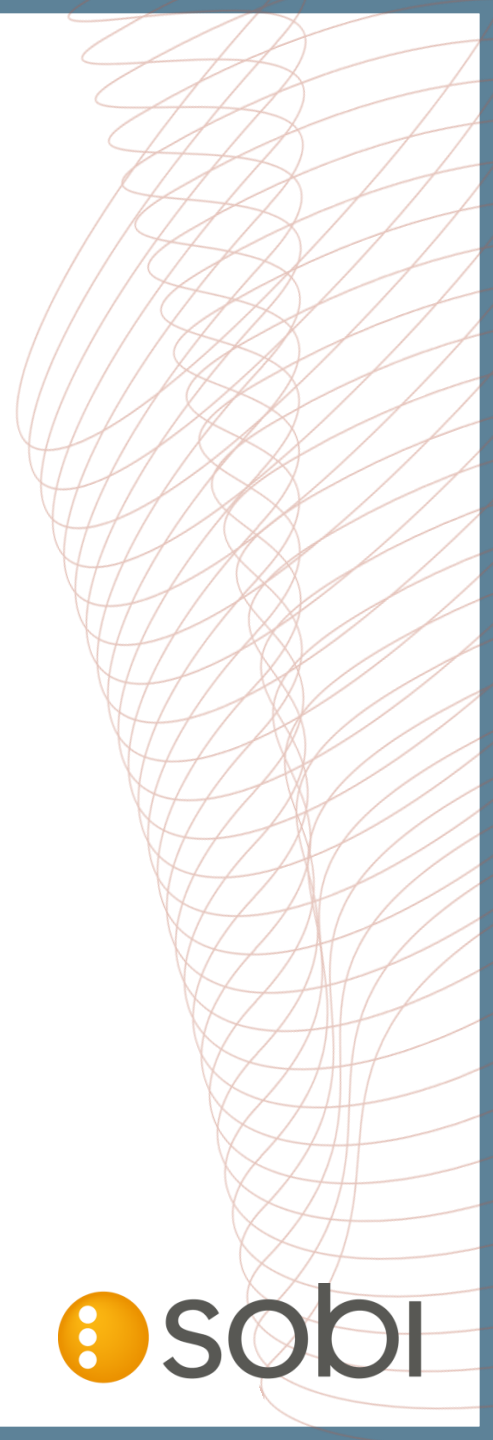


# Medical Affairs

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**ANIMATED VIDEO**

# **EARLY DIAGNOSIS AND MANAGEMENT OF SYNOVITIS IN HAEMOPHILIA**

**MAY 2026**

This programme has been sponsored by Sobi™ and is intended for healthcare professionals only  
NP-50289

# ACKNOWLEDGEMENT AND DISCLOSURES

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# EDUCATIONAL OBJECTIVES

1. Understand the pathophysiology of synovitis in haemophilia. How recurrent joint bleeds lead to synovial inflammation and progressive joint damage
2. Recognise synovitis as an early and partially reversible stage of haemophilic arthropathy and understand clinical relevance for long-term preservation and pain outcomes
3. Identify clinical signs, image findings and symptoms associated with synovitis, consider how they inform treatment optimization
4. Apply strategies to manage synovitis with the aim of reducing joint inflammation, preventing progression to irreversible arthropathy and improving quality of life

# HAEMARTHROSIS IN HAEMOPHILIA A

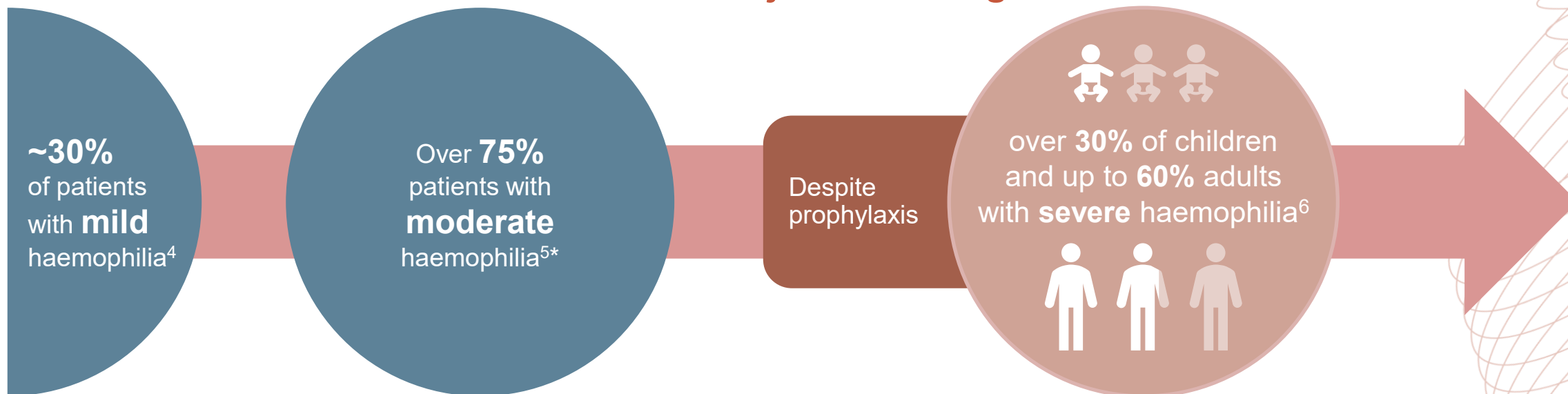
# HAEMARTHROSIS IS A HALLMARK OF HAEMOPHILIA<sup>1-6</sup>



