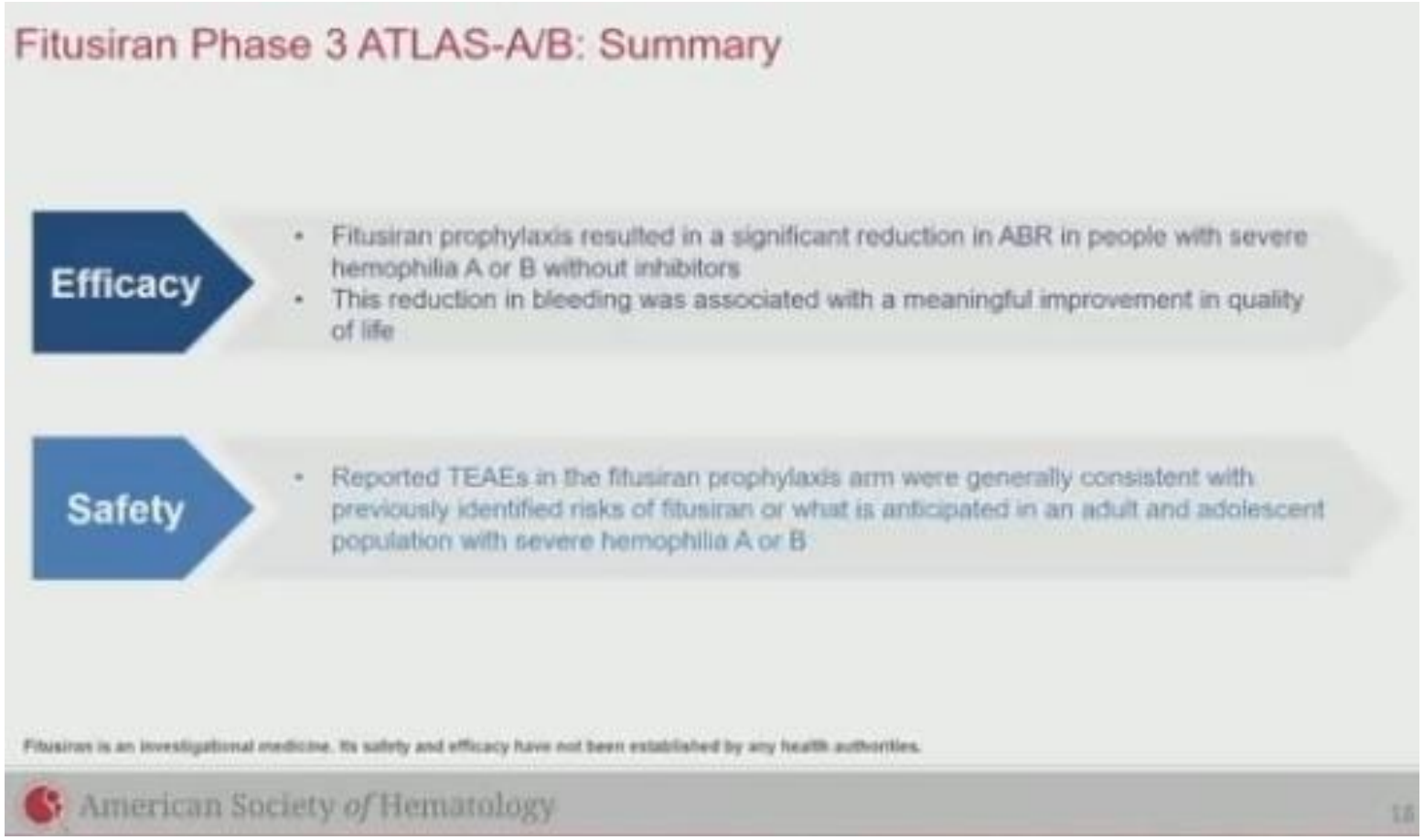
Fitusiran Phase 3 ATLAS-A/B: Safety and Tolerability

TEAE Category, n (%)	On-demand Factor Concentrates (n=40)	Fitusiran 80 mg Prophylaxis (n=79)
Any TEAE	18 (45.0)	62 (78.5)
Any TESAE	5 (12.5)	5 (6.3)
Any TEAE leading to treatment discontinuation[a]	-	2 (2.5)
Any TEAE leading to death	0 (0.0)	0 (0.0)
Any TEAESI	1 (2.5)	15 (19.0)
ALT increased	0 (0.0)	12 (15.2)
AST increased	1 (2.5)	3 (3.8)
Hepatic enzyme increased	0 (0.0)	1 (1.3)
Transaminases increased	0 (0.0)	1 (1.3)

No TEAESIs of thrombosis were reported. Differences in reported TEAESIs between the fitusiran prophylaxis arm and factor on-demand arm were consistent with previously identified risks of fitusiran

[a]In the fitusiran arm, 2 participants (2.5%) experienced TEAEs that resulted in fitusiran discontinuation (cholecystitis and increased ALT, in 1 participant each). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; TESAE, treatment-emergent serious adverse event.

The Rest of the Story-Fair Balance



5 thrombotic events total in program

Trial restarted: Dosing from 80mg/month to 50mg/every other month (~70% dose reduction)
Use lower doses of factor for breakthrough bleeds

All comparisons to on-demand, not to prophylaxis with other agents
gene tx, emi precedents

https://www.hemophilia.org/news/sanofi-revises-fitusiran-dosing-regimen-to-mitigate-risk-of-vascular-thrombosis

https://www.news.sanofi.us/2020-12-10-Sanofi-to-resume-dosing-in-fitusiran-clinical-studies-in-the-U-S

Emicizumab Prophylaxis in Persons with Mild or Moderate Hemophilia A: Results from the Interim Analysis of the HAVEN 6 Study

Claude Negrier,[1] Johnny Mahlangu,[2] Michaela Lehle,[3] Pratima Chowdary,[4] Olivier Catalani,[3] Víctor Jiménez-Yuste,[5] Benjamin M. Beckermann,[3] Christophe Schmitt,[3] Cédric Hermans,[6] Giuliana Ventriglia,[3] Jerzy Windyga,[7] Anna Kiialainen,[3] Roseline d'Oiron,[8] Paul Moorehead,[9] Vanda Teodoro,[3] Amy Shapiro,[10] Johannes Oldenburg[11]

[1]Louis Pradel Cardiology Hospital, Lyon 1 University, Lyon, France; [2]University of the Witwatersrand and NHLS, Johannesburg, South Africa; [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [4]Royal Free London, London, UK; [5]Hospital Universitario La Paz, Autónoma University, Madrid, Spain; [6]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Bicêtre Hospital AP-HP, University Paris-Saclay and UMR_S1176 INSERM, Le Kremlin-Bicêtre, France; [9]Memorial University of Newfoundland, NL, Canada; [10]Indiana Hemophilia & Thrombosis Center, IN, USA; [11]University of Bonn, Bonn, Germany

Emicizumab is subject to additional safety monitoring requirements in many countries. Healthcare professionals are asked to report any suspected adverse reactions to the regulatory authorities in your country according to your national requirements.

Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

63rd ASH® Annu

In this population of people with mild or moderate HA, no new safety signals were identified and there were no thrombotic events, thrombotic microangiopathies, or deaths at the time of the interim analysis*

Efficacy data were consistent across all bleeding endpoints and with other HAVEN studies

Data indicate emicizumab offers a favourable safety profile and an efficacious treatment option for people with mild/moderate HA while reducing treatment burden for those previously receiving either episodic or prophylactic FVIII treatment

Surgical Experience from the Phase IIIb STASEY Trial of Emicizumab Prophylaxis in Persons with Hemophilia A with FVIII Inhibitors: Final Analysis

Giancarlo Castaman,[1] Jerzy Windyga,[2] Hazza Alzahrani,[3] Susan Robson,[4] Fabian Sanabria,[4] Monet Howard,[5] Víctor Jiménez-Yuste[6]

[1]Center for Bleeding Disorders and Coagulation, Careggi University Hospital, Florence, Italy; [2]Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Blood Transfusion, Warsaw, Poland; [3]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [5]F. Hoffmann-La Roche Ltd, Mississauga, ON, Canada; [6]Hospital Universitario La Paz, Autónoma University, Madrid, Spain

- Most minor surgical procedures during the STASEY study were performed without additional prophylactic coagulation factor and did not result in post-operative treated bleeds
- Major surgeries during the STASEY study were safely performed with additional coagulation prophylaxis
- No thrombotic microangiopathies or thrombotic events related to emicizumab occurred in people who had on-study surgeries in the STASEY study
- A bleed management plan should be in place for anyone on emicizumab undergoing surgery, to optimize the prevention and treatment of bleeds

Annual Meeting & Exposition of the American Society of Hematology

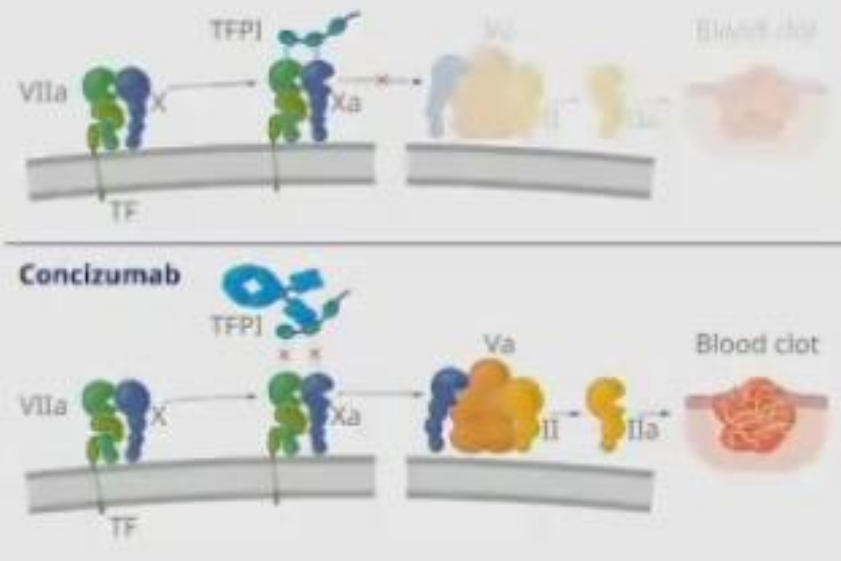
Publication #345

Surgeries and diagnostic procedures in hemophilia patients on concizumab prophylaxis: Results from the phase 2 explorer4 and explorer5 trials

Wheeler AP[1], Benson G[2], Eichler H[3], Tønder SM[4], Cepo K[4], Jimenez-Yuste V[5], Kavakli K[6], Wong Lee Lee L[7], Matsushita T[8]

[1]Vanderbilt Children's Hospital, TN, USA; [2]Northern Ireland Haemophilia Centre, Belfast, United Kingdom; [3]Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Homburg, Germany; [4]Novo Nordisk A/S, Søborg, Denmark; [5]Hospital Universitario La Paz, Madrid, [illegible]; [7]Hospital Queen Elizabeth, Kota Kinabalu, Malaysia; [8]Nagoya University, Nago

Concizumab is an anti-tissue factor pathway inhibitor (TFPI) antibody



- For subcutaneous prophylaxis across all hemophilia subtypes
- That acts independently from FVIII and FIX
- By enhancing the initiation phase of coagulation through increased FXa activity
- Allowing sufficient thrombin generation to prevent bleeds

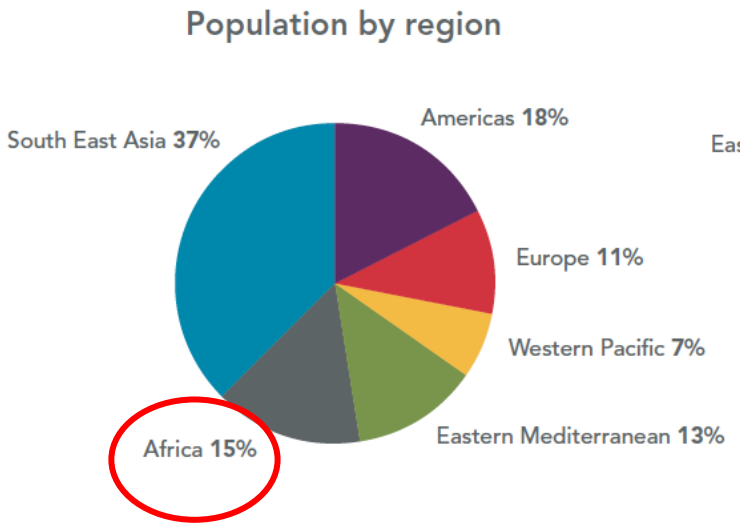
Financial Stewardship In an Era of Hematologic Advances in Care: Whose Value? What Price?

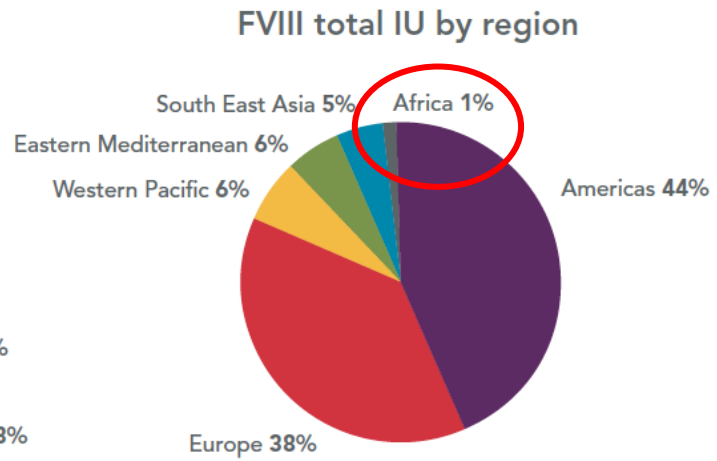
Aaron Kesselheim, MD
Glenn Pierce, MD,PhD
Derek Robertson, MBA, JD
Pedro Gascon, MD
John Lin, MD

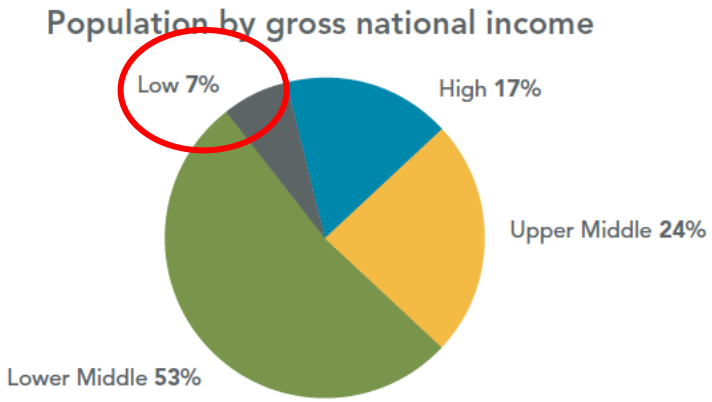
Estimating Escalating Costs Over 60 Years

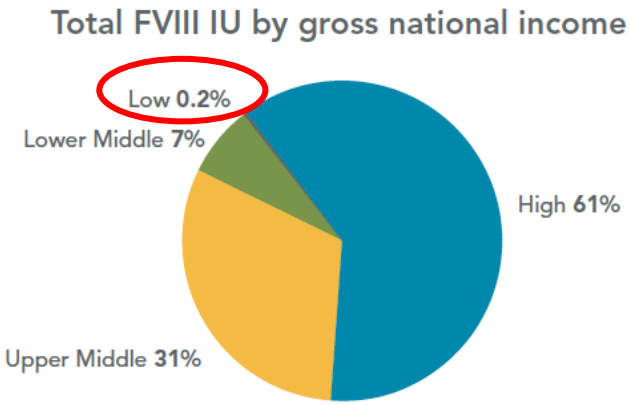
- 1965: Cryo, ~$8/bag, weight based dosing, 20 bags/adult bleed =$160
  - 20-40 bleeds/year = $3200-$6400/yr
- 1970: Lyophilized factor ~$0.08/unit, 2000-3000 units/adult bleed x 1-3 tx
  - 20-40 bleeds/year = $3200-$29,000/yr
- 1985: Virally inactivated factor 2x base charge; up to $58,000/yr
- 1987:Highly purified, virally inactivated factor 6x base charge; up to $180,000/yr
- 1992:Recombinant factor ~$1.00/unit, $40,000-$360,000/year
- 2014: Extended half life recombinant factor ~$2-3/unit, $600,000/year
- 2017: FVIII mimetic bispecific antibody ~$500,000/year

The Numbers: Global Distribution of FVIII Use







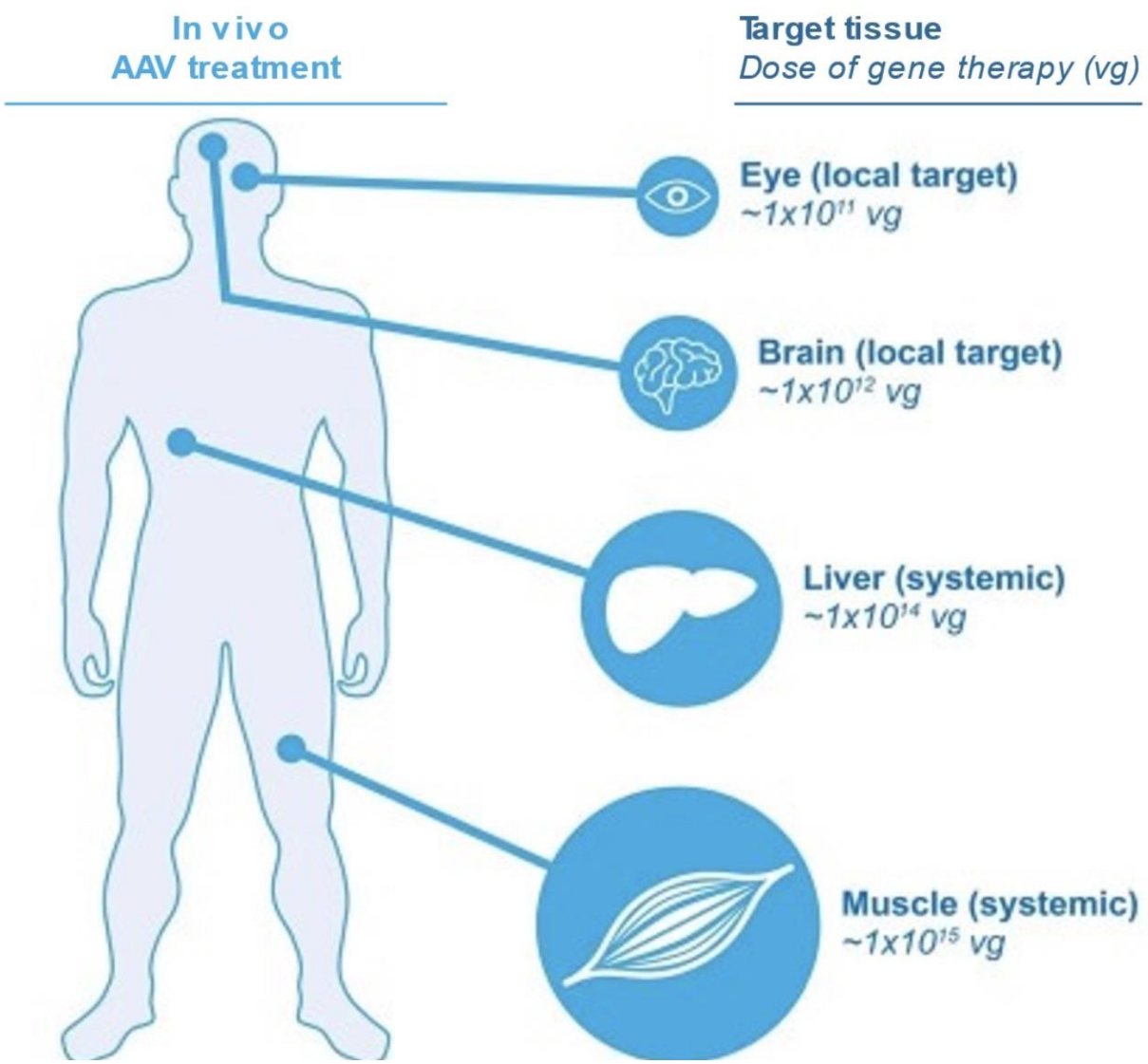


Equity in health care means equal utilization, distribution **according to need**, equal access, equal health outcomes

Pierce/ASH 2021

World Federation of Hemophilia Annual Global Survey 2019, https://www.wfh.org/en/our-work-research-data/annual-global-survey

Cost of Manufacture vs Charge for Gene Therapy



# of Doses and Manufacturing Cost of Goods (COGs)
Based on process modelling

$0.4M/eye

0.005L batch for 1 dose
$ 500/dose (HEK, Sf9 and Producer Cell Line)

0.05L batch for 1 dose
$ 5,000/dose (HEK)
$ 1,000/dose (Sf9 and Producer Cell Line)

$2.5M?

5L batch for 1 dose
$ 30,000/dose (HEK)
$ 7,000/dose (Sf9 and Producer Cell Line)

Scree

$2.2M

50L batch for 1 dose
$ 300,000/dose (HEK)
$ 50,000/dose (Sf9 and Producer Cell Line)

Image adapted from Realizing the Promise of Gene Therapy Through Collaboration and Partnering: Pfizer's View, Scientific American January 2019

Pierce/ASH 2021

Genotype-phenotype relationship among 1200 unrelated white patients with inherited FVII deficiency

Susan Halimeh[1], Gili Kenet[2], Lydia Koch[3], Piotr Kuta[3], Maria Shneyder[3], Tido Bajorat[3], & Ulrike Nowak-Göttl[3]

[Duisburg1 (G), Tel-Hashomer2 (IS), Kiel and Lübeck3 (G)]

FVII deficiency has high variability between genotype and phenotype

Genotype-phenotype relationship…

Symptomatic phenotype is influenced by

Factor of interest*	Odds Ratio	95% CI
Age at first onset	**1.01**	**1.007 - 1.025**
Female vs. male gender	**3.25**	**2.35 - 4.50**
Blood group 0 vs. non-0	**1.6**	**1.1 - 2.2**
Presence vs. absence of further bleeding diseases	**1.9**	**1.3 – 2.8**

*mild deficiencies related to FII, FV, von Willebrand disease, fibrinogen, FXIII

no significant influence (removed from regression model):
factor 5 1691 G>A; Prothrombin G20210A G>A, Prothrombin 19911 A>G, AT-, PC-, PS-deficiency

A Novel Methodology for Building Longitudinal, Patient-Centric Real-World Datasets in Hemophilia A

A Pilot Study in the Mild and Moderate Population

Mark W. Skinner,[1,2] Gillian Hanson,[3] Tao Xu,[4] Richard O
Emily Cibelli,[3] Francis Nissen,[4] Michelle Witkop,[7] Fabiar

[1]McMaster University, Hamilton, ON, Canada; [2]Institute for Policy Advancement Ltd, W
Francisco, CA, USA; [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [5]Roche Products
South San Francisco, CA, USA; [7]National Hemophilia Foundation, NY, USA; [8]Indiana
IN, USA

There are limited real-world data on people with mild or moderate hemophilia A

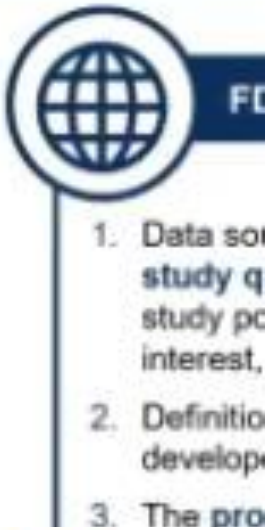
People with mild and moderate HA account for 40–52% of all PwHA, including nearly all women with HA, and this population is under-represented in scientific literature[1,2,3]

Available claims data from payer databases are confined to billing codes, and lack crucial data on outcomes and disease characterization (e.g., severity, treatment response)[4]

Registry datasets can require resource-intensive data entry and potentially miss key information about care received at outside facilities, at home, or after patients switch providers[5]

A patient-centered approach to fill this gap

- The aim of this study was to create a **longitudinal healthcare database** using a **novel, patient-centered approach** to collect RWD from individuals with mild and moderate HA in the United States
  - This online record management platform integrates **medical record data** collected during routine clinical care with **PROs**
  - Data are traced back to original notes from clinicians, fulfilling an important requirement highlight FDA's new draft **guidelines on RWD**[1]



Conclusions

The patient-centric data collection methods implemented in this study provide a novel approach to build longitudinal real-world datasets, with benefits for patients and physicians

Technology-enabled data abstraction showed consistent high quality; direct engagement with patients complements potential gaps in the clinical record

This approach provides needed data on groups under-represented in RWD and traditional PwHA cohorts, including those with mild and moderate disease and women with HA

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Efficacy of rFVIIIFc for First-Time Immune Tolerance Induction (ITI) Therapy: Final Results From the Glo

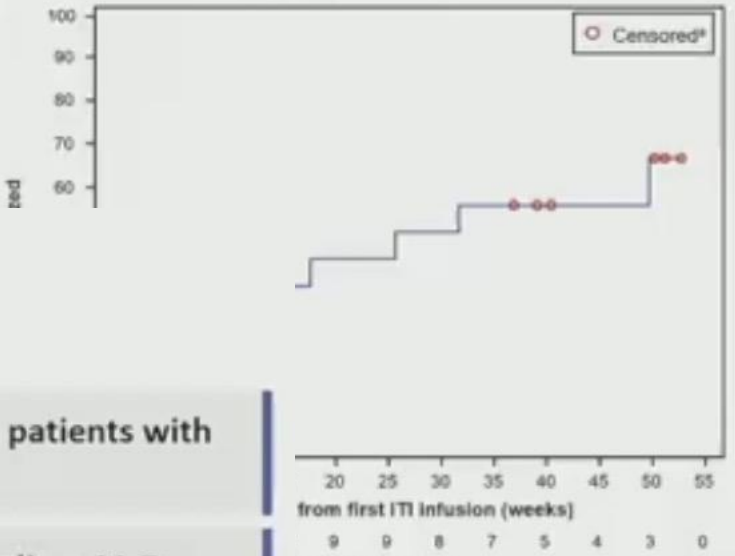
Lynn Malec,[1] An Van Damme,[2] Anthony Chan,[1] Jennifer Dumont,[3] Stefan Lethag

[1]Versiti Blood Research Institute, WI, USA. [2]Cliniques Universitaires Saint-Luc, B Bulgaria. [3]Sanofi, Cambridge, MA, USA. [4]Sobi, Stockholm, Sweden. [5]Hospital for Transplantation, University of Milan. [6]Angelo Bianchi Bonomi Hemophilia and Thr

*At the time of the study

63rd American Society of Hematology (ASH)

Rapid Tolerization Was Achieved in the Majority of First-Time ITI Subjects With rFVIIIFc ITI



The Kaplan–Meier estimate of the ITI success rate was 67%

Summary and Conclusion

- rFVIIIFc is the first EHL FVIII with prospective data for first-time ITI in patients with severe hemophilia A with high-titer inhibitors
- rFVIIIFc was well tolerated and offered rapid time to tolerization (median: 11.7 weeks [2.7 months]) with ITI success and no relapse in almost two-thirds of subjects
- Optimizing ITI to eradicate inhibitors remains a priority

THANK YOU

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Dental considerations for PWBD

Lochana Nanayakkara

Consultant In Restorative Dentistry, Royal London Dental Hospital

Dental Lead, North London Adult Haemophilia Network

Chair, Dental Committee, World Federation of Haemophilia

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Objectives:

- To understand the importance of oral health in PWBD
- To understand how oral health impacts the quality of life of PWBD
- To discuss how the haemophilia comprehensive care team can facilitate access to primary dental care.

