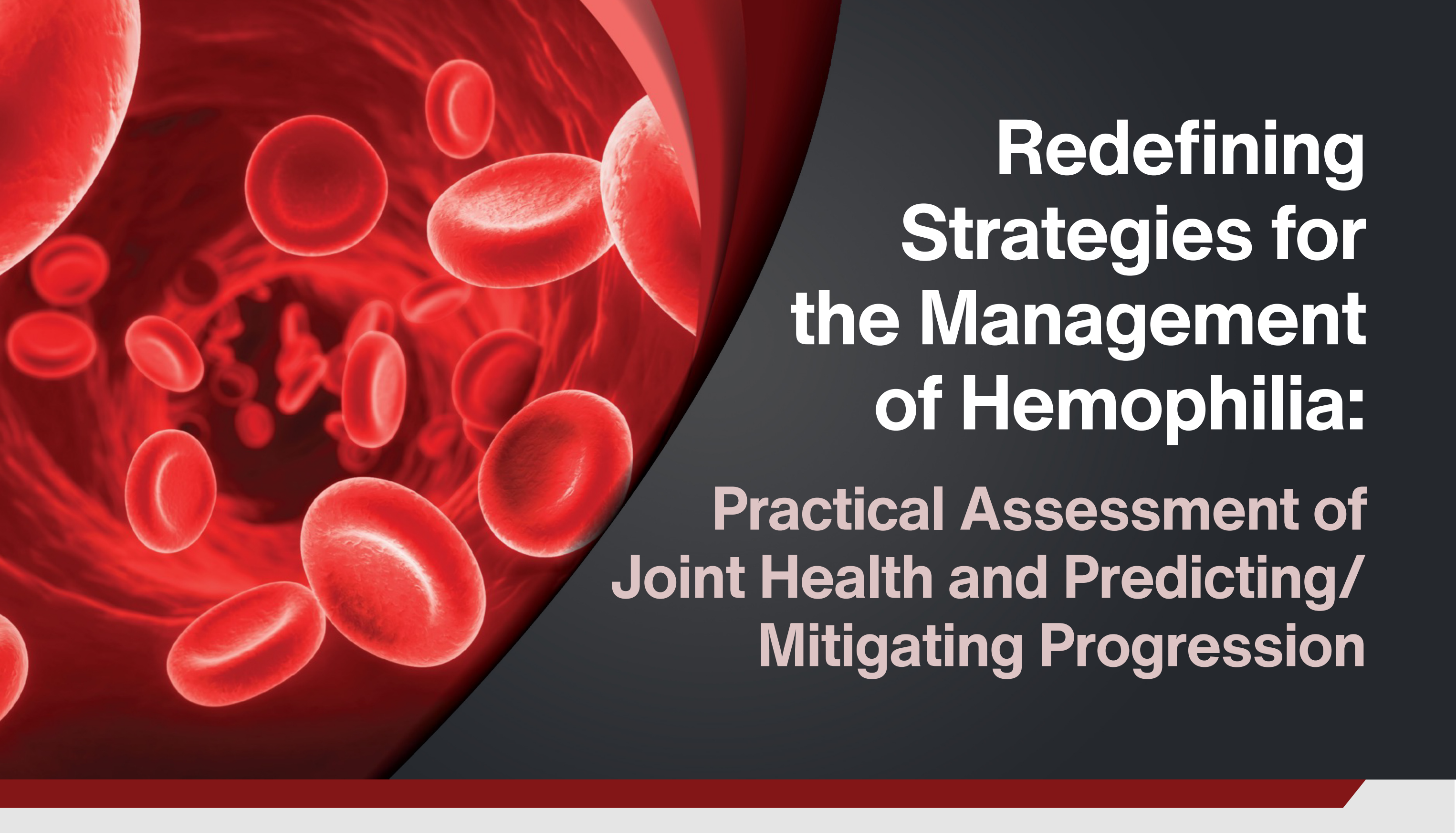
