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

Overview of World Federation of Hemophilia Treatment Guidelines, 3rd edition

Glenn Pierce, MD, PhD
World Federation of Hemophilia, VP Medical
Medical and Scientific Advisory Council, National Hemophilia Foundation
La Jolla, California

Housekeeping

- Upon joining the webinar, you will see two audio options. You can opt to listen via the speakers on your computer OR by using your phone to call in. If the phone option is chosen, the webinar toolbar will provide you with the phone and access number and audio pin.

- All audio will be muted. At the end of the presentation there will be time for questions. To submit a written question, please use the “Questions” area of your toolbar. The presenters will respond to as many questions as time allows.

- Today’s webinar will last approximately 1 hour. Please note that this webinar will be recorded.

- We will begin today’s webinar first with two brief audience polls. First, we are interested in knowing more about you. Please select your response to the poll question now.

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

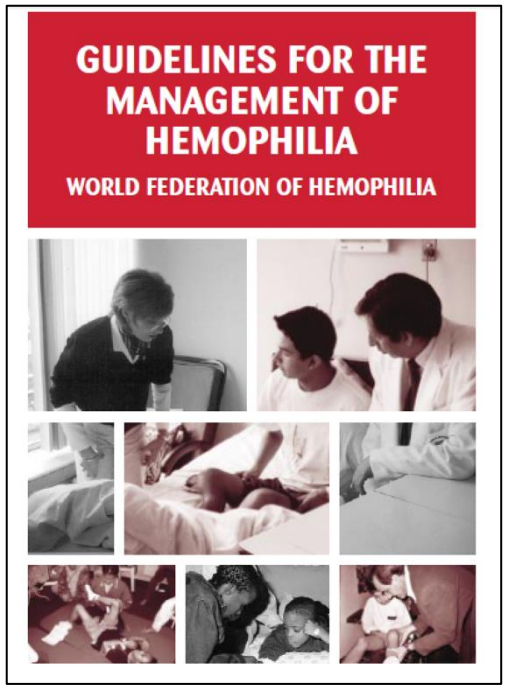
Disclosures for Glenn Pierce, MD, PhD

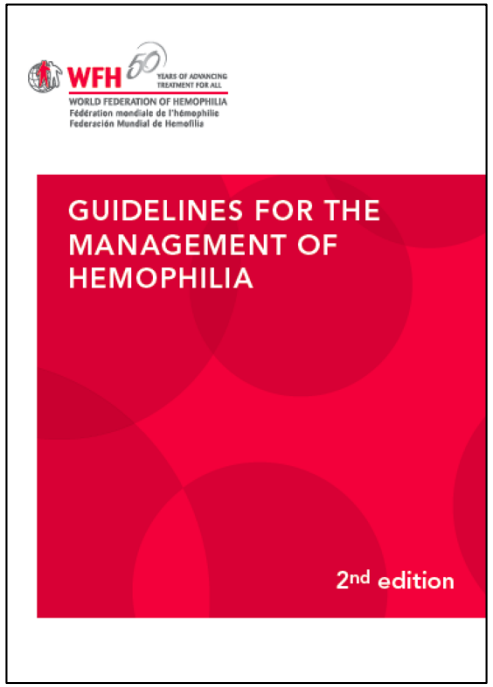
- **Director: Director, Global Blood Therapeutics, Voyager Therapeutics, World Federation of Hemophilia**
- **Advisory Boards: NHF Medical and Scientific Advisory Council (MASAC)**
- **Consultant: Ambys Medicines, BioMarin, CRISPR Therapeutics, Decibel Therapeutics, Frontier, Geneception, Generation Bio, Novo Nordisk, Pfizer, Third Rock Ventures**

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

WFH Guidelines for the Management of Hemophilia, 2005, 2012, 2020

https://onlinelibrary.wiley.com/doi/10.1111/hae.14046





1st Edition (2005)

6 member writing group
No references
Bibliography of 10 documents

2nd Edition (2012)

11 member writing group
literature search & grading of cited level of evidence on which recommendations were based

>1000 citations
>1 million downloads in 6 languages

3rd Edition (2020)

~50 expert panelists
Each chapter supported by a full systematic review
eDelphi
344 practical recommendations

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

DOI: 10.1111/hae.14046

SUPPLEMENT ARTICLE

Haemophilia WILEY

WFH Guidelines for the Management of Hemophilia, 3rd edition

Alok Srivastava[1] | Elena Santagostino[2] | Alison Dougall[3] | Steve Kitchen[4] | Megan Sutherland[5] | Steven W. Pipe[6] | Manuel Carcao[7] | Johnny Mahlangu[8] | Margaret V. Ragni[9] | Jerzy Windyga[10] | Adolfo Llinás[11] | Nicholas J. Goddard[12] | Richa Mohan[13] | Pradeep M. Poonnoose[14] | Brian M. Feldman[15] | Sandra Zelman Lewis[16] | H. Marijke van den Berg[17] | Glenn F. Pierce[18] | on behalf of the WFH Guidelines for the Management of Hemophilia panelists and co-authors*

https://onlinelibrary.wiley.com/doi/10.1111/hae.14046

Health Care Provider Panelists

Erik Berntorp, Margareth Castro Ozelo, Carlos D. De Brasi, Piet de Kleijn, Silmara A. de Lima Montalvão, Gerard Dolan, Alison Dougall, Carmen Escuriola Ettingshausen, Emna Gouider, Kate Khair, Barbara A. Konkle, Rolf C. R. Ljung, Gianluigi Pasta, Shrimati Shetty, Alison Street, Claude Tayou Tagny, Pierre Toulon

PWH/Parents Panelists

Abdelaziz Al Sharif, Manuel A. Baarslag, Lisa Bagley, Francisco Careta, Kim Chew, Gaetan Duport, Radoslaw Kaczmarek, Augustas Nedzinskas, Enrique David Preza Hernández, Bradley Rayner, R. Sathyanarayanan, Andrew Selvaggi, Ekawat Suwantaroj

Guidelines Methodology Leadership Team

Donna Coffin, Debbie Hum, Melanie Golob, Sonia O'Hara, Tom Schofield, Lucy T. Henry, Maura Sostack

Endorsed by

Asian-Pacific Society on Thrombosis and Hemostasis,
European Haemophilia Consortium
National Hemophilia Foundation (USA)

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

WFH Guidelines for the Management of Hemophilia, 3rd edition

3rd Edition, 2020
12 Chapters

1. **Principles of care***
2. Comprehensive care
3. Lab diagnosis and monitoring
4. **Genetic assessment***
5. Hemostatic agents
6. **Prophylaxis in hemophilia***
7. Treatment of specific hemorrhages
8. **Inhibitors to clotting factor***
9. Specific management issues
10. Musculoskeletal complications
11. **Outcome assessment***
12. **Methodology***

*New chapters in 3rd edition

344 practical recommendations

https://onlinelibrary.wiley.com/doi/10.1111/hae.14046

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

Hemophilia is a Global Disease

- Therapeutic advances in hemophilia arriving at breathtaking pace, uneven distribution
  - 60% of world (LMIC, LIC) use 7% of available product
- Treatment practices vary considerably around the world, related to access to treatment
- However, principles of care are universal, and decreased morbidity and mortality can be achieved even in lower resourced countries
- In higher resourced countries, management of hemophilia is not uniform, QoL and long-term outcomes vary
- Guidelines, established by both data and consensus make a difference

Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The World Federation of Hemophilia Annual Global Survey 1999-2018. Haemophilia. 2020;00:1–10. https://doi.org/10.1111/hae.14012. Pierce GF, Haffar A, Ampartzidis G, et al. First-year results of an expanded humanitarian aid programme for haemophilia in re- source-constrained countries. Haemophilia. 2018;24(2):229-235. WFH Annual Global Survey, https://elearning.wfh.org/resource/report-on-the-annual-global-survey-2019/

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

WFH Guidelines for the Management of Hemophilia, 3rd edition

3rd Edition, 2020
12 Chapters

1. **Principles of care***
2. Comprehensive care
3. Lab diagnosis and monitoring
4. **Genetic assessment***
5. Hemostatic agents
6. **Prophylaxis in hemophilia***
7. Treatment of specific hemorrhages
8. **Inhibitors to clotting factor***
9. Specific management issues
10. Musculoskeletal complications
11. **Outcome assessment***
12. **Methodology***

*New chapters in 3rd edition

344 practical recommendations

https://onlinelibrary.wiley.com/doi/10.1111/hae.14046

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

Speakers

Steven Pipe, MD
University of Michigan
Hemostatic Agents

Margaret Ragni, MD, MPH
University of Pittsburgh
Inhibitors

Manuel Carcao, MD
The Hospital for Sick Children in Toronto
Prophylaxis

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

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

Hemophilia Guidelines for All:

A new ambition of the World Federation of Hemophilia

Steven Pipe, MD
University of Michigan

The WFH Guidelines for the Management of Hemophilia, 3rd edition

Disclosures for Steven Pipe, MD

- **Research Support:** Siemens
- **Advisory Committee:** Sangamo Therapeutics (Scientific Advisor Board)
- **Consultant:** Apcintex, Bayer, Biomarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics, uniQure

Chapter 5: Hemostatic Agents 2020 Updates

Committee Members

S Pipe, M Carcao, K Chew (PPWH), R Kaczmarek (PWH),

S Kitchen, J Mahlangu, M Ozelo, E Suwantaroj (PWH), J Windyga,

G Pierce, A Srivastava

PWH is person with hemophilia, PPWH is parent of a person with hemophilia

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

Agenda

1. Corroboration
2. Clinical Tools
3. Controversy

Clinical Case – Liam @ 9 months

- Severe hemophilia A
- Diagnosed at birth based on family history (uncle and great-grandfather)
- No Factor VIII(FVIII) exposures to date
- Starting to show more bruising/hematomas over extremities now that he started crawling
- Family ready to consider initiating prophylactic FVIII replacement therapy

Which product to start?

- Recombinant?
- Plasma-derived?
- Emicizumab?

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

Corroboration

Recommendation 5.1.1:

- For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived factor concentrates.
- **Remark**: The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences.

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

Clinical Case – James @ 16 months

- Severe hemophilia A
- Diagnosed at birth after bleeding circumcision
- Presented at 4 months with intracranial hemorrhage, port placed for regular infusions
- Developed a high titer FVIII inhibitor, had 1 year of attempt at immune tolerance induction but inhibitor remained refractory
- Family no longer willing to continue intense infusion schedule

How should he be managed with a refractory FVIII inhibitor?

Corroboration

Recommendation 5.4.3:

- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events.

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

Corroboration

Recommendation 5.7.1:

- For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis.
- **Remark:** For patients with hemophilia A with no inhibitor, the WFH recommends that emicizumab can be used for regular prophylaxis.

Specific recommendations regarding use of emicizumab are covered in:

- Chapter 2: Comprehensive Care of Hemophilia
- Chapter 6: Prophylaxis in Hemophilia
- Chapter 8: Inhibitors to Clotting Factor
- Chapter 9: Specific Management Issues

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

Clinical Case – William @ 8 years

- Severe hemophilia A
- On primary prophylaxis since infancy
  - SHL-FVIII qOD
- Despite an aggressive regimen, he still has occasional breakthrough bleeds and family struggling with adherence

Would he benefit from an extended half-life (EHL) product?

- What regimen?
- How to evaluate?
- Does it matter which EHL-FVIII?

SHL is standard half-life; qOD is every other day

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

Clinical Tools

Recommendation 5.3.1:

- For people with hemophilia A receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends individualized pharmacokinetic (PK) monitoring.
- **Remark:** Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates.

Recommendation 5.3.9:

- For patients with hemophilia B.....WFH recommends pharmacokinetic monitoring.

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

Clinical Tools

Recommendation 5.3.11:

- Patients with hemophilia who are transitioning from standard half-life (SHL) factor concentrates to extended half-life (EHL) factor concentrates would typically require decreased dose frequencies, but EHL products may also be used to maintain higher trough levels to optimize prophylaxis.
- **Remark**: Pharmacokinetic-guided dosing as per Recommendations 5.3.1 and 5.3.9 provides for more individualized prophylaxis

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

Controversy

Recommendation 5.3.10:

- For patients with hemophilia A or B, there is no evidence for any *clinical safety* issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of factor concentrates.