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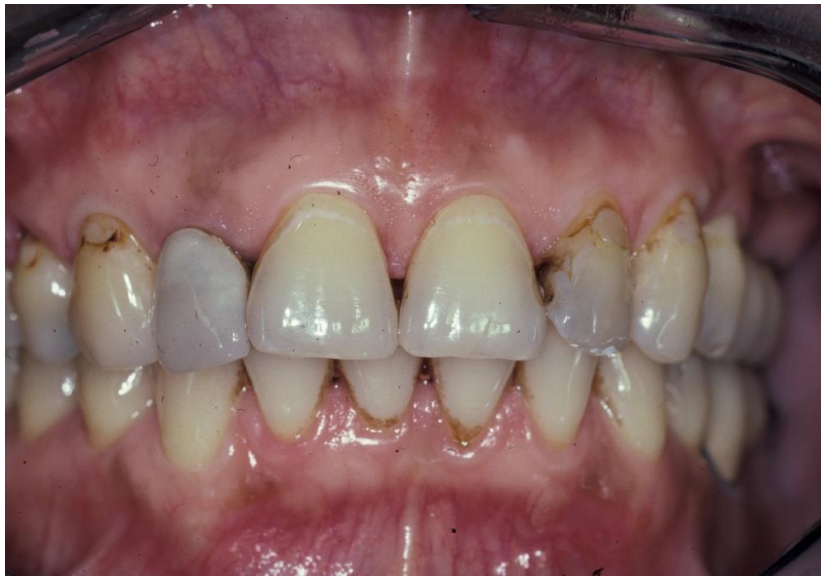
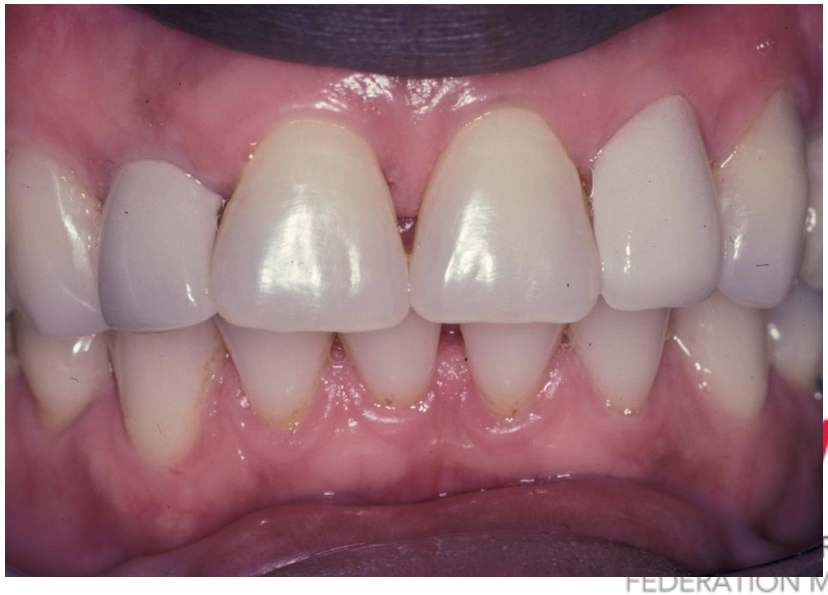
Restorative dentistry

"Our aim must be not merely the meticulous restoration of that which is missing, but also the perpetual preservation of that which remains."
M.M.DeVan





Current Guidelines

- Allows most dental treatments to be carried out safely whilst minimising the use of factor concentrates
- Majority of patients can be safely treated in general practice for routine dentistry
- Only severe cases of haemophilia (<1 IU/dl) and those with inhibitors should be routinely referred to the Dental Hospital, unless on prophylaxis
- All EXTRACTIONS should be referred to the Dental Hospital
- Factor replacement therapy is ONLY required for dental surgery extractions, Inferior Dental Alveolar blocks, injections, lingual infiltration and when prolonged bleeding is expected

Brewer A & Correa MA, Guidelines for dental treatment of patients with inherited bleeding disorders, Montreal:World Federation of Haemophilia 2006 (revised 2013)

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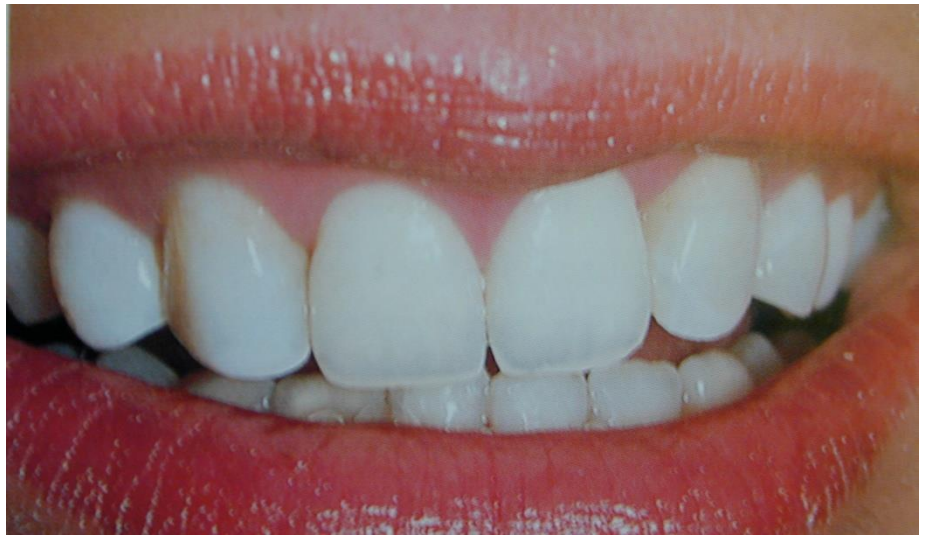
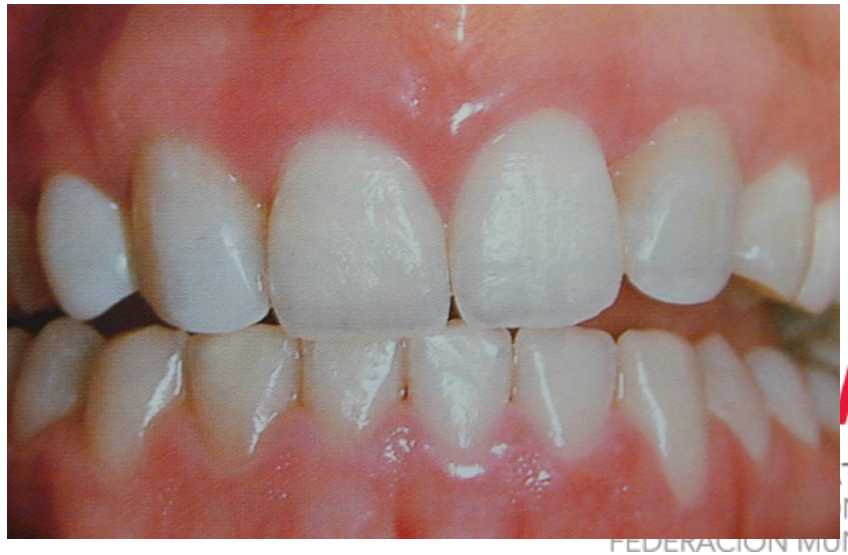
Current Guidelines – **Prevention** is a PRIORITY

- Prevention = Preservation of a healthy dentition and periodontium
- Prevention = Less need for invasive dental treatment
- Prevention = Less need for factor replacement therapy
- Prevention = Less complications for patients with inhibitors
- Prevention = Decreased costs for Haemophilia Centres





- Periodontal Disease is the most common chronic inflammatory condition in humans[1]

- It affects 50% of the world's adult populations[1, 2]

- 83% of the British population present with some level of periodontal inflammation[3]

1. Chapple I.L.C., Genco R., et al., (2013) Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. Journal of Clinical Periodontology. 40 (Supplement 14); 106–112.
2. Nazir, M.A. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int. J. Health Sci. 2017, 11, 72–80.
3. Fuller E, Steele J, Watt R, Nuttall N. (2011) 1: Oral Health and function – a report from the Adult Dental Health Survey. The Health and Social Care information centre.

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- A cohort study by Fiske et al showed that a high proportion of IBD patients have periodontal disease (49 out of 50 patients)

*Fiske J, McGeoch R, Savidge G, Smith M. The treatment needs of adults with inherited bleeding disorders. Journal of Disability and Oral Health 2002; **3**: 59-61.*

- Patients with mild vWD are NOT more susceptible to Periodontitis
- They do not have a more pronounced inflammatory response to oral biofilm

Mester et al. The presence of periodontitis in patients with von Willebrand Disease: A systematic review. Appl. Sci. July 2021, 11, 6408.

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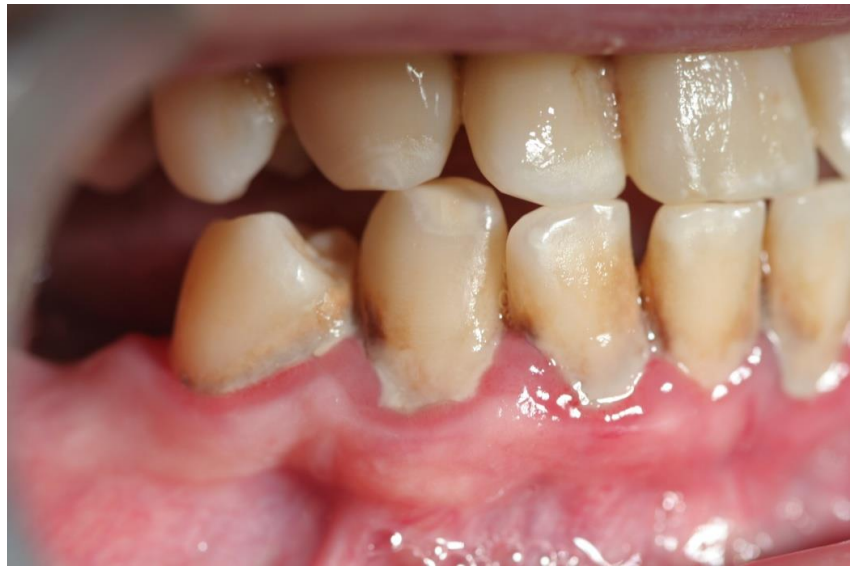
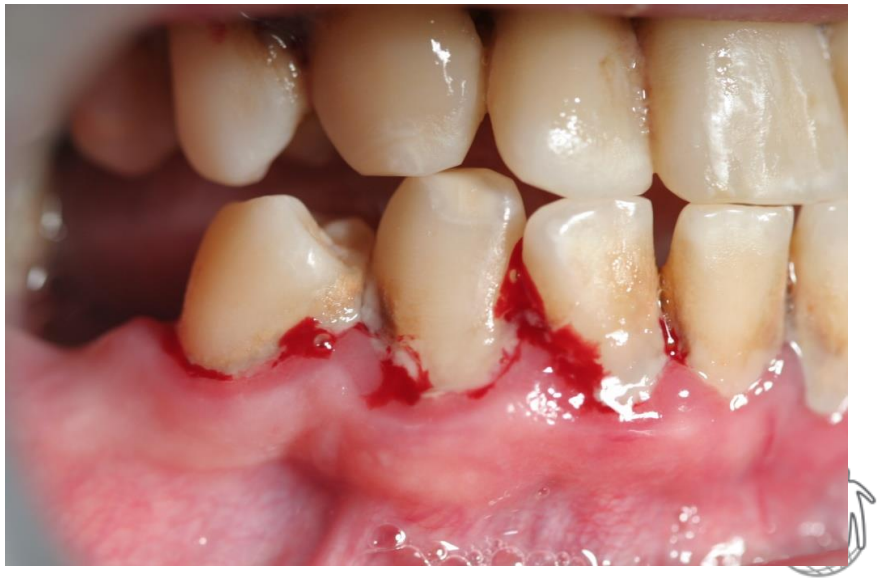
Periodontal disease

- Most common symptom is bleeding on tooth brushing
- In PWBD, prolonged bleeding can be encountered
- Tranexamic Acid Mouthwash is helpful





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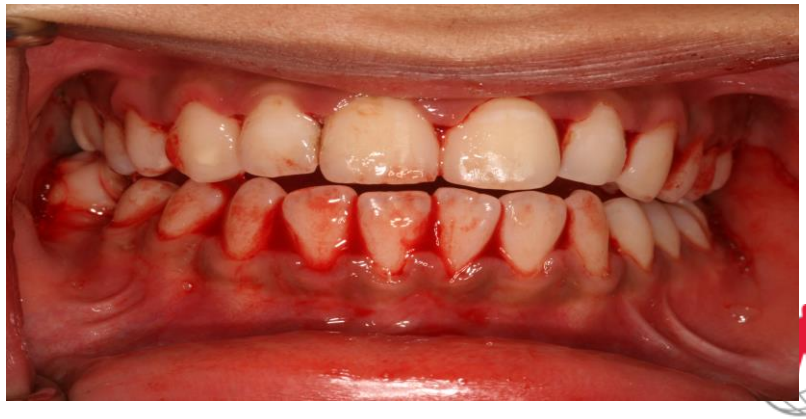
Challenges for the dentist

- Prevention and management of periodontal disease is focused on:
  - improving oral hygiene practices
  - root surface debridement
- Both processes can **cause** gingival bleeding



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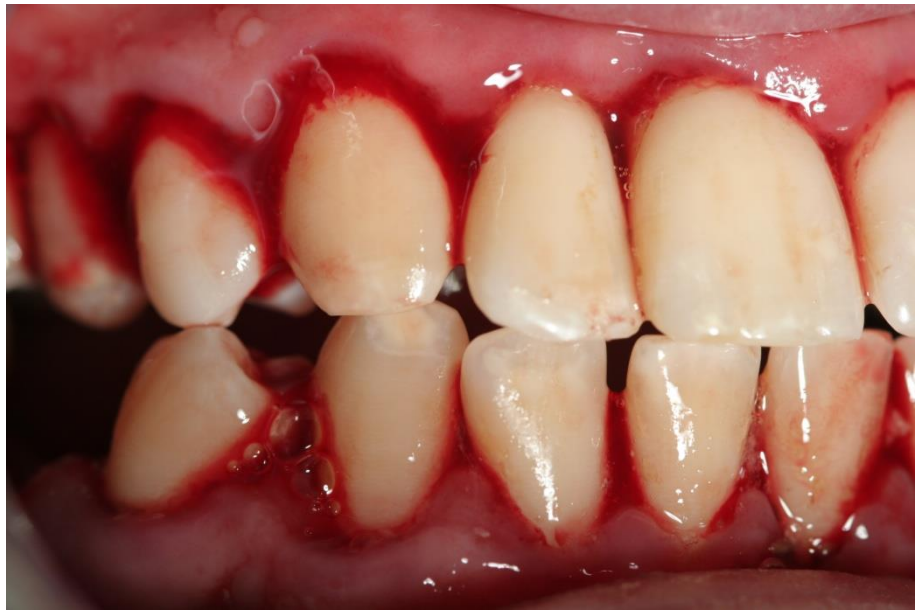
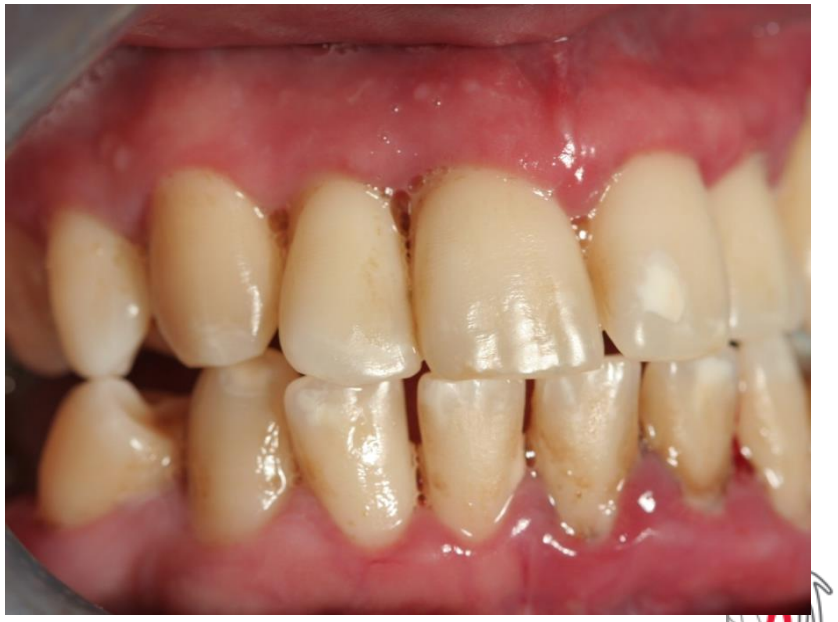
Periodontal disease

- Hygiene therapy with improved home care and regular maintenance with General dental practitioner / hygienist will stabilise disease



Hygiene visit



One week later

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PREVENTION…….

Healthy Gums Don't Bleed!

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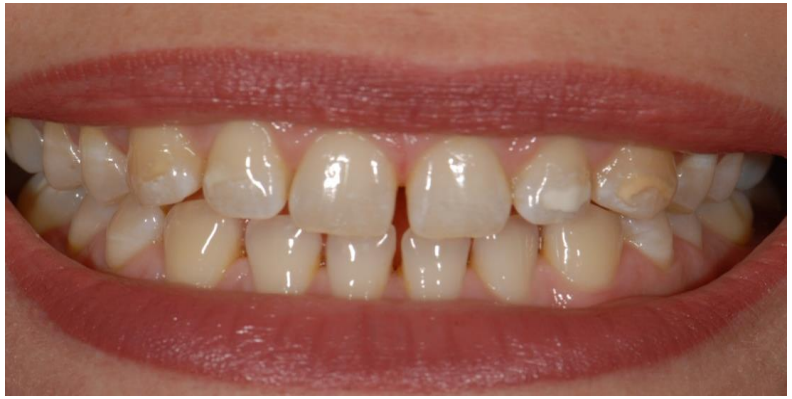
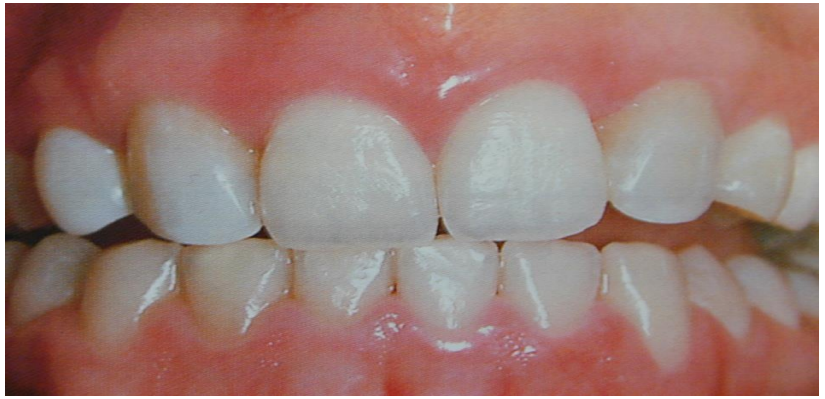
Good oral health is associated with *improved quality of life* in patients with inherited bleeding disorders





*Alpkilic Baskirt E, Ak G, Zulfikar B. Oral and general health-related quality of life among young patients with haemophilia. Haemophilia : the official journal of the World Federation of Hemophilia 2009; **15**: 193-198.*

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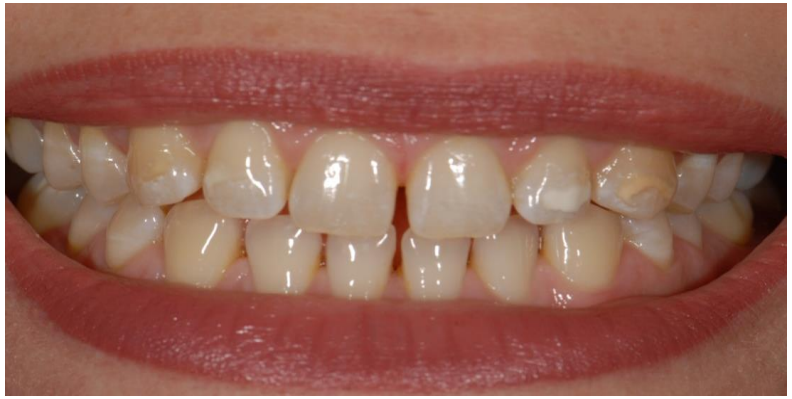
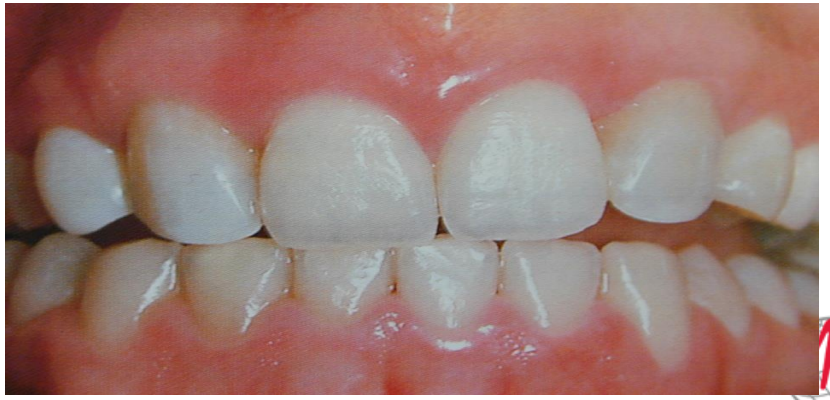
Quality of Life

- Absence of pain
- Altered taste
- Confidence to smile and function in social situations
- Halitosis related with oral bleeding
- Intimacy issues for women and men
- Association with systemic disease





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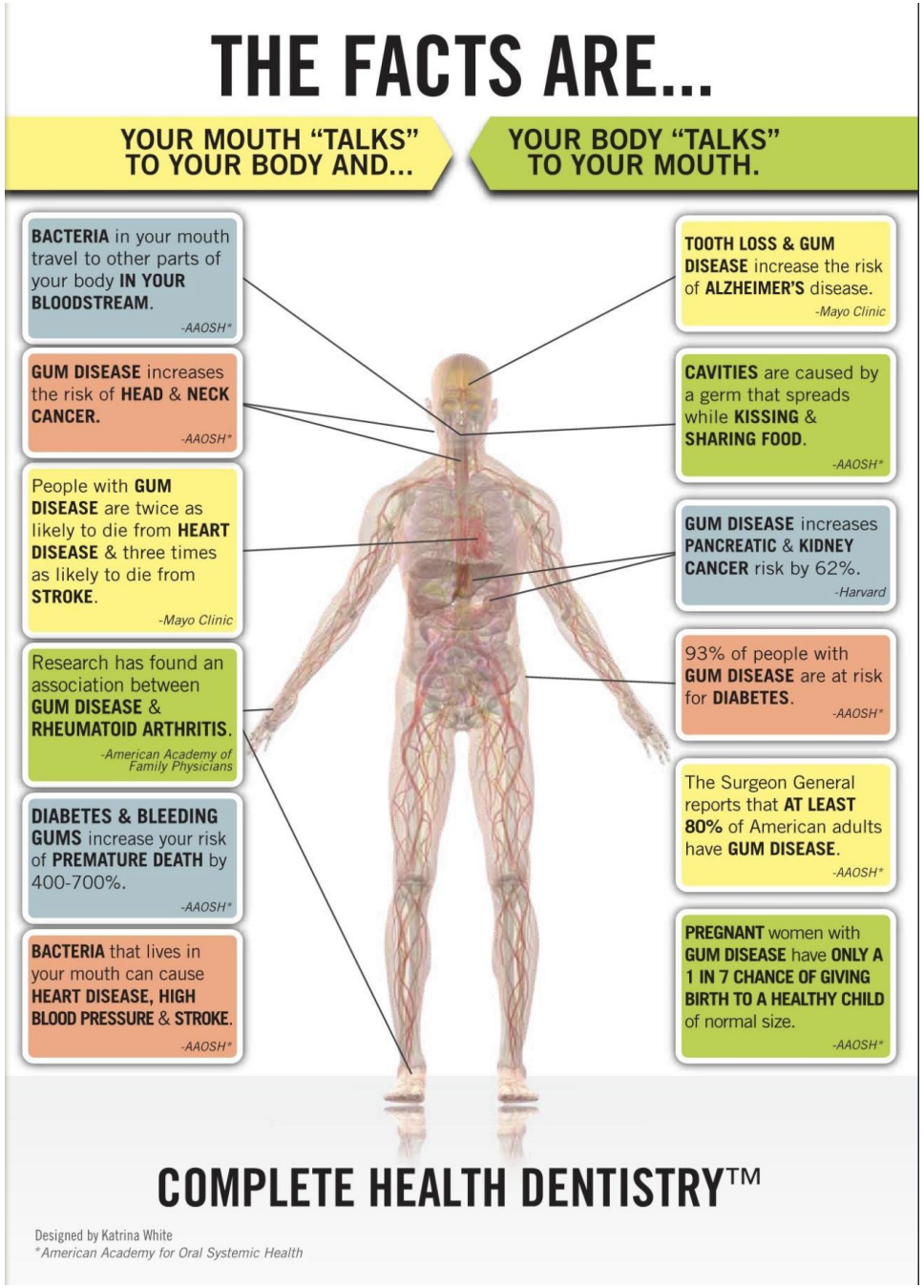
Head and Neck Cancer

Heart Disease

Stroke

Diabetes



Alzheimers Disease

Premature low birth weight babies

Rheumatoid Arthritis

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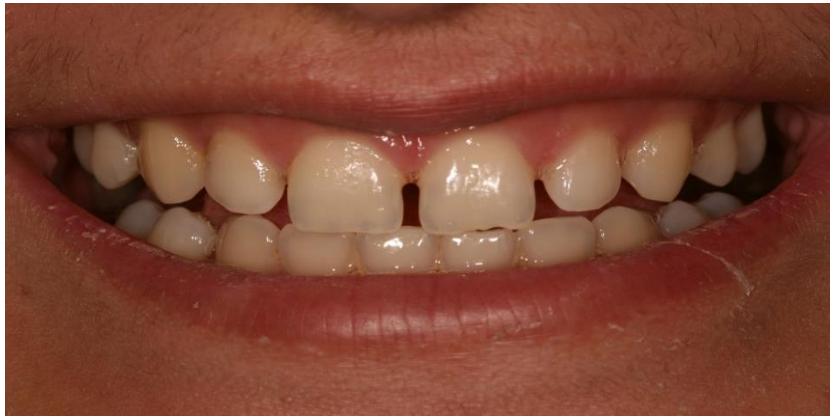
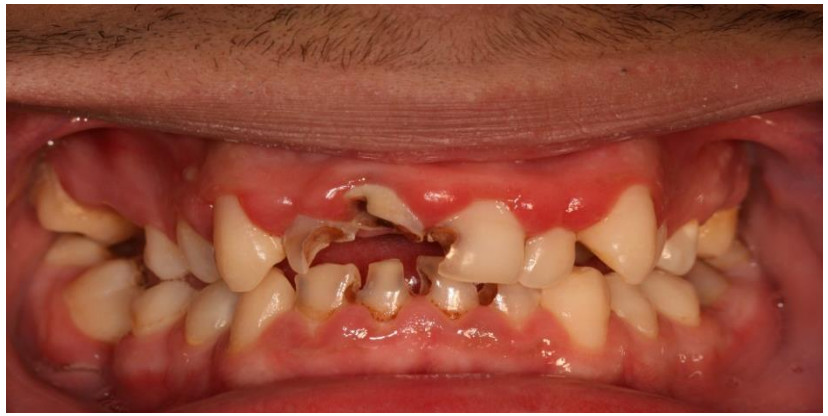
Prevention = A DENTAL ***HOME*** FOR ALL PATIENTS





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PATIENT and GDP SURVEY

- **Patient Survey** was completed online or in Haemophilia outpatient clinics at Royal London Hospital
- A total of 105 anonymous surveys collected over a 5-month period in 2010
- The **GDP Surveys** were posted to GDPs from local PCTs (Tower Hamlets, City & Hackney and Newham)
- Total 122 surveys were posted with 53 being returned (response rate 43%)

Haemophilia

Haemophilia (2012), **18**, 510–515 DOI: 10.1111/j.1365-2516.2011.02716.x

ORIGINAL ARTICLE *Clinical haemophilia*

Access to primary dental care for patients with inherited bleeding disorders

H. KALSI,* L. NANAYAKKARA,* K. J. PASI,† L. BOWLES† and D. P. HART†

*Royal London Dental Hospital, New Road, London, UK; and †Haemophilia Comprehensive Care Centre, Royal London Hospital, Barts and The London School of Medicine & Dentistry, Queen Mary University London & Barts and The London NHS Trust, London, UK

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The barriers to accessing dental care:

Disease specific barriers:

- 21 of 105 patients (20%) had been refused dental treatment by a local dentist due to their bleeding disorder

Patient Specific Barriers:

- 18 of 105 patients (17%) felt apprehensive about visiting their local dentist due to previous bad experiences
- 47 of 105 patients (45%) did not feel confident in their GDP's ability to look after them taking into account their bleeding tendency

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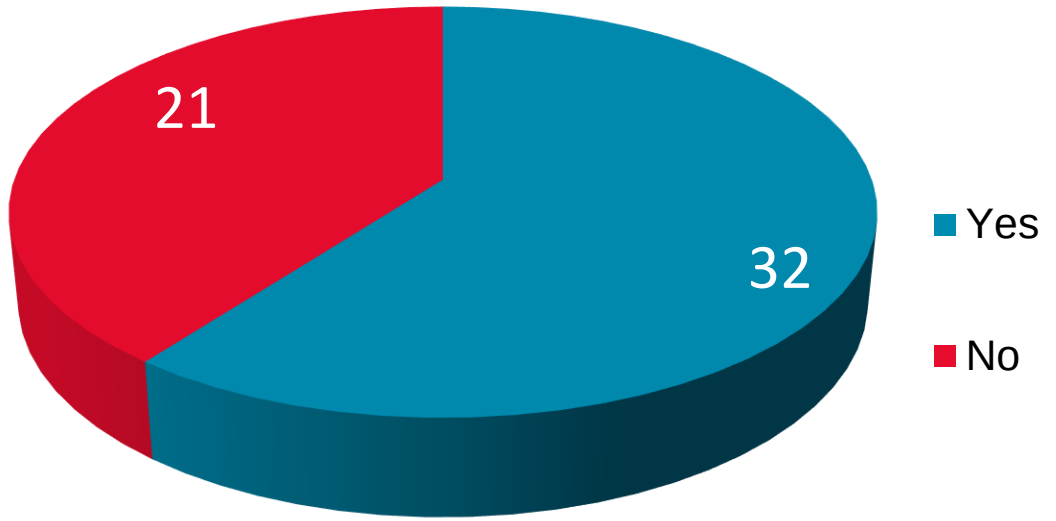
Do you feel confident in knowing how to manage a patient who has an inherited bleeding disorder?



- 21 of 53 GDPs (40%) surveyed did not feel confident in treating IBD patients in general dental practice

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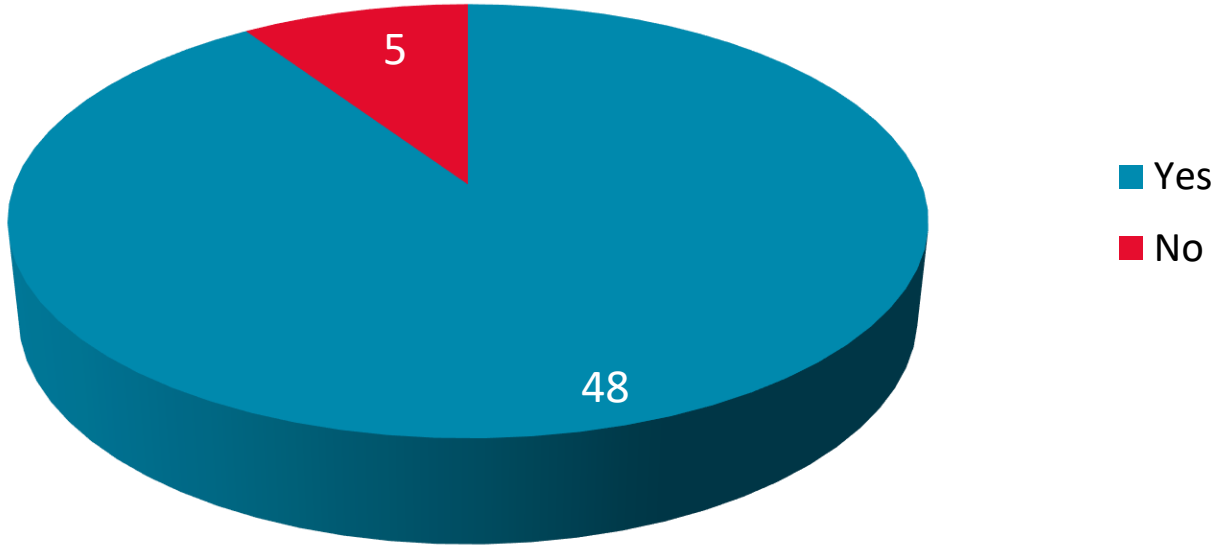
If a patient attended your practice with a co-authored letter from the haemophilia and dental teams outlining procedures that they felt could be treated safely in general practice, would you feel reassured and more likely to care for the patient in the long term?



- 48 of 53 GDPs (90%) would feel more reassured with a letter with specific details and advice

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Communication - Key to Success

Barts Health NHS
NHS Trust

Date:

Our Ref:

Dear Dental Colleague,

Re: **Primary dental care for patients with inherited bleeding disorders.**

Thank you for registering this patient for primary dental care. Although he/she suffers with an inherited bleeding disorder _____, routine check ups, hygiene treatment, and routine restorative work NOT requiring an inferior dental nerve block or lingual infiltration will be safe to perform at your Practice. We are fully supportive of trying to deliver primary care for our patients as locally as possible. Any concerns/questions should be referred to the haemophilia centre email address (above) for a reply within 48 hours.

Any interventional procedures requiring an inferior dental nerve block injection or lingual infiltration should be referred to Dr Lochana Nanayakkara, Consultant in Restorative Dentistry, at address XXXXXX or faxed directly on 020 XXX XXX.

Any dental extractions which are required should be addressed to Dr Judith Jones, Consultant in Oral Surgery at the above address or fax number.