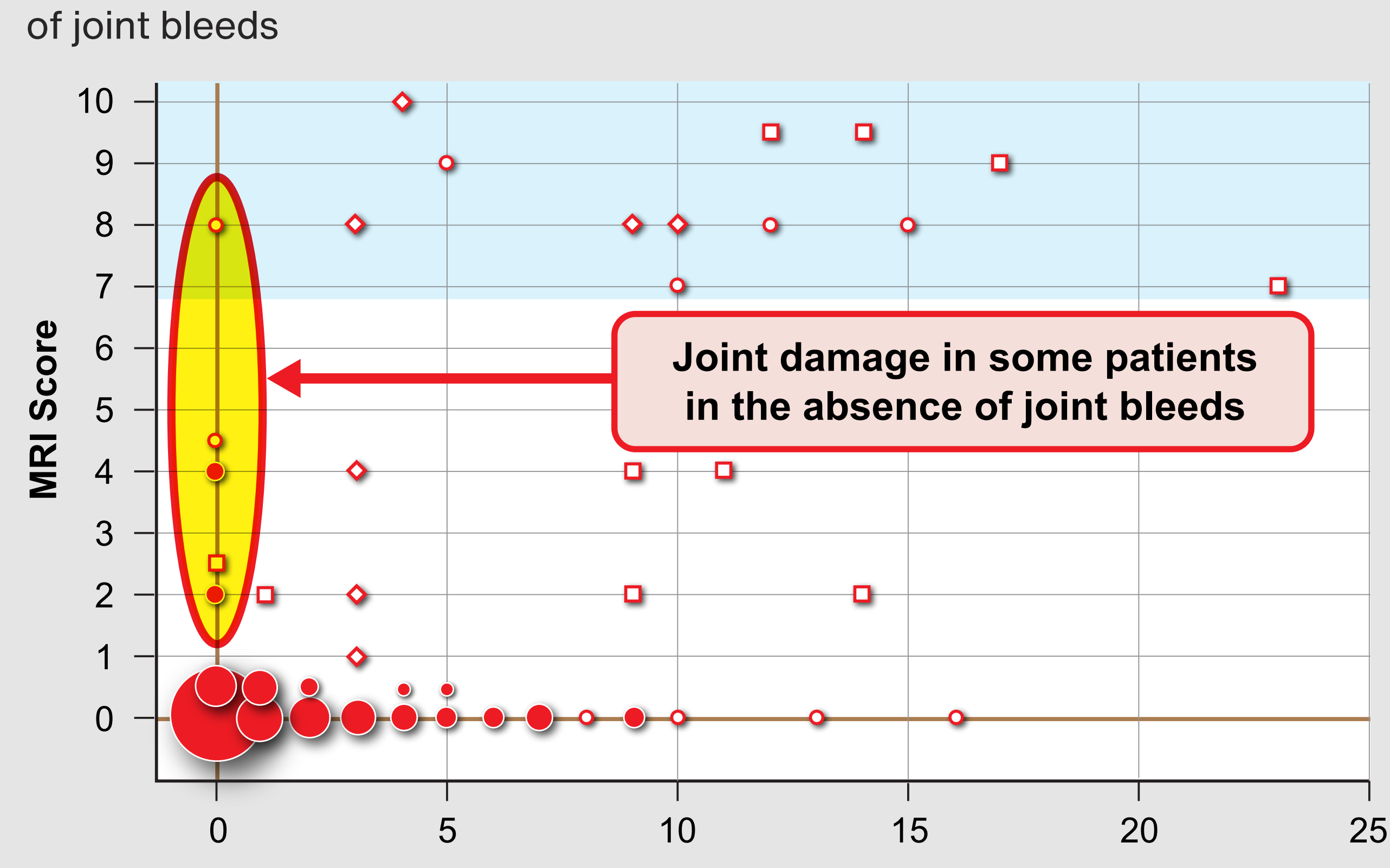