Haemophilia is characterised by recurrent haemarthroses (joint bleeds)<sup>1</sup>

Joint bleeds are observed across all severities of haemophilia<sup>4-6</sup>

## Prevalence of joint bleeding



\* Requiring treatment with clotting factor concentrates

1. Rodriguez-Merchan EC, et al. Haemophilia. 2011;17:1-23;
2. Dargaud Y, et al. Blood Rev. 2025;101304;
3. Gualtierotti R, et al. J Thromb Haemost .2021;19:2112-21;
4. Chiari JB, et al. Haemophilia. 2024;30:331-5;
5. Kloosterman FR, et al. Blood Av. 2022;6:4256-65;
6. Wilkins RA, et al. BMJ Open. 2022;12:e052358

# TYPES OF JOINT BLEEDING<sup>1-6</sup>

## Signs and symptoms of joint bleeds<sup>3-5</sup>

Type of bleed	Symptoms	Impact on movement
Subclinical	None	Normal motion
Early bleed	Sensation of fullness, stiffness, discomfort, pain or tingling (aura) in the joint (similar to arthritic pain)	Normal motion
Moderate	Pain, swelling	Restricted movement
Severe	Severe pain, marked swelling	Limited movement (joint immobilising bleeds)



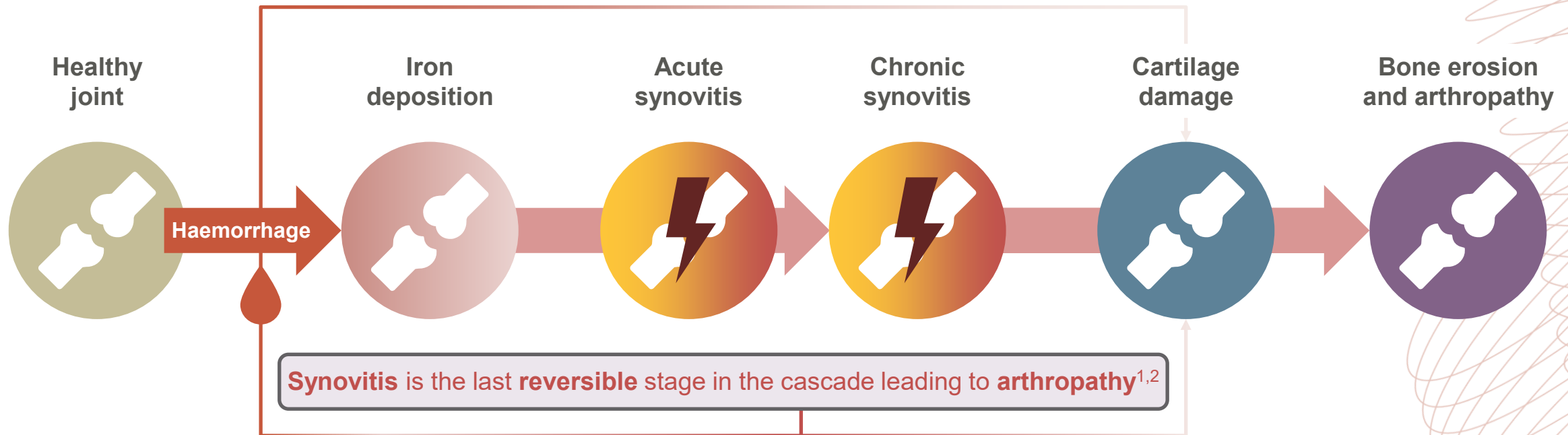
**Joint bleeds** can be difficult to distinguish from **arthritic pain**<sup>3,6</sup>

The onset of joint bleeding is often described by patients as a tingling sensation, increased warmth, and pressure<sup>1-6</sup>

1. Zwagemaker AF, et al. J Thromb Haemost. 2022;20:1126-37;
2. van Leeuwen FHP, et al. J Thromb Haemost. 2023;21:1156-63;
3. Hanley J, et al. Haemophilia. 2017;23:511-20;
4. Srivastava A, et al. Haemophilia. 2020;26:1-158;
5. Rodriguez-Merchan EC & Valentino LA. World J Orthop. 2016;7:370-5;
6. Blanchette VS, et al. J Thromb Haemost. 2014;12:1935-9