The Royal London Hospital provides an emergency out of hour's service for acute dental problems. Patients with inherited bleeding disorders needing to access this service should also contact the Royal London Hospital Haemophilia Registrar via switch board (020 XXX XXX) to ensure appropriate factor replacement follow up.

Yours faithfully,

Dr Dan Hart
Consultant Haematologist
Senior Lecturer in Haematology

Yours faithfully,

Dr Lochana Nanayakkara
Consultant in Restorative Dentistry
Dental Hospital

- Empower people with bleeding disorders to seek primary dental care …… regularly
- Dentists – Educate/De-mystify
- Haemophilia Team – Engage in Oral health PROMOTION
- Routinely ask patients about their oral health and if they experience bleeding on brushing

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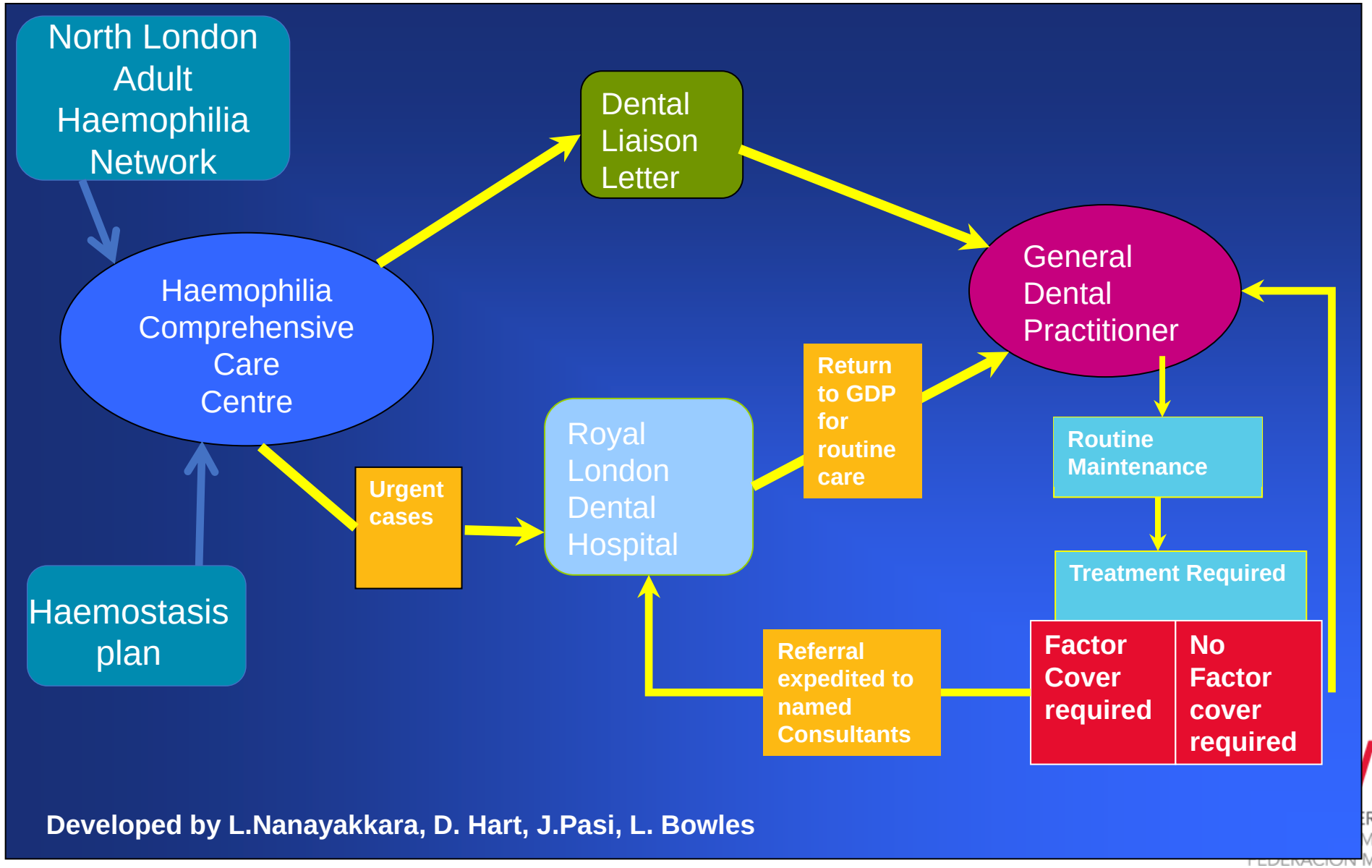
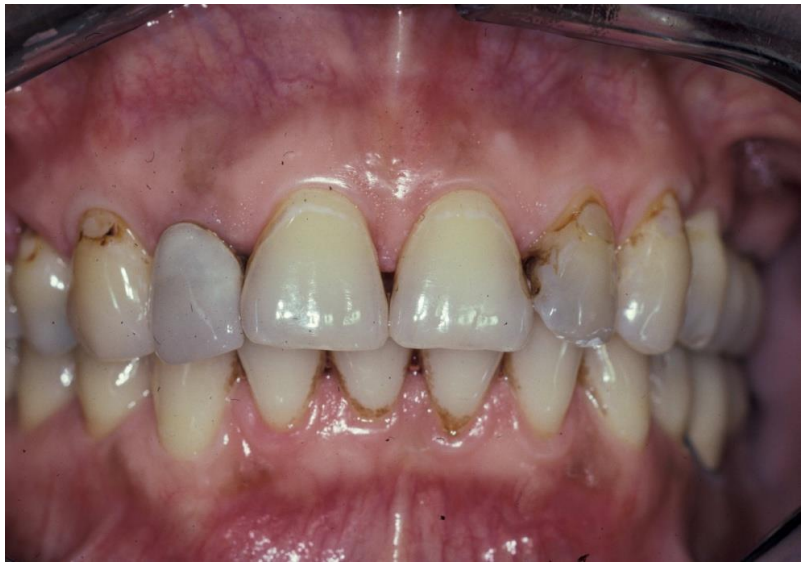
Shared Care Approach

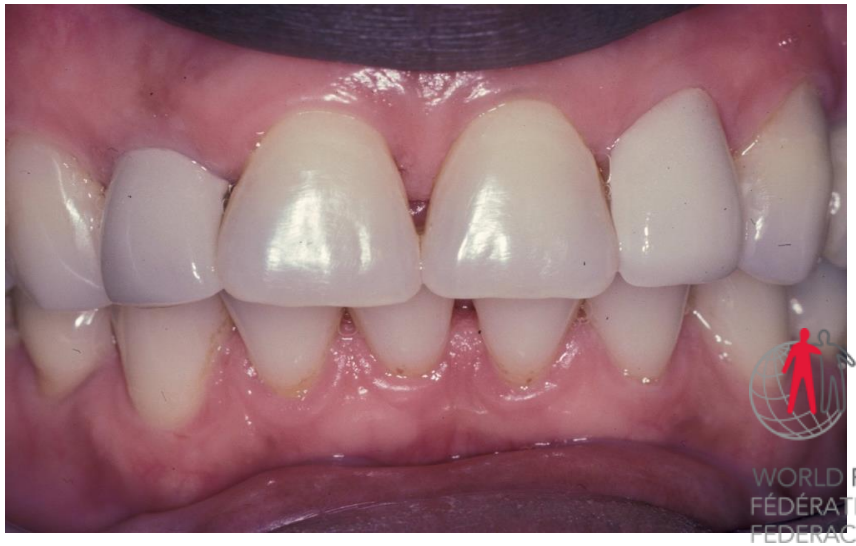


Reinforce Dental Prevention in Haematology clinics with simple advice



Dental caries occurs when oral bacteria ferment sugar to produce acid which destroys tooth tissue

Dental caries is prevented by decreasing the frequency of eating sugary foods



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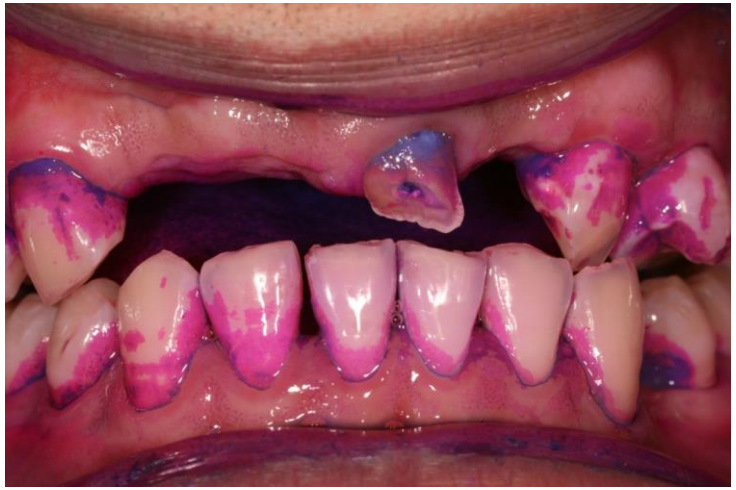
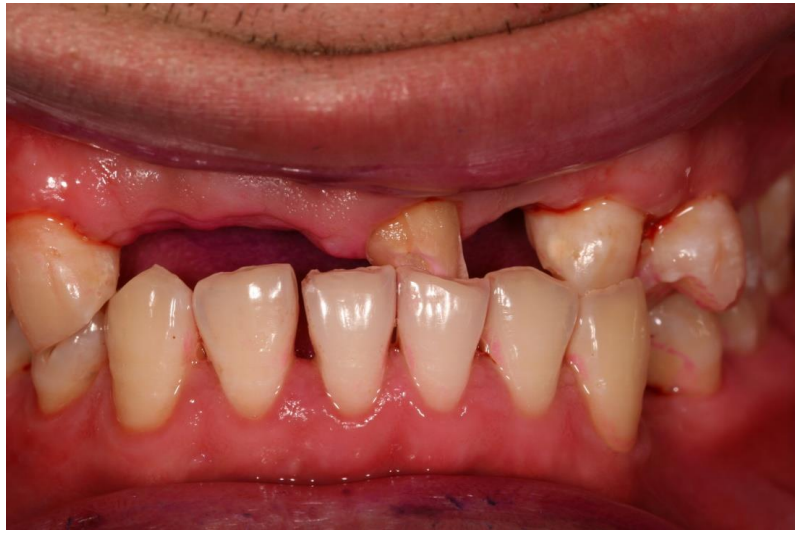
Reinforce Dental Prevention in Haematology clinics with simple advice



Gingival inflammation is caused by dental plaque, a biofilm that coats the surface of teeth and is linked to genetic, environmental and host risk factors

Gingival inflammation is prevented by effective plaque control



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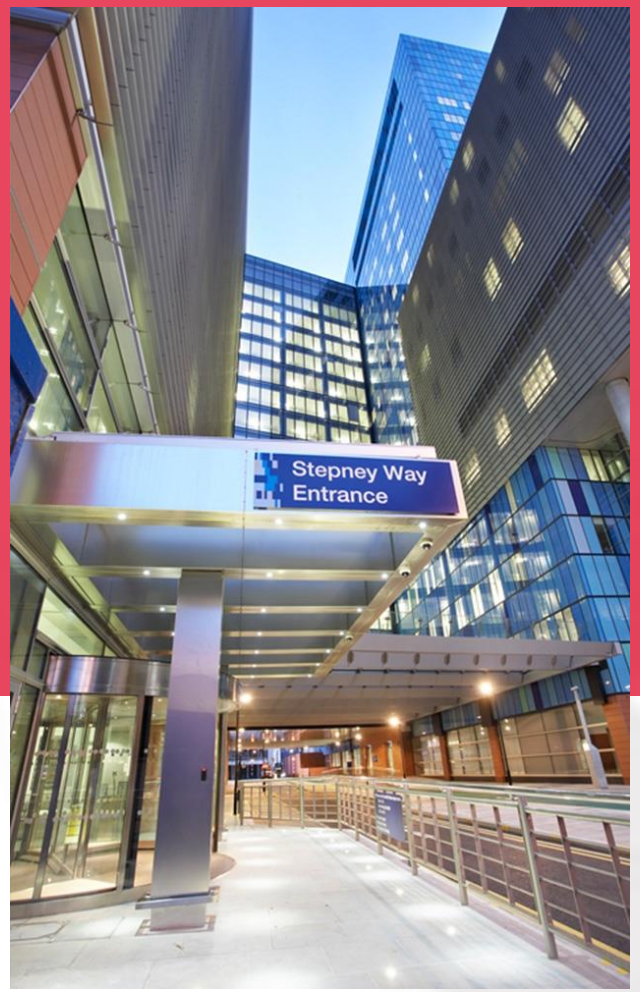
Fluoride reduces dentine sensitivity.

Fluoride makes dental enamel more insoluble to acids produced by the fermentation of sugar by bacteria which causes dental decay

Chlorhexidene Gluconate resists the adherence of bacterial plaque to the tooth surface.

It is used as a short-term adjunct to oral hygiene practices



THANK YOU

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Post Hepatitis C Care: How to Monitor Liver Health

Bruce A. Luxon, M.D., Ph.D.
Anton and Margaret Fuisz Chair in Medicine
Professor and Chairman
Department of Medicine
Georgetown University

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Speaker bureau	No conflicts of interest to disclose
Employee	No conflicts of interest to disclose
Shareholder	No conflicts of interest to disclose

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Plan for Today

- Basic facts on treating hepatitis C
  - What are treatment options?
  - What are the success rates?

} Shortened version

- What happens after an HCV “CURE”?
  - How do I assess liver health?
  - What are the complications from HCV infection?
  - How do I know if a patient is at risk of these complications?

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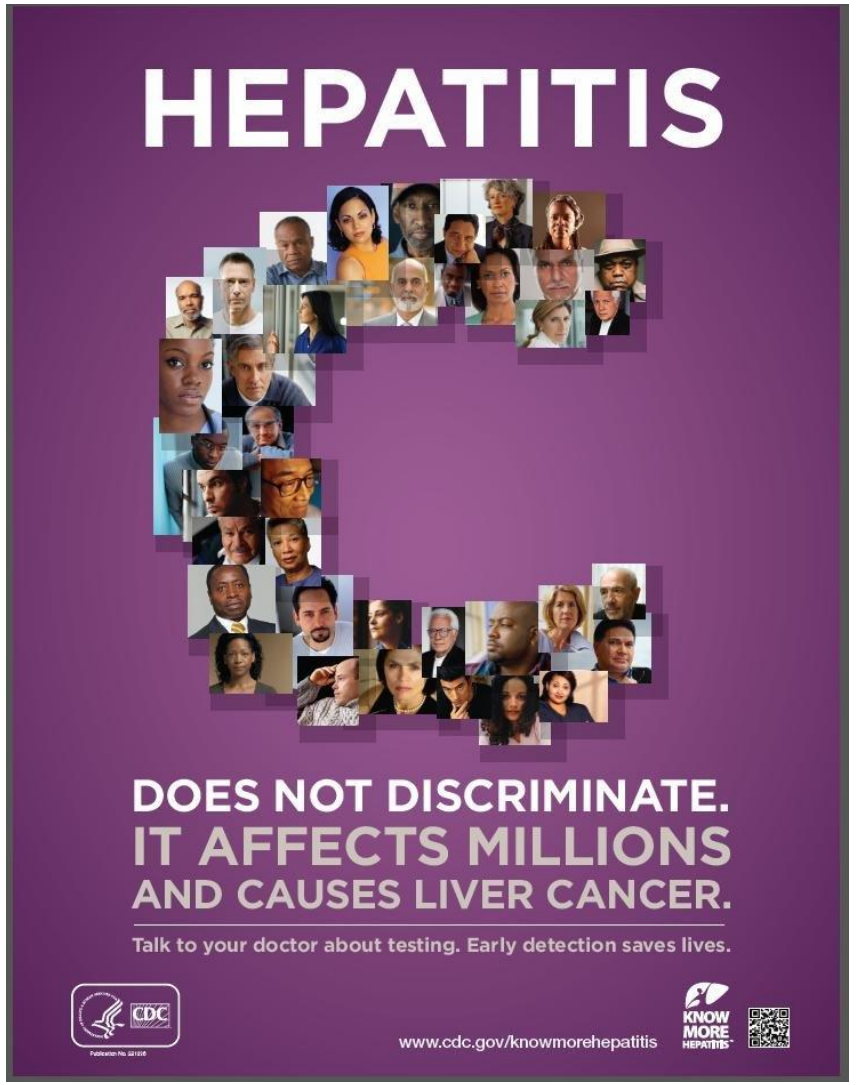
“A Silent Epidemic”

Previously number 1 cause of underlying liver disease requiring transplant

Leading cause of liver cancer



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Poster from: CDC Foundation. www.cdcfoundation.org/FY2011/Protecting-People-Liver-Disease (Accessed September 2021)

1. Dennis BB, et al. *World J Gastro* 2021;27:4818-30; 2. CDC, Hepatitis C. www.cdc.gov/dotw/hepatitisc/index.html (Accessed September 2021).

Typical Patient

- Mr. Jones is a 56 yo man with hemophilia who got human derived factor when he was a teenager.
- He developed hepatitis C and was treated in the early 2000's with interferon but was not cured.
- He was monitored with annual ultrasounds that eventually showed a cirrhotic appearing liver.
- He received a direct acting antiviral (DAA) and was cured of his hepatitis C in 2018.

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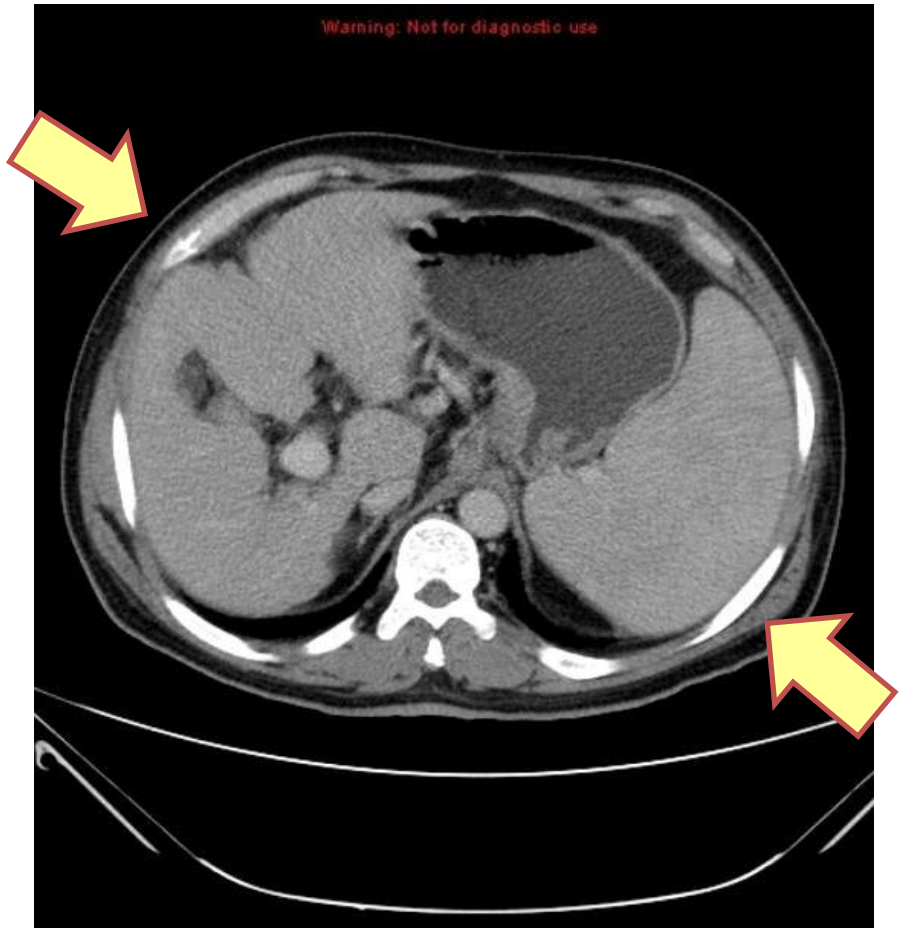
What do you tell this patient?

- His hepatitis C is cured
- ***But his liver disease is not***
- What are complications of his liver disease?
- How do you monitor him for complications?
- Will his liver improve?
- How long until his risk of complications is lowered?



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Typical Patient

- CT scan shows nodular liver consistent with cirrhosis
- Blood tests (specialized) show “high probability of advanced fibrosis”
- Platelets are 100K; AST is twice normal (APRI is 2.0)
- APRI predicts 91% chance of cirrhosis

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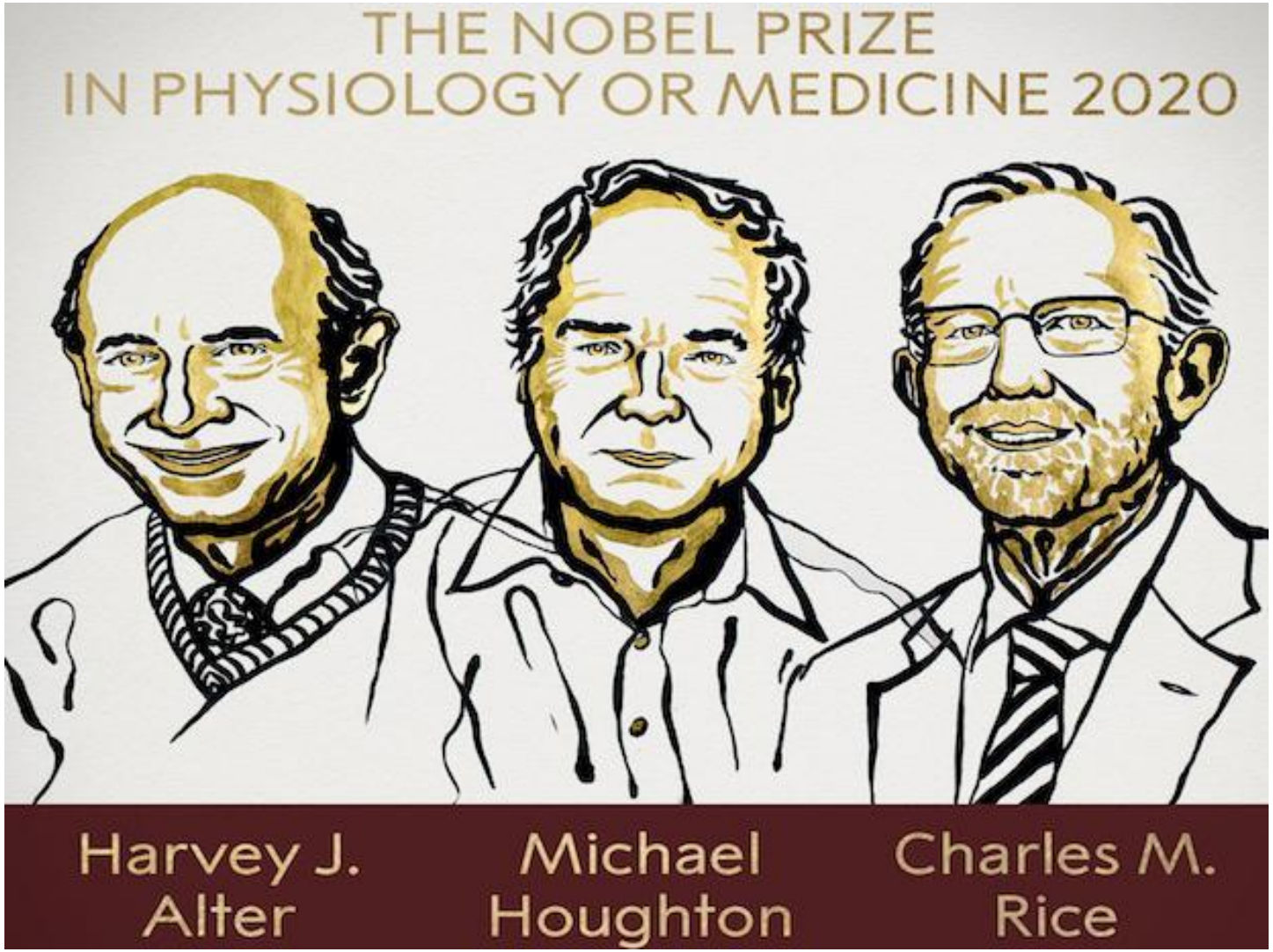
Brilliant science led to HCV cure



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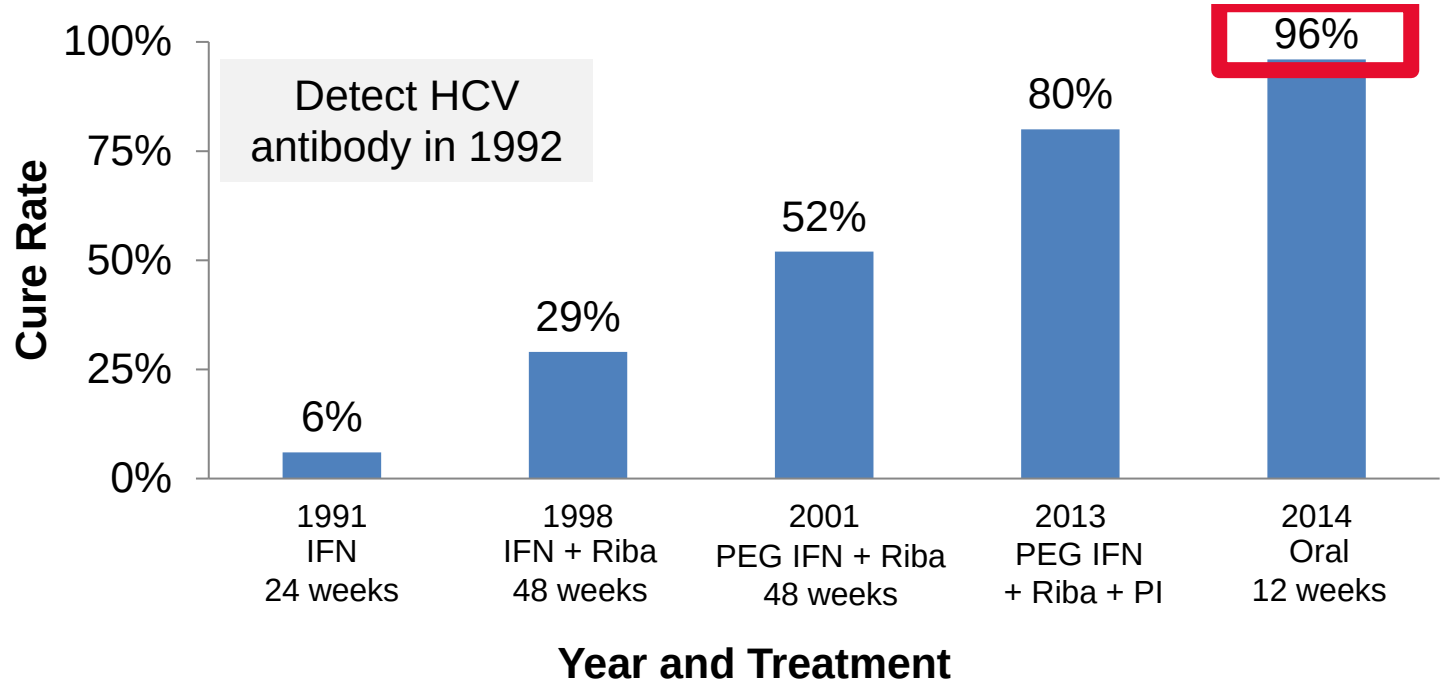
Progress in Curing Hepatitis C



HCV: Hepatitis C; IFN: Interferon; PI: Protease inhibitor; Riba: Recombinant immunoblot assay; PEG: Polyethylene glycol.

Jaekel E, et al. *N Engl J Med* 2001;345:1452–7; Rebetron Product Information, Schering Corporation; Olysio Prescribing Information, Janssen, 2013; Twenty-Five Years of Progress Against Hepatitis C: http://phrma-docs.phrma.org/sites/default/files/pdf/Hep-C-Report-2014-Stepping-Stones.pdf (Accessed September 2021).

What Are the Success Rates?*

- **Genotype 1a**: 92–100%
- **Genotype 1b**: 95–100%
- **Genotype 2**: 96–100%
- **Genotype 3**: 89–99%
- **Genotype 4**: 94–100%
- **Genotype 5**: 95–100%
- **Genotype 6**: 95–100%

Potentially cured but wide geographic variability of access to treatment

No evidence that PWH have different cure rates than listed

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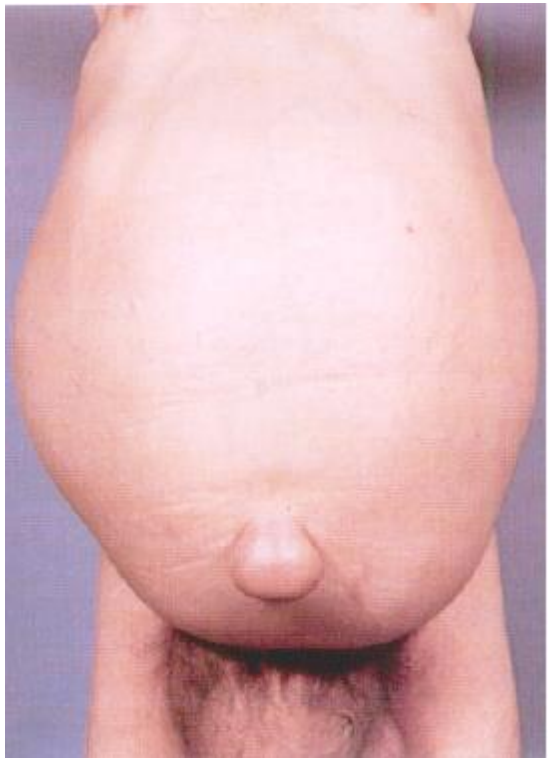
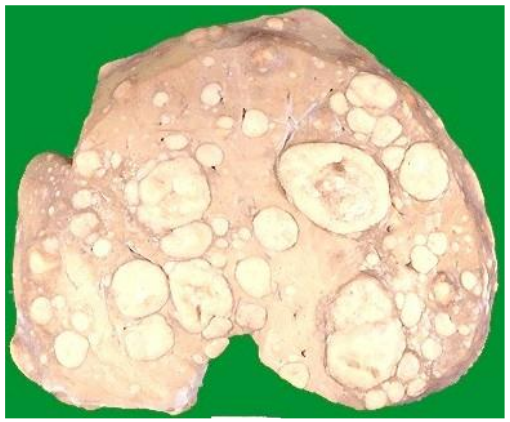
*For patients without liver cirrhosis.
HCV guidelines: www.hcvguidelines.org/ (Accessed September 2021).

What Can Happen to Patients After Curing Their Hepatitis C?