Redefining Strategies for the Management of Hemophilia:

Practical Assessment of Joint Health and Predicting/ Mitigating Progression

Hemophilia treatment should aim to prevent the permanent sequelae of bleeding (overt and subclinical) in any part of the body

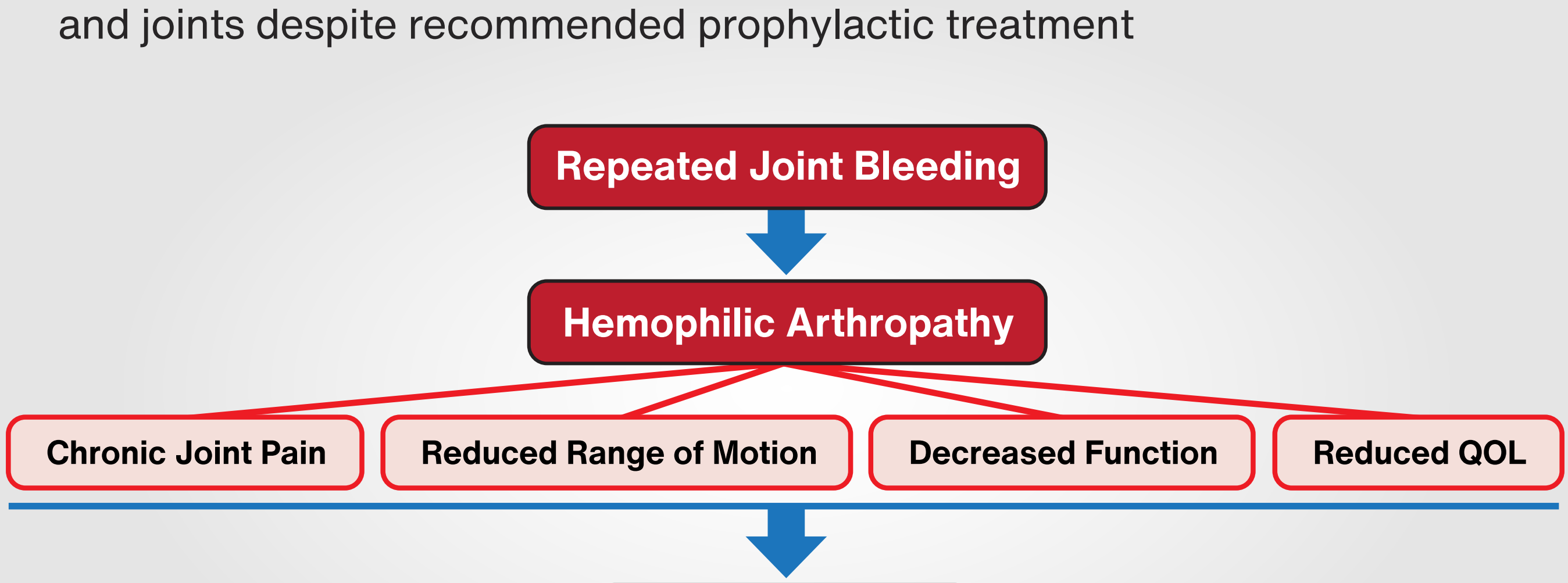
- The Joint Outcome Study showed that joint damage occurs, even in the absence of joint bleeds



Joint damage in some patients in the absence of joint bleeds

Image used for educational purposes only from Manco-Johnson MJ, et al. *N Engl J Med.* 2007.

- Even a single joint bleed may lead to irreversible joint damage
- Subclinical bleeding can also lead to joint damage
- Patients with hemophilia may experience spontaneous bleeding into muscles and joints despite recommended prophylactic treatment



Repeated Joint Bleeding

Hemophilic Arthropathy

Chronic Joint Pain | **Reduced Range of Motion** | **Decreased Function** | **Reduced QOL**

Disease Burden

- Factors influencing progression:
  - Disease severity
  - Gene mutations
  - Age at prophylaxis initiation
  - Prophylaxis adherence/persistence

Active joint health monitoring is essential because the threshold amount of blood that results in a symptomatic bleed differs among patients.

- Patients have different pain thresholds
- Thresholds change for each patient over time (as the patient grows from a child to an adult)
- Thresholds are different for every joint bleed within each patient

Despite advances in prophylactic treatment:

- Patients treated with FVIII prophylaxis to trough levels >1% may still experience subclinical joint damage. The WFH now recommends FVIII trough levels of 3% to 5%.
- FVIII trough levels of up to 15% may not be enough to prevent arthropathy (depending on lifestyle, joint status, and other factors).