# JOINT BLEEDING CAN LEAD TO IRREVERSIBLE ARTHROPATHY<sup>1,2</sup>

Permanent joint damage can occur from just one joint bleed due to initiation of the inflammatory process<sup>2-4</sup>



Failure to manage acute synovitis results in **chronic inflammation** and **osteoarthropathic damage**<sup>5</sup>

Figure adapted from Gringeri et al. Haemophilia 2014;20:459-63

1. Dargaud Y, et al. Blood Rev. 2025;101304; 2. Gringeri A, et al. Haemophilia. 2014;20:459-63; 3. Gualtierotti R, et al. J Thromb Haemost. 2021;19:2112-21; 4. van Vulpen LFD, et al. Osteoarthritis Cartilage. 2015;23:63-69; 5. Srivastava A, et al. Haemophilia. 2020;26:1-158

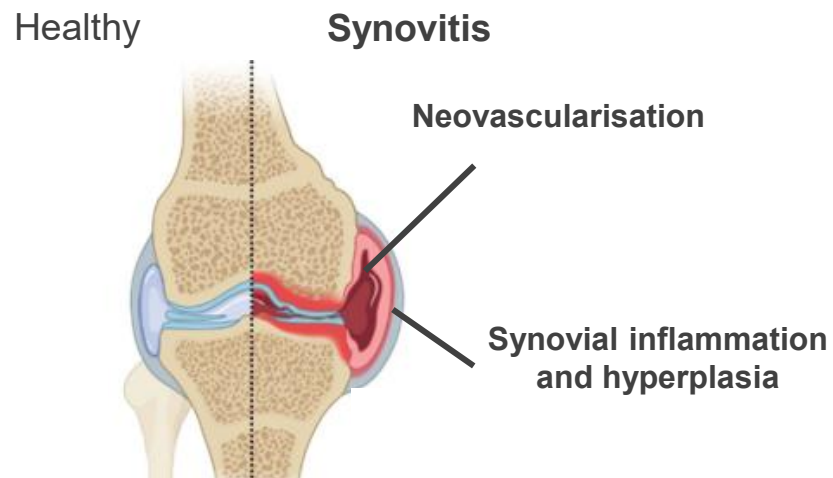
# DETECTING SYNOVITIS

# SYNOVITIS IS THE LAST REVERSIBLE STAGE IN THE CASCADE LEADING TO ARTHROPATHY<sup>1</sup>

Synovitis is the inflammation and hypertrophy of the synovial membrane, often driven by repeated joint bleeds<sup>1</sup>

## Synovitis can be asymptomatic<sup>2</sup>

### Synovitis in a knee joint



## Synovitis (acute → chronic)

### Acute synovitis<sup>1-3</sup>

- ✓ Swelling
- ✓ Warmth ± pain
- ✓ Limited range of motion
- ✓ Can take several weeks to resolve<sup>4</sup>

### Chronic synovitis

- ✓ Synovitis lasting >3 months<sup>4</sup>
- ✓ Symptoms of acute synovitis; however, movement may be more limited<sup>2,3</sup>
- ✓ Presence of inflammation, joint effusion and synovial hypertrophy<sup>2</sup>



**Failure to manage synovitis results in a vicious cycle of inflammation and bleeding, leading to irreversible arthropathy, highlighting the importance of early detection<sup>4</sup>**

Image adapted from Nicholson HJ, et al. Appl Sci. 2024;14:6292, used under CC BY 4.0

1. Dargaud Y, et al. Blood Rev. 2025;101304; 2. Rodriguez-Merchan EC & Valentino LA. World J Orthop. 2016;7:370-5; 3. van Vulpen LFD, et al. Haemophilia. 2021;27:96-102; 4. Srivastava A, et al. Haemophilia. 2020;26:1-158

# HAEMOPHILIC SYNOVITIS IS DRIVEN BY RECURRENT HAEMARTHROSIS AND IRON DEPOSITION

This **self-perpetuating cycle** of inflammation and structural damage can be asymptomatic<sup>1-3</sup>

## Characteristics of haemophilic synovitis



**Silent symptoms** Haemophilic synovitis is not necessarily associated with pain and swelling<sup>4</sup>



**Dual-hit mechanism** Iron-driven “chemical hit” and cytokine triggered “inflammatory hit”<sup>5</sup>



**Importance of bleeding** Bleeding triggers a self-perpetuating inflammatory cascade<sup>1-3</sup>

Unlike haemophilic synovitis, synovitis in the absence of haemophilia (e.g. in rheumatoid arthritis or osteoarthritis) is commonly associated with excessive mechanical loading<sup>6</sup>