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

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

THANK YOU

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

Hemophilia Guidelines for All:

A new ambition of the World Federation of Hemophilia

Margaret Ragni, MD, MPH
University of Pittsburgh

The WFH Guidelines for the Management of Hemophilia, 3rd edition

Disclosures for Margaret V. Ragni, MD, MPH

- **Research Funding:** Alnylam/Sanofi, BioMarin, Bioverativ/Sanofi Takeda/Shire, Sangamo, Spark Therapeutics
- **Advisory Boards:** Alnylam/Sanofi, BioMarin, Takeda/Shire, Spark Therapeutics

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

Chapter 8: Inhibitors to Clotting Factors, 2020 Updates

Committee Members

M Ragni, E Berntorp, M Carcao, C Ettingshausen

A Nedzinskas (PWH), M Ozelo, E Hernandez (PWH),

A Selvaggi (PWH), HM van den Berg,

G Pierce, A Srivastava

PWH is person with hemophilia

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

Inhibitors 2020

Disease Burden

- More serious bleeding, complications
- More allergic reactions
- Higher rate of hospitalization
- Greater treatment costs
- Higher mortality rate

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

Inhibitors 2020

What's New

- **Bleed management**
- **Inhibitor screening**
- **Immune tolerance induction (ITI)**
- **Surgery and invasive procedures**
- **Product switching**

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

Clinical Case 1

An 11-month-old-male with severe hemophilia A develops a large gluteal hematoma and small scattered hematomas over the last week. He has been on on-demand recombinant FVIII (rFVIII) for a target right knee bleed, but it is poorly responsive to his usual rFVIII. There is no family history of inhibitors, but a 3-year-old cousin also has severe hemophilia A.

At the HTC visit, laboratory tests are drawn and reveal: Hgb 11.0 g/dL, FVIII <0.01 IU/ml, and anti-FVIII 12.0 BU.

His family asks how to treat bleeds now that he has an inhibitor. They also wonder if his cousin should be tested for inhibitors.

BU is Bethesda unit, used to measure inhibitor titer

Bleed management

Treatment is based on inhibitor type: low-responding (LR) or high-responding (HR)

Hemophilia A patients with inhibitors

	Low-responding inhibitors (LR)	High-responding inhibitors (HR)
Agent	**FVIII**	**rFVIIa** or **aPCC** or FVIII*
Monitoring	FVIII activity (FVIII:C) assay	Thromboelastography / thrombin generation

Hemophilia B patients with inhibitors

Agent	**FIX**	**rFVIIa** or **aPCC**** or porcine FVIII
Monitoring	FIX activity (FIX:C) assay	Thromboelastography / thrombin generation

* **HA**: In HR, with low inhibitor titer, FVIII may be used, monitoring for anamnestic response.
****HB**: With FIX-containing products, there is risk for allergic reactions, nephrotic syndrome.

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

Inhibitor screening

- **After initial factor exposure, at least every 6-12 months, then annually**
- **After intensive factor exposure, e.g. > 5 days, within 4 weeks of last exposure**
- **For recurrent bleeds or target joint bleeds, despite adequate CFC replacement therapy**
- **For failure to respond to adequate CFC replacement therapy**
- **For lower factor recovery or half-life than expected after CFC replacement therapy**
- **For suboptimal clinical or laboratory response to CFC replacement therapy**
- **Before surgery**
- **For suboptimal postoperative response to CFC replacement therapy**

CFC is clotting factor concentrate

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

Clinical Case 2

The bleed resolves with rFVIIa. You introduce the concept of ITI with the parents. They ask what is the most effective approach to rid the inhibitor. They ask if a port is needed?

They recently attended the INHIBITOR summit and met several families who had a good experience with emicizumab.

If they decide to switch to emicizumab will it rid the inhibitor, or can the inhibitor "come back" years later?

How would they treat bleeds?

Brand name of emicizumab is Hemlibra®

Immune tolerance induction*

	Hemophilia A patients with inhibitors	Hemophilia B patients with inhibitors
Drug	**rFVIII, pdVIII, rFVIIIFc** – success 70%	**rFIX** – success lower than in HA
Dose	**rFVIII:** 100 IU/kg daily	High-dose (as in HA); consider immunosuppression
Success	Persistently negative titer, recovery > 66%, half-life > 6 hours	Persistently negative titer
Failure	If ITI unachieved in 2-3 years	rFIX may increase allergic reactions, nephrotic syndrome

ITI is immune tolerance induction

* Few data exist on ITI in hemophilia B, so WFH makes no specific recommendations for hemophilia B ITI.

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

Immune tolerance induction

General guidance

- All inhibitor patients should undergo a trial of ITI
- Data on the impact of EHL products in ITI are limited
- After successful ITI, FVIII prophylaxis should be initiated
- Non-factor therapies may reduce disease burden
- Use of non-factor therapies in ITI is not established

EHL is extended half-life

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

Bleed management and emicizumab

Hemophilia A patients with inhibitors on emicizumab prophylaxis

	Low-responding inhibitors (LR)	High-responding inhibitors (HR)
Agent	**FVIII**	**rFVIIa** preferred over aPCC due to TMA* risk
Monitoring	Bovine reagent-based chromogenic assay (bovine FX in kit reagent)	Thromboelastography / thrombin generation

*TMA is thrombotic microangiopathy, which has been reported in patients receiving aPCC and emicizumab. Close monitoring is recommended in those with thrombosis risk factors: *past VTE, obesity, smoking, chronic infection and inflammation;* and also in those receiving rFVIIa in whom risk appears low.

Adamkewicz JI, *Haemophilia* 2017;23:11-17; Levy GG, *JTH* 2019;17:1470-77; Neufeld EJ, *Blood Rev* 2015; 29(Suppl 1): S34-41.

Clinical Case 3

The child's maternal uncle is a 43-year-old man with severe hemophilia A and past anti-FVIII 5.7 BU. He was begun on ITI 2 years after inhibitor detection but was refractory to ITI, so he has been taking rFVIIa for bleeds.

Now he has painful arthritis of the right ankle. The surgeon says ankle fusion surgery is indicated. Lab studies reveal anti-FVIII 4.5 BU.

He says his nephew recently started weekly emicizumab and he would also like to switch, but he has a few questions. Can he switch to emicizumab or should he wait until after surgery? Once he switches, can he still take rFVIIa to treat bleeds?

Surgery and invasive procedures

General recommendations:

- Determine factor coverage, bypass, follow-up; or use adjusted-dose continuous infusion.
- Once hemostasis is achieved, maintain regimen 3-5 days, then taper over 1-3 weeks.

	Low-responding inhibitors (LR)	**High-responding inhibitors (HR)**
HA-I, HB-I:	Higher, more frequent doses or adjusted-dose continuous infusion	Single-agent bypass **(rFVIIa or aPCC)** or, if fails, consider sequential bypass
HA-I: Emicizumab prophylaxis	**FVIII** products advised for surgery	**rFVIIa** preferred over aPCC for surgery
HB-I: Factor IX allergy	**rFVIIa** advised for surgery	**rFVIIa** is advised for surgery

HA-I is hemophilia A with inhibitor; HB-I is hemophilia B with inhibitor.

Surgery and invasive procedures

General recommendations:

- Determine factor coverage, bypass, follow-up; or use adjusted-dose continuous infusion.
- Once hemostasis is achieved, maintain regimen 3-5 days, then taper over 1-3 weeks.

	Low-responding inhibitors (LR)	**High-responding inhibitors (HR)**
HA-I, HB-I:	Higher, more frequent doses or adjusted-dose continuous infusion	Single-agent bypass **(rFVIIa or aPCC)** or, if fails, consider sequential bypass
HA-I: Emicizumab prophylaxis	**FVIII** products advised for surgery	**rFVIIa** preferred over aPCC for surgery
HB-I: Factor IX allergy	**rFVIIa** advised for surgery	**rFVIIa** is advised for surgery

HA-I is hemophilia A with inhibitor; HB-I is hemophilia B with inhibitor.

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

Immune tolerance induction (ITI)

When should ITI be initiated?

- ITI should start immediately after detection, no matter the titer

What agent should be used in ITI?

- The optimal regimen is undefined; **rFVIII** 100 IU/kg/day preferred

How should bleeds be managed in ITI?

- In LR, **rFVIII** should be used to treat acute bleeds
- In HR, **rFVIIa or aPCC*** bypass; or, if low titer, **FVIII** is advised

How should ITI-refractory or ITI-naïve be managed?

- **Emicizumab** prophylaxis is recommended over rFVIIa

Can ITI be delayed, avoided?

- Whether ITI can be delayed or avoided is unknown

*aPCC should be avoided in those taking emicizumab prophylaxis to avoid TMA.

Immune tolerance induction (ITI)

When should ITI be initiated?

- ITI should start immediately after detection, no matter the titer

What agent should be used in ITI?

- The optimal regimen is undefined; **rFVIII** 100 IU/kg/day preferred

How should bleeds be managed in ITI?

- In LR, ~~**rFVIII** should be used to treat acute bleeds~~
- In HR, **rFVIIa or aPCC*** bypass; or, if low titer, **FVIII** is advised

How should ITI-refractory or ITI-naïve be managed?

- **Emicizumab** prophylaxis is recommended over rFVIIa

Can ITI be delayed, avoided?

- Whether ITI can be delayed or avoided is unknown

*aPCC should be avoided in those taking emicizumab prophylaxis to avoid TMA.

Inhibitors 2020: Summary

- All inhibitor patients should undergo a trial of ITI.
- Data on impact of EHL products on ITI are limited.
- After successful ITI, FVIII prophylaxis should be initiated.
- For hemostasis in surgery in inhibitor patients on emicizumab, use rFVIIa,
- Bleeds while on emicizumab should be managed with rFVIIa.
- Non-factor therapy prophylaxis may reduce disease burden.
- Use of non-factor therapies in ITI is not established.

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

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

Hemophilia Guidelines for All:

A new ambition of the World Federation of Hemophilia

Manuel Carcao, MD
Hospital for Sick Children, Toronto

Disclosures for Manuel Carcao, MD

- **Research Support from:**
  - Bayer, Bioverativ/Sanofi, CSL-Behring, Novo Nordisk, Octapharma, Pfizer and Shire/Takeda

- **Honoraria for speaking/participating in advisory boards from:**
  - Bayer, Bioverativ/Sanofi, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche and Shire/Takeda

Chapter 6: Prophylaxis in Hemophilia 2020 Updates

Committee Members

Manuel D. Carcao (Chair), Manuel A. Baarslag (Patient), Lisa Bagley (Patient), Francisco Careta (Patient), Emna Gouider, Kate Khair, Rolf C. R. Ljung, Margaret V. Ragni, Elena Santagostino, H. Marijke van den Berg, Glenn F. Pierce, Alok Srivastava

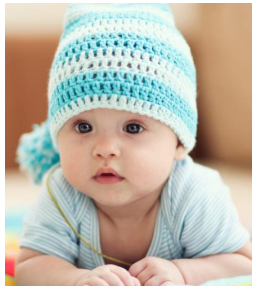
WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

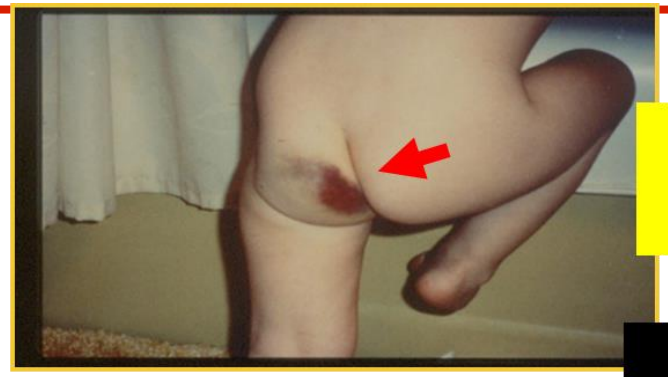
Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

Hemophilia = life-long severe bleeding disorder [without regular factor infusions=prophylaxis]

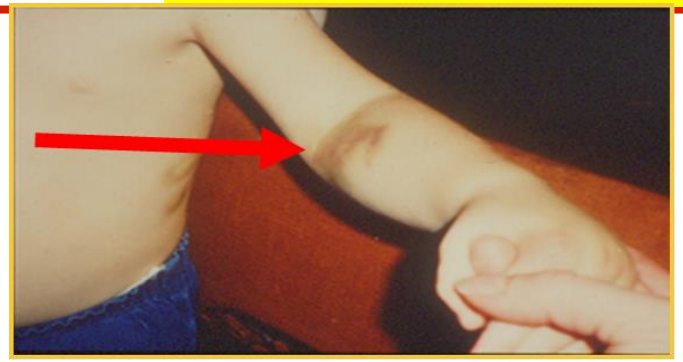
WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

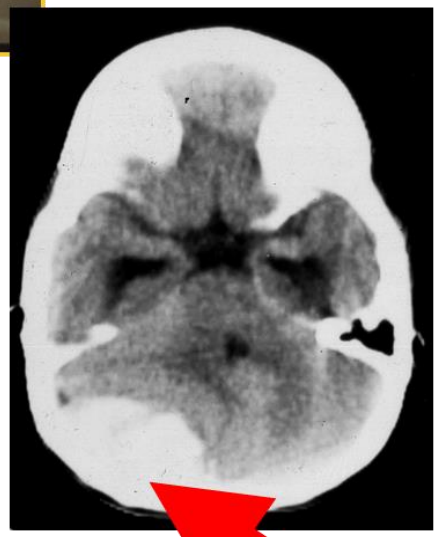
Hemophilia = life-long severe bleeding disorder [without regular factor infusions=prophylaxis]