Joint Health Monitoring

- MRI and X-ray are the traditional methods to assess and monitor joint health; MSUS may offer some additional advantages

MRI

- Gold standard for early detection of joint changes
- High spacial resolution; ability to distinguish between different intra-articular elements
- Drawbacks include limited accessibility, complexity, need for sedation in children, and lack of standardized assessment criteria

MSUS

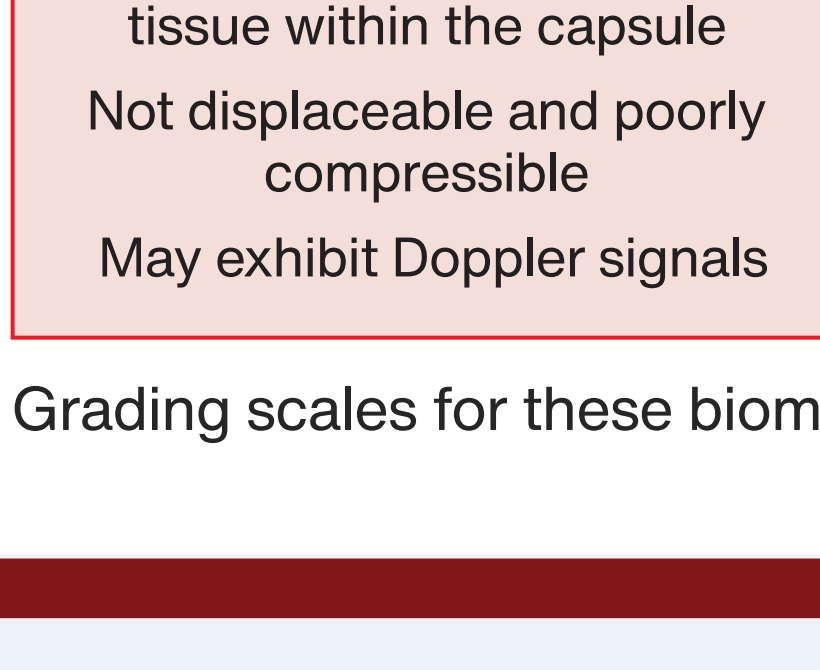
- Economical, readily available, noninvasive; no sedation required
- High sensitivity in detecting low intra-articular blood concentrations
- Good correlation with MRI for cartilage damage and gradual bone changes
- Can be performed in multiple joints at the same time in children

X-ray

- Least sensitive; not recommended for early arthropathy detection
- Low correlation with MRI; underestimates the degree of joint pathology in soft tissues
- Main use is in evaluating advanced joint pathology in adult patients with hemophilia

MSUS allows for the study of 3 hemophilia biomarkers:

Synovitis



Presence of a hypoechoic synovial hypertrophy, regardless of the presence of effusion or any grade of Doppler signal