1. Van Vulpen LFD, et al. Haemophilia. 2021;27: 96-102; 2. Gringeri A, et al. Haemophilia. 2014;20:459-63;  
3. Gualtierotti R, et al. J Thromb Haemost 2021;19:2112-21; 4. De la Corte-Rodriguez H, et al. Haemophilia. 2022;28:138-44;  
5. Calcaterra I, et al. Front Physiol. 2020;11:541; 6. Ishikura H, et al. Sci Rep. 2026;16:8007

# SUBCLINICAL BLEEDS CAN OCCUR DESPITE PROPHYLAXIS<sup>1</sup>



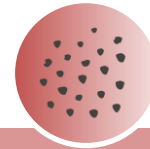
MRI can reveal the presence of subclinical bleeds in patients with haemophilia<sup>1-3</sup>

## DYNAMO study

N=51  
Median age 43 years

Adult patients with non-severe haemophilia (median factor VIII level 10 IU/dL)<sup>2,\*</sup>

14%



Haemosiderin depositions are considered signs of previous subclinical bleeding<sup>1-3</sup>

## BEGIN study

N=43  
Median age 23.5 years

Patients ≥16 years with severe haemophilia and lifelong access to prophylaxis<sup>3,\*†</sup>

16%

of joints contained haemosiderin depositions

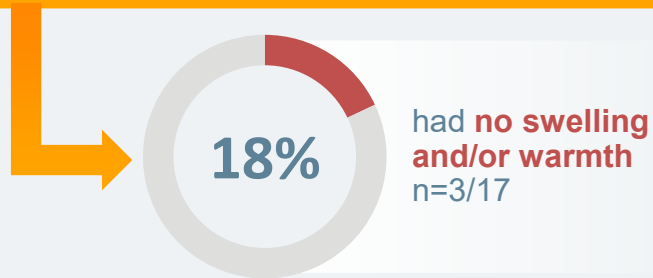
\* Joints investigated were knees, elbows and ankles; † With/without synovial hypertrophy; Patients had to be on prophylaxis for at least 12 months before inclusion MRI, magnetic resonance imaging

1. Gringeri A, et al. Haemophilia. 2014;20:459-63;
2. Zwagemaker AF, et al. J Thromb Haemost. 2022;20:1126-37;
3. van Leeuwen FHP, et al. J Thromb Haemost. 2023;21:1156-63

# SYNOVITIS IS A MARKER OF EARLY JOINT DISEASE BUT CAN OCCUR IN THE ABSENCE OF CLINICAL SYMPTOMS<sup>1,2</sup>

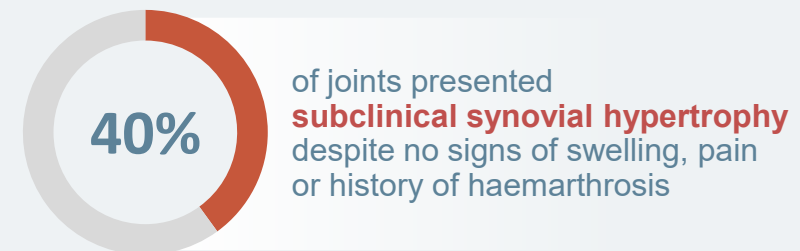
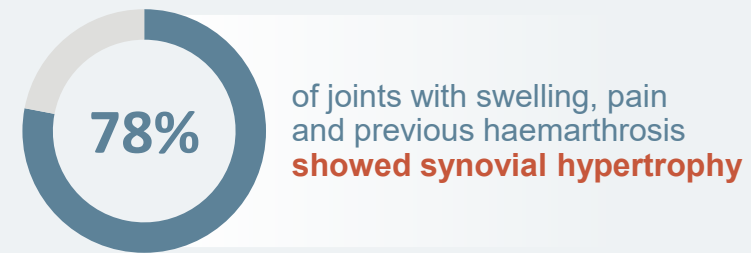
A single-centre analysis of 474 joints  
79 patients\* with haemophilia without a recent joint bleed<sup>1</sup>

N=17 (22%) had active synovial proliferation  
at ultrasound in at least one joint



A single-centre analysis of 203 joints from  
66 patients<sup>†</sup> with haemophilia<sup>2</sup>

Severity:  
Mild 5/66 (7.6%), moderate 8/66 (12.1%), severe 53/66 (80.3%)



\* With severe haemophilia A, aged  $\geq 16$  years who had access to prophylaxis. <sup>†</sup> 56 patients had haemophilia A and 10 haemophilia B (aged 16-69 years). Nine patients (13.6%) were being treated with primary prophylaxis, 33 (50%) with secondary prophylaxis, 18 (23.3%) with tertiary prophylaxis and 5 (7.6%) were treated on-demand. Synovial hypertrophy was assessed by ultrasound

1. van Bergen EDP, et al. Haemophilia. 2023;29:1580-8; 2. De la Corte-Rodriguez H, et al. Haemophilia. 2022;28:138-44