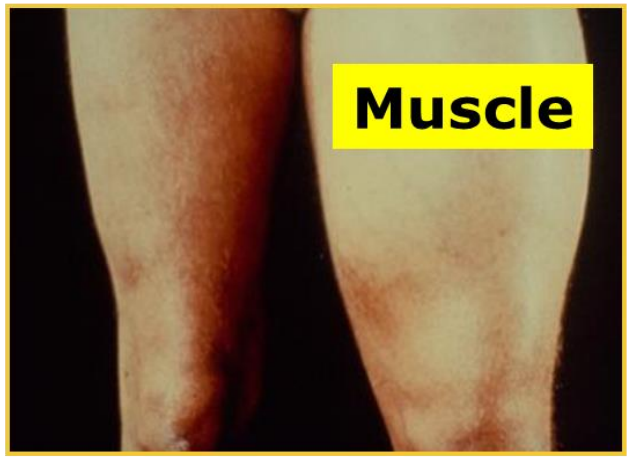




Soft Tissue







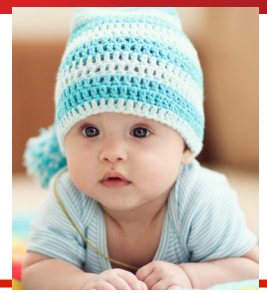
Muscle

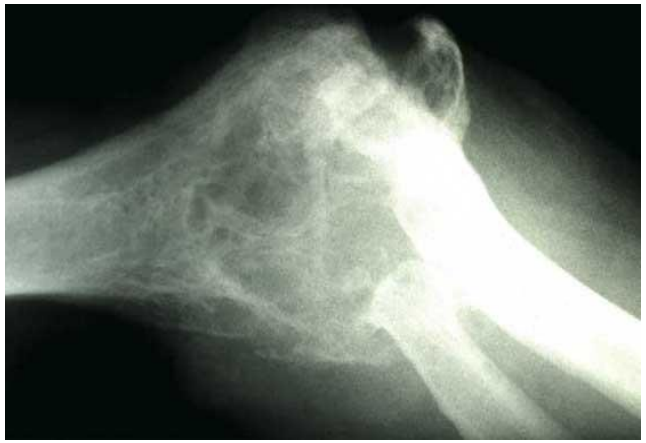
Joint

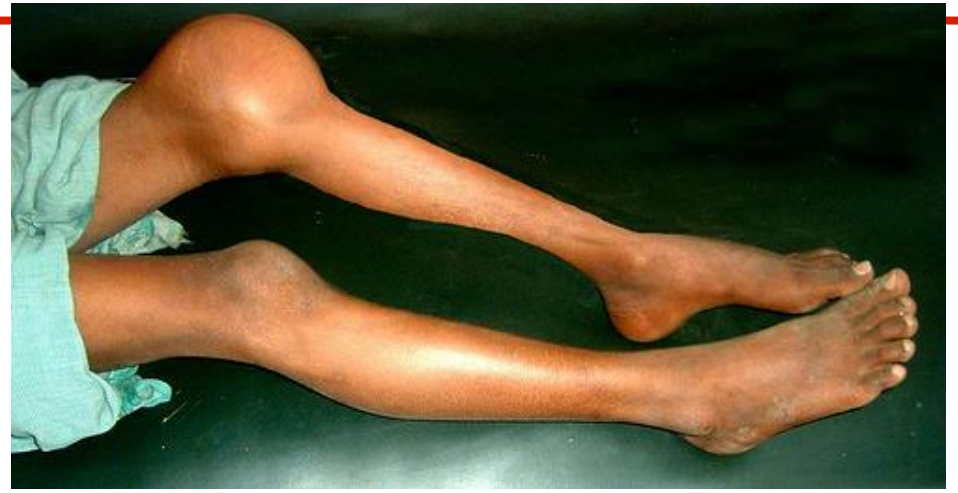
Intracranial

*Photographs used are with patient consent or are sourced from stock images

And this would lead to…

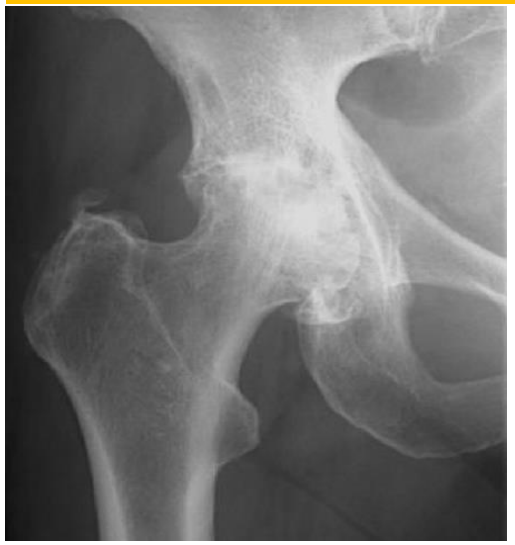


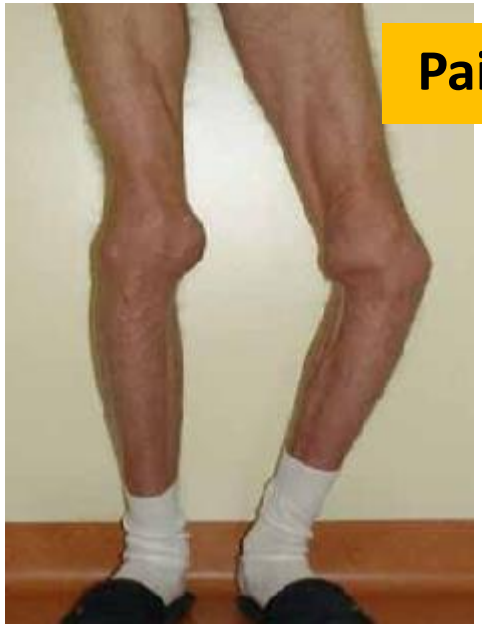




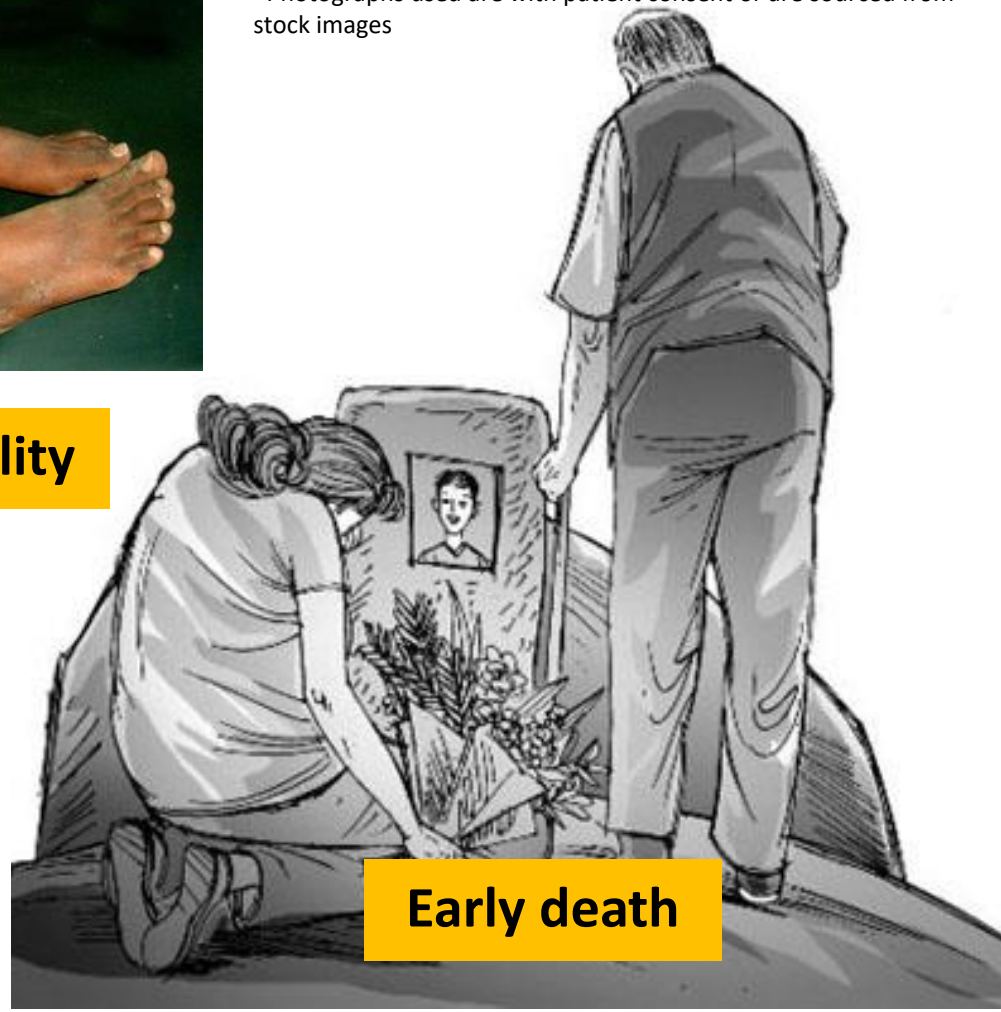
*Photographs used are with patient consent or are sourced from stock images