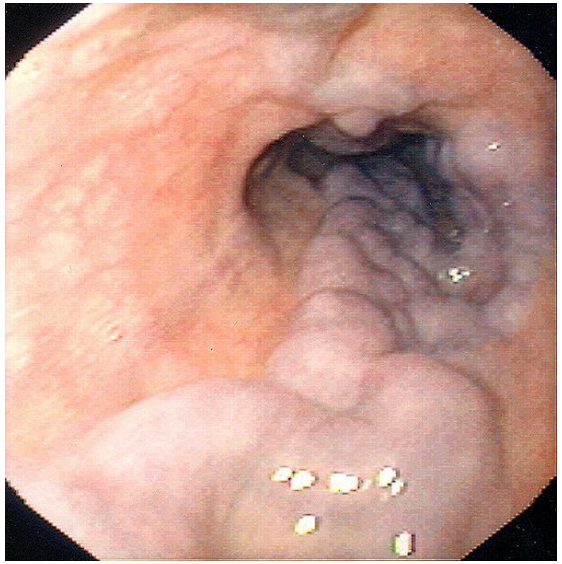


Ascites

Sometimes Nothing Happens



Liver cancer



Esophageal varices

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- Hepatitis C cirrhosis is like a trail along a cliff.

- Where you are on the trail makes all the difference to your risk.

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How to Quantify Liver Health

- Traditional serum tests are notoriously insensitive to quantify liver health
- Liver biopsy was initially the “gold standard” to assess fibrosis, the replacement of liver parenchyma by scar tissue
- Many non-invasive techniques are now available to assess fibrosis
  - Innovative combinations of standard tests (e.g.; APRI)
  - Specialized proprietary tests (e.g.; Fibrosure™, Fibrotest™)
  - Elastography (ultrasound or MRI)

Complications Occur

METAVIR Fibrosis Scale

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Typical Patient

- Patient wants to know *“how his liver is doing”*
- Blood tests show AST now normal; platelets are 150K (APRI is 0.67)
- Still high likelihood of “advanced fibrosis”
- *“When will I get better?”*

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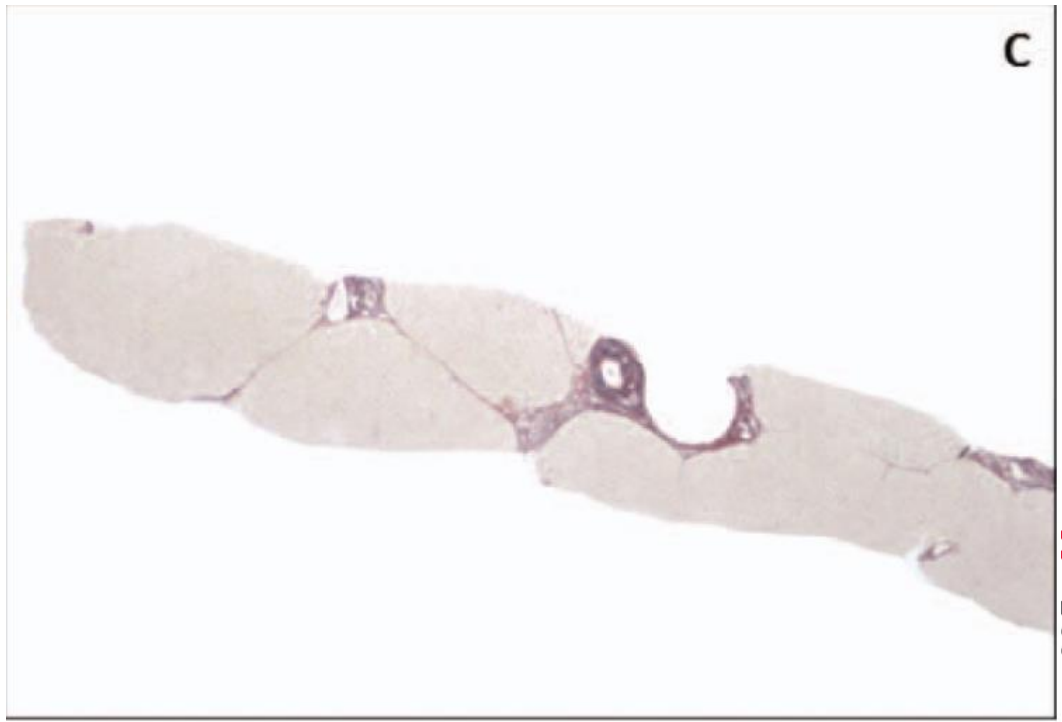
Pre treatment biopsy

Post treatment biopsy: SVR achieved four years previously



Hepatitis C

D'Ambrosio, Hepatology 2012

Hepatitis C - Fibrosis Reversal

OLD News

Poynard 2002

67% cirrhosis regression

Histological outcomes of sustained virological responders with regard to inflammation and fibrosis.

Reference	Number of patients	Time to biopsy	Therapy	Staging system	Biopsy length	Improved inflammation (%)	Maintained inflammation (%)	Progressive inflammation (%)	Fibrosis regression (%)	Fibrosis maintenance (%)	Fibrosis progression (%)	Cirrhosis regression (%)
Marcellin et al. (1997)	48	2.2 years (mean)	IFN	Knodell	10 mm	94	2	4				
Shiratori et al. (2000)	183	3.7 years	IFN	Metavir/ Desmet	>10 mm	89	10	1	59	40	1	na
Manns et al. (2001)	1034	24 months	PEG/ RBV, IFN/ RBV	Knodell	na	90	na	na	21–26	na	na	na
Poynard et al. (2002)	1094	20 months (mean)	IFN/ RBV, PEG, PEG/ RBV	Metavir	30 mm	86	12	2	25	68	7	67
Toccaceli et al. (2003)	87	29.5 months (median)	IFN	Knodell	na	87	10	2	33	64	3	na
Maylin et al. (2008)	126	6 months (median)	IFN, IFN/ RBV, PEG/ RBV	Metavir	15 mm	57	39	4	56	32	12	64
George et al. (2009)	49	62 months (mean)	IFN/ RBV, PEG/ RBV	Ishak	na	82	12	6	82	na	na	na
Balart et al. (2010)	195	24 weeks	PEG/ RBV	Ishak	10 mm or > 4 PT	na	na	na	48.20	37	14	53
Mallet et al. (2008)	35 (F4 cirrhosis at baseline)	17 months (median)	IFN, IFN/ RBV, PEG/ RBV	Metavir	15 mm	na	na	na		51	na (already F4 cirrhosis)	49
D'Ambrosio et al. (2012)	38 (F4 cirrhosis at baseline)	61 months (median)	IFN/ RBV, PEG/ RBV	Metavir	30 mm (median)	na	na	na		39	na (already F4 cirrhosis)	61
				Morphometry	10 mm or >12 PT	na	na	na		3	8	89
				Necroinflammation (0–3)	10 mm or >12 PT	84	16	0				
				Ishak (portal inflammation)	10 mm or >12 PT	34	66	0				
				Ishak (lobular/ interface inflammation)	10 mm or >12 PT	87/97	13/3	0				

Lee and Friedman, Antiviral Res. 2014 107:23-30.

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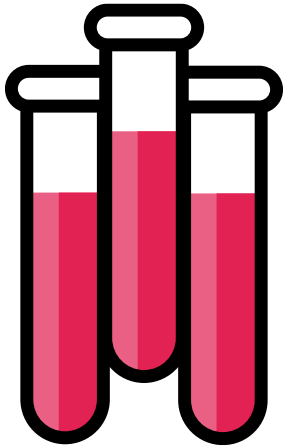
Specialized Lab tests

- These serum or plasma tests use commonly available lab values and patient variables (e.g.; age, gender)
- Lab values can be “standard” like platelets, AST, bilirubin or more unique “matrix turnover proteins”
- Lab values and variables combined into a “fibrosis score”
  - Need to be disease specific
  - Can predict probability of “advanced fibrosis” or likelihood of minimal fibrosis
  - Some tests correlate with Metavir fibrosis



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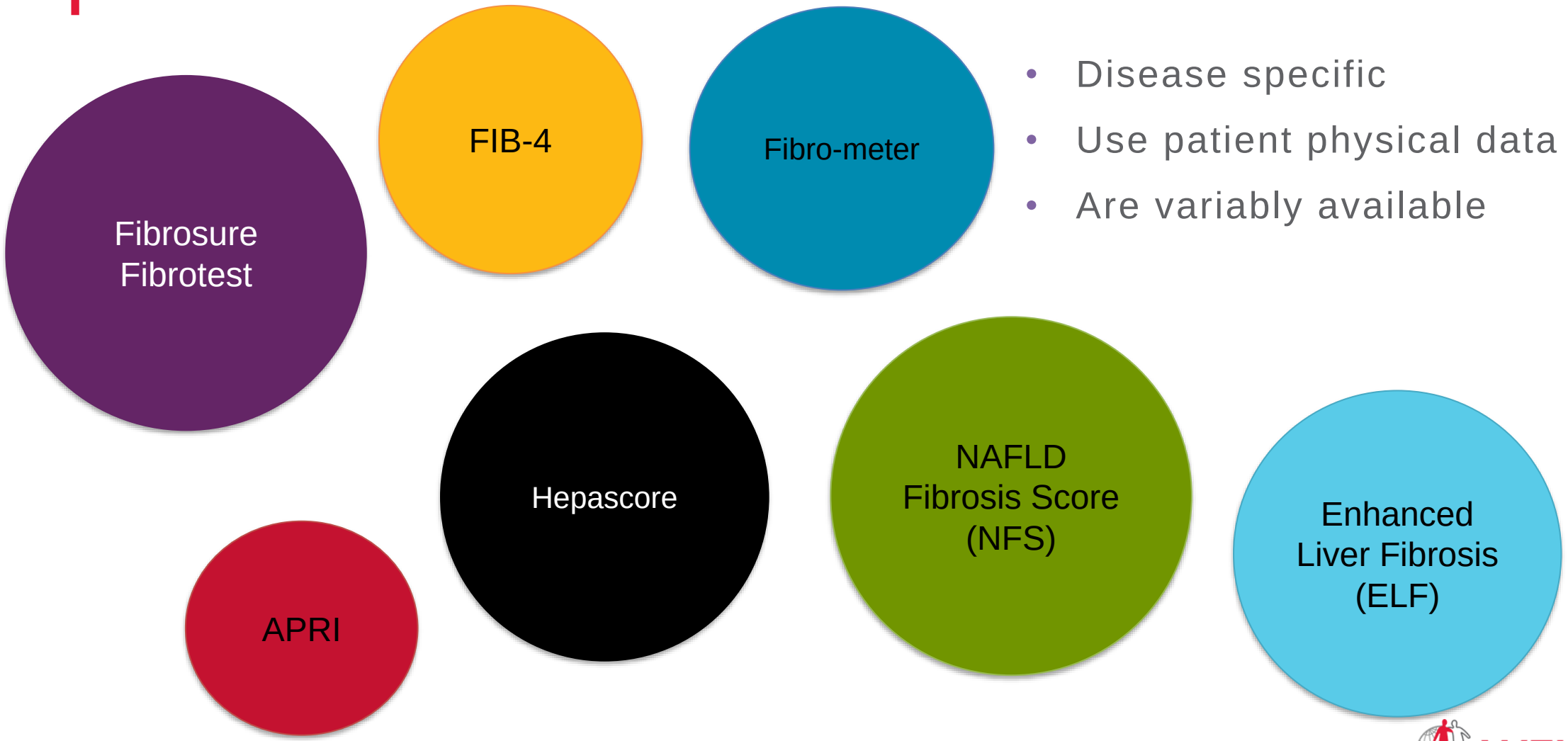
Specialized Lab tests



- Disease specific
- Use patient physical data
- Are variably available

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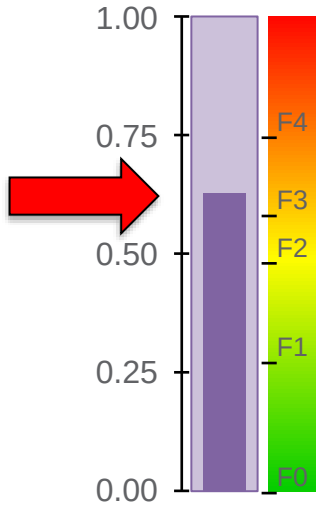
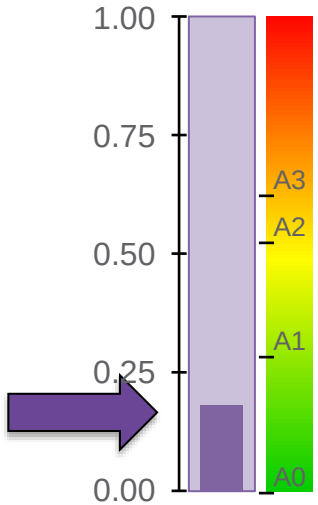
Example of a Non-invasive Fibrosis and Activity Biomarker

Liver Fibrosis, FibroTest™
Fibro Test
FibroTest assesses the fibrosis of the liver



Score : 0.62
(F3)
advanced fibrosis

ActiTest™ Panel
Acti Test
ActiTest assesses the activity (inflammation in chronic viral hepatitis C or B)



Score : 0.18
(A0-A1)
no activity

This FibroTest is designed for fibrosis estimation in chronic hepatitis B or C.

Also provides estimate of “activity, inflammation.”

High Risk

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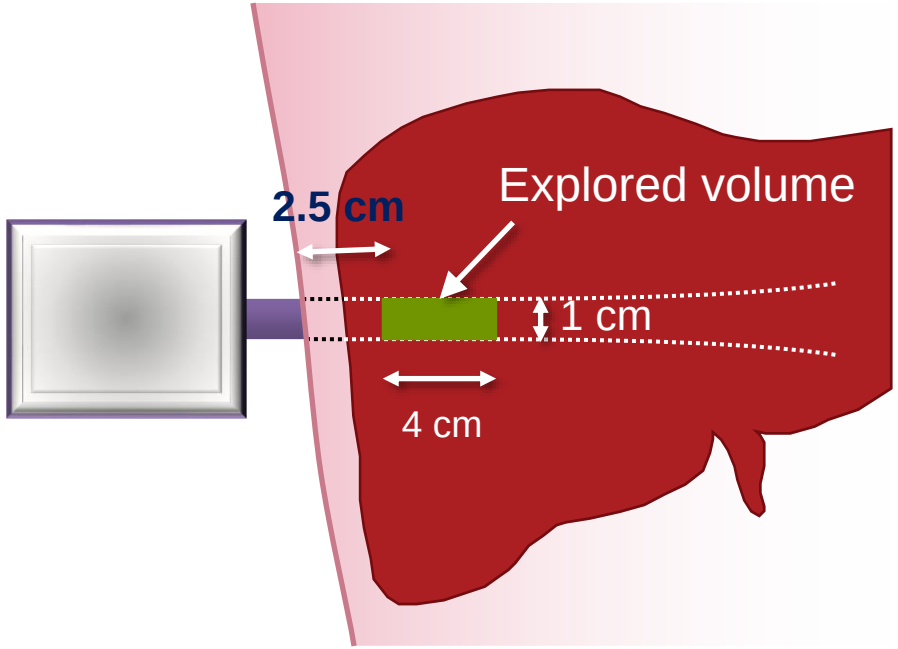
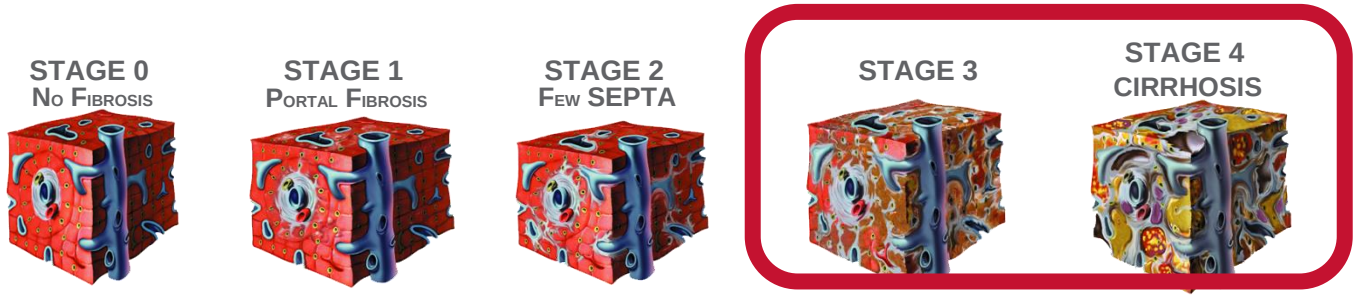
Elastography

- Very popular
- Easy to do in office
- Instant results
- Requires interpretation



Measures speed of sound wave through liver
Speed is proportional to “stiffness”
Stiffness is related to fibrosis



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Hepatitis C

- Can fibrosis be reversed?
  - **Yes**
- Can cirrhosis be reversed?
  - **Yes**
- Can complications still occur?
  - **Yes!**
- What is the time frame for improvement?
  - Early changes (improvements) seen at one year
  - Five year benefit clearly seen, even in cirrhotics

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Hepatitis C
Long Term Follow Up

- For patients with confirmed advanced fibrosis or cirrhosis
  - Risk of HCC: screen with ultrasound every 6 months
  - Risk of variceal bleeding: Screen with EGD every 1-2 years
  - Monitor for complications of ascites and encephalopathy

Hepatitis C
Long Term Follow Up

- For patients with confirmed advanced fibrosis or cirrhosis
  - Determine if fibrosis has improved so that patient is no longer at risk (no longer F3 or F4)[1]
  - Use combination of blood tests and elastography (interval 12-18 months)[2]

1 Nahon, et al Gastro 2017
2 Author personal experience

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Summary (1)

- Treatment of hepatitis C is now very routine: multiple oral regimens with nearly universal cure
- Curing the viral infection does **not** cure the liver disease
- Patients still can have complications
  - Ascites
  - Variceal bleeding
  - Liver cancer

Summary (2)

- Confirmation of extent of liver fibrosis can be made easily by non-invasive measures
  - Specialized blood tests (e.g.; Fibrosure, APRI)
  - Elastography
- Patients with advanced fibrosis **(F3 or F4)** are at risk of complications
- Assessment of liver fibrosis and risk of complications should be made with aid of a hepatologist, especially if a gene therapy research protocol is an option

THANK YOU

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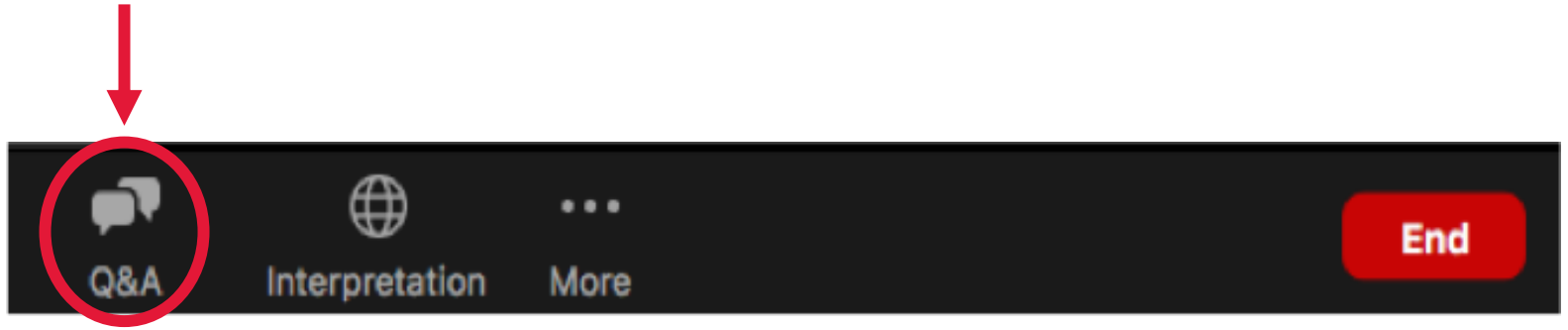
QUESTION & ANSWER

Please submit your questions in the Q&A box



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Obesity and hemophilia

Cedric Hermans, MD, PhD

UCL Université catholique de Louvain

Cliniques universitaires SAINT-LUC UCL BRUXELLES

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Prevalence of obesity in haemophilia

The Netherlands

Adults (n=716)	1992	2001
Overweight	27%	35%
Obesity	4%	8%
All	31%	43%
Children (n=264)	**1992**	**2001**
Overweight	6%	10%
Obesity	2%	6%
All	8%	16%

All (n=1014)	severe	non-severe
Overweight	22%	31%
Obesity	8%	7%

Hofstede FG, et al. Haemophilia 2008;14:1035-8.

United States

Adults (n=59)	2009
Overweight	32%
Obesity	36%
All	68%
Children (n=55)	**2009**
Overweight	16%
Obesity	21%
All	37%

All (n=132)	severe	non-severe
Overweight	25%	22%
Obesity	29%	26%

Majumdar S, et al. Haemophilia 2010;16:455-9.

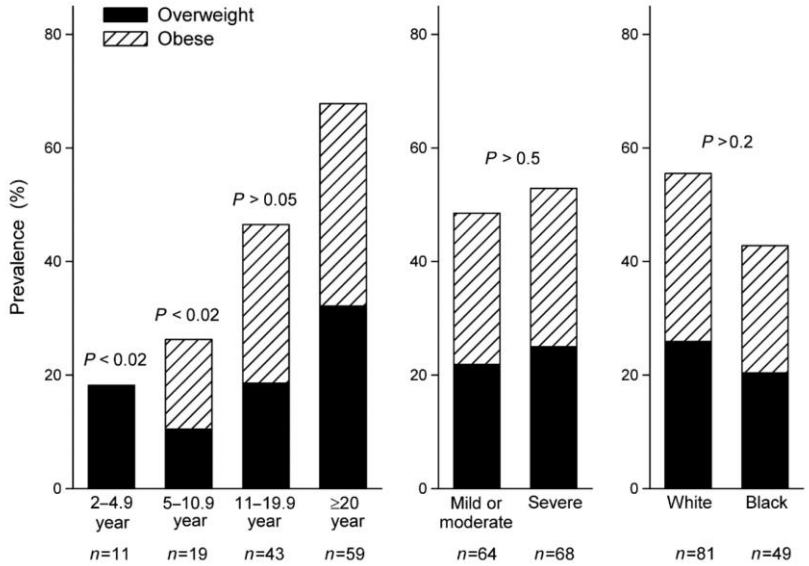

Fig. 1. Prevalence of being overweight and obese among haemophiliacs based on age, severity of disease and ethnicity. The significance of differences from the adult (≥20 year) group is shown above the respective bar for each of the younger age groups. The results of statistical comparisons on the basis of disease severity and ethnicity are above the relevant pairs or bars.

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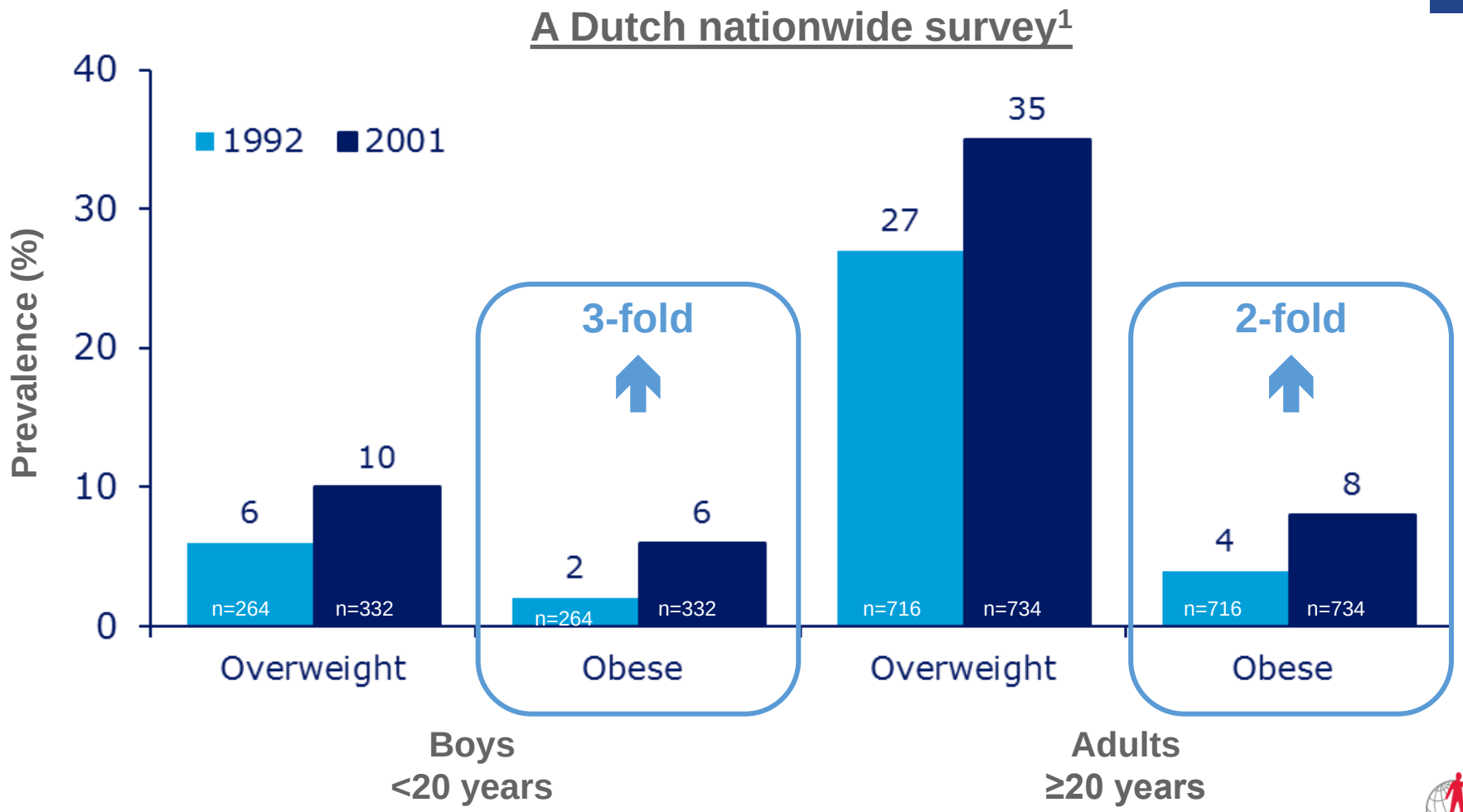
People with haemophilia are getting heavier



Hofstede FG et al. Haemophilia. 2008; 14: 1035–8

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Prevalence of obesity and overweight in haemophilia patients according to age

	Children	Teens	Adults
BMI above normal level	36 %	38 %	63 %
Obesity	20 %	22 %	28 %
Overweight	16 %	16 %	35 %

Based on data from 10,814 US male patients with HA and HB (45 % with severe disease) aged 6-79 years enrolled in the Centers for Disease Control and Prevention Universal Data Collection surveillance between 1998 and 2008

Haemophilia 2014, 20: 340-48

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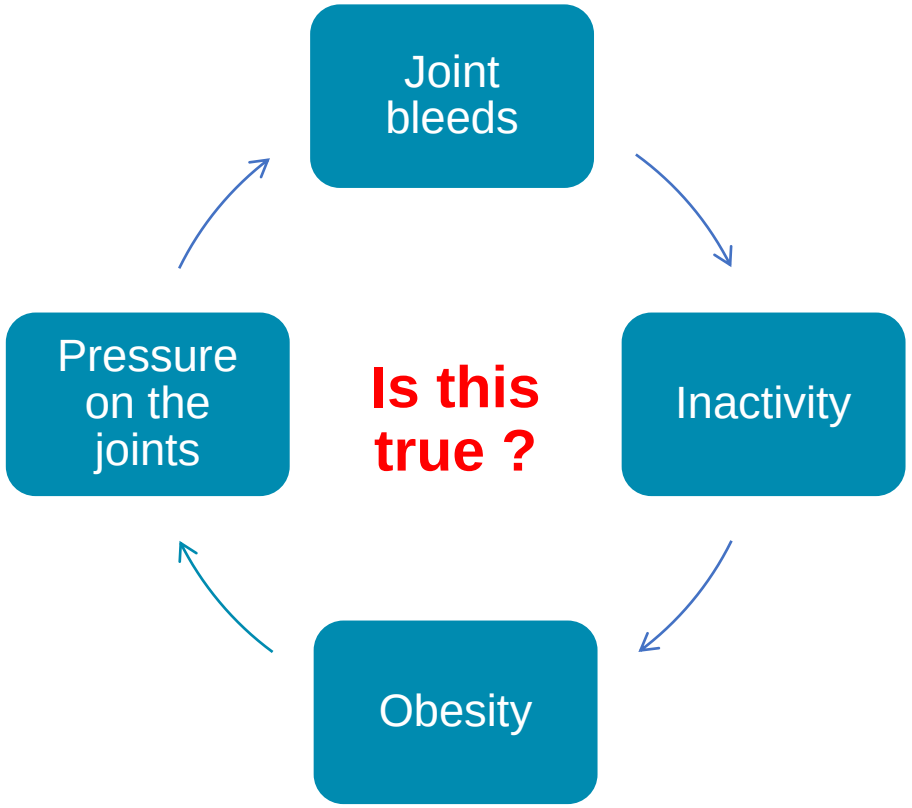
Prevalence of obesity in haemophilia

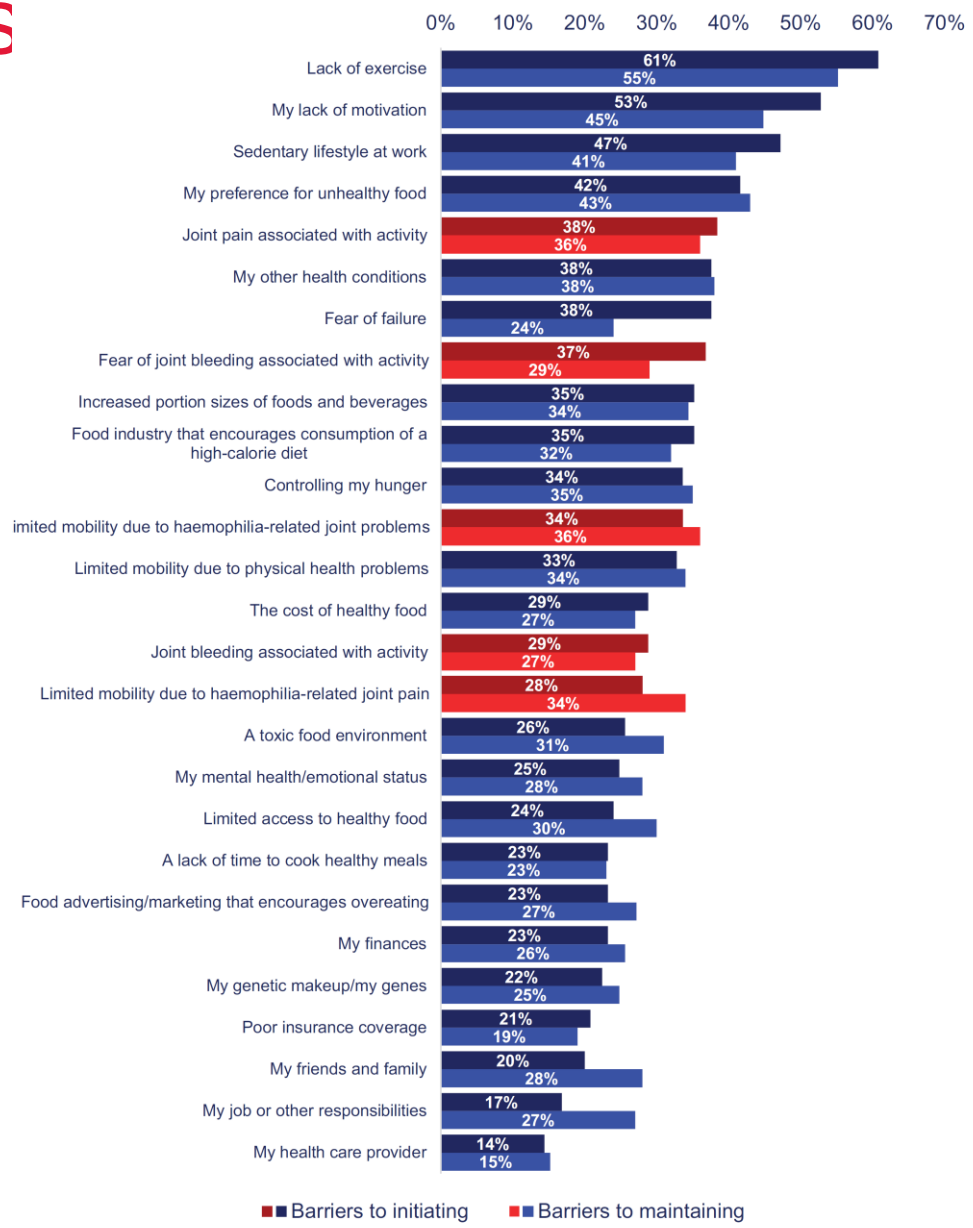
Study	Study location	No. of haemophilia patients	Definitions used	Age, years	Prevalence (%)					
					Overweight		Obese		At Least Overweight	
					Control	Haemo-philia	Control	Haemo-philia	Control	Haemo-philia
Hofstede (2008)	All Netherlands	1066	OW: BMI 25-29.9; Obese: BMI ≥30	>20	50	35	8	8	58	42
				≤20	14	10	3	6	17	15
Sartori (2008)	Padova, Italy	40	OW + Obese: BMI ≥26	>20	NR	NR	NR	NR	50	42
Miesbach (2009)	Frankfurt, Germany	29	OW: BMI 25-29.9; Obese: BMI ≥30	60-85	53	52	21	10	74	62
Majumdar (2010)	Mississippi, US	132	Adults: OW: BMI 25-29.9; Obese: BMI ≥30	≥20	39.5	32	31.6	36	71.1	68
			Paediatric: OW: BMI 85th-95th PCTL; Obese: BMI ≥95th PCTL	2-19.9	17.5	16	24.2	21	41.7	37
Soucie (2011)	140 centres in the US	6347	OW: BMI 85th-95th PCTL; Obese: BMI ≥95th PCTL	2-20	NR	15.1	NR	17.4	32.7	32.5
Sharathkumar (2011)	Indiana, US	185	Obese: BMI ≥30	>35	NR	NR	36.2	34.6	NR	NR
Lim (2011)	Minnesota, US	58	Obese: BMI ≥30	>35	NR	NR	31.9	19.6	NR	NR
Revel-Vilk (2011)	Ontario, Canada	173	OW: BMI 85th-94th PCTL; Obese: BMI ≥95th PCTL	<18	18	14.1	8	14.7	26	28.8

Wong TE, et al. Am J Prev Med 2011;41:S369-75.