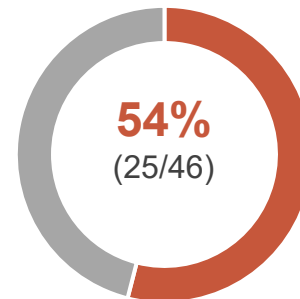
# SYNOVITIS IN CHILDREN CAN OCCUR EVEN WITHOUT EVIDENT BLEEDING

Subclinical bleeds could lead to synovitis, which is the first reversible step in the process towards irreversible joint damage<sup>1,2</sup>



## Synovitis in Children<sup>3</sup>

Severe Haemophilia A, median age, 11.4 years



**synovial hypertrophy** and **haemosiderin deposition, without evident bleeding** on dose and frequency-escalated **primary prophylaxis**<sup>3\*</sup>

Preventing and monitoring subclinical bleeds and synovitis with **ultrasound** is key to protecting joints from long-term irreversible structural damage<sup>2,4,5</sup>

\* 54% of study participants had detectable soft-tissue changes in at least one index joint and 39% had detectable osteochondral changes in at least one index joint; and 5 (7.6%) were treated on demand

Synovial hypertrophy was assessed by ultrasound

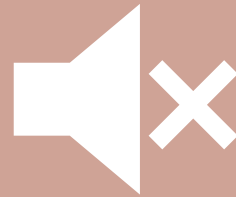
1. Dargaud Y, et al. Blood Rev. 2025;101304; 2. Mancuso ME, et al. Haemophilia. 2023;29:619-28; 3. Stimec J, et al. Res Pract Thromb Haemost. 2021;5:e12565; 4. Gringeri A, et al. Haemophilia. 2014;1:459-63; 5. van Bergen EDP, et al. Haemophilia 2023;29:1580-8

# ASSESSMENT OF SYNOVITIS

# ROUTINE ASSESSMENT OF JOINTS SHOULD BE PERFORMED USING A MULTIMODAL APPROACH<sup>1-6</sup>

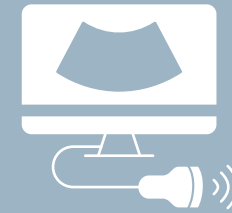


**Joint assessment** should be performed on a **regular basis** (at least annually)<sup>1,2</sup>



**Synovitis can be asymptomatic**, and may not be detected during physical examination<sup>2,4-6</sup>

**Functional HJHS lacks sensitivity for detecting early joint abnormalities<sup>7</sup>**



**Imaging** should be routinely used to ensure **detection of early joint damage**<sup>1,2</sup>

HJHS, Hemophilia Joint Health Score

1. Seuser A, et al. Blood Coagul Fibrinolysis. 2018;29:509-20;
2. Srivastava A, et al. Haemophilia. 2020;26:1-158;
3. van Leeuwen FHP, et al. Haemophilia 2023;29:445-55;
4. Gualtierotti R, et al. Haemophilia. 2024;30:1018-24;
5. Álvarez-Román MT, et al. Haemophilia. 2024;30:513-22;
6. van Bergen EDP, et al. Haemophilia. 2023;29:1580-8;
7. Ay C, et al. Haemophilia. 2024;30:1265-71

# STANDARDISED US IMAGING PROTOCOLS ENSURE CONSISTENT DETECTION OF SYNOVITIS ENABLING TIMELY INTERVENTION<sup>1-7</sup>

Interpretation of US images can be challenging; however, standardised protocols exist that increase reproducibility and comparability across clinics<sup>1-4</sup>

- HEAD-US and JADE are the most widely used scanning protocols<sup>8</sup>
- Both include evaluation of synovial hypertrophy, cartilage integrity and bony changes in<sup>8</sup>:



## HEAD-US<sup>2</sup>



**Simplified scoring system** based on an **additive scale** used to define joint status in people with haemophilia<sup>2</sup>



Grey-scale US



Assess synovial hypertrophy without measuring thickness<sup>8</sup>



## JADE<sup>4</sup>



**Quantifies soft tissue and osteochondral abnormalities** in haemophilic joints using a standardised algorithm<sup>4</sup>



Grey-scale + Doppler US



Measures synovial thickness and disease activity (Power Doppler)<sup>8</sup>

\* When compared with MRI


HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; JADE, Joint tissue Activity and Damage Exam; MRI, magnetic resonance imaging; US, ultrasound

1. Soliman M, et al. Haemophilia. 2017;23:660-72; 2. Martinoli C, et al. Thromb Haemost. 2013;109:1170-9; 3. De la Corte-Rodriguez H, et al. Expert Rev Hematol.