Destroyed joints





Pain & Disability



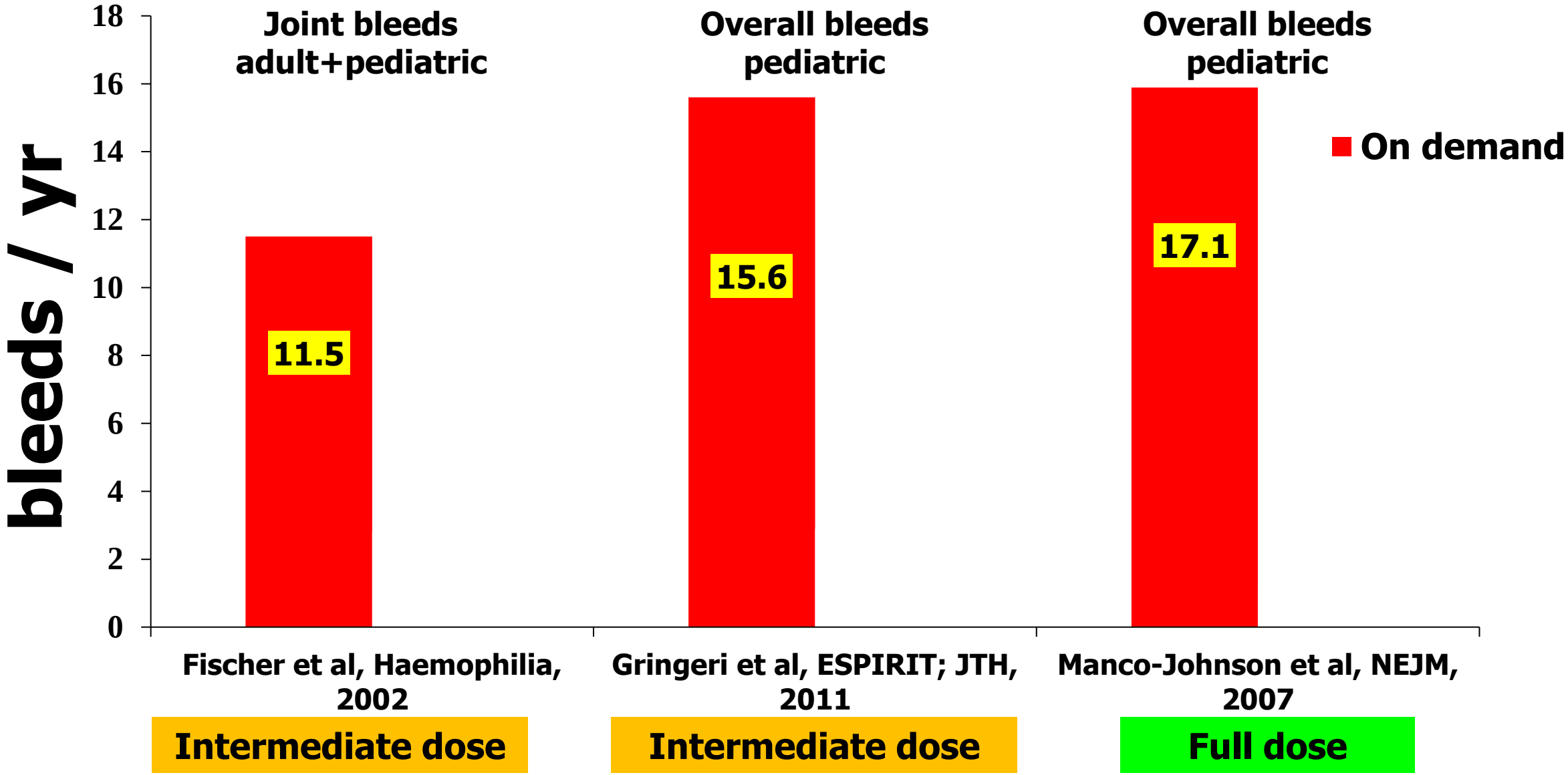
Early death

But with Prophylaxis

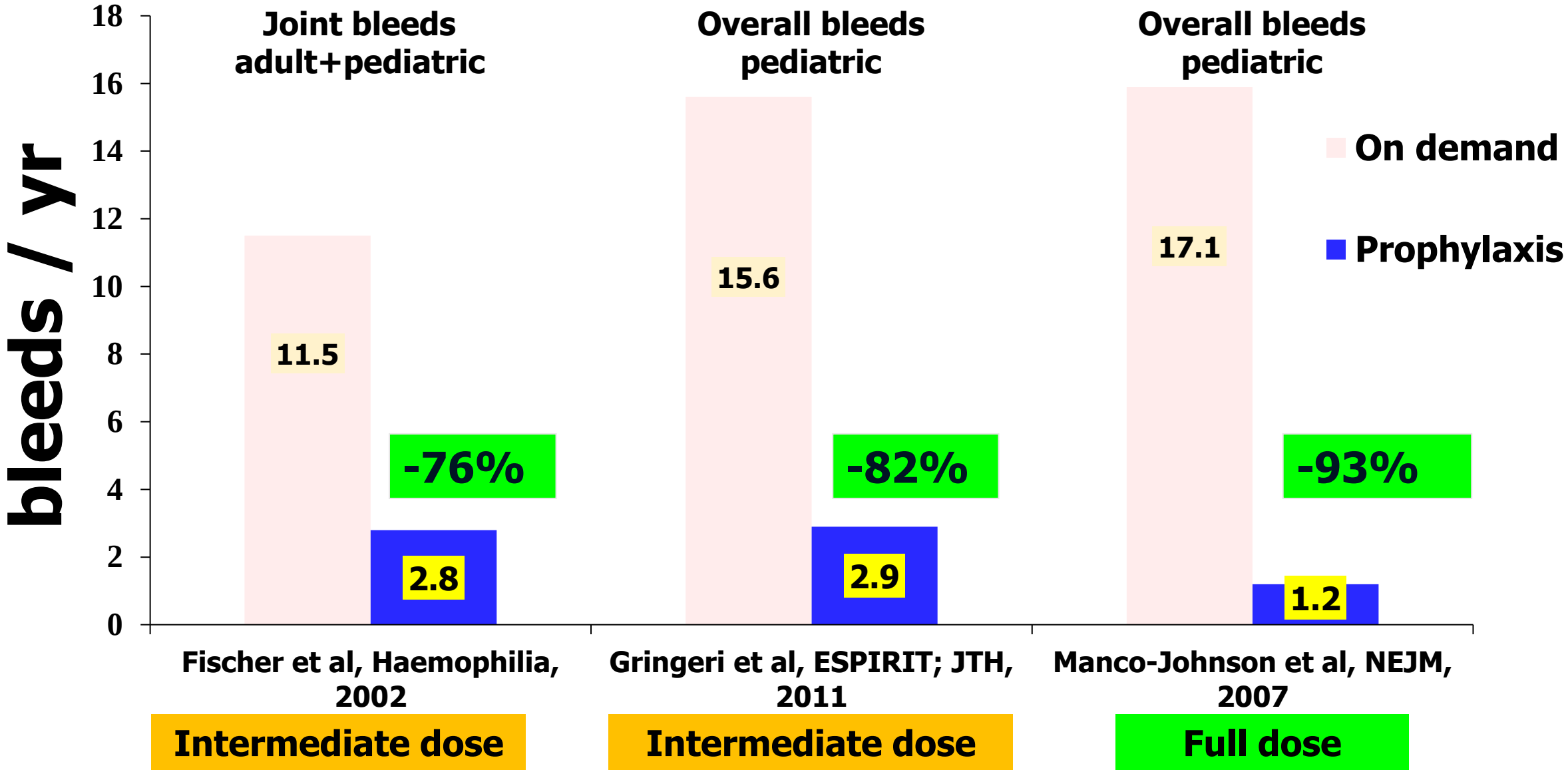
They don’t have to experience these things!

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

Prophylaxis with Standard $T_{1/2}$ factor → huge ↓ in bleeding



Prophylaxis with Standard $T_{1/2}$ factor➔huge ↓ in bleeding



Prophylaxis with Standard $T_{1/2}$ factor➔huge ↑ in QOL

WFH Guidelines 2020 (Prophylaxis)

PROPHYLAXIS IS STANDARD OF CARE

EVERYWHERE

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

Prophylaxis Standard of care-everywhere

WFH guidelines 2020 (Prophylaxis)

- ***"For patients with severe .. haemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care .... When prophylaxis is not feasible, episodic (on demand) therapy is essential treatment for acute hemorrhages, but will NOT PREVENT long-term joint damage."***

Chapter 6: Prophylaxis in Hemophilia in Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

Prophylaxis Standard of care-everywhere

WFH guidelines 2020 (Prophylaxis)

"In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic (on demand) therapy but recognizes that less intensive prophylaxis may be used."

Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

Prophylaxis Start early

WFH guidelines 2020 (Prophylaxis)

… The WFH recommends early initiation of prophylaxis … prior to the onset of joint disease and ideally before age 3, …

(i.e. primary prophylaxis)

Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

Prophylaxis Aim to prevent all bleeds

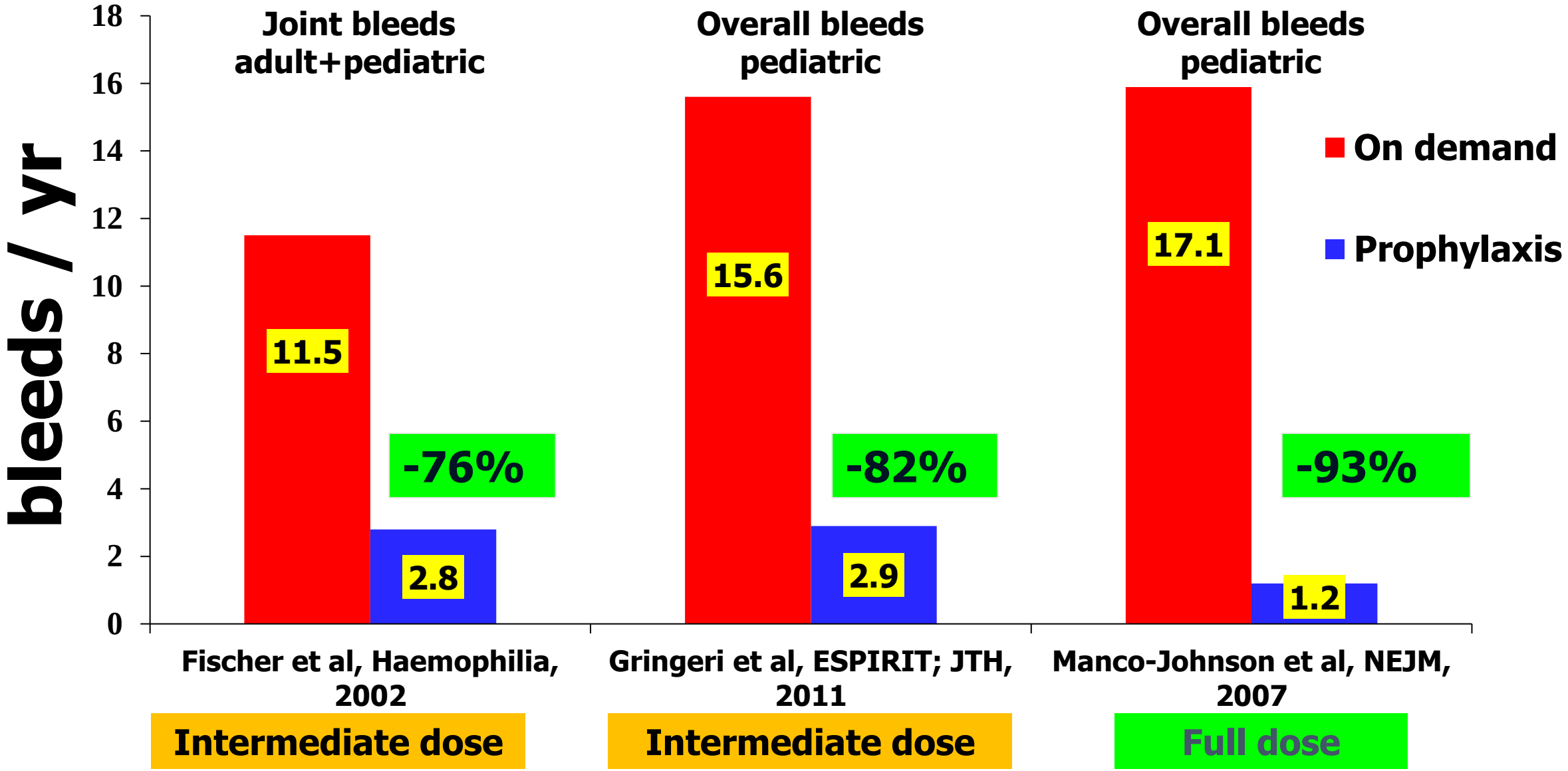
WFH guidelines 2020 (Prophylaxis)

- ***"For patients with haemophilia A or B with a severe phenotype (may include patients with moderate haemophilia), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times"***

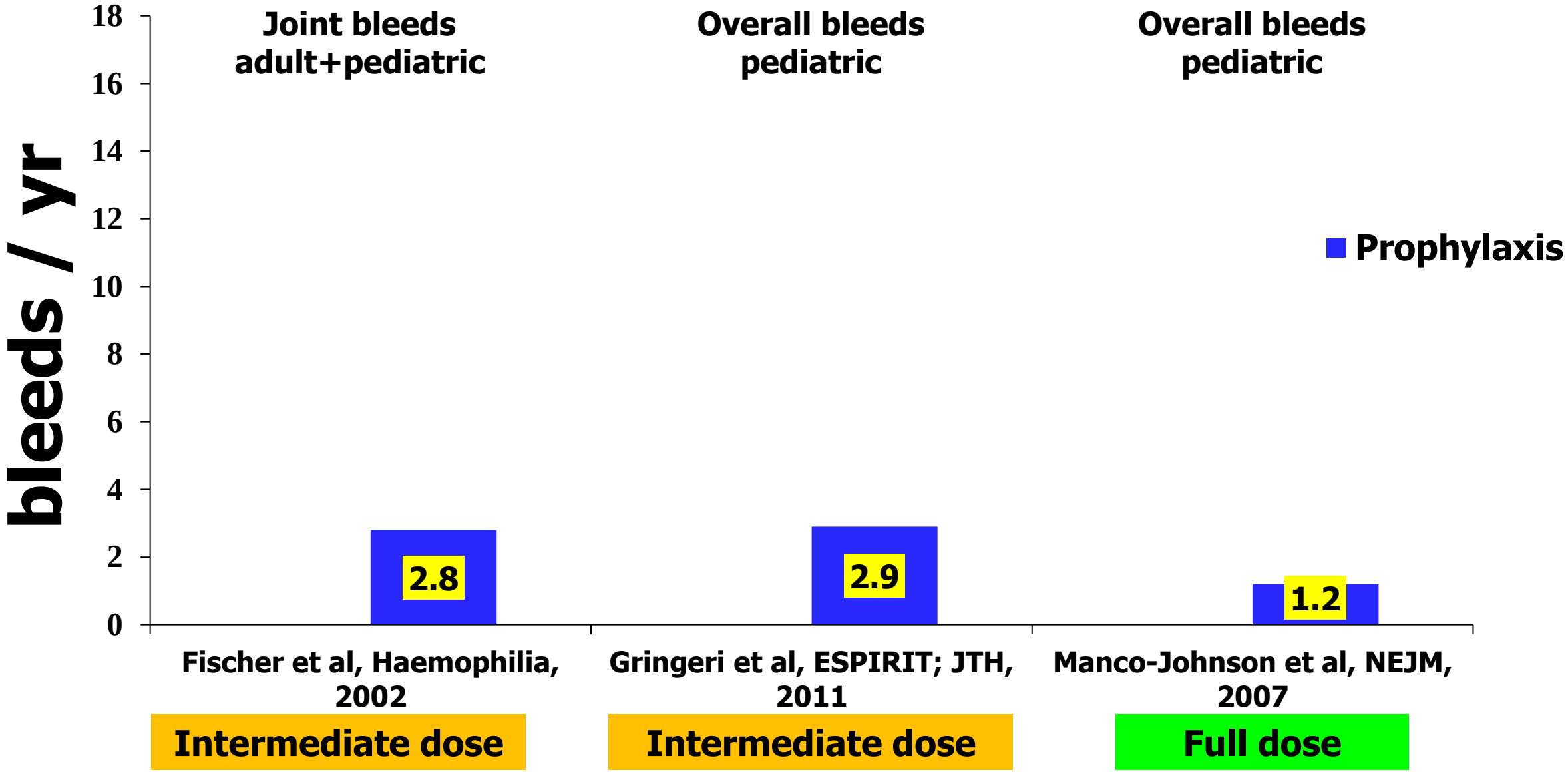
Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