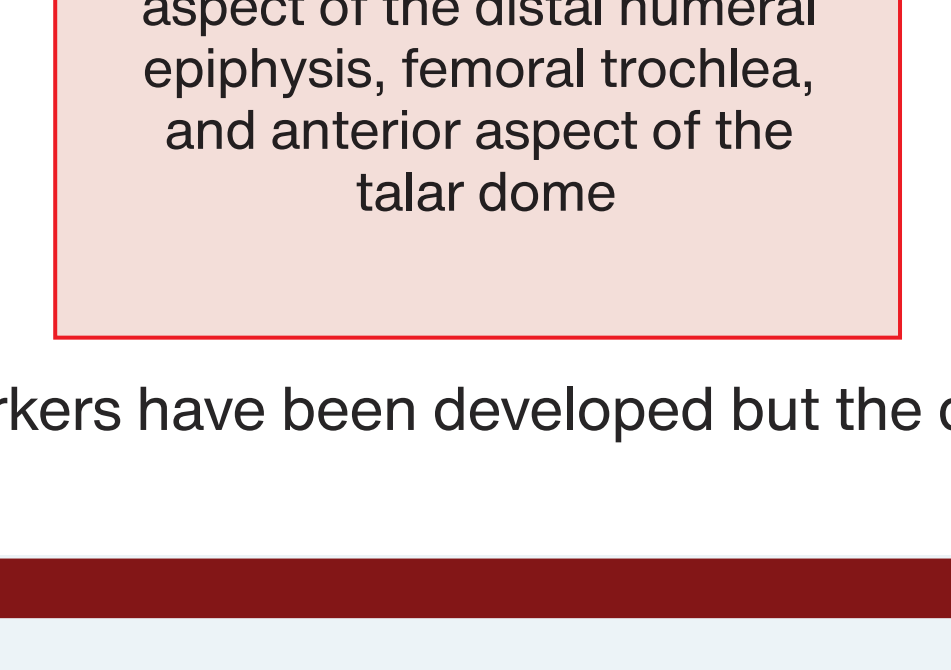
Synovial hypertrophy

Abnormal hypoechoic synovial tissue within the capsule

Not displaceable and poorly compressible

May exhibit Doppler signals

Osteochondral Damage

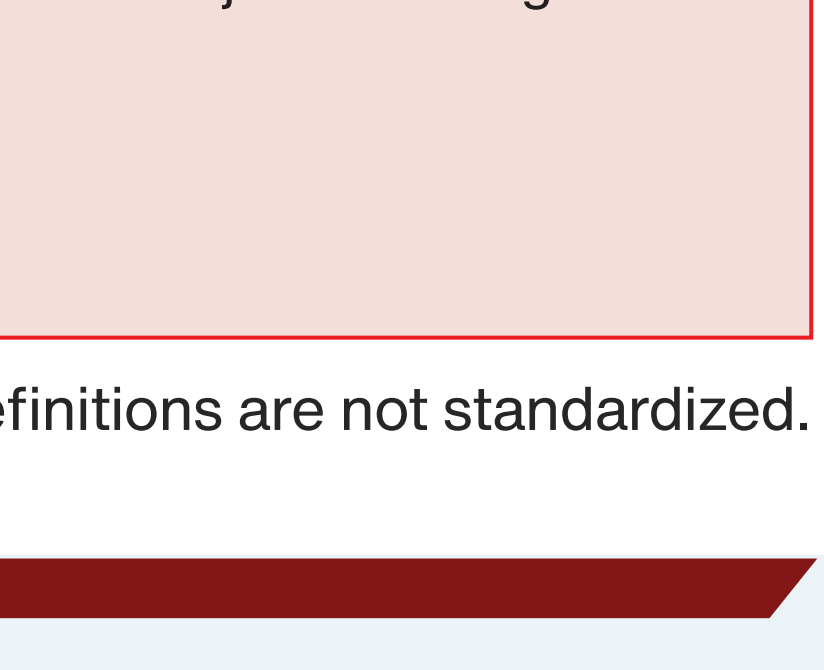


Variable degree of loss of thickness of the cartilage—*but damage should be considered irreversible*

Variable degree of irregularity of subchondral bone

Look for this in anterior aspect of the distal humeral epiphysis, femoral trochlea, and anterior aspect of the talar dome

Hemarthrosis



Can be used in point-of-care study for differential diagnosis of painful joints and detection of joint bleeding

Can describe acute joint bleeding

Grading scales for these biomarkers have been developed but the definitions are not standardized.

Rebalancing Therapies

- Rebalancing therapies (fitusiran, concizumab) may play an important role in mitigating joint damage and improve the patient's ability to participate in physical activity, a key indicator for QOL

Fitusiran

An siRNA molecule that acts by binding to the mRNA for antithrombin and inhibits its production (and therefore allows thrombin to form).

Studied in 3 phase 3 clinical trials (in patients aged >12 years with hemophilia A or B; pediatric studies are ongoing):

- ATLAS-INH trial in patients with inhibitors
- ATLAS-A/B trial in patients without inhibitors
- ATLAS-PPX prophylaxis trial in patients with or without inhibitors