Pathophysiology of obes in haemophilia patients

- Why are patients with haemophilia obese / overweighted ?
- Does haemophilia predispose to obesity ?
- Obesity = more fat and less muscle mass





PwH reported barriers to initiating and maintaining weight loss.

Calculation and communication of the BMI in routine practice

- A survey of 87 hemophilia treatment centers (HTC) in the U.S. found that two thirds (67%) of centers calculated BMI.
- Of those, less than half shared the results of the BMI calculation with the patient.

- 81.25% of treaters calculate BMI for every patient of these 38.46% do this once a year and 61.65% ‘occasionally’
- 81.25% of treaters inform the patient about their BMI
- 18.75% of treaters do not calculate BMI

McAlister S et al. National Conference on Blood Disorders in Public Health Program Book, March 9–11, 2010;Sec2:36. www.blooddisordersconference.com.

EHTSB European Survey

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Consequences of obesity on haemophilia

- Physical
  - Joint range of motion, joint status / impairment
  - Physical functioning and use of mobility aids (crutches / walkers and wheel chairs)

- Comorbidities
  - Co-morbidities : high blood pressure, high cholesterol, impaired glucose tolerance, insulin resistance and type 2 diabetes, asthma, joint problems, risk for social and psychological problems, malignancies
  - Liver disease (NASH fatty liver disease, progression of HCV)

- Blood coagulation
  - Haemostatic parameters (influence on haemostatic and fibrinolytic parameters) that could influence the phenotype

Sequelae of overweight and obesity in haemophilia patients

Joint disease	Range of motion in lower extremities decreases as BMI increases
Bone health	Increased bone mineral density Obese haemophilia patients protected from osteoporosis and osteopenia
Other MS complications	Greater muscle strength Less joint pain
Cardiovascular health	Increased risk of atherothrombosis, increased PAI
Diabetes	
Liver disease	Fatty non-alcoholic liver disease
PK	Inverse correlation between BMI and recovery and volume of distribution

Wong et al. Am J Prev Med 2011; 41(6S4) : S369-375

Obesity worsens range of motion

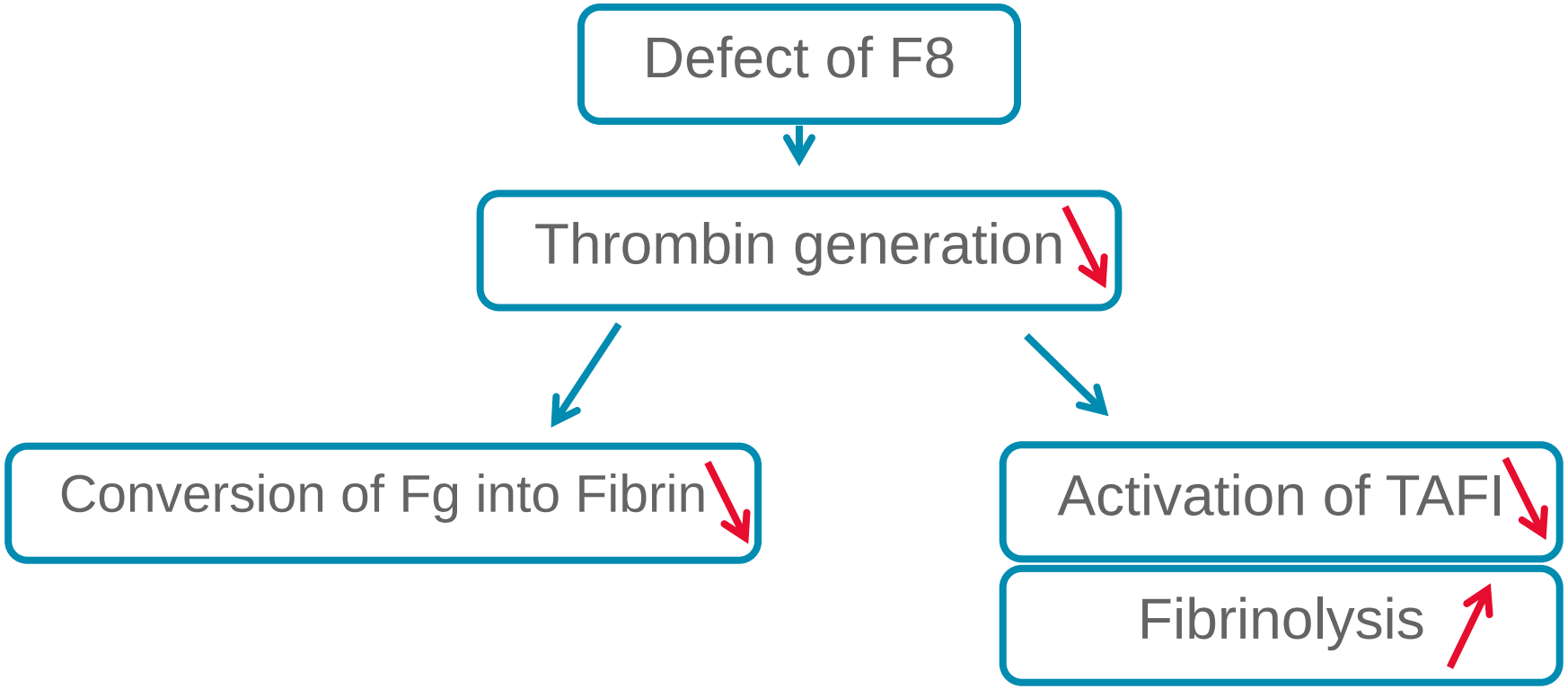
Body mass index	Mild, *n* = 917				Moderate, *n* = 1048				Severe, *n* = 2378			
	No.	%	% Limitation	*P* value	No.	%	% Limitation	*P*-value	No.	%	% Limitation	*P value*
13.0 to 17.0	271	29.6	-0.6	< 0.001	328	31.3	-0.1	< 0.001	816	34.3	0.4	< 0.001
17.1 to 21.1	319	34.8	-0.2		352	33.6	0.6		742	31.2	2.1	
21.2 to 42.0	309	33.7	0.9		345	32.9	2.4		760	32.0	4.1	

Obesity worsens hip anomalies

Baseline BMI	Total [*N* = 8192] *N* (% of column)	Hip abnormality [*N* = 1372] *N* (% of row)	Normal [*N* = 6820] *N* (% of row)	*P* value
Normal	5094 (69)	806 (16)	4288 (84)	< 0.0001
Overweight	1446 (20)	292 (20)	1154 (80)	
Obese	851 (12)	200 (24)	651 (76)	

Soucie JM, et al. Blood 2004;103:2467-73 Ullman M, et al. Haemophilia 2014;20:340-8.

Bleeding in patients with haemophilia



Bleeding complications

Obese patients have attenuated hyperfibrinolysis (Increased PAI-1) that could influence the phenotype protective effect

Do obese haemophilia patients consume more clotting factor per year?

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Bleeding frequency and clotting factor concentrate usage

Variable		Obese PWH (*N* = 51)	Non-obese PWH (*N* = 46)
Number of bleeds/PM	Severe PWH	0.62 (0.12-0.78)	0.50 (0.06-1.17)
	Moderate PWH	0.04 (0.01-0.06)	0.06 (0.00-0.42)
	Mild PWH	0.00 (0.00-0.01)	0.00 (0.00-0.04)
CFC used/PM (unadjusted) [IU]	Severe PWH	19,167 (10,486-28,535)*	13,338 (4,982-16,458)*
	Moderate PWH	211 (0-411)	333 (0-2,135)
	Mild PWH	0 (0-300)	0 (0-160)
CFC used/PM (weight adjusted) [IU kg^{-1}]	Severe PWH	176 (100-289)	173 (65-213)
	Moderate PWH	2 (0-4)	5 (0-27)
	Mild PWH	0 (0-3)	0 (0-2)

Values are expressed as median and interquartile range
CFC, clotting factor concentrate
PM, patient-month
PWH, patients with haemophilia
* $P < 0.05$ obese vs. non-obese PWH

Tuinenburg A, et al. Haemophilia 2013;19:744-52.

Impact of obesity on concentrate use, joint status and bleeding phenotype

- Consumption of concentrate :
  - Obese severe patients use 1.4 more concentrate/month than non-obese patients
  - Almost Extra 6000 units/month

- More severe joint mobility loss of the lower limbs (osteoarthritis)

- **No more (clinically patent) bleeding episodes in patients with obesity compared to non-obese patients**
  - Sedentarity
  - Over-treatment related (favourable PK)
  - Hypofibrinolysis (next slide – Increased PAI-1)

Tuinenburg A. Haemophilia 2013, 19: 744-752

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Is it justified that obese haemophilia patients use more clotting factor?

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Examples : Calculation of the FVIII dose to administer in order to reach a FVIII level of 80 %

$$\text{Dose FVIII} = \frac{60\text{kg} \times 80\%}{2} = 2400\ \text{U}$$

$$\text{Dose FVIII} = \frac{75\text{kg} \times 80\%}{2} = 3000\ \text{U}$$

$$\text{Dose FVIII} = \frac{90\text{kg} \times 80\%}{2} = 3600\ \text{U}$$

$$\text{Dose FVIII} = \frac{105\text{kg} \times 80\%}{2} = 4200\ \text{U}$$

Asterix

Panoramix

Cetautomatix

Obelix

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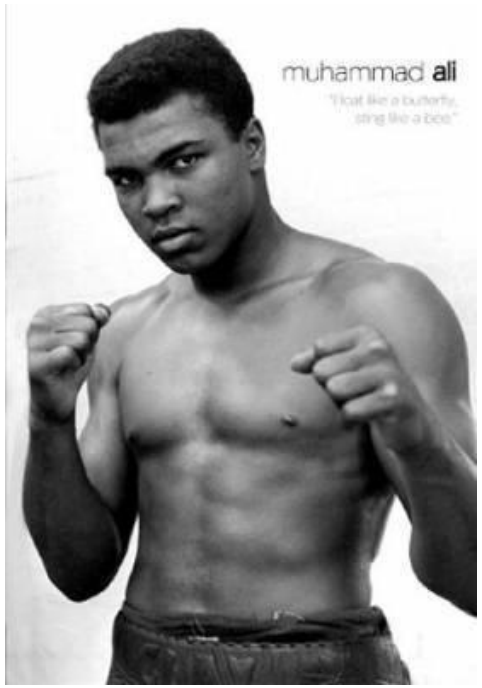
Other examples

Rafael Nadal
85 kg; 185 cm

Usain Bolt
94 kg; 196 cm



Mohamed Ali
100 kg; 189 cm

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Clinical case: A 45-year-old male with severe HA and obesity

- Severe HA / Diffuse arthropathy / Hypertension
- Obesity
  - Body weight: 120 kg
  - Height: 177 cm
  - Body mass index (BMI): 38 kg/m^2
  - Body fat (impedance): 40.7%
  - Ideal body weight: 70 kg
- Measurement of the FVIII *in vivo* recovery
  - Dose of FVIII given: 1960 units
  - FVIII before infusion: 11%; after: 56%
  - **Recovery = 45 (delta) x 120 (BW) divided by 1960 = 2.75 (much higher than 2) (Over-treatment?)**

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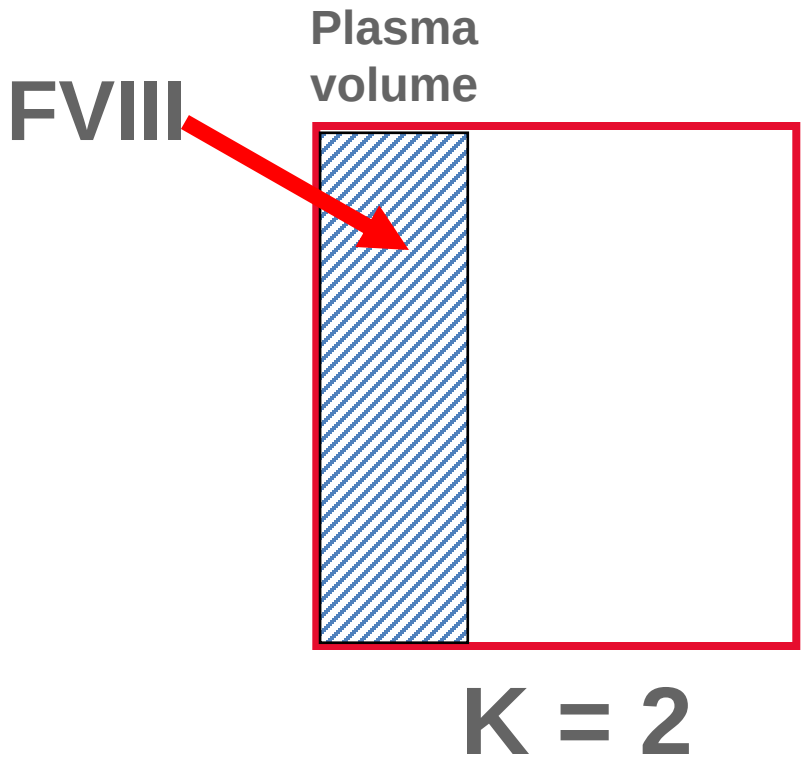
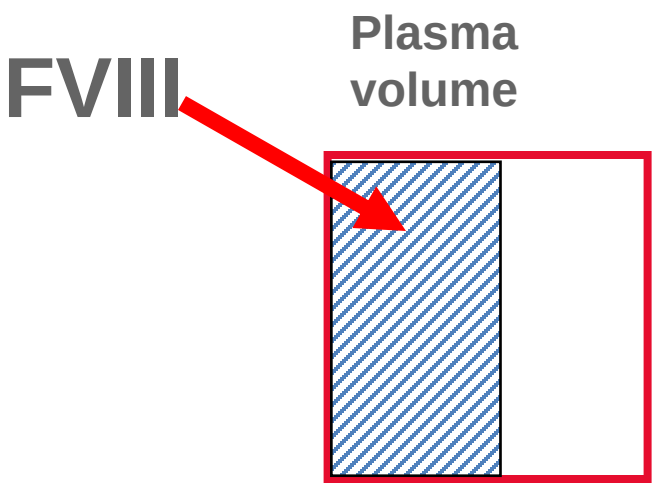
Effects of body weight / surface on recovery

ADULTS



K = 2

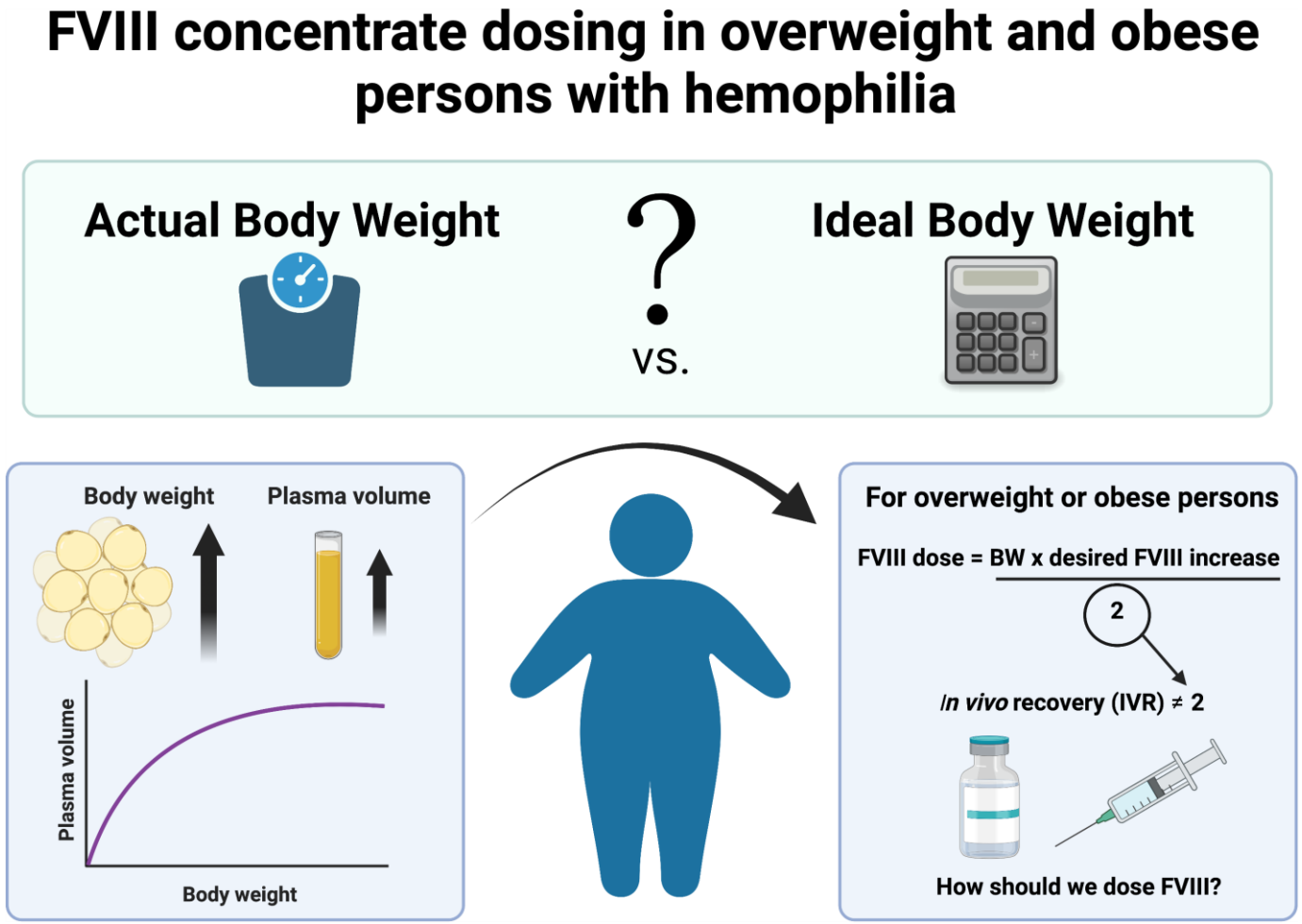
CHILDREN



K = 1.5

Body surface < 1.7 m²
Weight < 40 kg

Am. J Pathol 1982; 35 : 289



Nicoletta Machin, Ming Y. Lim, Evidence-Based Minireview: For overweight or obese persons with hemophilia A, should factor VIII dosing be based on ideal or actual body weight?, Hematology Am Soc Hematol Educ Program, 2021,

Impact of body weight on F8 recovery

Journal of Thrombosis and Haemostasis, **9**: 1784–1790 DOI: 10.1111/j.1538-7836.2011.04431.x

ORIGINAL ARTICLE

Body weight and fat mass index as strong predictors of factor VIII *in vivo* recovery in adults with hemophilia A

S. HENRARD,*† N. SPEYBROECK* and C. HERMANS†
*Institute of Health and Society, Université catholique de Louvain, Brussels; and †Haemostasis and Thrombosis Unit, Division of Adult Haematology, Cliniques universitaires Saint-Luc, Brussels, Belgium

haematologica
the Hematology Journal
Open Access Publication

Disorders of Coagulation
ARTICLES

Impact of being underweight or overweight on factor VIII dosing in hemophilia A patients

Séverine Henrard,[1,2] Niko Speybroeck,[1] and Cedric Hermans[2]

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For overweight or obese persons with hemophilia A, should factor VIII dosing be based on ideal or actual body weight?

Nicoletta Machin[1,2] and Ming Y. Lim[3]

[1]Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, PA; [2]Hemophilia Center of Western Pennsylvania, Pittsburgh, PA; and [3]Department of Internal Medicine, Division of Hematology and Hematologic Malignancies, University of Utah, Salt Lake City, UT

LEARNING OBJECTIVES

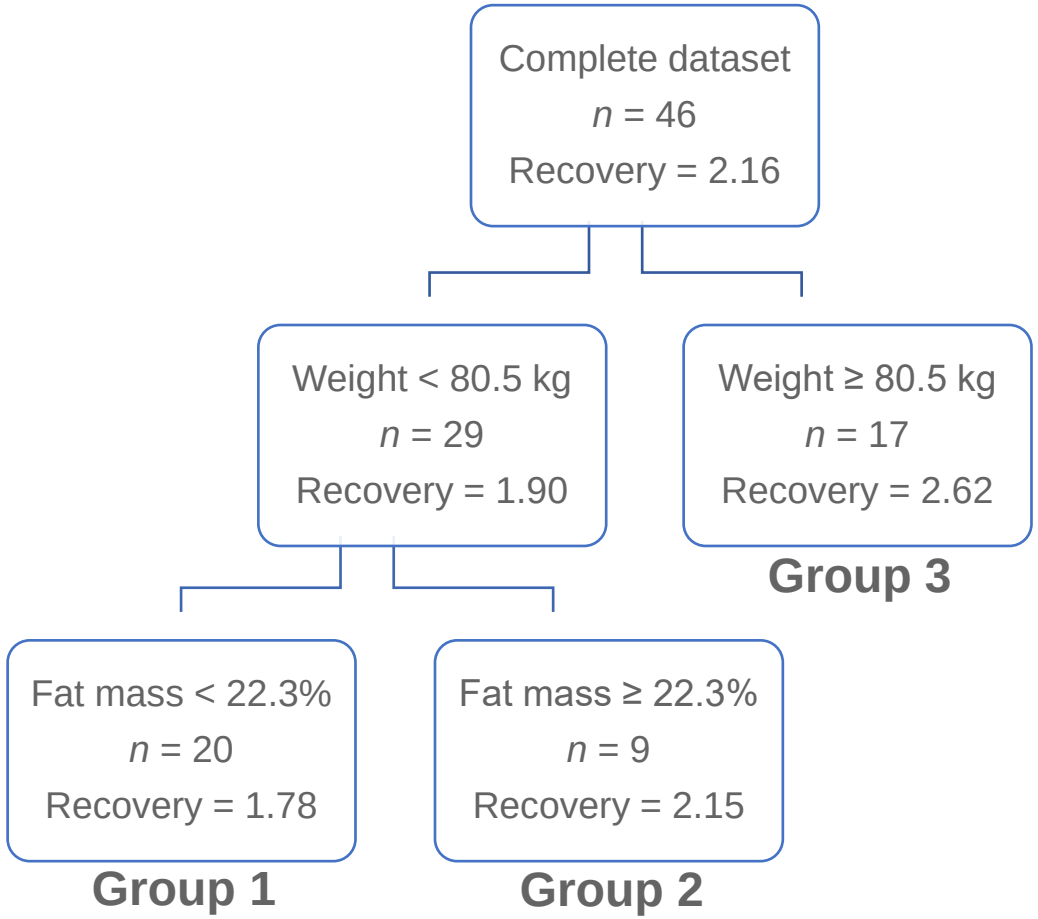
- Review evidence of the impact of body weight on FVIII in vivo recovery
- Review evidence of using ideal body weight for FVIII dosing in overweight and obese persons with hemophilia A

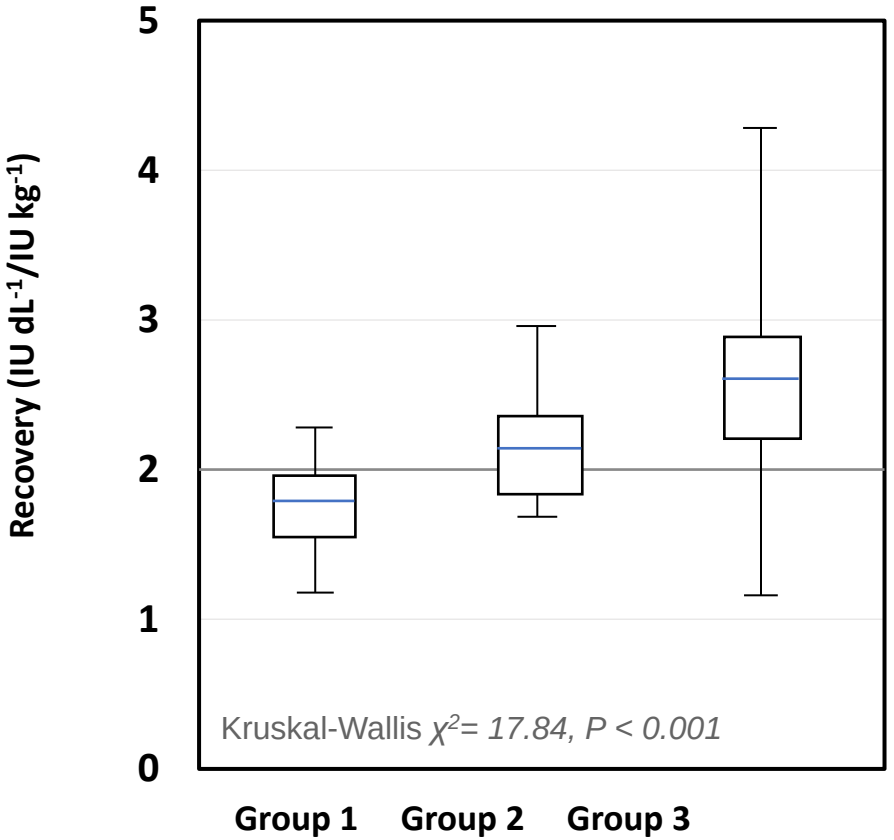
Table 1. Summary of clinical studies evaluating FVIII IVR stratified by BMI

Reference	Study design (age, years)	n	Intervention (median IU, range)	BMI groups (kg/m²) (n)	IVR (IU dL⁻¹/IU kg⁻¹)	Strongest predictor of IVR
Henrard et al[5]	Prospective observational (mean, 40.4±12.3)	46	A dose of rFVIII (2000, 980–4200)	18.5–24.9 (26) 25.0–29.9 (14) ≥30.0 (6)	1.88 2.30 2.70	BW
Henrard et al[6]	Retrospective pooled analysis of 8 PK trials (median, 26; IQR, 21–38)	201	A dose of rFVIII (3745, 1953–8794)	<18.5 (9) 18.5–24.9 (105) 25.0–29.9 (52) >30.0 (35)	1.72 2.03 2.18 2.68	BMI
Henrard et al[7]	Retrospective pool analysis of 6 PK trials (median, 14.5; IQR, 12.8–15.6)[a]	66	A dose of rFVIII (2778, 1675–5420)	Normal (43) Overweight (7) Obese (16)[b]	1.93 2.12 2.65	BMI-for-age
Tiede et al[8]	Prospective observational (mean, 37.4; range, 23.0–57.0)	35	rFVIII 50 IU/kg by ABW	<18.5 (5) 18.5–24.9 (7) 25.0–29.9 (9) 30.0–34.9 (7) ≥35 (7)	2.2[c] 2.9[c] 2.9[c] 3.2[c] 3.5[c]	BMI

[a]Only trial in children.
[b]Based on the BMI-for-age percentiles (normal, 5th-84th; overweight, 85th-94th; obese, >95th).
[c]End point reported as IVR at 30 minutes using a geometric mean.
IQR, interquartile range.

Recovery in overweight





Henrard S, et al. J Thromb Haemost 2011;9:1784-90.

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Which parameter should we use?

Parameter		Unit	Variables	Con
Body weight	BW	kg	weight	No correction for fat
Body mass index	BMI	kg/m^2	weight, height	No correction for fat
Body surface area	BSA	m^2	weight, height	No validation in obesity
Ideal body weight	IBW	kg	sex, height	No correction for body composition
Lean body weight	LBW	kg	sex, BMI	Inaccurate at extremes
Predicted normal weight	PNWT	kg	corrected LBW	Inaccurate at extremes
Fat Free Mass Index	FFMI	kg/m^2	fat mass, height	Not validated in haemophilia

Hanley MJ, et al. Clin Pharmacokinet 2010;49:71-87.