2018;11:253-61; 4. Volland LM, et al. J Ultrasound Med. 2019;38:1569-81; 5. Barnes RFW, et al. BMC Musculoskelet Disord 2023;24:299;


6. Di Minno MND, et al. J Clin Med. 2017;6:77; 7. Srivastava A, et al. Haemophilia. 2020;26:1-158; 8. Mancuso ME, et al. Haemophilia. 2022;29:619-28

# MRI AND ULTRASOUND ALLOW DETECTION OF EARLY JOINT ABNORMALITIES ENABLING EARLY INTERVENTIONS<sup>1-5</sup>



## Point-of-care ultrasound

- ✓ POC-US allows detection of joint defects that may be missed during physical examination<sup>5</sup>
- ✓ Standardised protocols like HEAD-US and JADE ensure consistent detection and reproducibility across different operators and centres<sup>6-11</sup>
- € Low cost<sup>4</sup>
- 🕒 Quick to perform<sup>4</sup>
- 🏥 Widely accessible<sup>4</sup>



## MRI


- ✓ Considered the gold standard of joint assessment<sup>2,4,5</sup>
- ✓ Subclinical bleeding is more readily detected by MRI than US<sup>1,2</sup>
- € High cost<sup>3,4</sup>
- 🕒 Lengthy procedure time<sup>3,4</sup>
- 👤 Requirement for sedation in children<sup>3,4</sup>


HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; JADE, Joint tissue Activity and Damage Exam; MRI, magnetic resonance imaging; POC, point of care; US, ultrasound

1. van Leeuwen FHP, et al. J Thromb Haemost. 2023;21:1156-63;
2. Aisa CS, et al. Haemophilia. 2014;20:e51-7;
3. Di Minno MND, et al. Haemophilia. 2013;19:e167-73;
4. Plut D, et al. Radiol Oncol. 2019;53:178-86;
5. Dargaud Y, et al. Blood Rev. 2025;101304;
6. Martinoli C, et al. Thromb Haemost. 2013;109:1170-9;
7. De la Corte-Rodriguez H, et al. Expert Rev Hematol. 2018;11:253-61;
8. Volland LM, et al. J Ultrasound Med. 2019;38:1569-81;
9. Gualtierotti R, et al. Haemophilia. 2024;30:1018-24;
10. Álvarez-Román MT, et al. Haemophilia. 2024;30:513-522;
11. van Bergen EDP, et al. Haemophilia 2023;29:1580-8

# TREATMENT

# TREATMENT OF SYNOVITIS AIMS TO PREVENT THE DEVELOPMENT OF IRREVERSIBLE DAMAGE<sup>1-4</sup>

 Following identification of acute synovitis, patients should be treated as early as possible with<sup>1,2</sup>

 If synovitis does not improve, synovectomy may be required<sup>2,5</sup>



Intensified haemostatic treatment



Suppress synovial activation



Prevent new bleeds



Analgesics



Anti-inflammatory treatment



Treat pain and inflammation

Non-surgical



Radio



Chemical



Reduce synovitis

Surgical



Arthroscopic



Open



Reduce bleed frequency

Early and continuous physiotherapy to support rehabilitation<sup>2</sup>

# EARLY AND CONTINUOUS PHYSICAL THERAPY IS CRUCIAL TO PRESERVE FUNCTIONAL ABILITY<sup>1,2</sup>

## Physical therapy is an integral part of comprehensive haemophilia care<sup>1,2</sup>



### Physical therapy following haemarthrosis/acute synovitis<sup>1</sup>

- Should begin as soon as pain symptoms subside
- **Active and proprioceptive exercises** should be performed until joint motion and function return to pre-bleed levels and acute synovitis resolves



### Physical therapy for chronic synovitis<sup>1</sup>

- Performed **throughout rehabilitation**
- **Individualised** based on patient functional levels
- Exercises begin slowly with **increasing progression** of weight-bearing activities



WFH recommends people with haemophilia to engage in regular physical activity.<sup>1</sup>