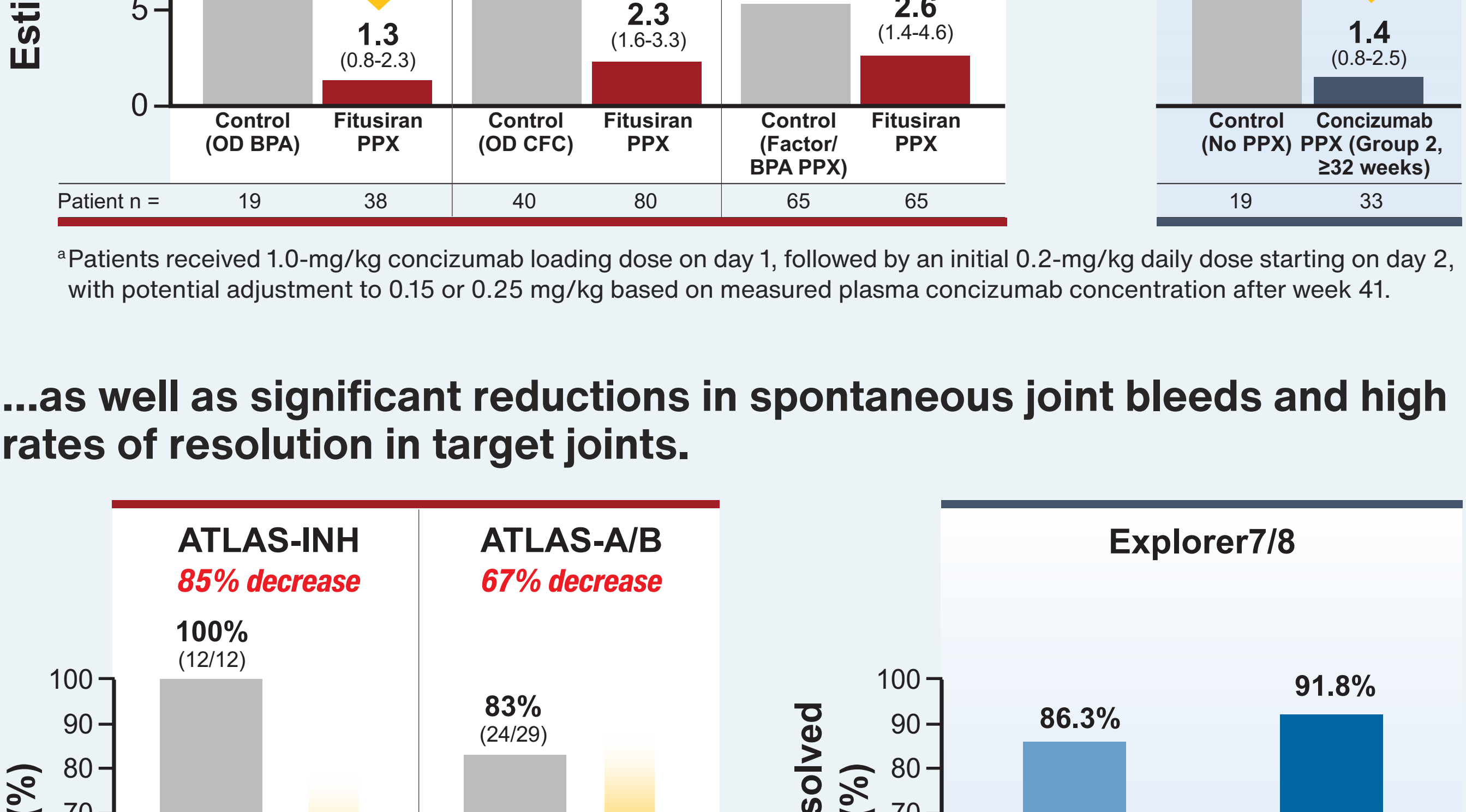
Concizumab

An anti-TFPI antibody that restores FXa production.

Studied in 2 phase 2 trials and several phase 3 trials (some ongoing) in patients aged >12 years with hemophilia A or B with or without inhibitors.