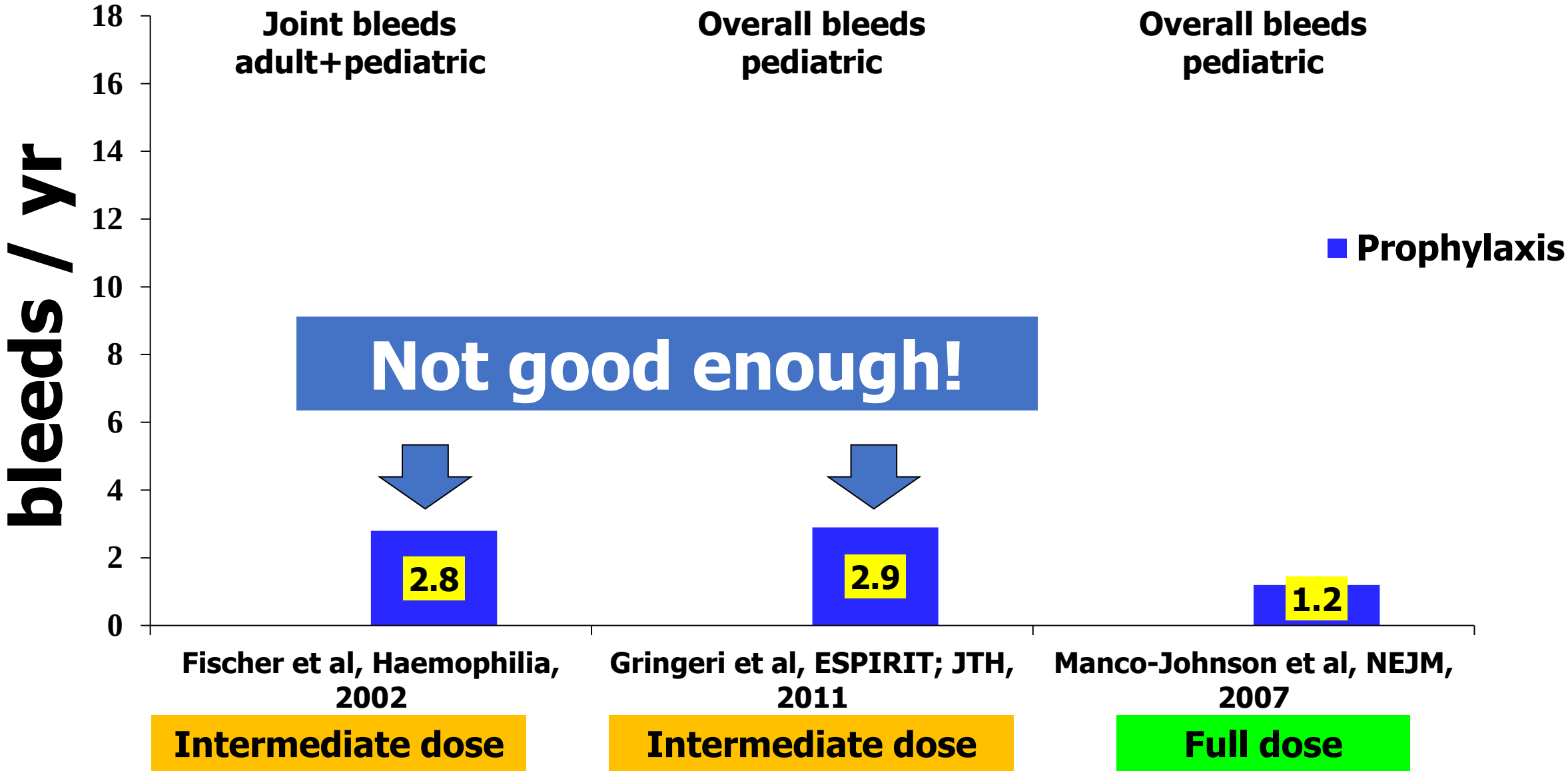
Prophylaxis with Standard $T_{1/2}$ factor → huge ↓ in bleeding



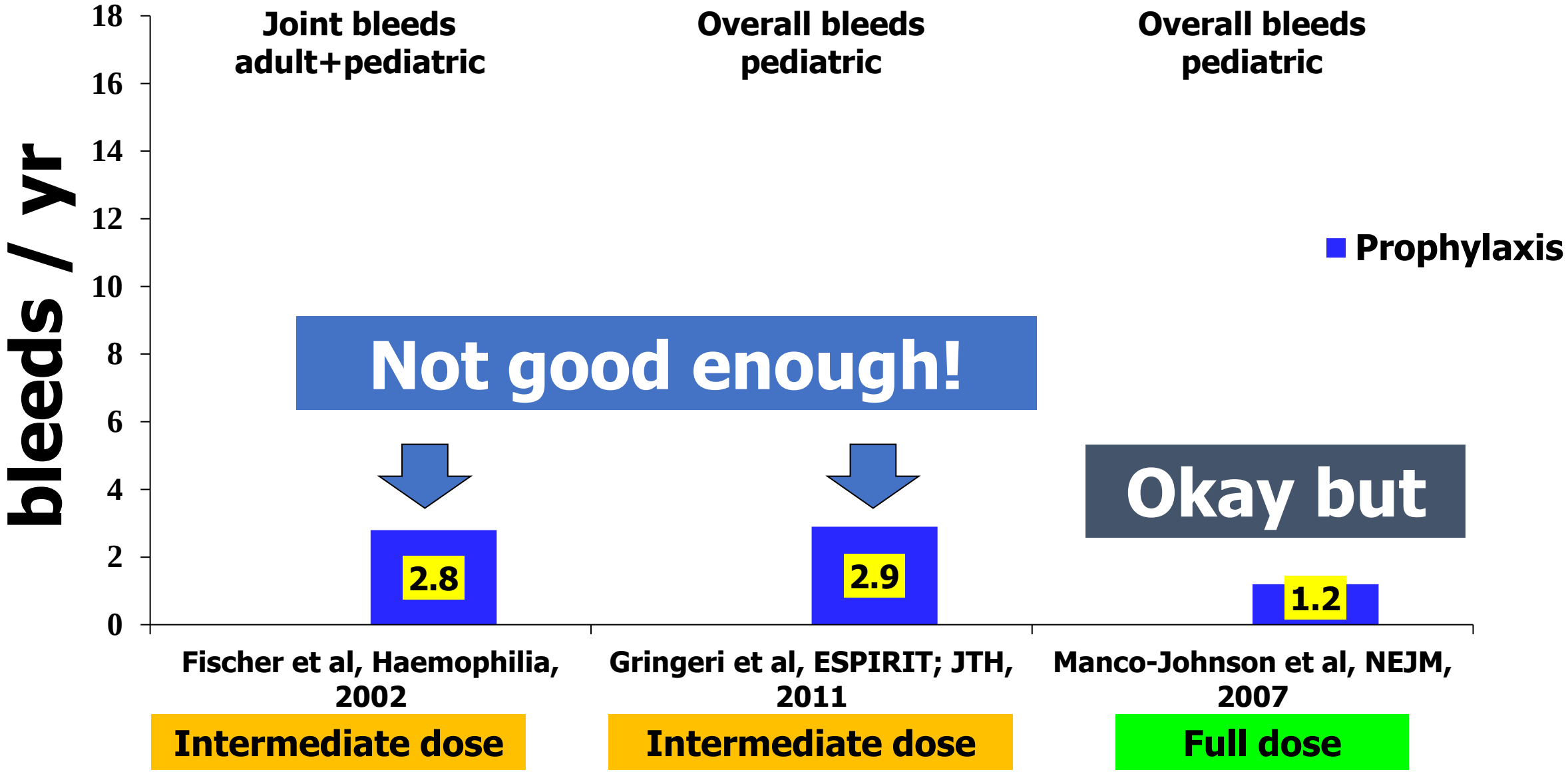
Prophylaxis with Standard $T_{1/2}$ factor➔huge ↓ in bleeding



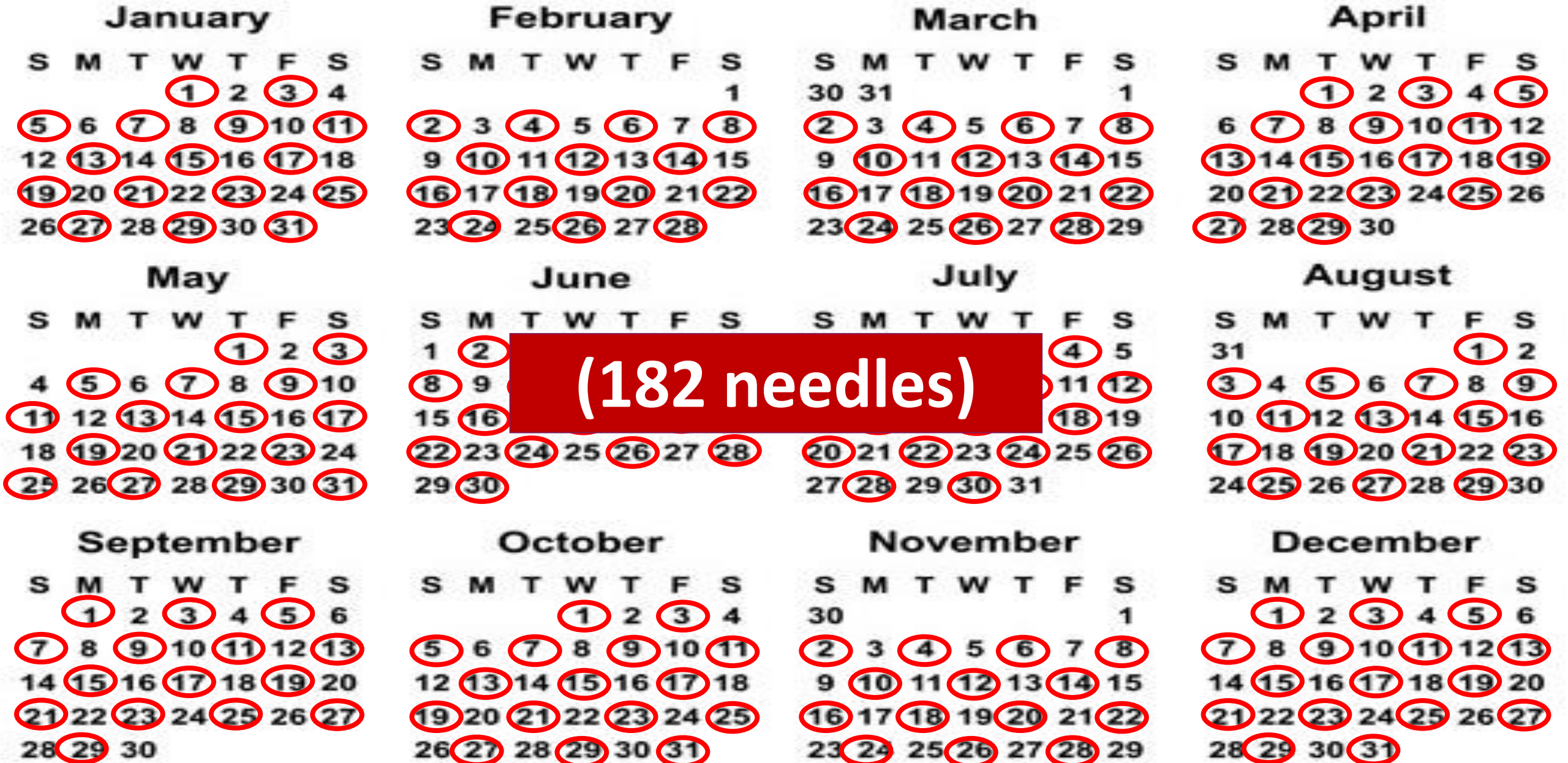
Prophylaxis with Standard $T_{1/2}$ factor → huge ↓ in bleeding



Prophylaxis with Standard $T_{1/2}$ factor → huge ↓ in bleeding

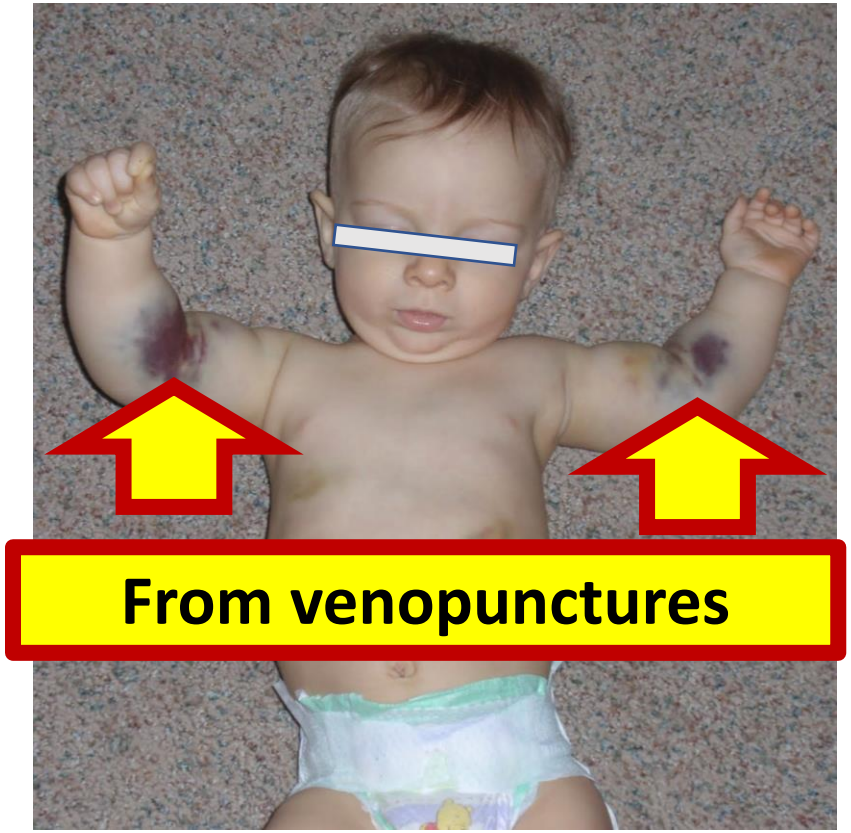


Full dose Prophylaxis with SHL-FVIII



(182 needles)

Even 1 needle is hard enough!