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2014), **20**, 226–229 DOI: 10.1111/hae.12300

ORIGINAL ARTICLE *Clinical haemophilia*

Pharmacokinetic analysis of anti-hemophilic factor in the obese patient

A. GRAHAM and K. JAWORSKI
Hemophilia Center of Western Pennsylvania, Pittsburgh, PA, USA

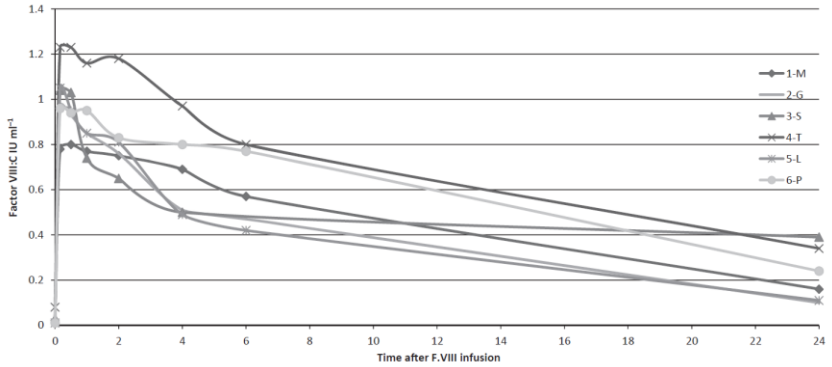


Table 2. Comparison of standard and ideal body weight (IBW) dosing in six hemophilia patients.

								Factor VIII dosing		IBW dosing: PK	
Pt	Age (year)	Severity (U mL^{-1})	HCV/HIV	Weight (kg)	Height (inches)	BMI	IBW (kg)*	Actual	IBW	Peak	Half-life (h)
1	33	<0.01	+/–	151	71.5	45.8	76.0	7550	3800	0.78	13.92
2	25	0.02	–/–	91	69	30.0	70.7	4550	3535	0.97	5.25
3	35	<0.01	+/–	100	67.5	33.8	67.0	5000	3350	1.04	3.73
4	47	<0.01	+/+	115	75	31.5	84.5	5750	4225	1.23	13.24
5	31	<0.01	+/–	118	72	35.1	78.0	5900	3900	1.06	3.75
6	33	<0.01	+/–	122	69	39.7	70.7	6100	3535	0.97	15.72

PK, pharmacokinetic FVIII data; BMI, body mass index.
*IBW weight is 50 kg + 2.3 kg per inch over 5 feet.

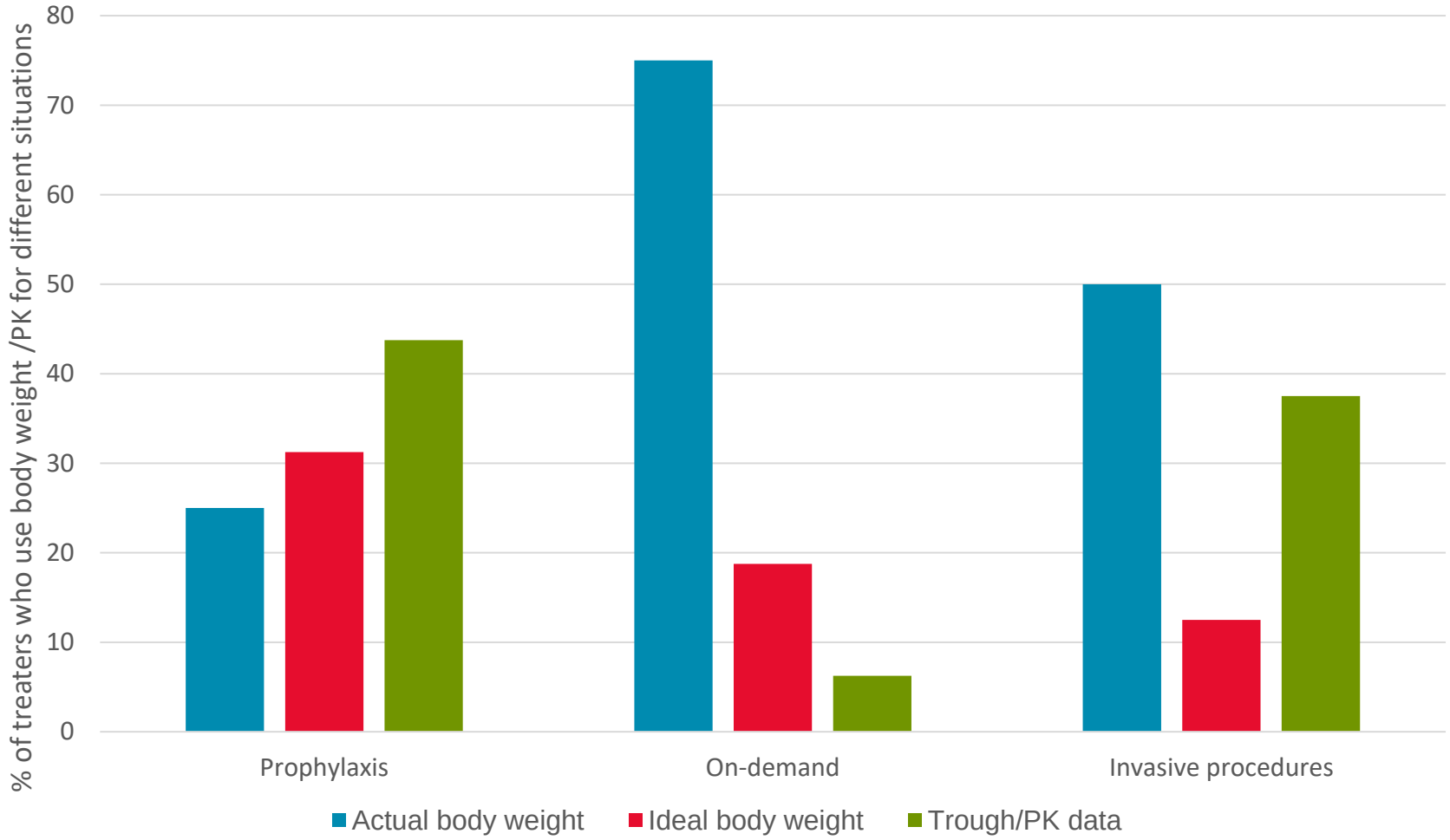
Dosing based on Ideal Body Weight

Pt	Age (year)	Severity (U mL^{-1})	HCV/HIV	Weight (kg)	Height (inches)	BMI	IBW (kg)[a]	Factor VIII dosing		IBW dosing: PK	
								Actual	IBW	Peak	Half-life (h)
1	33	<0.01	+/-	151	71.5	45.8	76.0	7550	3800	0.78	13.92
2	25	0.02	-/-	91	69	30.0	70.7	4550	3535	0.97	5.25
3	35	<0.01	+/-	100	67.5	33.8	67.0	5000	3350	1.04	3.73
4	47	<0.01	+/+	115	75	31.5	84.5	5750	4225	1.23	13.24
5	31	<0.01	+/-	118	72	35.1	78.0	5900	3900	1.06	3.75
6	33	<0.01	+/-	122	69	39.7	70.7	6100	3535	0.97	15.72

PK, pharmacokinetic FVIII data
BMI, body mass index
IBW, ideal body weight; [a]IBW weight is 50 kg + 2.3 kg per inch over 5 feet

Graham A, et al. Haemophilia 2014;20:226-9.

Determining dose of factor concentrate in obese patients – Prescribing practices among physicians of the EHTSB / Survey 2016



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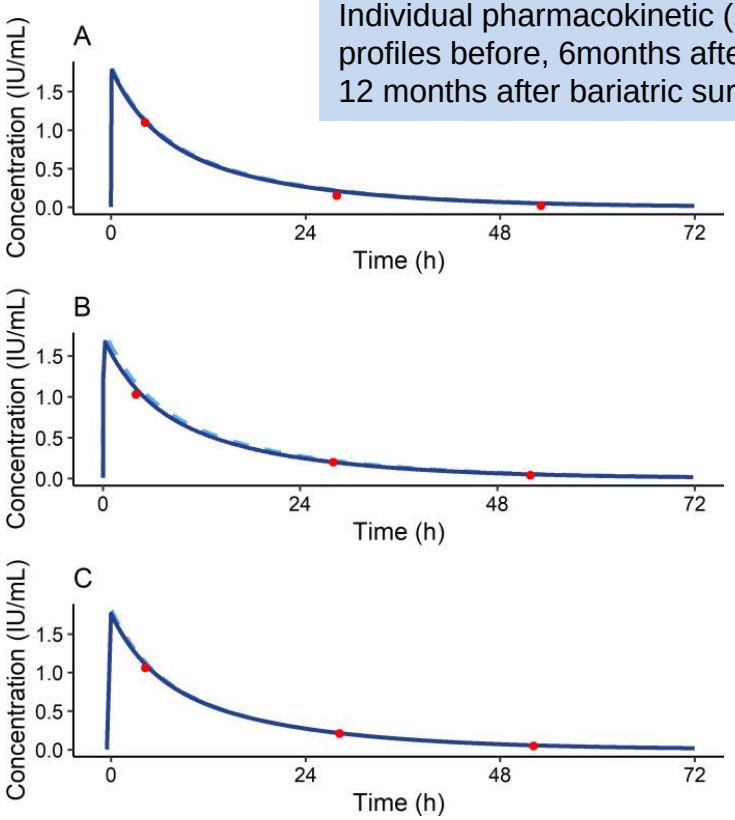
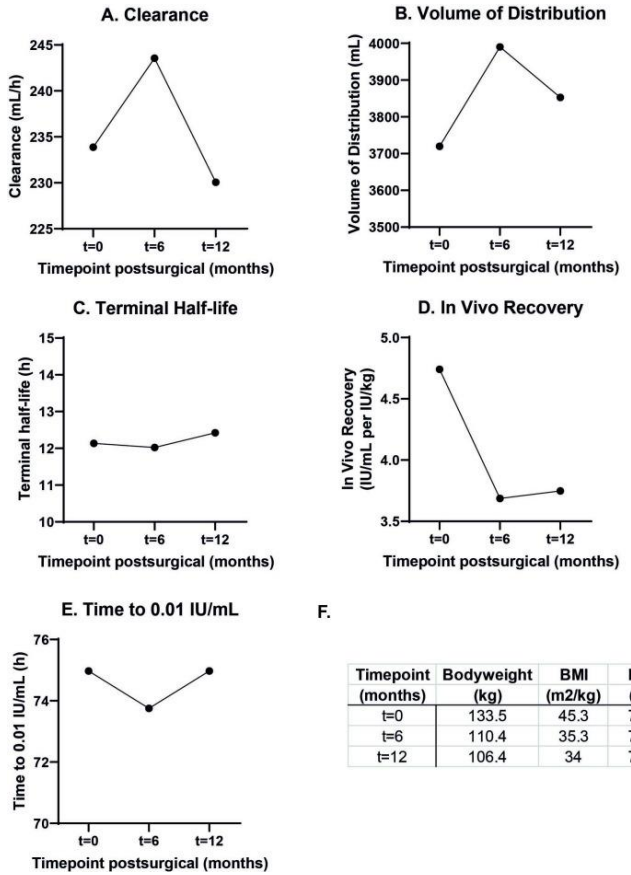
Impact of extreme weight loss on factor VIII concentrate pharmacokinetics in haemophilia

Iris van Moort ,[1] Laura H Bukkems,[2] Laurens Nieuwenhuizen,[3] Marjon H Cnossen[1]

Individual pharmacokinetic (PK) profiles before, 6months after and 12 months after bariatric surgery .





F.

Timepoint (months)	Bodyweight (kg)	BMI (m2/kg)	IBW (kg)
t=0	133.5	45.3	70.3
t=6	110.4	35.3	70.3
t=12	106.4	34	70.3

van Moort I, et al. BMJ Case Rep 2021;14:e238036. doi:10.1136/bcr-2020-238036

Received: 17 December 2020 | Revised: 21 January 2021 | Accepted: 15 February 2021

DOI: 10.1111/hae.14285

Haemophilia WILEY

REVIEW ARTICLE

Factor VIII concentrate dosing with lean body mass, ideal body weight and total body weight in overweight and obesity: A randomized, controlled, open-label, 3 × 3 crossover trial

Craig D. Seaman[1,2] | Jonathan G. Yabes[3] | Christina M. Lalama[3] | Margaret V. Ragni[1,2]

IBW (ideal body weight) is more likely to achieve a targeted FVIII recovery than based on TBW in overweight and obese patients with haemophilia A

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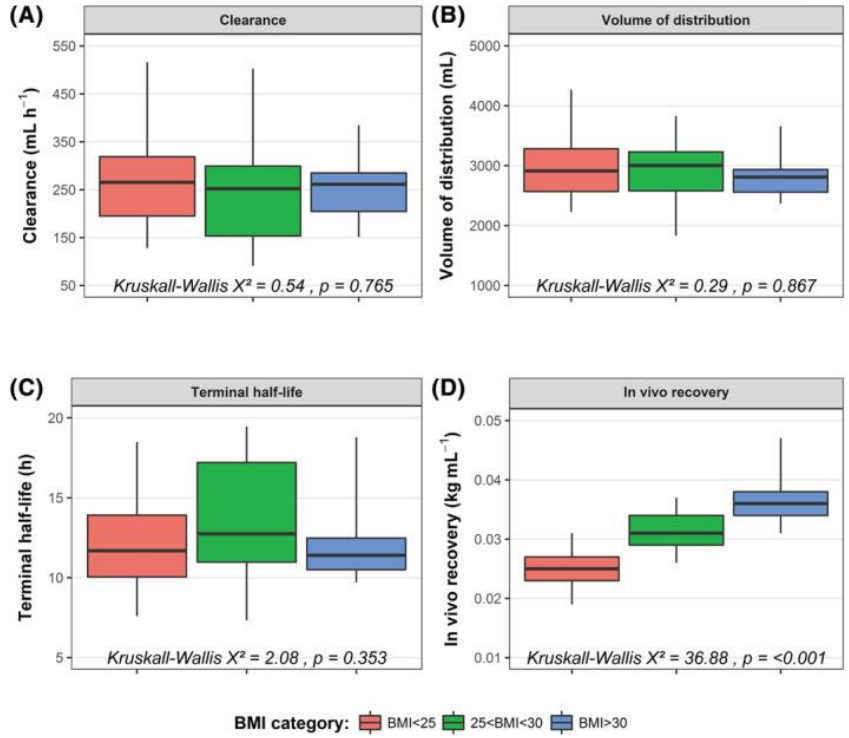
Received: 18 December 2019 | Revised: 15 October 2020 | Accepted: 3 November 2020
DOI: 10.1111/bcp.14670

ORIGINAL ARTICLE

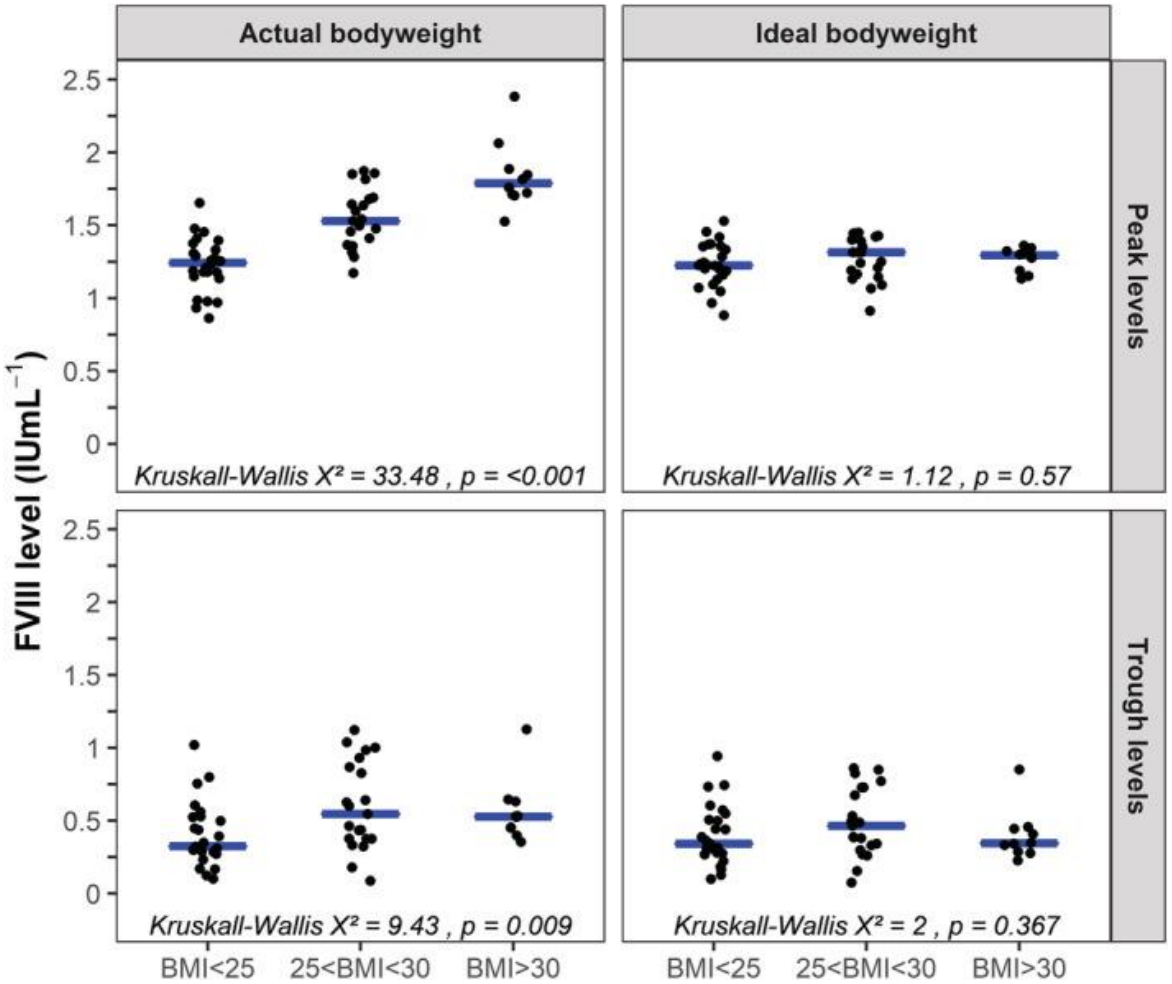
Dosing of factor VIII concentrate by ideal body weight is more accurate in overweight and obese haemophilia A patients

Iris van Moort[1] | Tim Preijers[2] | Hendrika C.A.M. Hazendonk[1] | Roger E.G. Schutgens[3] | Britta A.P. Laros-van Gorkom[4] | Laurens Nieuwenhuizen[5] | Felix J.M. van der Meer[6] | Karin Fijnvandraat[7,8] | Frank W.G. Leebeek[9] | Karina Meijer[10] | Ron A.A. Mathôt[2] | Marjon H. Cnossen[1] | for the OPTI-CLOT study group



No differences in individual pharmacokinetic (PK) parameters (clearance, volume of distribution and terminal half-life) between BMI categories. (A) Clearance. (B) volume of distribution of the central compartment. (C) Terminal elimination half-life. (D) Calculated in vivo recovery.

Are the other PK parameters (T1/2 and AUC) influenced by obesity ?



Dosing based on ideal body weight results in adequate coagulation factor VIII (FVIII) peak and trough levels when treating a life-threatening bleed.

Br J Clin Pharmacol. 2021;87:2602–2613.

Association of overweight and obesity with the use of self and home-based infusion therapy

- Obese persons with haemophilia are less likely to use Home-Infusion and Self-Infusion, possibly because of the increased difficulty of venipuncture caused by adiposity.

- The inability to perform HI and SI may lead to :
  - delayed treatment of bleeds,
  - reduce the effectiveness of the treatment
  - place those with elevated BMI at increased risk of haemophilic complications.

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Haemophilia, 2014, 20 : 340-348

DOI: 10.1111/hae.13918

SUPPLEMENT ARTICLE

Haemophilia WILEY

Awareness, Care and Treatment In Obesity maNagement to inform Haemophilia Obesity Patient Empowerment (ACTION-TO-HOPE): Results of a survey of US patients with haemophilia and obesity (PwHO) and their partners and caregivers

Stacy E. Croteau[1] | Susan Cutter[2] | Grace Hernandez[3] | Brian Wicklund[4] | Meredith L. Dreyer Gillette[4] | Kimberly Haugstad[5] | David L. Cooper[6] | Vlady Ostrow[6] | Joe Nadglowski[7]

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Obesity and comprehensive haemophilia care

- Patients who are overweight or obese should be identified
- Particular attention should be paid to the BMI at each clinic visit
- A nutritionist should be an integral part of comprehensive care and discuss and educate patients on the importance of diet and physical exercise
- If functional limitations restrict physical activities, a physical therapist familiar with haemophilia should provide assistance
- Referral should be made to a weight reduction programme and if necessary an obesity clinic to help haemophilic patients reduce weight

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Majumdar S et al. *Haemophilia* 2010;16:455–9.

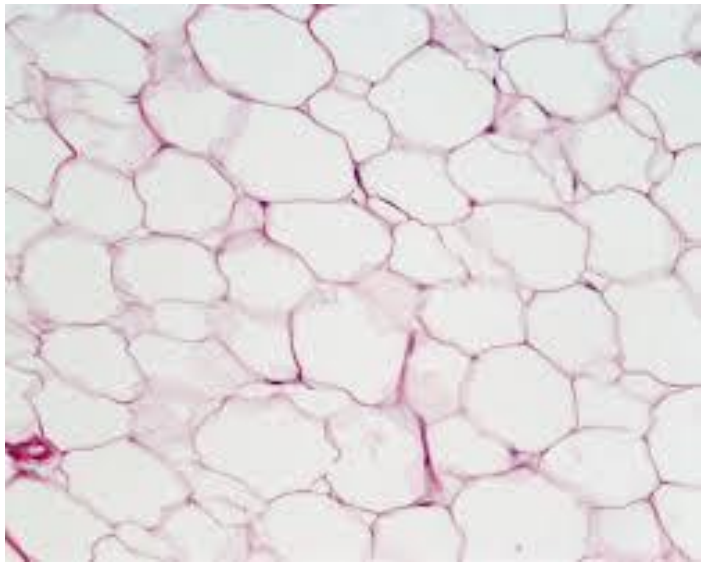
What should be done ?

- Promoting a healthy lifestyle and managing obesity needs to be highly integrated into haemophilia care, rather than treated as an additional disease.

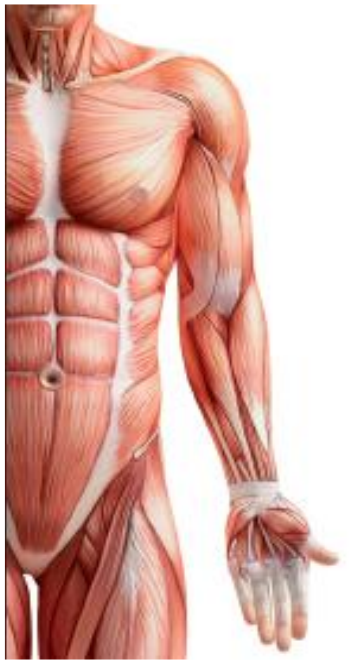
- Physical activity is a key feature of overweight and obesity management, but can be challenging for haemophilia patients with joint problems.

- Individualised exercise plans need to be developed and implemented with the support of specialist physiotherapists.

Obesity



- More FAT
- Less MUSCLES



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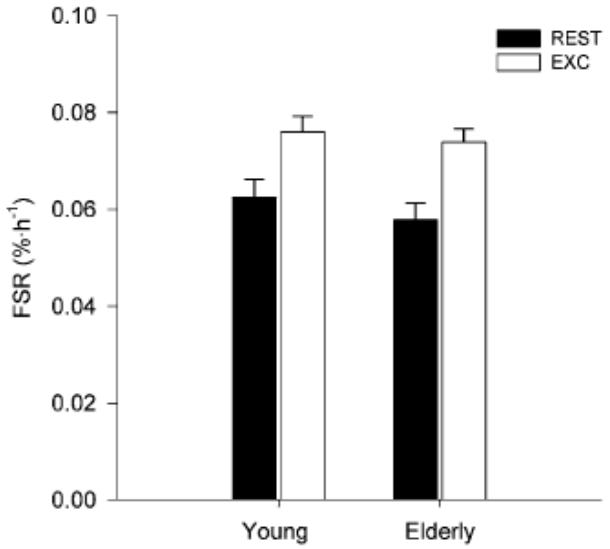
Physical activity in patients with haemophilia should be promoted



Individual or group sessions

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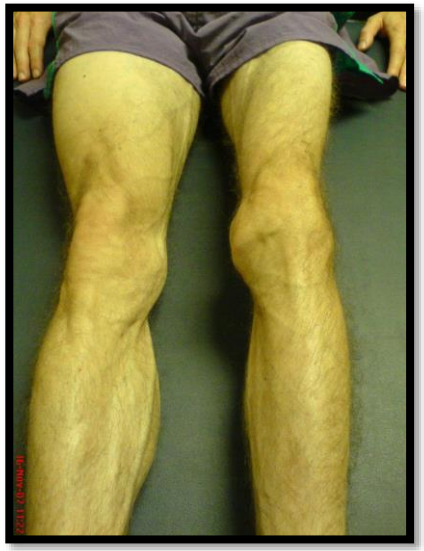
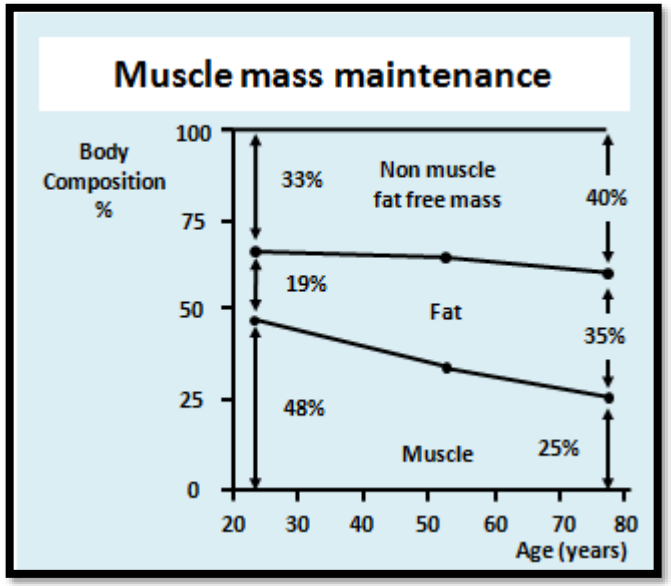
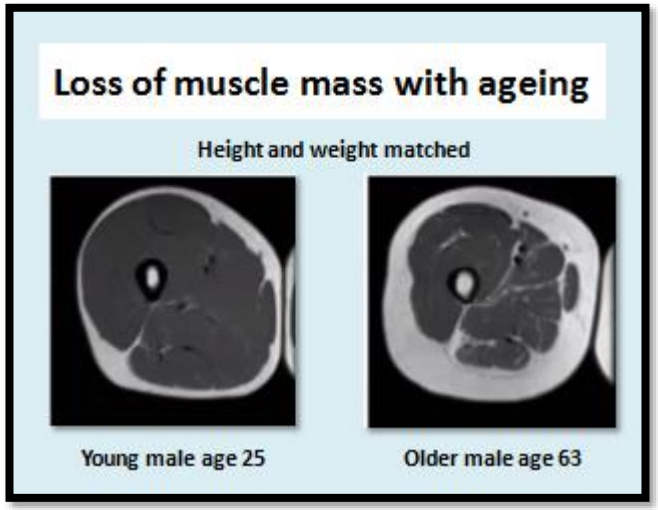
The many causes for muscular loss in patients with haemophilia

- Arthropathy
- Immobilisation
- Age (sarcopenia)
- Diabetes type 2
- Comorbidities







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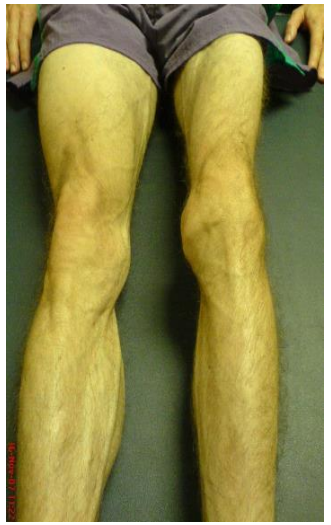
Skeletal muscle tissue has a tremendous plasticity!

- Muscle TURNOVER : 1-2 %/day
- 7 days in a bed = -1.3 kg Muscles
- 6 Months Physical Activity = +1.2 Kg Muscles



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Conclusions : obesity in haemophilia

- It is an increasing global concern
- It has a negative influence on physical functioning
- It increases clotting factor consumption and replacement therapy should be adjusted. Patients may be reluctant to reduce their FVIII dose due to perceived safety risks.
- Deserves more research as many questions remain unanswered

THANK YOU

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Pain in people with haemophilia: What-Why-How to cope?

Nathalie Roussel, PhD
Associate Professor
University of Antwerp

University of Antwerp

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Speaker disclosures

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Consultant	Bayer, SOBI, Pfizer, NovoNordisk
Employee	No relevant conflicts of interest to declare
Paid Instructor	No relevant conflicts of interest to declare
Speaker bureau	No relevant conflicts of interest to declare
Other	No relevant conflicts of interest to declare

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Pain in People with Hemophilia (PwH)

Management of pain in hemophilia?