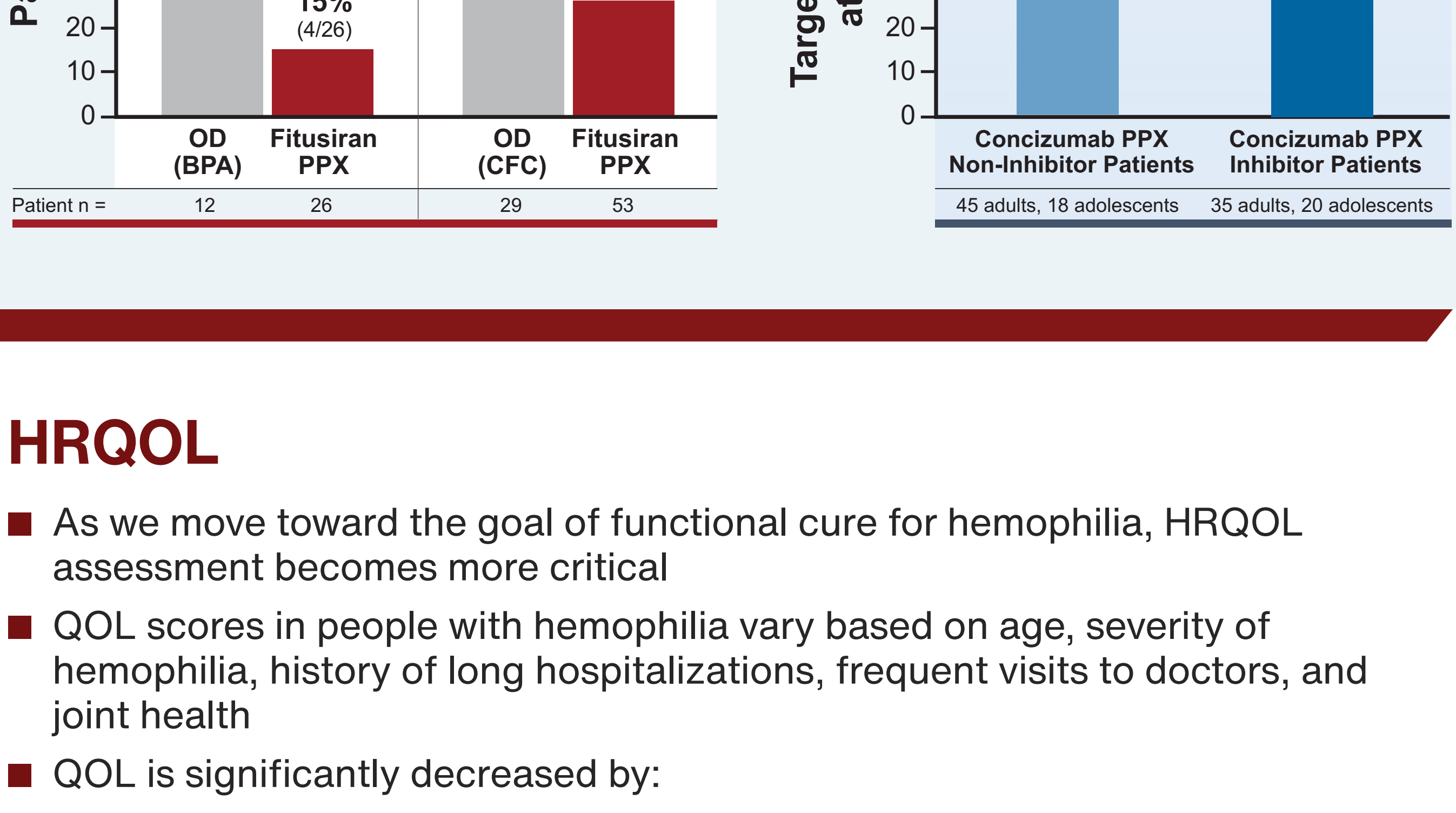
Significant reductions in joint bleeding after both agents:

Both agents showed significant reductions in mean AjBR...



[a] Patients received 1.0-mg/kg concizumab loading dose on day 1, followed by an initial 0.2-mg/kg daily dose starting on day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 41.