**Physiotherapists** facilitate this by:

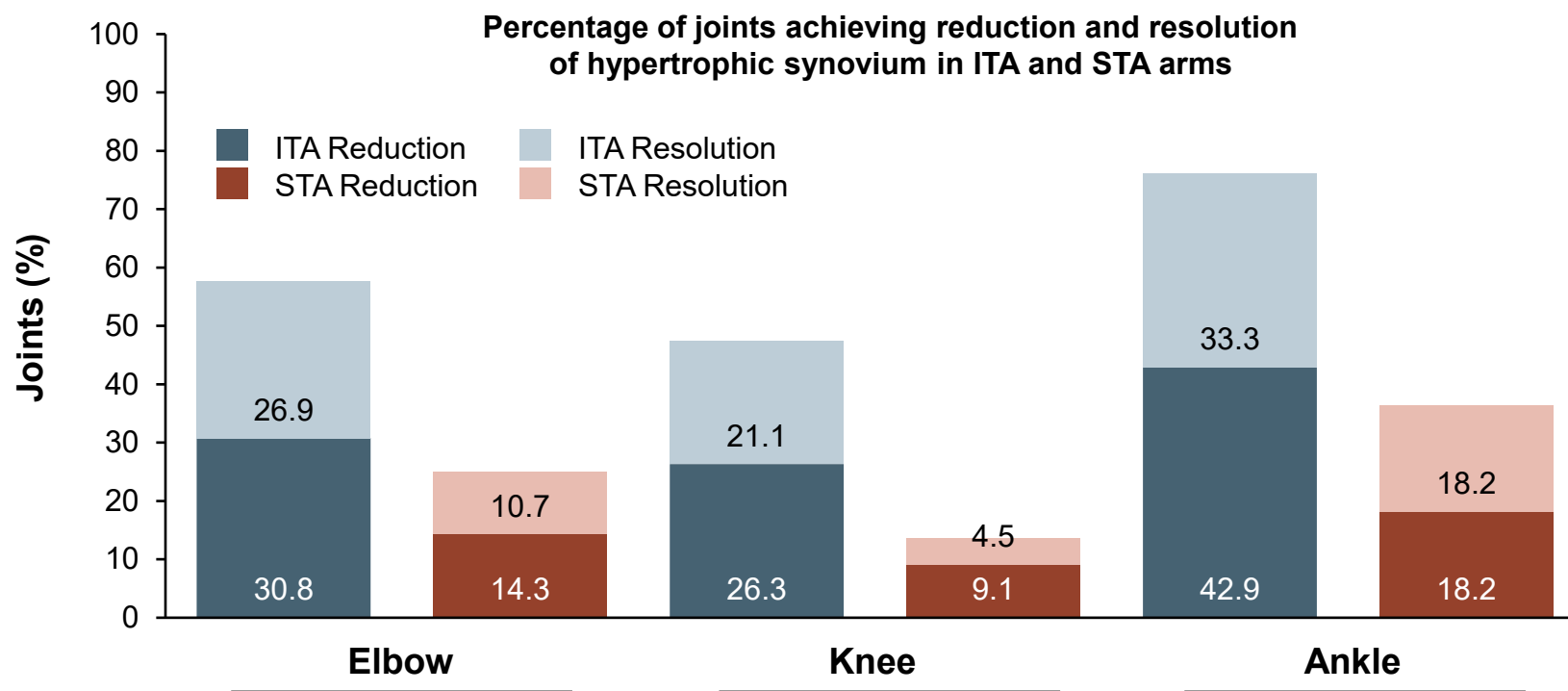
**Educating** on activities and prevention<sup>2</sup>

**Monitoring and managing** musculoskeletal complications<sup>2</sup>

**Preservation** of muscle strength and function<sup>1,2</sup>

# SYNOVIAL HYPERTROPHY MAY BE REVERSED WITH APPROPRIATE TREATMENT

Intensive FVIII replacement was associated with a reduction or resolution of synovial hypertrophy in 35.9% of cases compared with 8.4% with standard treatment in severe/moderate PwHA\*



Median time of treatment  
 ITA: 12 months (IQR: 9.8-14)  
 STA: 16 months (IQR: 11-16))

ITA targeted FVIII trough level of 8%-12% (n=39)  
 STA targeted FVIII trough level of 3%-5% (n=36)

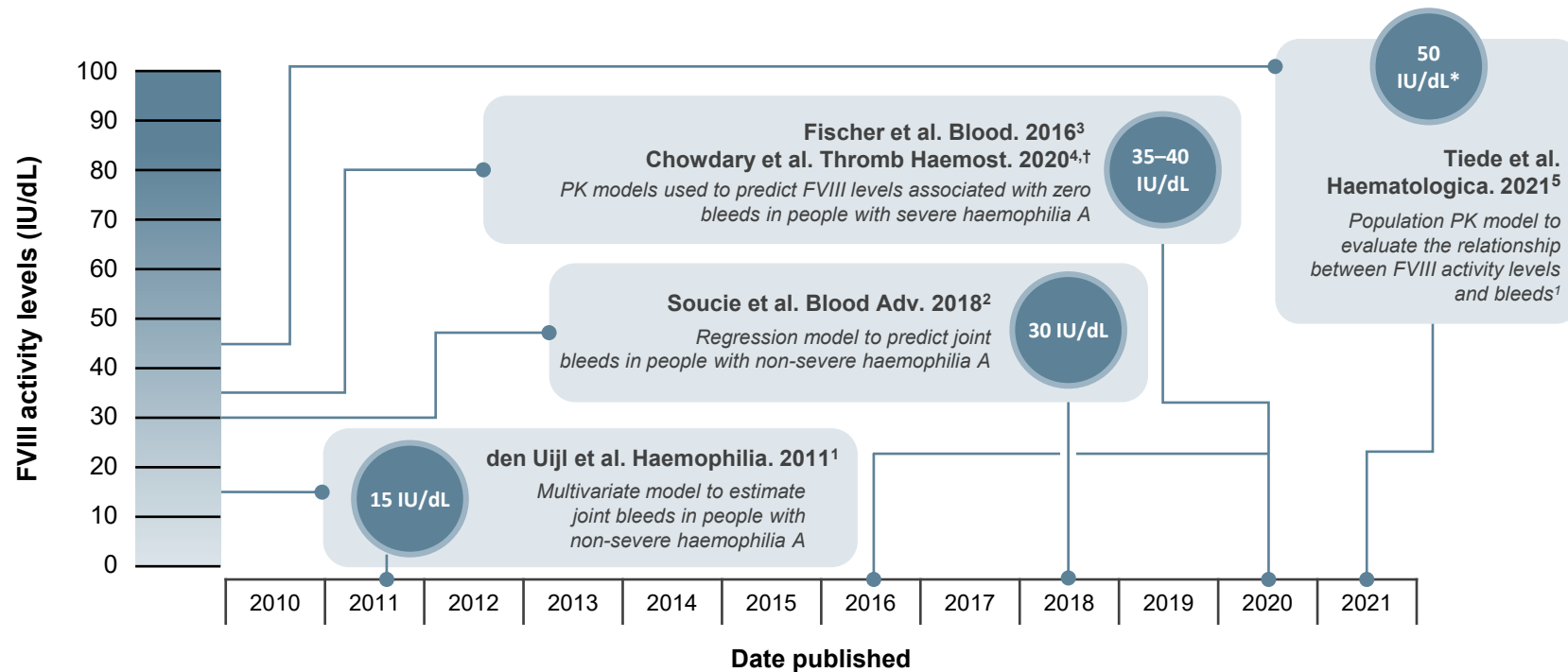
\* Patients ≥12 with severe or severe/moderate haemophilia A. Cox regression-hazard ratio: 10.79; 95%CI 1.38-84.45; p=0.023