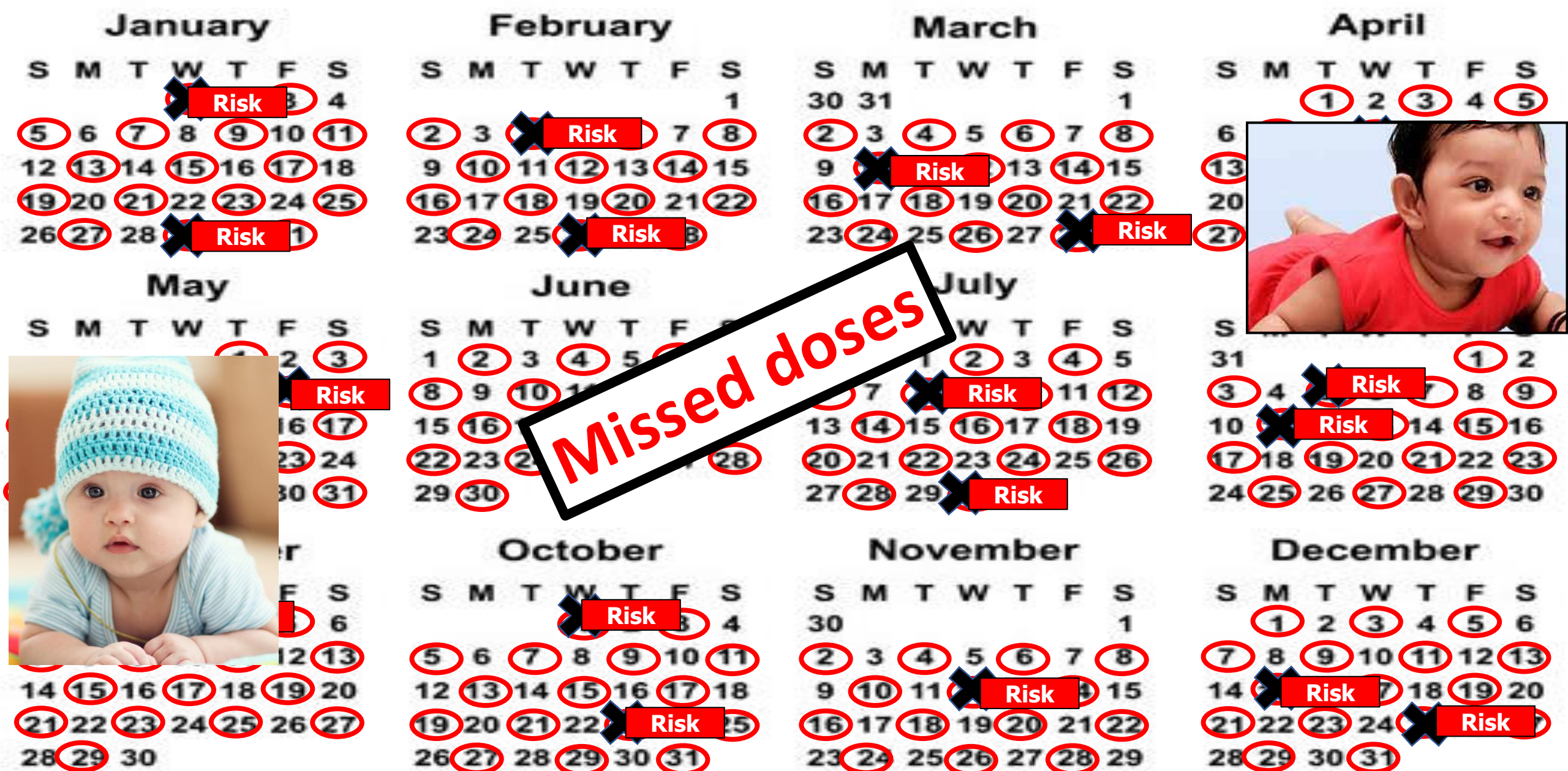
*Photographs used are with patient consent or are sourced from stock images

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

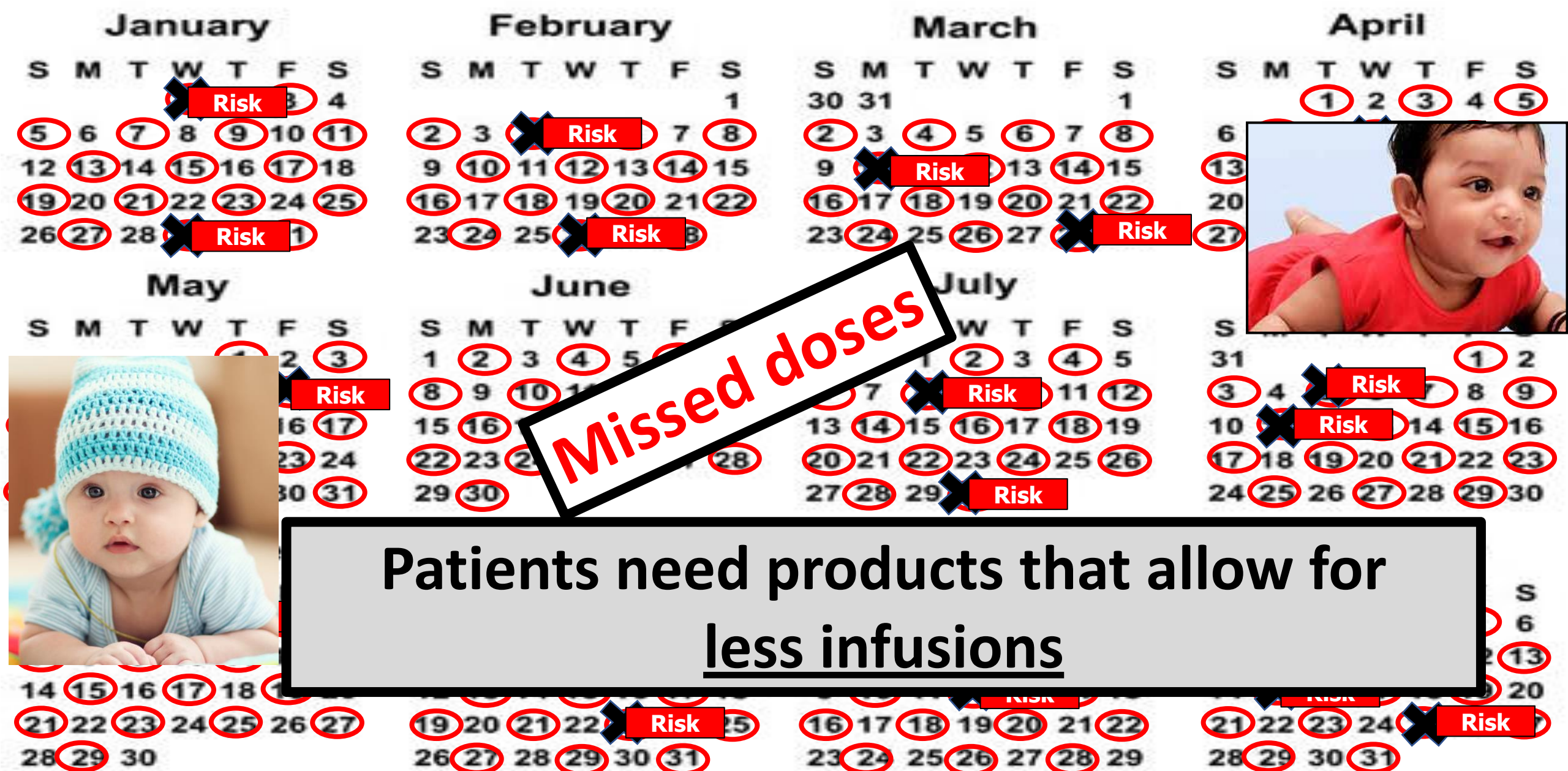
Full dose Prophylaxis with SHL-FVIII – this is very hard

(182 needles)

Full dose Prophylaxis with SHL-FVIII – this is very hard



Full dose Prophylaxis with SHL-FVIII – this is very hard



Patients need products that allow for less infusions

Full dose Prophylaxis with SHL-FVIII

What do patients achieve with this?

(182 needles)

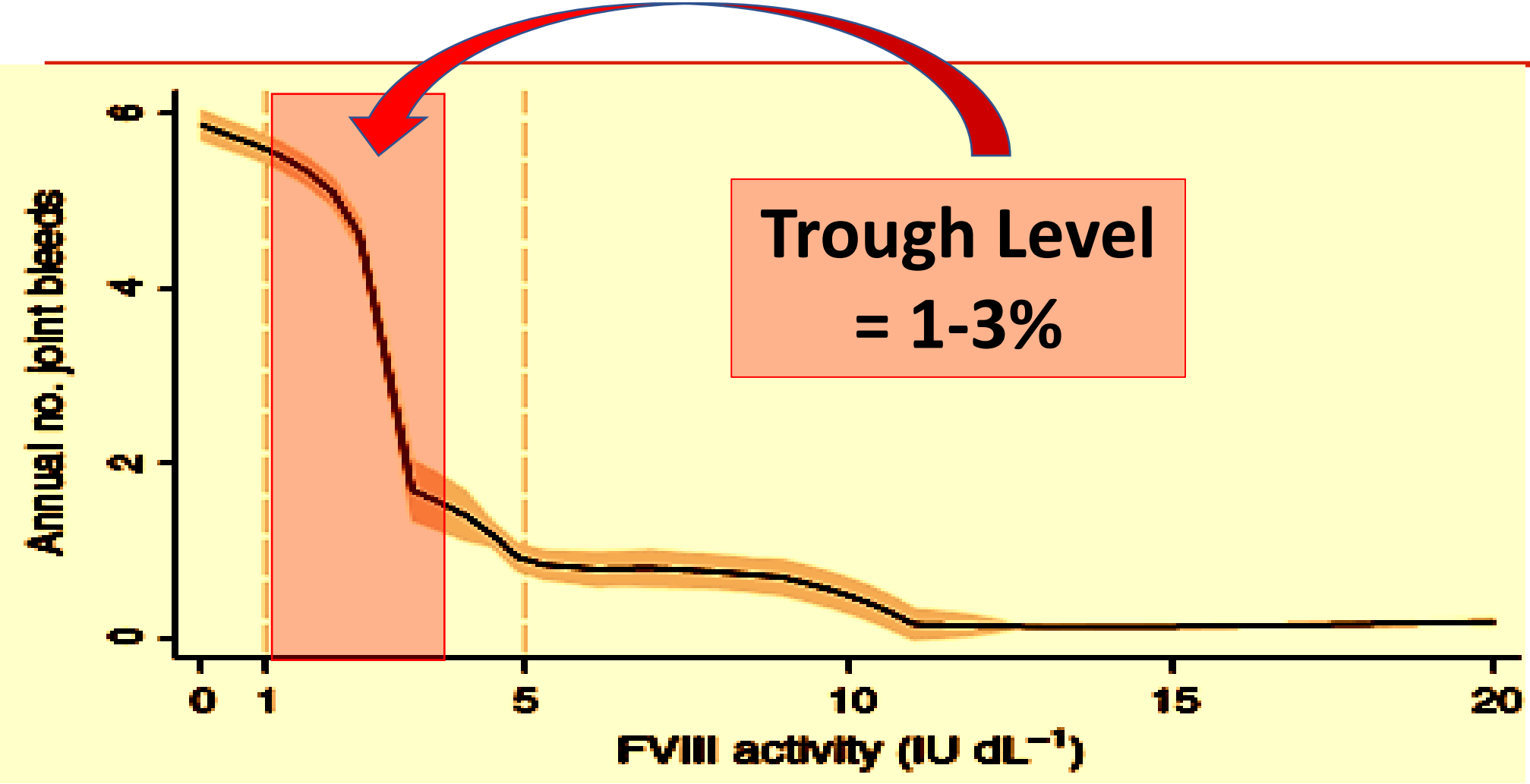
Full dose Prophylaxis with SHL-FVIII

What do patients achieve with this?