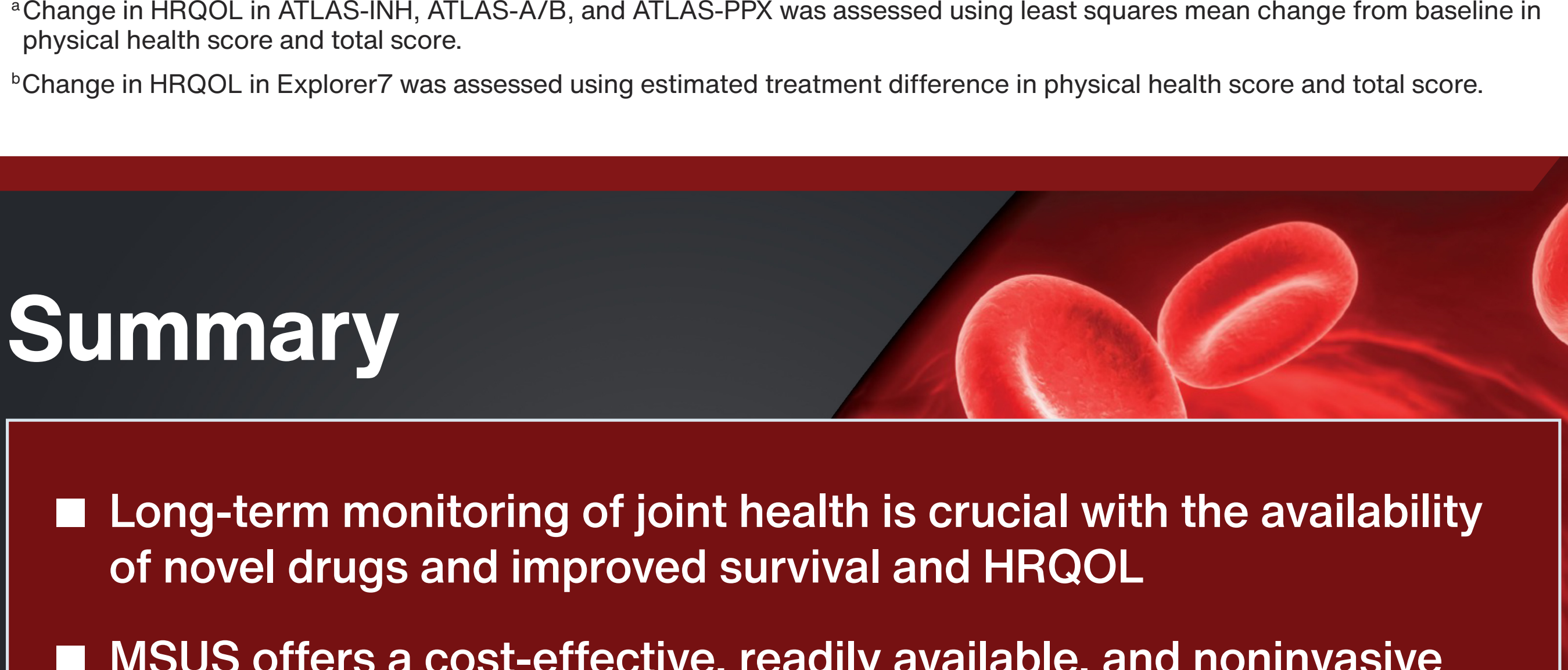
...as well as significant reductions in spontaneous joint bleeds and high rates of resolution in target joints.



HRQOL

- As we move toward the goal of functional cure for hemophilia, HRQOL assessment becomes more critical
- QOL scores in people with hemophilia vary based on age, severity of hemophilia, history of long hospitalizations, frequent visits to doctors, and joint health
- QOL is significantly decreased by:
  - ≥2 target joints
  - Higher frequency of joint pain
  - History of joint surgery

Balancing agents have shown significant improvements in HRQOL, in particular in the physical health score:



[a] Change in HRQOL in ATLAS-INH, ATLAS-A/B, and ATLAS-PPX was assessed using least squares mean change from baseline in physical health score and total score.

[b] Change in HRQOL in Explorer7 was assessed using estimated treatment difference in physical health score and total score.

Summary

- **Long-term monitoring of joint health is crucial with the availability of novel drugs and improved survival and HRQOL**
- **MSUS offers a cost-effective, readily available, and noninvasive modality for assessment of arthropathy**
- **Standardization of currently available biomarkers for joint damage and joint bleeding will further improve the management of patients with hemophilia in the near future**
- **Emerging rebalancing agents offer an unprecedented opportunity to mitigate joint damage and improve patients' ability to participate in physical activities**

Abbreviations

AjBR: annualized joint bleeding rate
ABR: annualized bleeding rate
BPA: bypassing agent
CFC: clotting factor concentrate
FVIII: factor VIII
FXa: activated factor X
Haem-A-QoL: Haemophilia Quality of Life Questionnaire for Adults
HRQOL: health-related quality of life
LSM: least squares mean
MRI: magnetic resonance imaging
MSUS: musculoskeletal ultrasound
N/A: not applicable
OD: on-demand
PPX: prophylaxis
QoL: quality of life
siRNA: small interfering RNA
TFPI: tissue factor pathway inhibitor
WFH: World Federation of Hemophilia

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