ITA, intensive treatment arm; PwHA, people with haemophilia A; STA, standard treatment arm

Adapted from: Di Minno MND, et al. J Thromb Haemost. 2025;23:458-65

# HIGHER FVIII LEVELS OF UP TO 50% MAY BE REQUIRED TO ACHIEVE A NEAR-ZERO JOINT BLEED RATE<sup>1-3</sup>

## FVIII activity levels associated with a near-zero joint bleed rate



The **GTH** recommends treatment with coagulation agents in **chronic synovitis** to prevent recurrent bleeding that may require levels of  $\geq 30\%$  for 6 months and regular check ups and monitoring<sup>6</sup>



A **European e-Delphi consensus** statement recommends that joint bleeds and microbleeds need to be avoided through effective prophylaxis<sup>7</sup>

FVIII, Factor VIII; WFH, World Federation of Hemophilia.

\*In children; †Zero spontaneous joint bleeds in all patients with estimated FVIII activity level  $\geq 40$  IU/dL.

1. den Uijl I, et al. Haemophilia 2011; 17(1):41-44; 2. Soucie J, et al. Blood Adv 2018;2:2136-44; 3. Fischer K, et al. Blood. 2016;128:2576; 4. Chowdary P, et al. Thromb Haemost 2020; 120:728-736; 5. Tiede A, et al. Haematologica 2021;106:1902-9; 6. GTH [S2k-Leitlinie Synovitis bei Hämophilie](#). 2022 (accessed February 2026) 7. Mancuso ME, et al. Haemophilia 2023;29:619-28

# SUMMARY



A **single** haemarthrosis or subclinical bleeding can lead to **synovitis**<sup>1</sup>



**Bleeds** can occur despite patients receiving prophylaxis<sup>2</sup>



**Synovitis** is the last reversible step leading to arthropathy<sup>2,3</sup>



Routine assessment of joints should include imaging such as **ultrasound** to facilitate detection of early abnormalities<sup>4</sup>



Haemophilia A patients with **synovitis** should be treated **as early as possible** targeting increased **haemostasis** by intensifying haemostatic treatment<sup>5-7</sup>

1. Dargaud Y, et al. Blood Rev. 2025;101304; 2. Gringeri A, et al. Haemophilia. 2014;20:459-63; 3. Di Minno MND, et al. J Thromb Haemost. 2025;23:458-65; 4. Seuser A, et al. Blood Coagul Fibrinolysis. 2018;29:509-20; 5. Seuser A, et al. Haemophilia. 2007;1326-31; 6. Srivastava A, et al. Haemophilia. 2020;26:1-158; 7. S2k-Leitlinie Synovitis bei Hämophilie, 2nd edition 2022

# CLINICAL TAKEAWAYS

# CLINICAL TAKEAWAYS

- Bleeding, including subclinical bleeding can occur despite patients receiving prophylaxis
- Synovitis is the last reversible step prior further deterioration leading to arthropathy
- Routine assessment of joint health status is therefore essential and should include imaging such as ultrasound to facilitate the detection of early abnormalities
- In patients with haemophilia A and synovitis, prophylaxis should be intensified to resolve and/or reduce the synovial hypertrophy, alongside other measures (anti-inflammatory drugs, physiotherapy, etc) to promote long-term joint health

# REFERENCES

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