(182 needles)

Factor VIII Trough levels = 1-3%

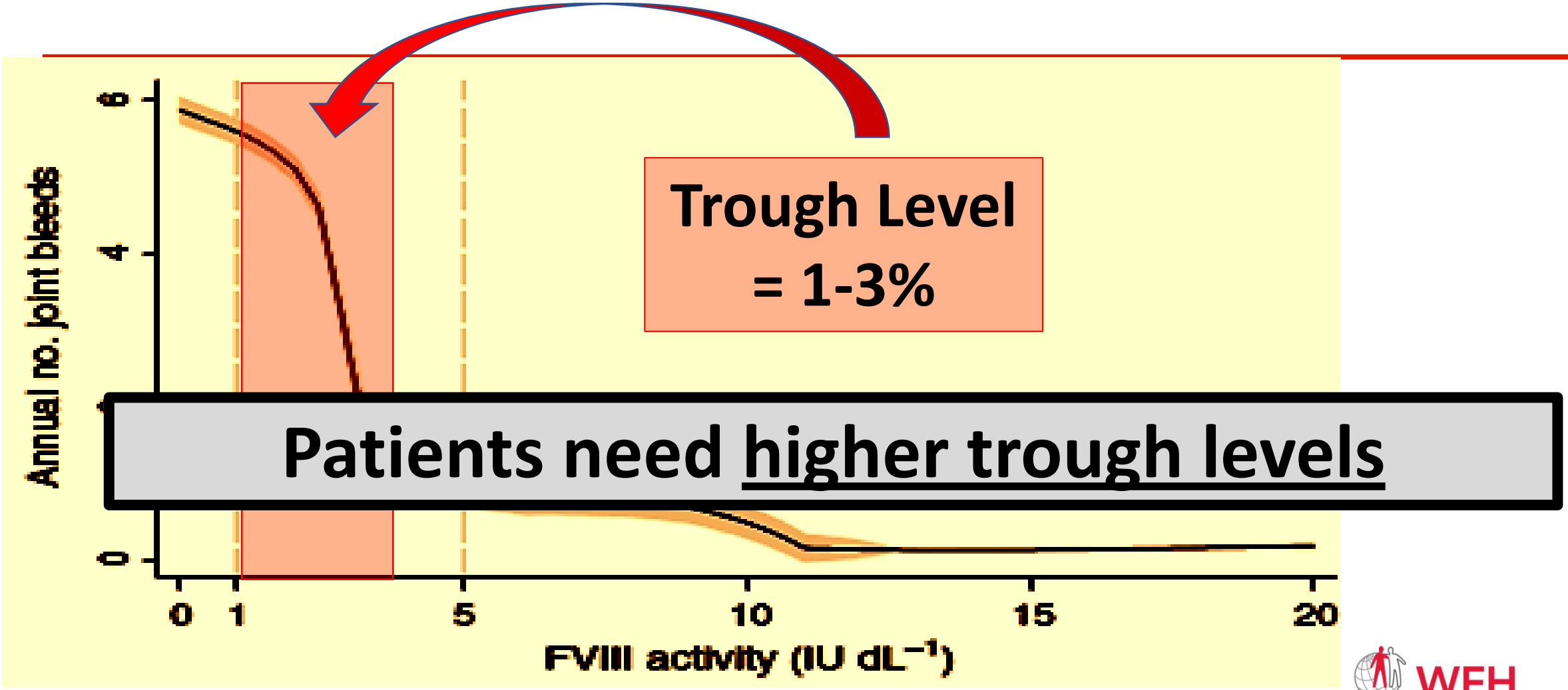
of joint bleeds vs baseline FVIII



Den Uijl I et al. Hemophilia 2011.

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

of joint bleeds vs baseline FVIII



Den Uijl I et al. Hemophilia 2011.

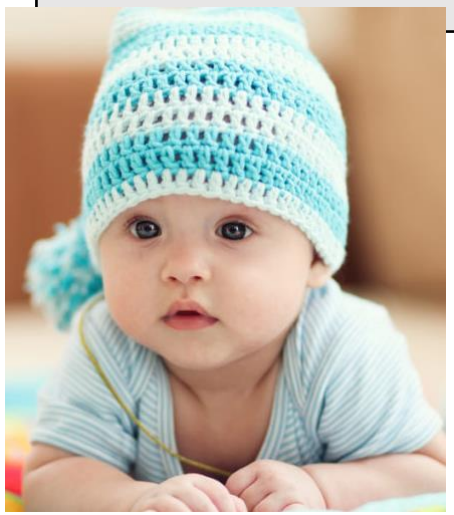
WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Prophylaxis: Patients need more

1)
Less infusions

2)
Higher factor trough levels

3)
Non-IV administered



Or a combination

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

WFH Guidelines 2020 (Prophylaxis)

PROPHYLAXIS

WE CAN NOW DO

BETTER

Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

WFH Guidelines 2020 (Prophylaxis)

PROPHYLAXIS

WE CAN NOW DO

(AND SHOULD DO)

BETTER

Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

Prophylaxis We can now do better

WFH guidelines 2020 (Prophylaxis)

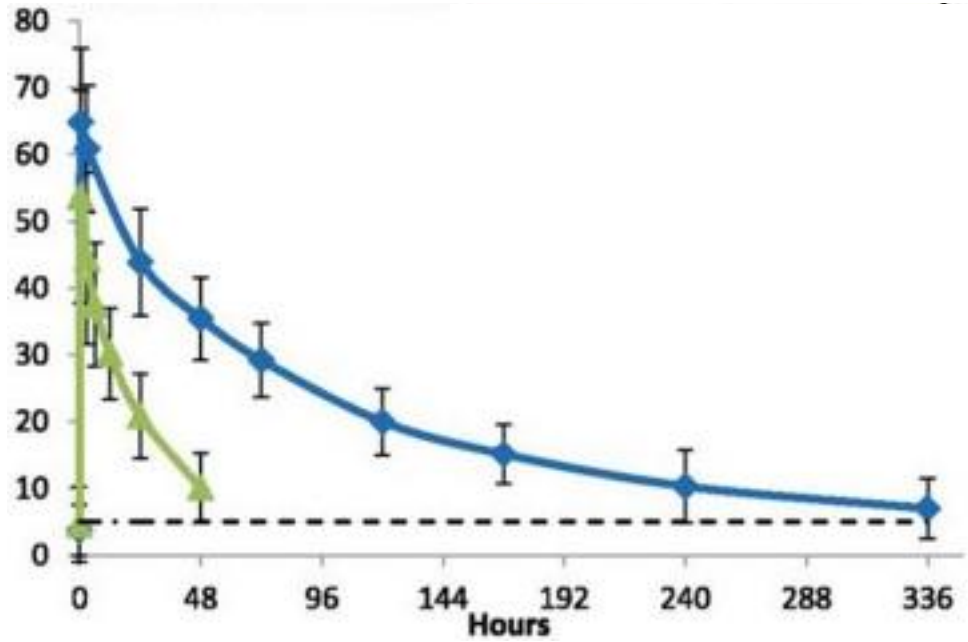
- ***"Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%, or higher)."***

Chapter 6: Prophylaxis in Hemophilia in Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

Prophylaxis We can now do better

Extended half-life (EHL) Clotting factor concentrates	Non-factor therapies (e.g. emicizumab)



Allow us to achieve better protection than simply a 1% factor level

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

Benefits of Extended half-life (EHL) CFC

1)

Less infusions

2)

Higher factor trough levels

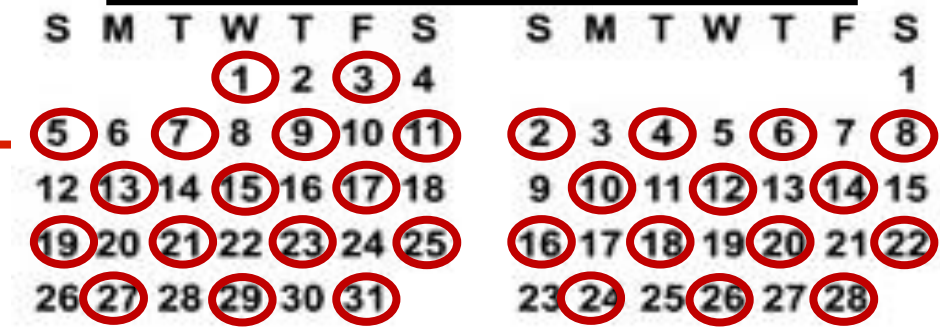
3)

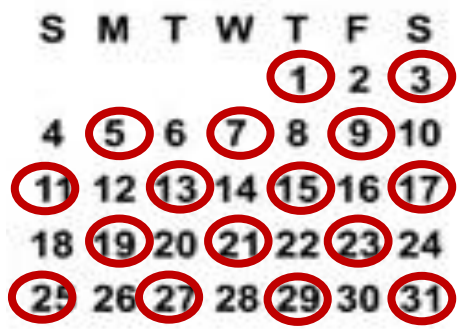
Non-IV administered

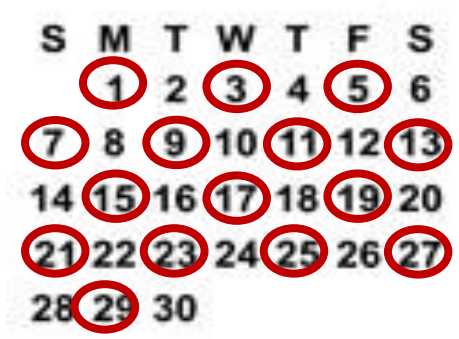
Or a combination

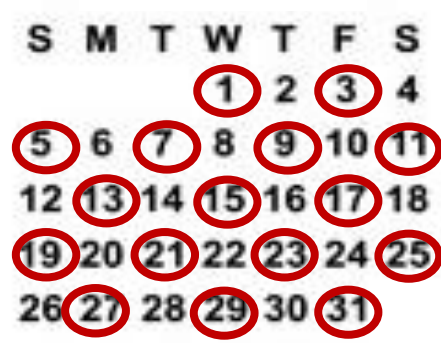
WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Current FVIII