Hemophilia Treatment Centers

Need for a better understanding of pain

Need for treatment recommendations

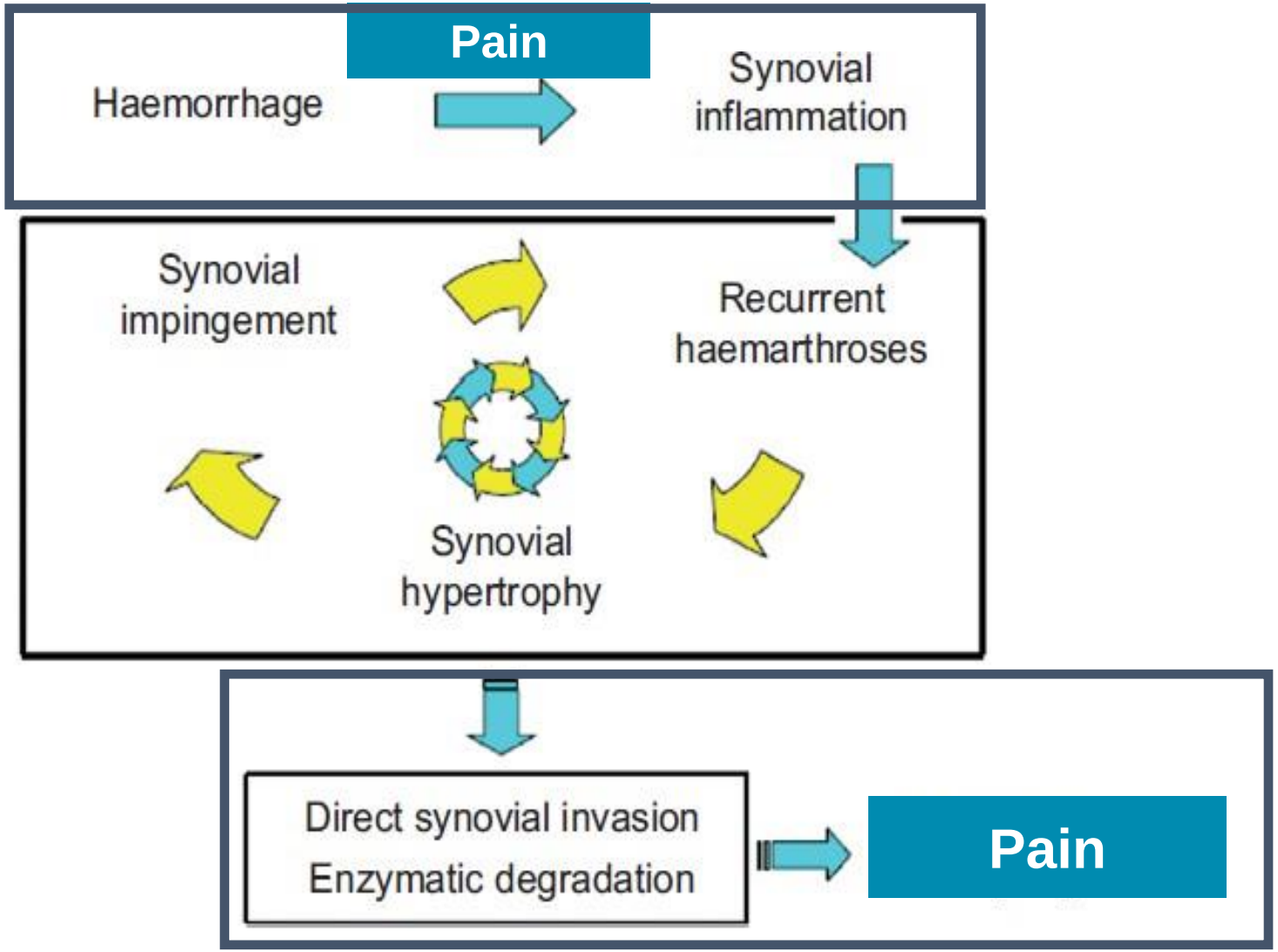
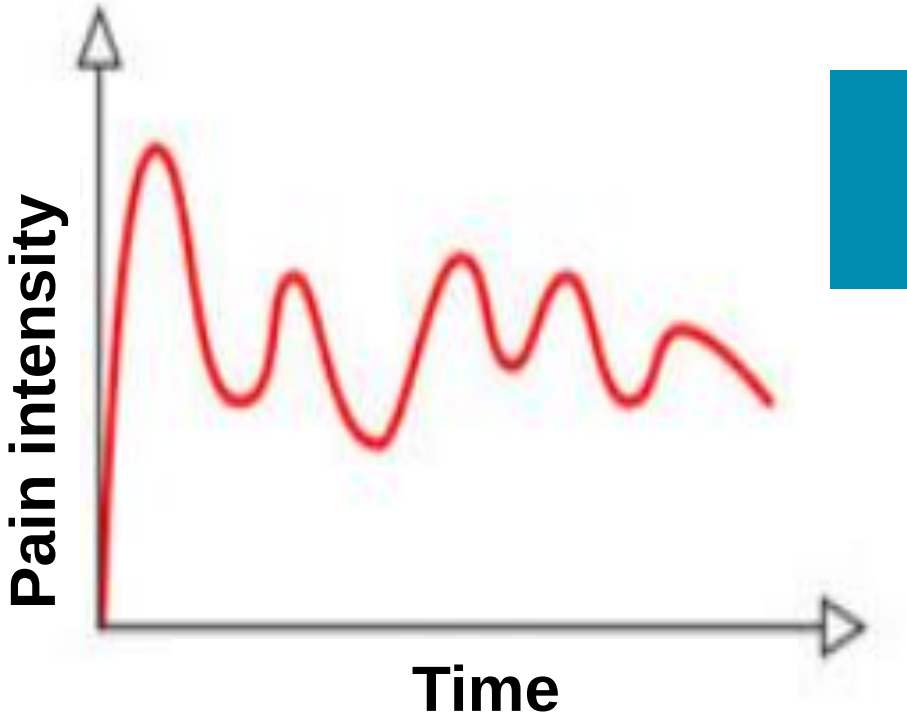
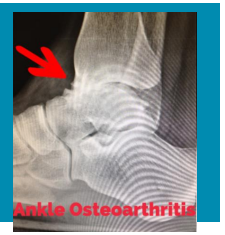


Figure 1 A chronic, self-perpetuating cycle of haemarthrosis–synovitis–haemarthrosis [29]. Reproduced with permission. © World Federation of Hemophilia, 2004.

Pain intensity varies in Osteoarthritis

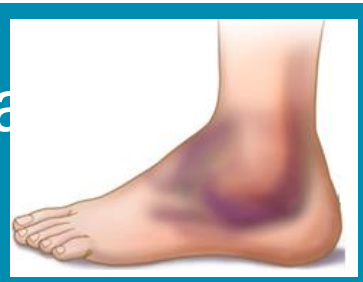


‘Flare-up’ in patients with OA

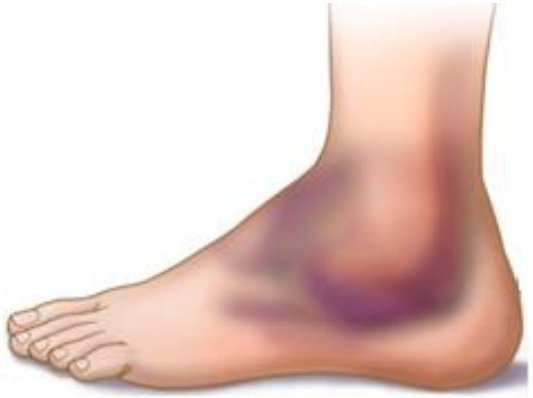


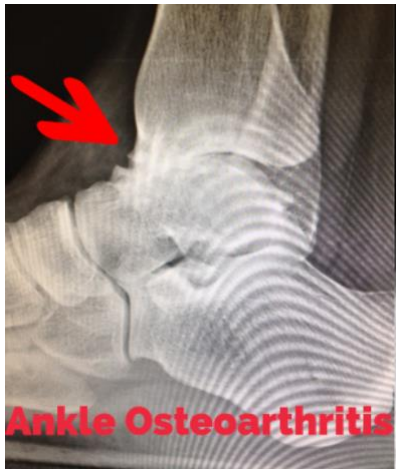
Parry et al, *Osteoarthritis Cartilage*, 2019

Increase of pain intensity is considered a
‘acute’ pain and hence as a bleeding



Causes of pain

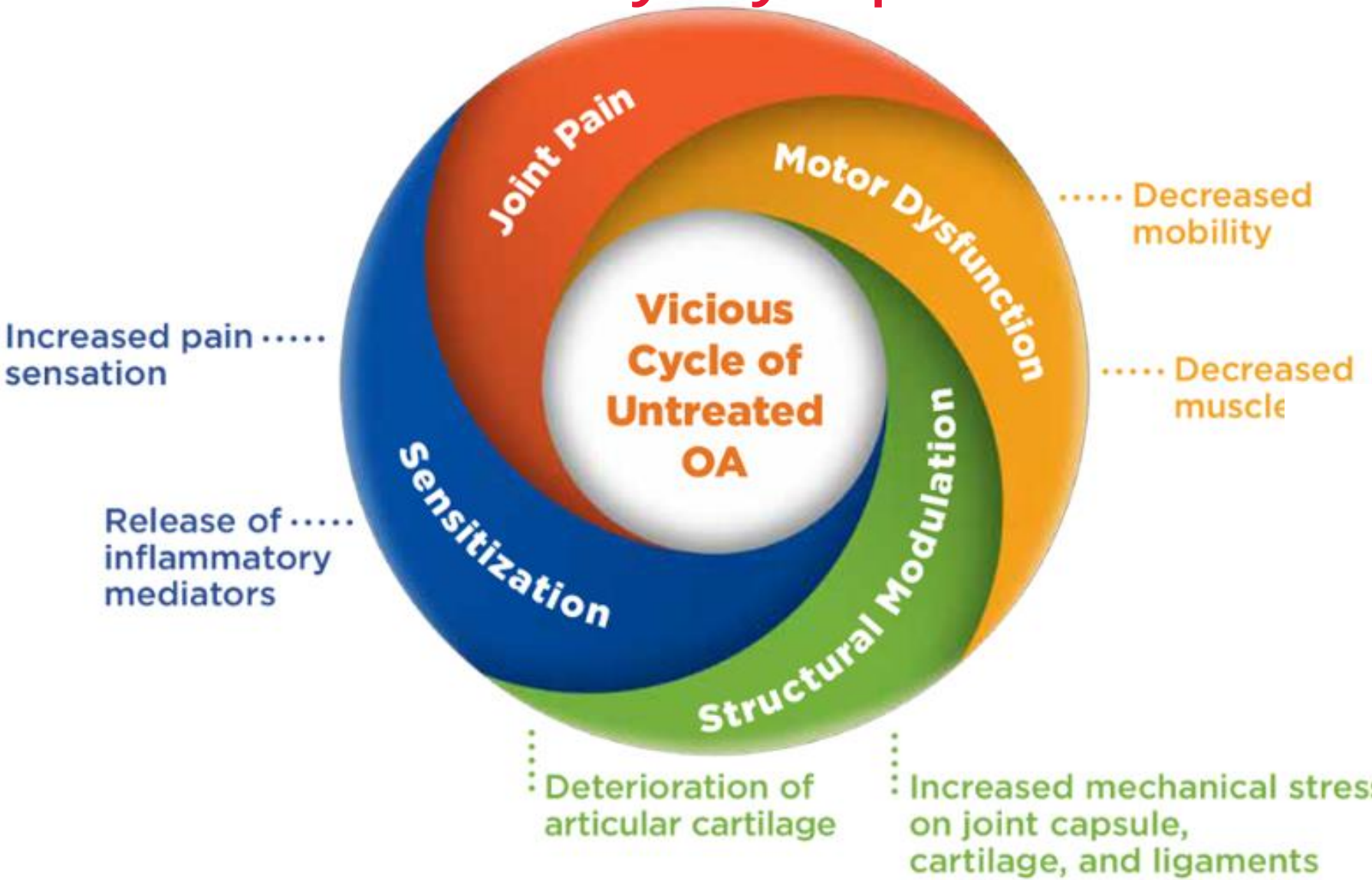




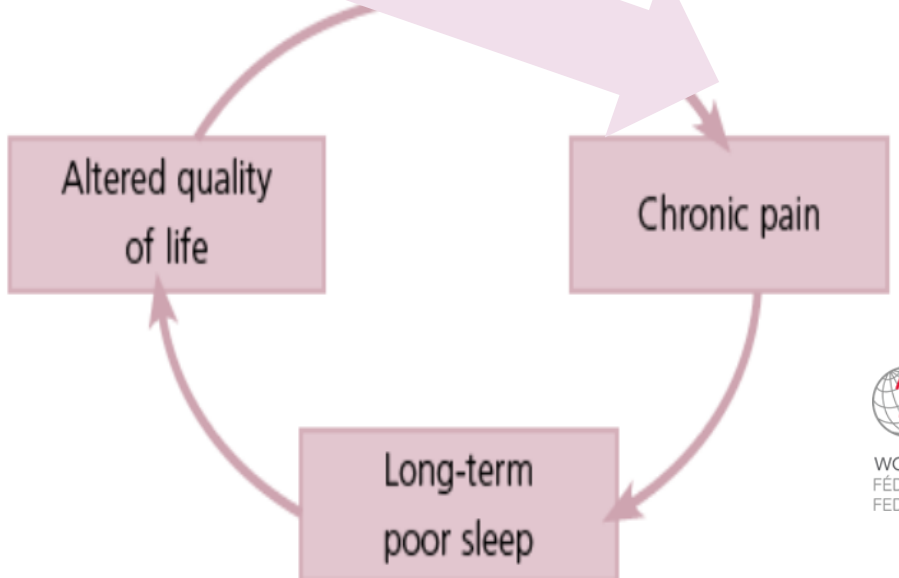
Bleeding	Joint damage

It is more complex than that

Pain is not the only symptom

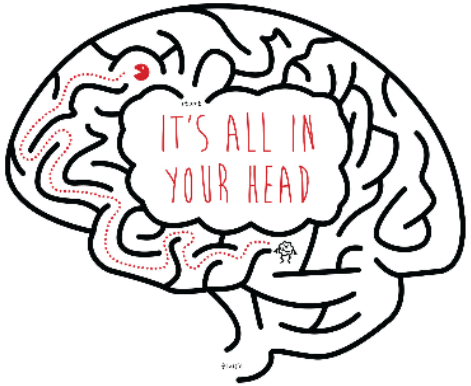


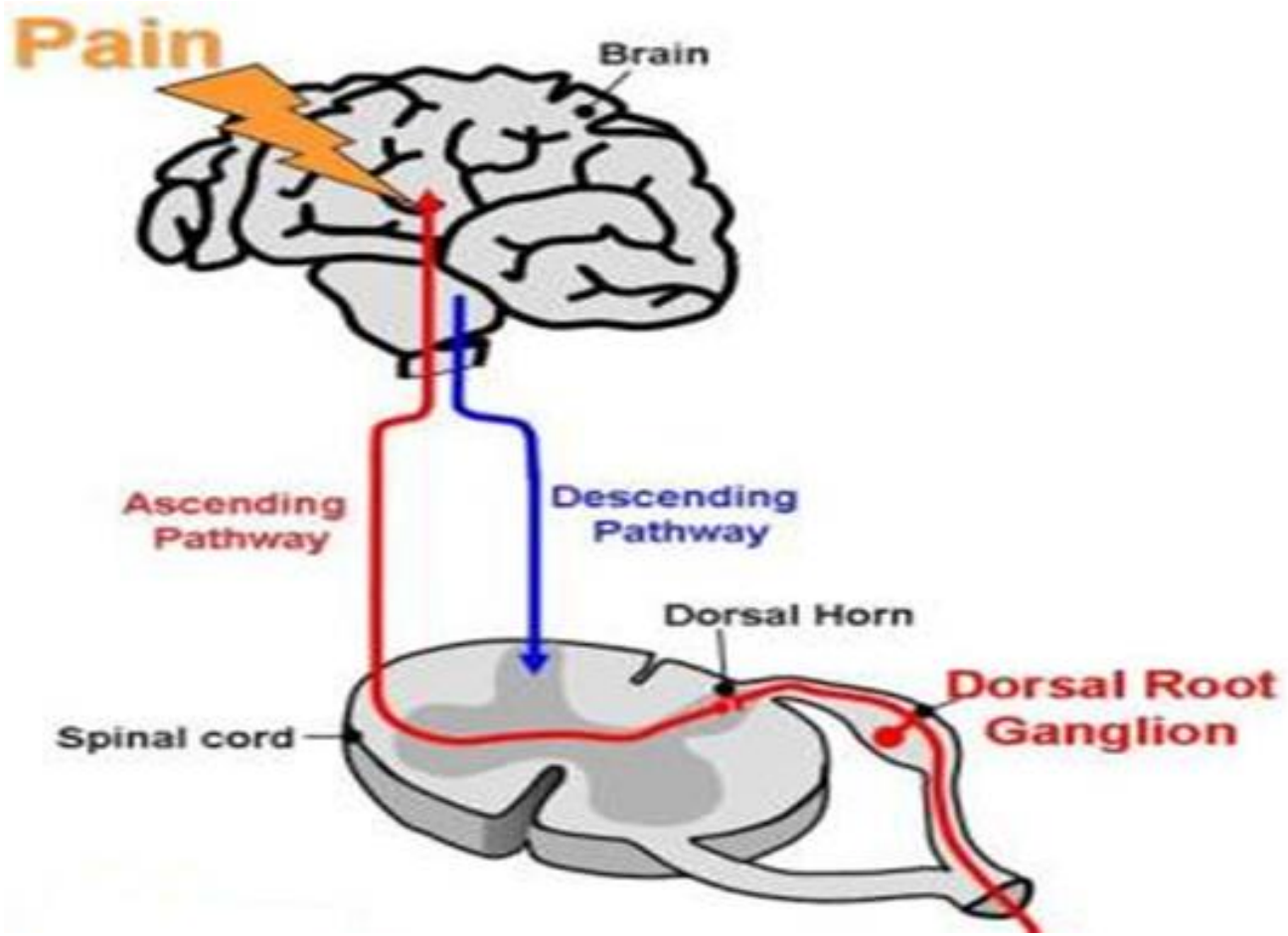
Consequences of pain



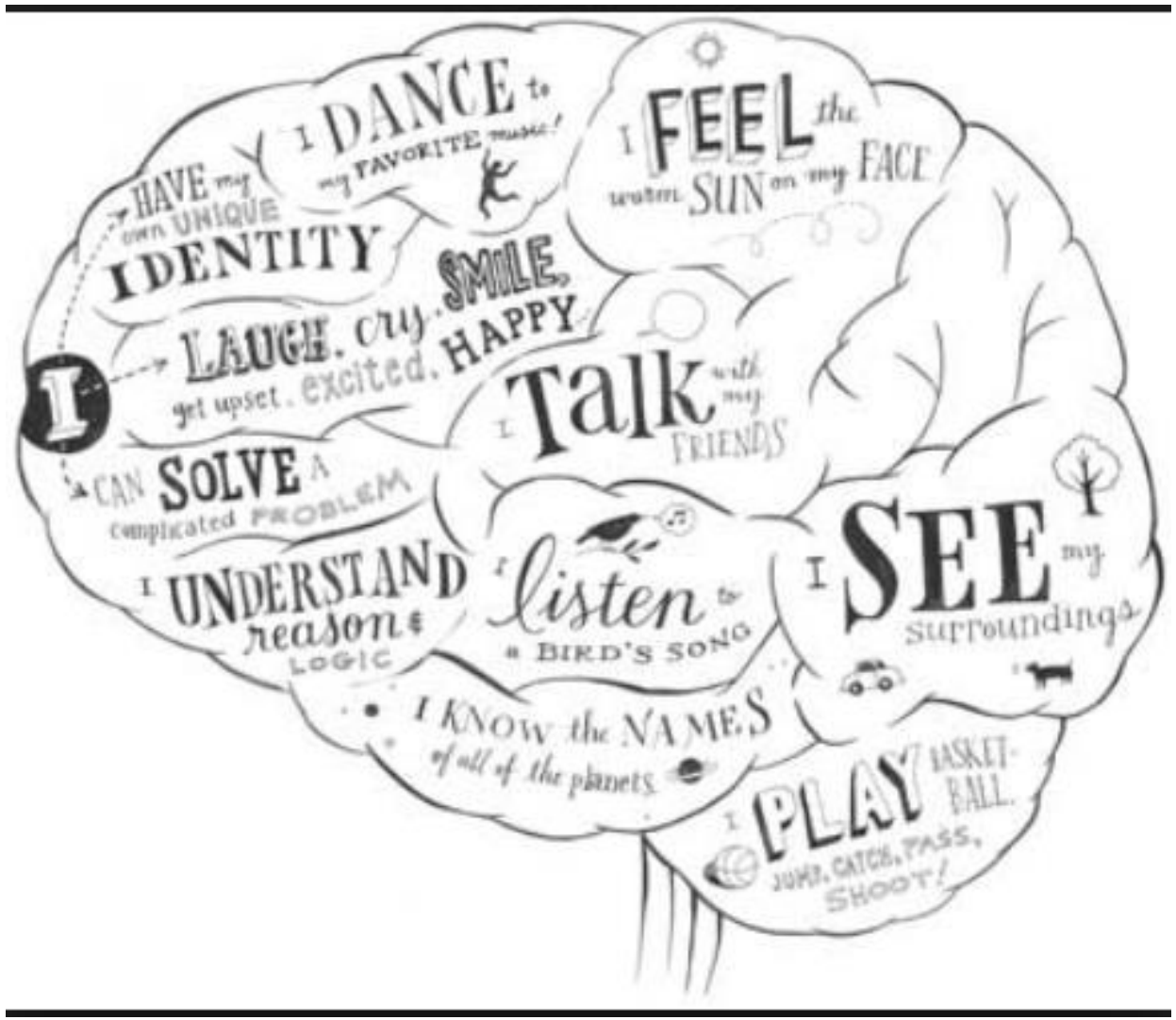
Complexity of pain

Interpretation of signals in the brain

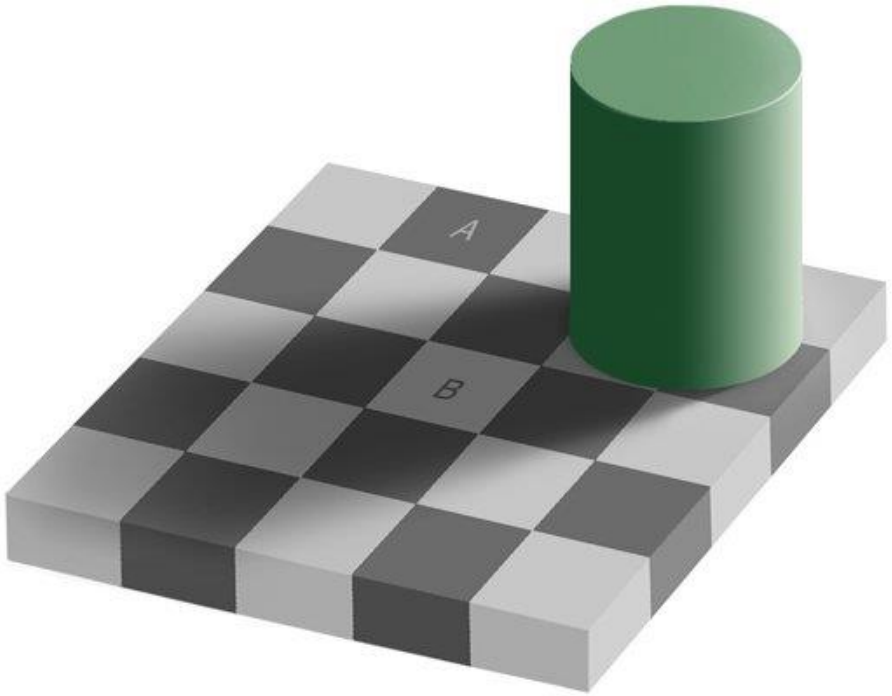


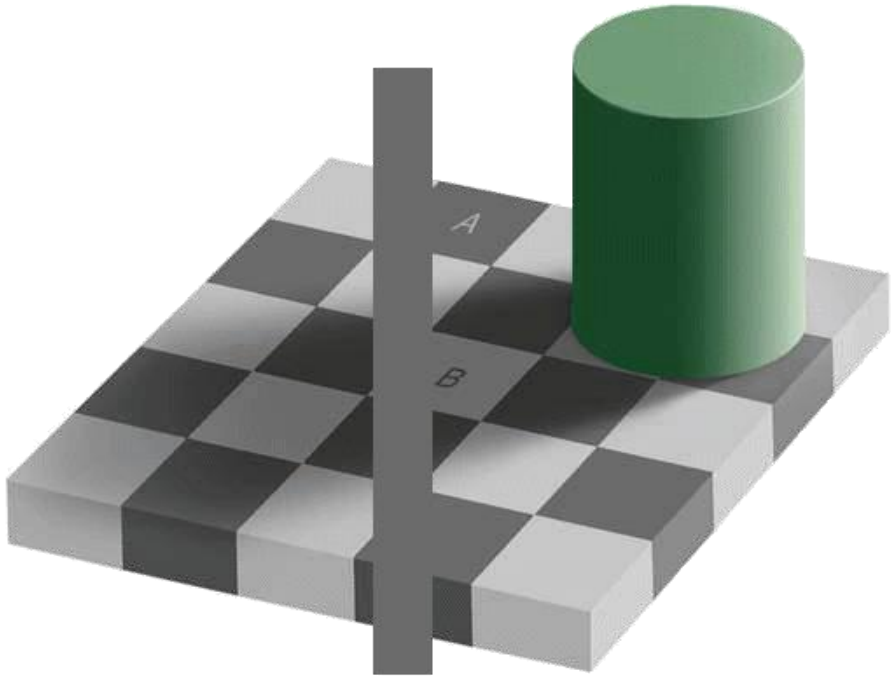


Complexity !!!


I HAVE my own UNIQUE IDENTITY
I DANCE to my FAVORITE music!
I FEEL the warm SUN on my FACE
I LAUGH, cry, SMILE, get upset, excited, HAPPY
I Talk with my FRIENDS
I CAN SOLVE A complicated PROBLEM
I UNDERSTAND reason & LOGIC
I listen to a BIRD'S SONG
I SEE my surroundings
I KNOW the NAMES of all of the planets
I PLAY BASKET-BALL. JUMP, CATCH, PASS, SHOOT!

Perception of signals can be unreliable





Pain assessment

Underassessment of pain

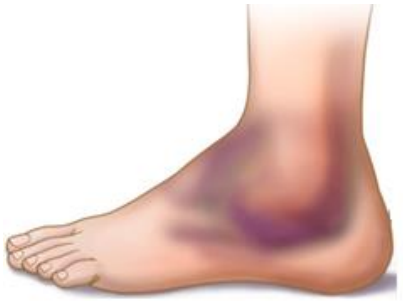
- Cause of inadequate pain management

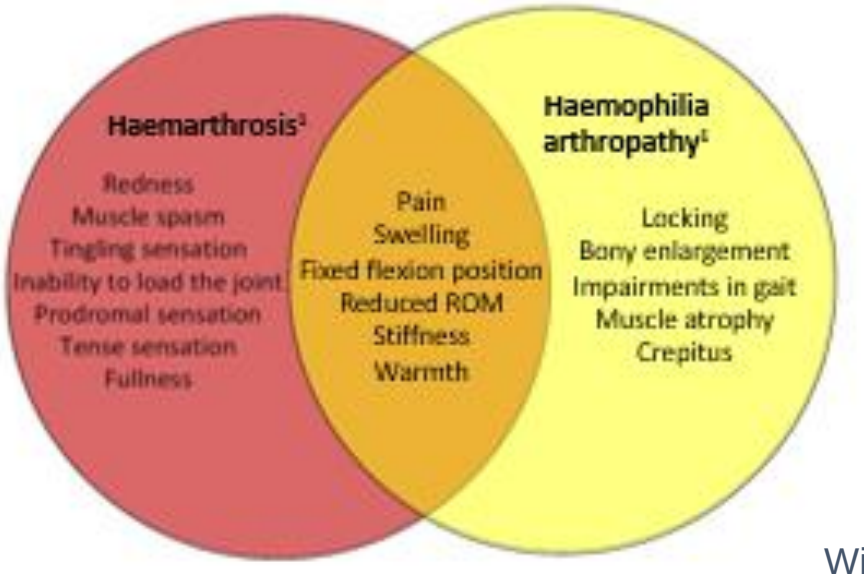
Pain is subjective and multidimensional

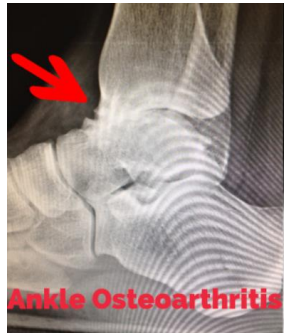
- Include physical and psychological assessment

1. **Patients' history**
2. Questionnaires
3. Clinical tests

Perception of pain







Witkop et al, *Haemophilia*, 2011

PwH and health care providers have difficulties to distinguish symptoms resulting from bleeding versus arthropathy

Increase of pain intensity is not always a bleed

Patients' history

National Pharmaceutical Council
http://www.npcnow.org

Table 8. Information From the Patient History

Parameter	Information To Be Obtained	Sample Questions
Pain characteristics	Onset and duration	When did the pain begin?
	Location(s)	Where does it hurt? (Use diagram, when possible.)
	Quality	What does the pain feel like?
	Intensity (severity)	How severe is the pain right now? (Use numeric rating scale to obtain score, when possible.)
	Associated symptoms	
	Exacerbating or alleviating factors	What increases or decreases the pain?
Management strategies	Past and current: • Medications ("natural," nonprescription, and prescription) • Nonpharmacologic treatments • Coping strategies (e.g., prayer, distraction)	What methods have you used to manage the pain? What methods have worked?
Relevant medical history	Prior illnesses (including psychiatric illnesses and chemical dependence), surgeries, and accidents	How is your general health?
	Coexisting acute or chronic illnesses	Have you had any problems with pain in the past?
	Prior problems with pain and treatment outcomes	If so, how did you manage the pain?

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Patients' history

National Pharmaceutical Council
http://www.npcnow.org

Relevant family history	Health of family members Family history of chronic pain or illnesses	How is the health of your family? Do any family members have problems with pain?
Psychosocial history	Past or current: • Developmental, marital, or vocational problems • Stressors or depressive symptoms • "Reinforcers" of the pain (e.g., compensation-litigation issues)	Are there any recent sources of increased stress? How has the pain affected your mood?
Impact of the pain on the patient's daily life	Impact of the pain on the patient's: • Work • Other daily activities (e.g., chores, hobbies) • Personal relationships • Sleep, appetite, emotional state	How has the pain affected your work and relationships with others? How is your sleep? How is your appetite?
Patient's expectations and goals	Expectations and goals for pain management in regard to pain intensity, daily activities, and quality of life	What are your goals for treatment?

Pain assessment

Underassessment of pain

- Cause of inadequate pain management

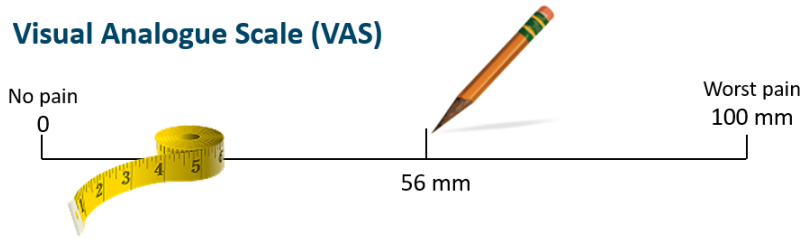
Pain is subjective and multidimensional

- Include physical and psychological assessment

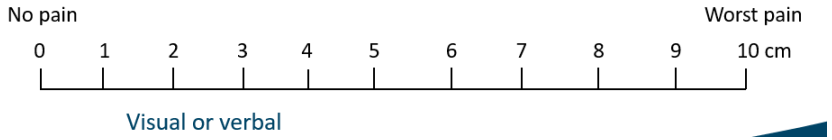
1. Patients' history
2. **Questionnaires**
3. Clinical tests

Unidimensional Pain Scales

Visual Analogue Scale (VAS)

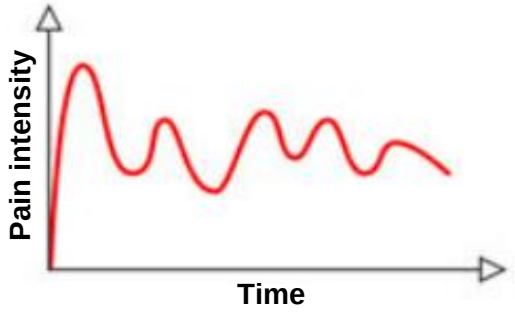


Numeric Rating Scale (NRS)



Wong-Baker Faces Rating Scale

These scales evaluate the pain intensity, not the cause!!!