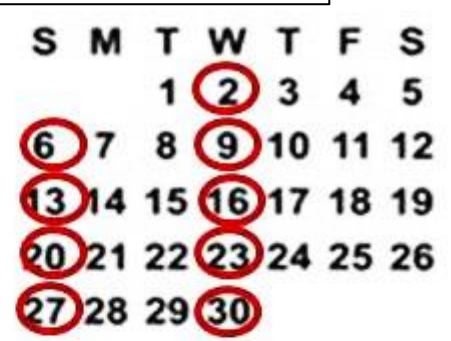


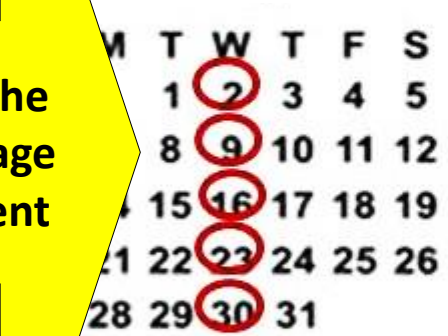


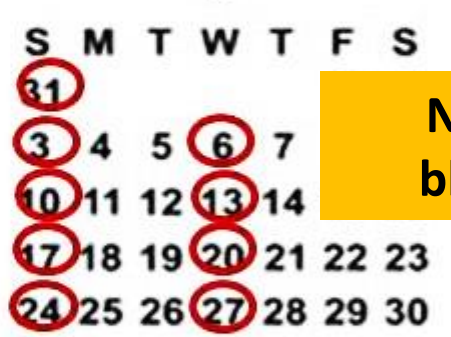


For the average patient

EHL FVIII



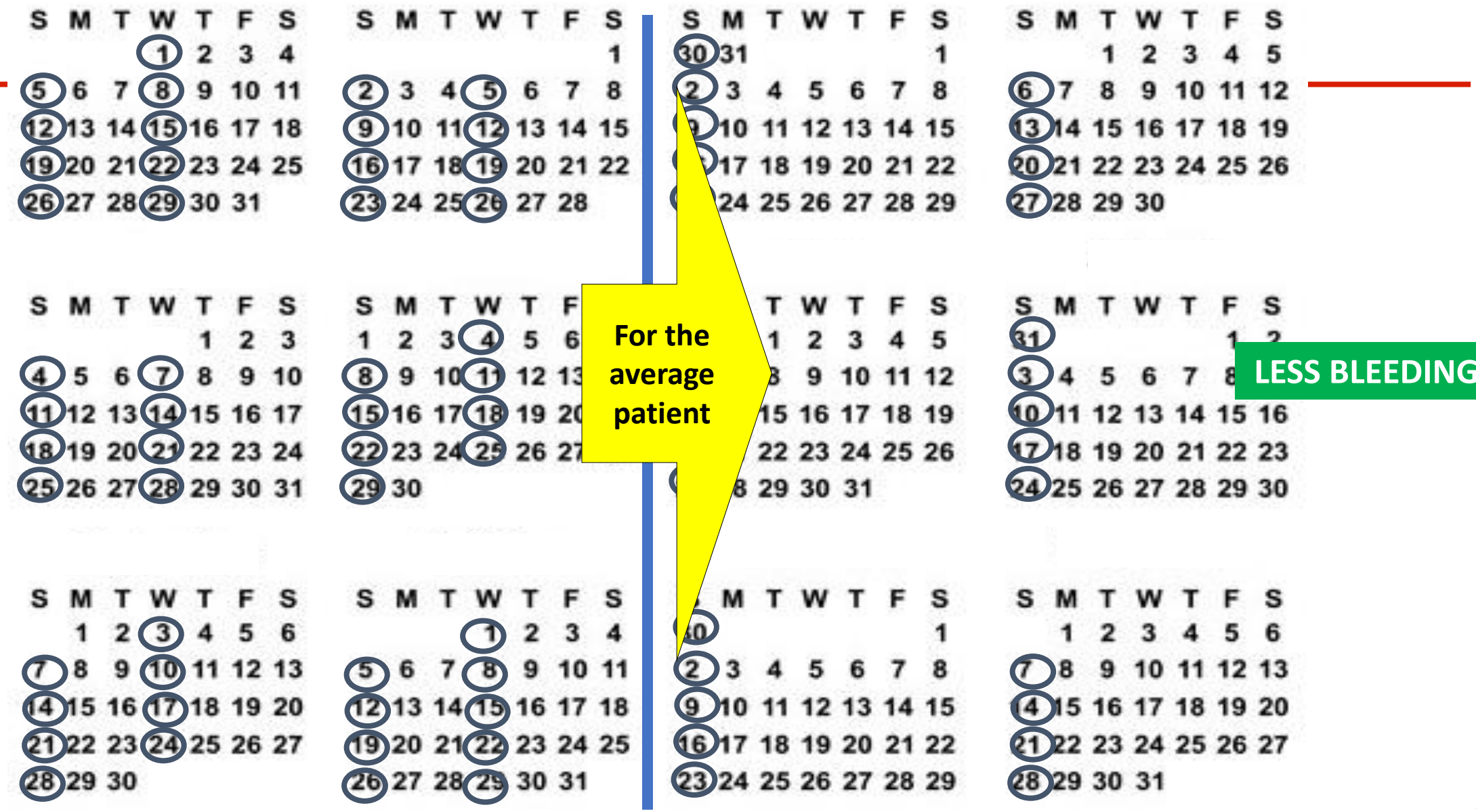




No ↑ in bleeding

Current FIX

EHL FIX



Emicizumab (SQ) prophylaxis

Studies show a >90% ↓ in bleeds (vs on demand therapy)

January

S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

February

S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29

March

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

April

S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

May

S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

June

S	M	T	W	T	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

July

S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

August

S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

September

S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

October

S	M	T	W	T	F	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

November

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

December

S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

52 times/yr

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

Emicizumab (SQ) prophylaxis

Studies show a >90% ↓ in bleeds (vs on demand therapy)

January						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

February						
S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29

March						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

April						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

May						
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

June						
S	M	T	W	T	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

July						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

August						
S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

September						
S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

October						
S	M	T	W	T	F	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

November						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

December						
S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

26 times/yr

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

Benefits of Emicizumab

1)

Less infusions

2)

Higher factor trough levels

Sort of!

3)

Non-IV administered

Or a combination

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

Prophylaxis No longer just factor

WFH Guidelines 2020 (Prophylaxis)

For patients with severe phenotype hemophilia A <u>WITHOUT INHIBITORS</u>, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.

Remark: … long term data on patient outcomes with such an approach … be obtained.

Chapter 6: Prophylaxis in Hemophilia in
Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.

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

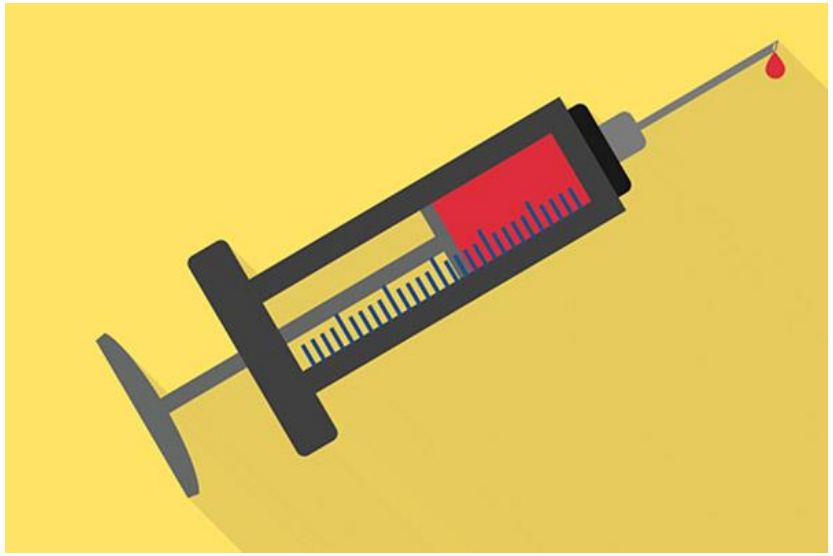
What is prophylaxis?

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

What is prophylaxis?

OLD

…the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding.



Blanchette VS, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.

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

What is prophylaxis?

OLD	NEW
…the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding.	***The regular administration of a hemostatic agent/ agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals.***
Blanchette VS, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.	**Chapter 6: Prophylaxis in Hemophilia in Srivastava A et al. WFH Guidelines for the Management of Hemophilia, 3rd ed, Haemophilia, 2020.**

KEY RECOMMENDATIONS: PROPHYLAXIS

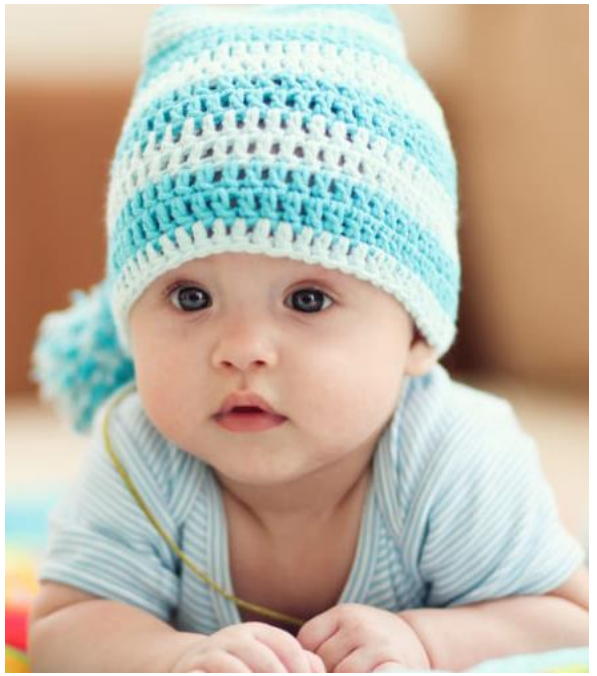
WFH Guidelines 2020 (Prophylaxis)

- **Standard of care – everywhere**
- **We can now do (and should do) better**
- **No longer just factor**

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

KEY RECOMMENDATIONS: PROPHYLAXIS

WFH Guidelines 2020 (Prophylaxis)



Can look forward to a better life!

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

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

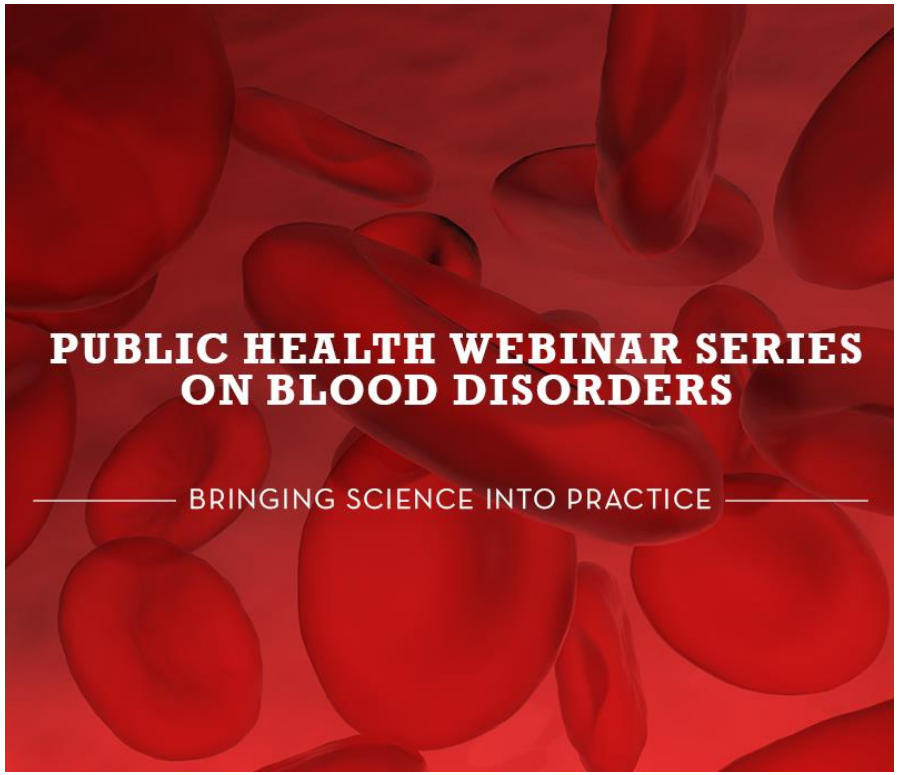
Questions & Answers

Conclusions

- Many new advances leading to new concepts since 2012 Guidelines
- Highlights from the new WFH Guidelines
  - Hemostatic agents
  - Inhibitor management
  - Prophylaxis
- Changing patterns of comprehensive care management
- Use of newer agents to drive toward a bleed-free existence
- Long term benefits clearly established
- Full implementation remains the challenge

https://onlinelibrary.wiley.com/doi/10.1111/hae.14046

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



This webinar was brought to you by CDC's Division of Blood Disorders. We thank the Hemophilia Federation of America for hosting today's webinar.

HFA
Hemophilia Federation of America™

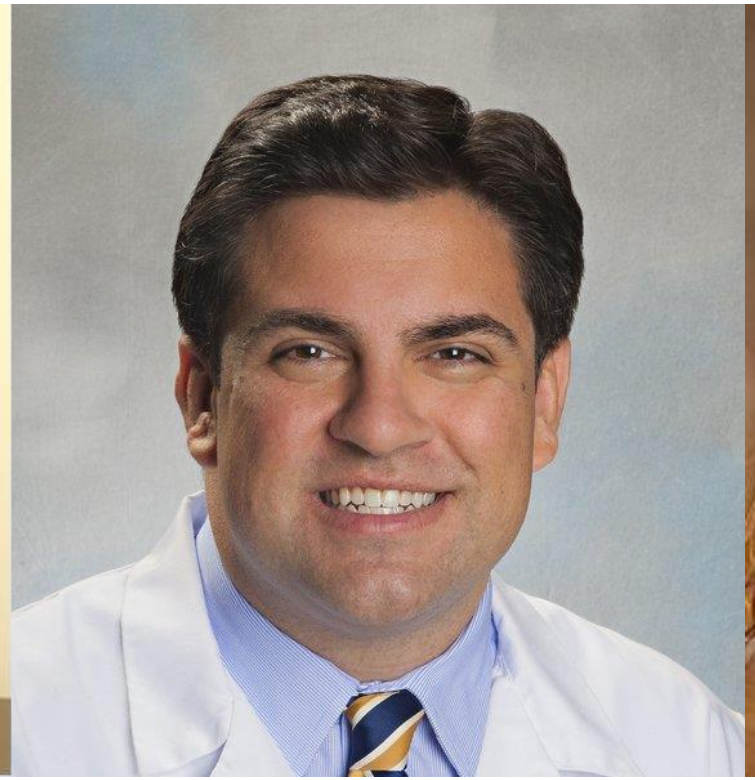
Questions about this webinar series? Please contact Cynthia Sayers at CSayers@cdc.gov.

CDC Webinar Archive: https://www.cdc.gov/blooddisorderswebinars/

Joint Guidelines on the Diagnosis and Management of von Willebrand Disease

February 25, 2021, 2–3 pm Eastern

Jean Grow, PhD
Marquette University



Nathan T. Connell, MD, MPH
Brigham and Women's Hospital
Harvard University

Angela Weyand, MD
University of Michigan
Hospitals & Health Center

More information, contact Cynthia Sayers; CSayers@cdc.gov