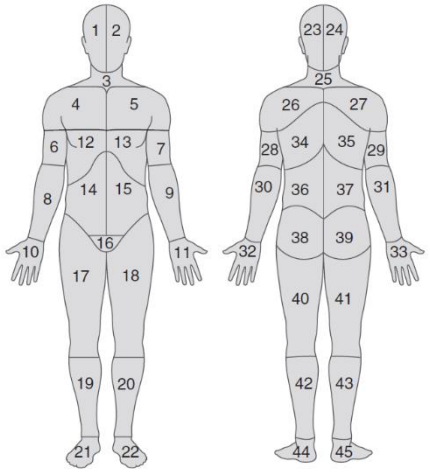


Pain intensity often fluctuates over time

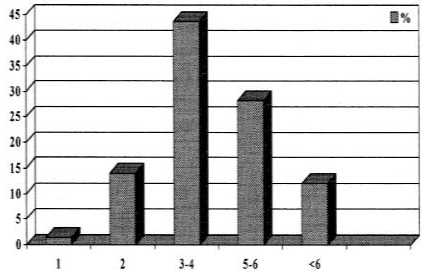
2. Questionnaires

Location & Extent

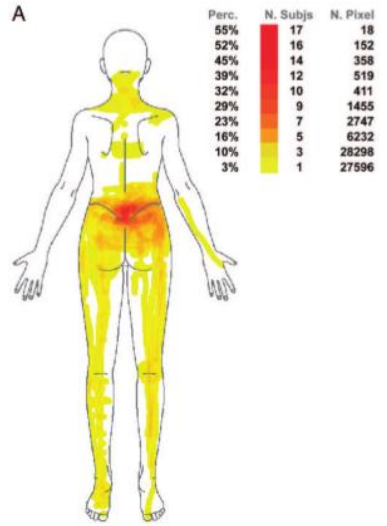
Body Chart



Margolis diagram → **pain location**



Barbero, *Eur J Pain*, 2015



Pain drawing → **extent of pain**

Questionnaires

IPQ-Brief

→ **Illness perceptions**

The Brief Illness Perception Questionnaire

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?											
	0	1	2	3	4	5	6	7	8	9	10
	no affect at all										severely affects my life
How long do you think your illness will continue?											
	0	1	2	3	4	5	6	7	8	9	10
	a very short time										forever
How much control do you feel you have over your illness?											
	0	1	2	3	4	5	6	7	8	9	10
	absolutely no control										extreme amount of control
How much do you think your treatment can help your illness?											
	0	1	2	3	4	5	6	7	8	9	10
	not at all										extremely helpful
How much do you experience symptoms from your illness?											
	0	1	2	3	4	5	6	7	8	9	10
	no symptoms at all										many severe symptoms
How concerned are you about your illness?											
	0	1	2	3	4	5	6	7	8	9	10
	not at all concerned										extremely concerned
How well do you feel you understand your illness?											
	0	1	2	3	4	5	6	7	8	9	10
	don't understand at all										understand very clearly
How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?											
	0	1	2	3	4	5	6	7	8	9	10
	not at all affected emotionally										extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused your illness. *The most important causes for me:-*

1. _____
2. _____
3. _____

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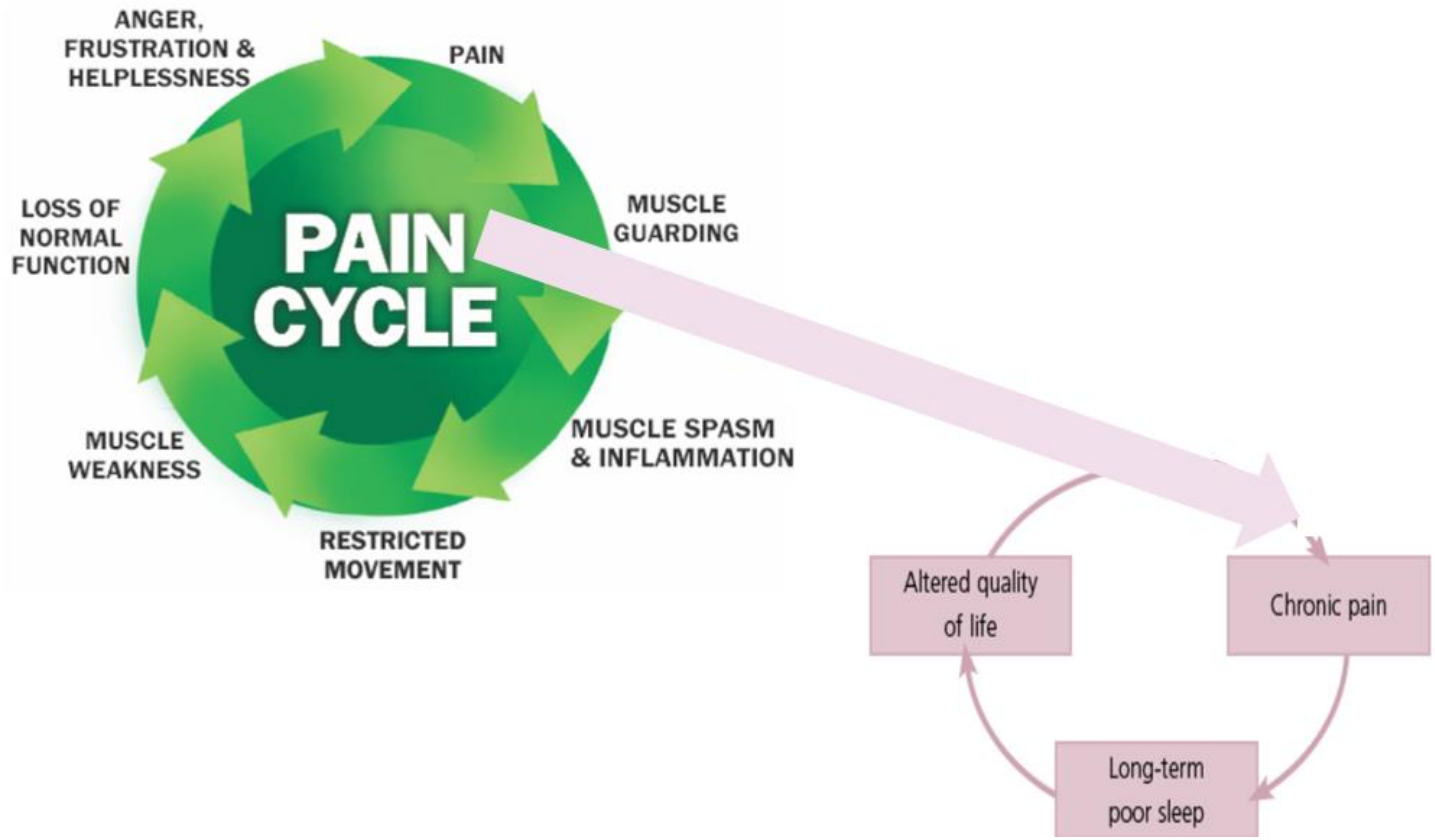
Questionnaires

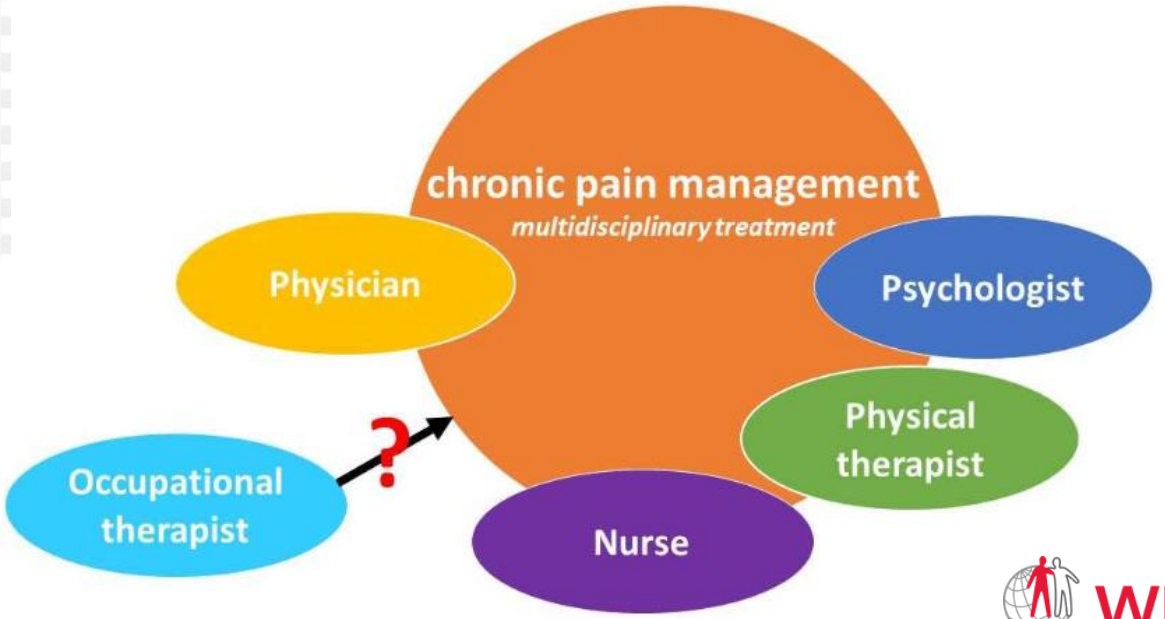
Activities of daily living

Quality of sleep

Quality of life



Pain management



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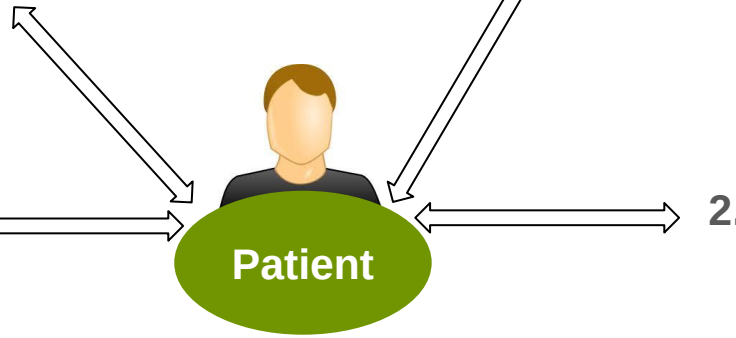
Multidisciplinary approach

4. Modification of strategy

1. Pain assessmen



3. Re-assessment

2. Pain management strategy

Surgery

Advice

Painkillers

Physiotherapy

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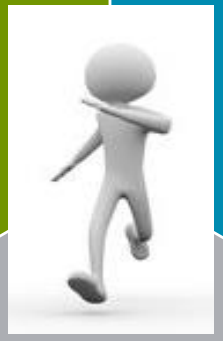
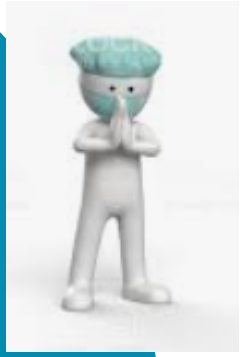
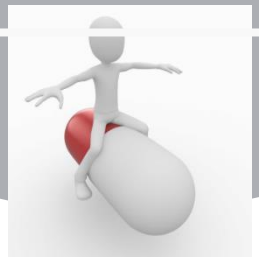
Pain management







Non-Pharma cological

Surgery

Pharmacological

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Pharmacological treatment

WFH guidelines for the management of hemophilia

TABLE 1–5: STRATEGIES FOR PAIN MANAGEMENT IN PATIENTS WITH HAEMOPHILIA

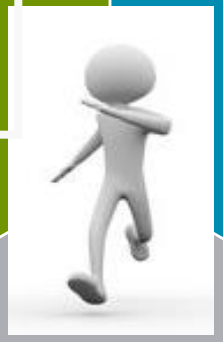
1	Paracetamol / acetaminophen *If not effective*
2	COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide and others) **OR** Paracetamol / acetaminophen plus codeine (3–4 times/day) **OR** Paracetamol / acetaminophen plus tramadol (3–4 times/day)
3	Morphine: Use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more that 4 times/day

Notes:

- If for any reason medications have been stopped for a period of time, patients who have been taking and tolerating high-dose narcotic drugs should re-start the drug at a lower dose, or use a less powerful painkiller, under the supervision of a physician
- COX-2 inhibitors should be used with caution in patients with hypertension and renal dysfunction

Srivastava, *Haemophilia,* 2013

Pain management



Non-pharmacological treatment

Physiotherapy

Psychotherapy

Active

Therapy

Lifestyle

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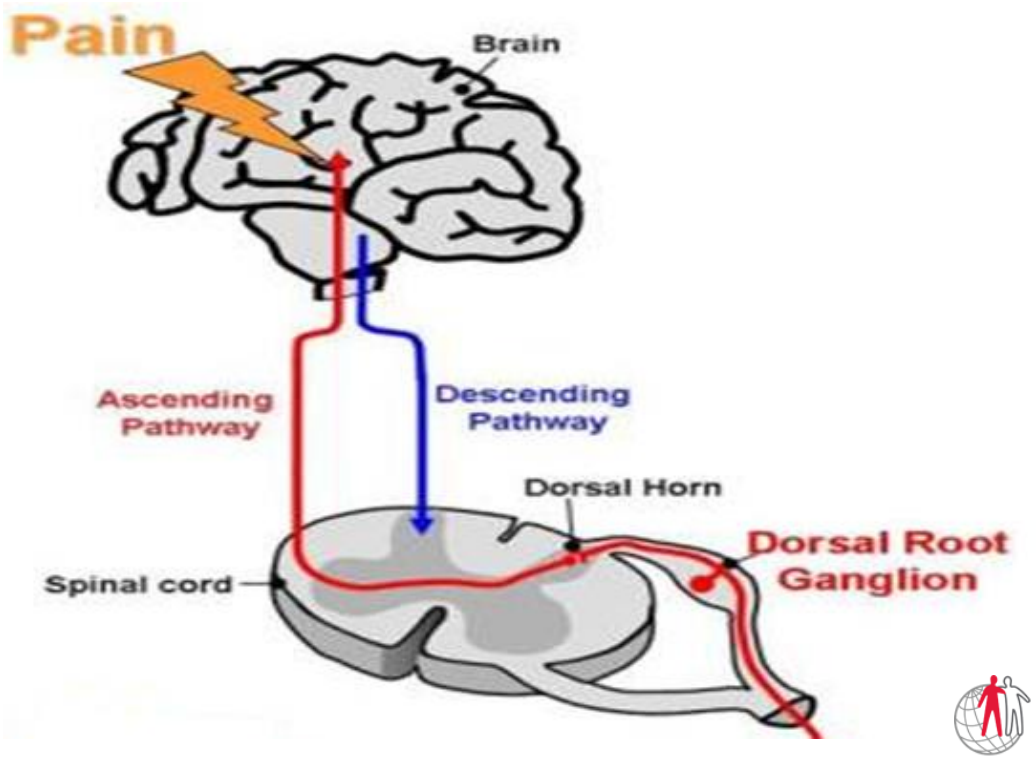
Non-pharmacological treatment

Main predictors of positive treatment outcome in chronic musculoskeletal pain

- Physical activity
- Depression
- Pain catastrophizing
- Self-efficacy



Miles, *Eur J Pain,* 2011

Non-pharmacological treatment

Main predictors of positive treatment outcome in chronic pain

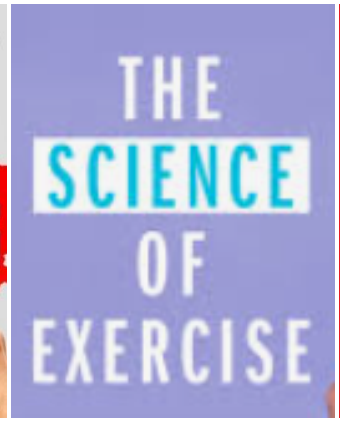
- Physical activity
- Depression
- Pain catastrophizing
- **Self-efficacy**

Miles, *Eur J Pain,* 2011


chronic pain
algiatry
medicine
morphine
pain management
health
hospice
opioids
analgesics
palliative care
relief
suffering


RELIEF
PAIN


customer
complex
data
identification
process
risk
plan
analysis
planning
implementation
monitor
retention
impact
management
opportunity
cost
context
treatment
plan
strategy
research
resources
important
evaluation


THE
SCIENCE
OF
EXERCISE


activity
TIME


RELIEF
ASHWAGANDHA
AYURVEDA
YOGA
TREATMENT
CULTURE
VIVEKANANDA
HEALTH
FIT
NATUROPATHY
STRESS MANAGEMENT
HEAL
CULTURE
REMEDIES
CARE
LIFE
VHG
HOLISTIC
REJUVENATION
HAPPINESS
CALMNESS


CHRONIC
THERAPIST
DEPRESSION
THOUGHT
TECHNIQUE
TREAT
TRAINING
ANXIETY
COGNITIVE
SHOWN
PSYCHOTHERAPEUTIC
COGNITION
PATIENT
MULTIMODAL
EXPOSURE
BEHAVIORAL
PSYCHOANALYSIS
HYPOCHONDRIASIS
THINKING
ROLE
BEHAVIORIST
SCHIZOPHRENIA
THERAPY
IMAGINAL
BEHAVIOR
BEHAVIORAL
APPROACH

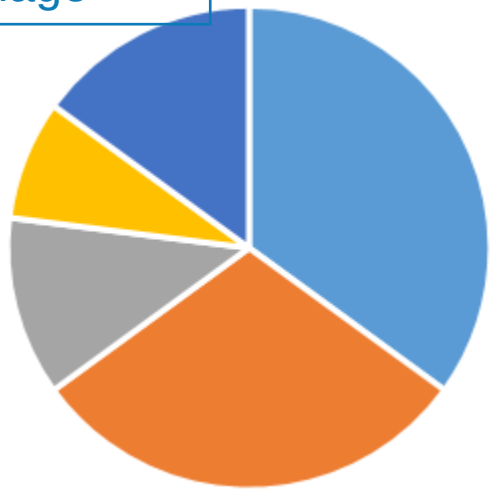
Take home messages

Pain analysis

Structural damage

Inflammation

Overweigth, sedentary



Deconditioning

Altered central pain mechanisms

Pain management

Brace/Surgery

Medication

Exercise & Physiotherapy

Lifestyle

Altered central pain mechanisms

EAHAD
European Association for Haemophilia and Allied Disorders

AHVH
Hemofilievereniging
Association de l'Hémophilie

University of Antwerp

BAYER

sobi
rare strength

CSL Behring
Biotherapies for Life™

UCLouvain

UZA

Cliniques universitaires
SAINT-LUC
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Un hôpital pour la Vie

BERGISCHE
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Mental Health and People with Bleeding Disorders (and their family members)

Kate Khair, PhD
Director of Research, Haemnet
Kate@Haemnet.com
U.K.

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Speaker disclosures

Shareholder	Haemnet Ltd
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Sponsored lectures	Bayer, CSL Behring, Novo Nordisk, Roche, Sobi, Takeda, Pfizer, uniQure

Day of diagnosis

>90% of mothers will be carriers
- Even in 30-50% with no family history

Loss
- ‘this is not the child I thought I was having’

Maternal guilt and sorrow
- Gender genetics!

Blame
- Cultural need for a ‘normal’ son

Learn to live with this child
- Impact now and into whole life going forward

Parenting a child (with haemophilia)

Mothers[1]

Move from a state of sad, guilty chaos to reconciling themselves with the (new) situation

- Time post diagnosis
- The turning point
- Reconciliation with a changing life

Fathers[2]

Grow through 'A tortuous road to a capable fatherhood'

- Sorrow
- Powerlessness
- Concern
- Loss of a regular fatherhood
- Insufficiency with treatment

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[1]Myrin-Westesson L, et al. Haemophilia. 2013 Mar;19(2):219-24.
[2]Myrin Westesson L, et al. Haemophilia. 2015 Nov;21(6):799-805.

Parental distress

- Child's pain, emotional stress, financial concerns, transportation, sacrifice and medical management[1]
- Out of pocket expenses[2]
- Worse with children with inhibitors[3]
  - Mothers report more personal pain than fathers[4]
- Normalisation[5]
  - Integration of care in to daily life
  - NOT just about prophylaxis!
  - (But that could be seen as a burden)

[1]DeKoven et al. Haemophilia 2014;20(4):541-9.
[2]Khair & Pelentsov. Haemophilia 2019;25(5):831-837.
[3]DeKoven et al. Haemophilia 2014;20(6):822-30.
[4]Lindvall K et al. Pediatr Blood Cancer 2014;61(4):706-11.
[5]Emiliani et al. Qual Health Res 2011;21(12):1667-78.

Treatment Burden

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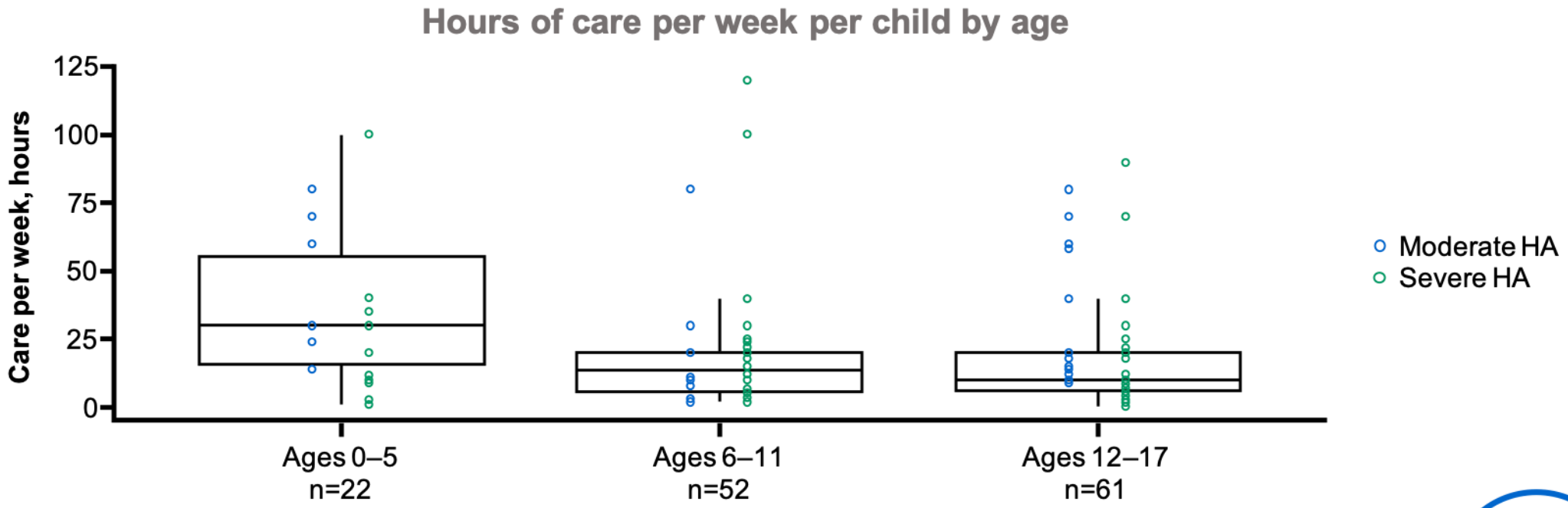
Caregivers – The BBC study

- Greater burden was seen in caregivers of children who
  - Had joint bleeds
  - Had target joints or reduced range of motion
  - Had a current inhibitor (significantly higher burden)
  - Lived with chronic pain1
- 66% caregivers reported that haemophilia affected their life
- 26.8% reported an economic impact
- Caregivers lost an average of 8.35 ± 14.5 days work due to haemophilia
  - spending ≥5 h/month infusing and ≥3 h/month travelling to the HTC2

[1]Khair et al. Haemophilia 2019;25(3):416-423.
[2]von Mackensen et al. Haemophilia 2019;25(3):424-432.

CHESS PAEDS



- Median (IQR) hours of care provided per week decreased from 30.0 (15.5, 55.0) for children aged 0–5 to 10.0 (6.0, 20.0) for children aged 12–17 years

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Khair K et al (oral presented at ASH 2020)

Treatment burden

Lack of parental attention[1]
Less of an issue (in haemophilia) with new therapies?
Fewer treatments, less burden?[1,2]
Personalised treatment
Responsibility lies with the PWH

Data records
'a valuable tool that may improve treatment compliance and optimize treatment regimen'[3]

Evidence – requires instrument completion:

- Compliance tools!
- QoL
- Anxiety
- Pain
- Burden

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[1]Khair et al Haemophilia 2019;25(5):814-820.
[2]van Balen at al. The Patient 2020;13(2):201-210.
[3]Hay et al. Haemophilia 2017;23(5):728-735.

Siblings

Lack of parental attention[1]

Negative social emotions[1]

Carrier status anxiety[1,2]

- ‘Mothers of the future’[3]
- Parental coping strategy[4]

[1]Tregidgo & Elander. Haemophilia 2019;25(1):84-91.
[2]Fujii T et al. Haemophilia 2019;25(6):1059-1065.
[3]von der Lippe et al. J Genet Couns. 2017;26(6):1324-1332.
[4]Vears DF et al. J Genet Couns. 2016;25(6):1257-1266.

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Adults – ‘haemophilia related distress’

US Data[1]

- Feelings of isolation and vulnerability
- Physical functioning
- Lack of trust in knowledge and care provided by staff in community healthcare settings,
- Concerns about the future (insurance, ageing/disability)
- Being different from others and feeling like an outsider
- Treatment burdens and fear of acute bleeds

CHESS[2]

- Clinical outcomes and quality of life are impaired in young adults despite primary prophylaxis
- Primary prophylaxis is not associated with lower levels of anxiety and depression than on-demand treatment
- Pain is common

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[1]Mattis S et al. Haemophilia 2019 Nov;25(6):988-995.
[2]O'Hara S et al. Haemophilia 2021 Jan;27(1):113-119.

Women’s issues

CARRIERS	Or people affected by haemophilia?
PSYCHOLOGY	Little data on of impact on women as ‘bleeders’
GUILT AND BLAME	Impact on carriers[1] (affected women with any bleeding disorder)
NEW AND EMERGING AREA	Increasingly recognized by patient associations

[1]von der Lippe et al. J Genet Couns. 2017;26(6):1324-1332.

Past history with viruses

Impact on parenting choices

- Anxiety of ‘carriers’ to have affected babies

Impact on perceptions of gene therapy?

- How can a virus be a good thing?

Survivor guilt / PTSD

- Surviving sibling/family member/peer
- Impact of ongoing inquiry

Managing expectations around gene therapy

Gene therapy may lead to

Reduction in anxiety/depression

Positive feelings – joy, ease of living, new outlook on life[1]

Emotional support may be required to deal with

Feelings of loss of identity or community[2]

Uncertainty (duration of expression)[1]

Loss of past opportunity

If we don't ask the right questions – we will never know

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[1]Miesbach et al Patient Prefer Adherence. 2020 Apr 22;14:767-770.
[2]Fletcher S et al. Haemophilia. 2021 Sep;27(5):760-768

Outcome Assessments

Haemophilia — WILEY 137

Chapter 11: Outcome Assessment

Pradeep M. Poonnoose[1] | Brian M. Feldman[2] | Piet de Kleijn[3] | Manuel A. Baarslag[4] | Radoslaw Kaczmarek[5] | Johnny Mahlangu[6] | Margaret V. Ragni[7] | Glenn F. Pierce[8] | Alok Srivastava[9]

- Frequency of bleeding
- Pain
- Body structure & function
- Activities and participation

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Outcome Measures and Mental Health

11.5 Environmental & personal factors
(E) Access to treatment
Insurance
(P) Resilience
treatment adherence

11.6 Economic Factors
Direct: Medicines, care and services
Indirect: Loss of work, 'out of pocket costs'
Burden

11.7 Health related QoL
Generic: EQ5D
Specific: CHO-KLAT
Haemo-QoL-A
PROBE

11.8 Patient reported outcomes
EQ5D
Pain
Activity
Burden

11.9 Core set of measures for use in clinic or research

- Value of care created for patients (outcomes achieved relative to cost)
- HCP's usually select instruments we think are relevant for you!
- Standardized measures should be encouraged
- Measuring a minimum set for every major medical condition
  - (not just severe hemophilia)
- WFH World Bleeding Disorders Registry (WBDR) collects uniform standardized patient data and outcomes
  - (WFH Gene Therapy Registry will do same)
- Advancing clinical care and studies on treatment outcomes

WFH Compendium of Assessment Tools webpage http://elearning.wfh.org/resource/compendium-of-assessment-tools/

CONCLUSIONS

- Mental health is as important as physical health
- Individual patients come with a family
- Treatment (or lack of it) impacts on physical AND mental health
- We need better focus on mental health outcomes
  - That are relevant to people with bleeding disorders
  - Enable better provision of support and care
  - New therapies on horizon
- The importance of talking about mental health is gaining visibility

THANK YOU

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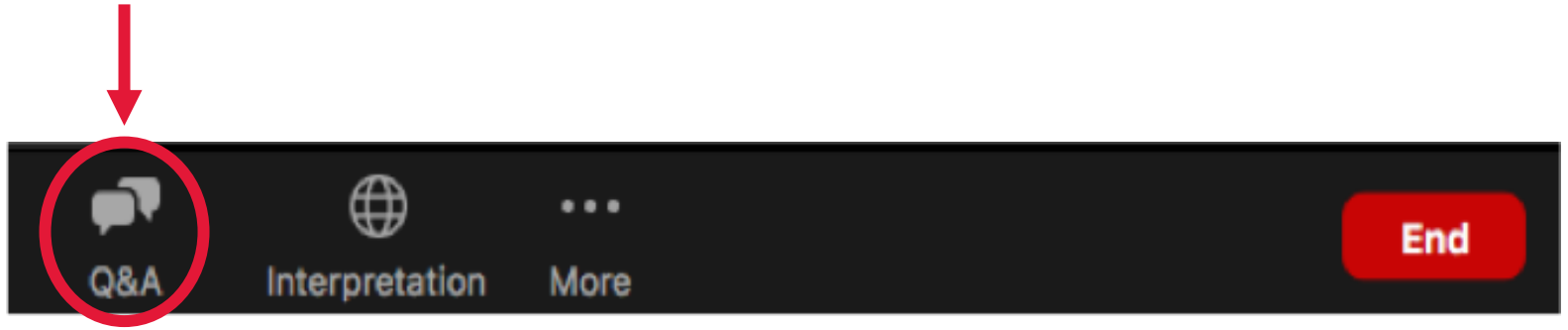
QUESTION & ANSWER

Please submit your questions in the Q&A box



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COMPASSION to ACTION
Together we can

THANK YOU!

¡GRACIAS!

MERCI!

شكرا

СПАСИБО

STAY SAFE!

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