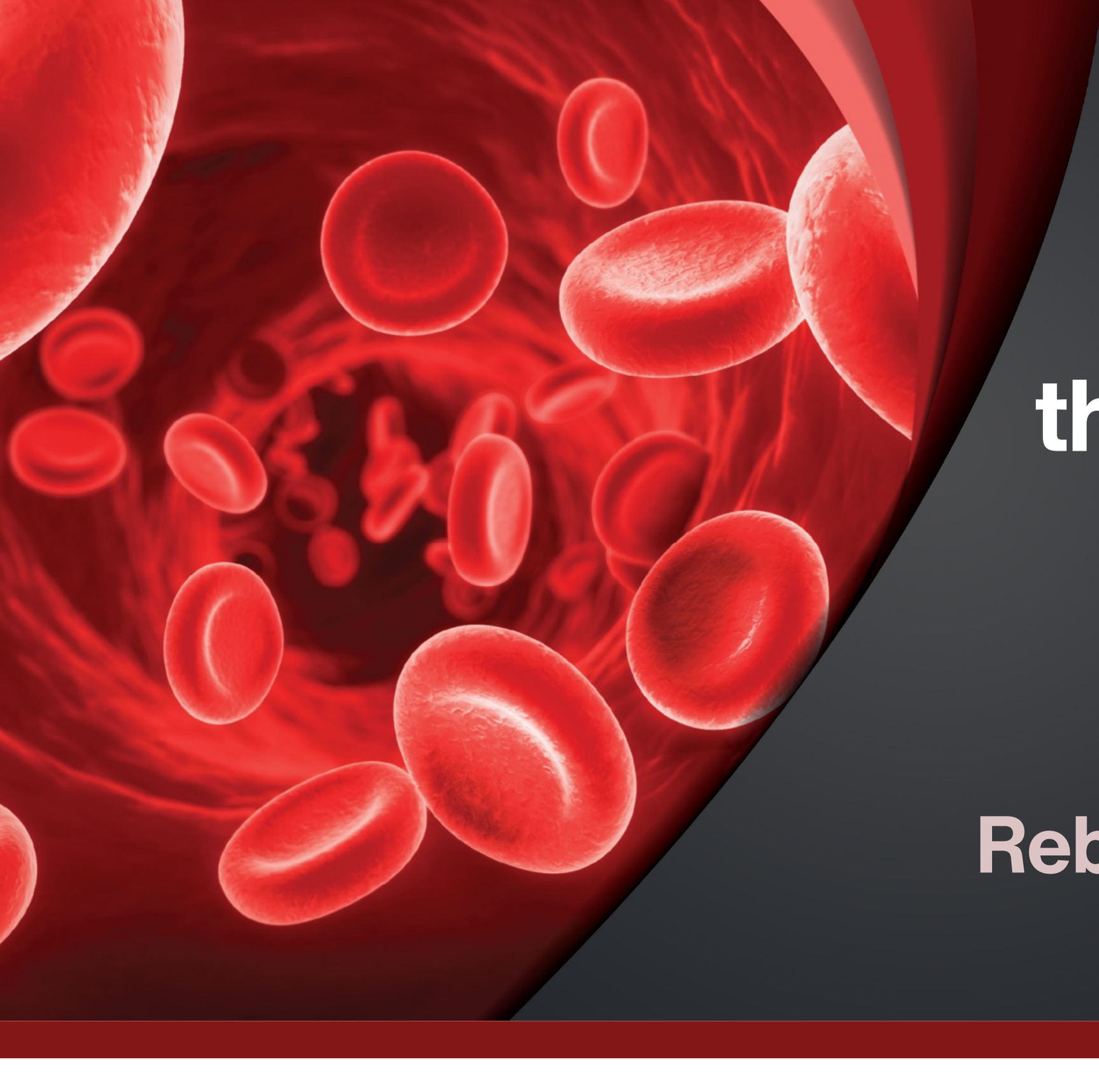
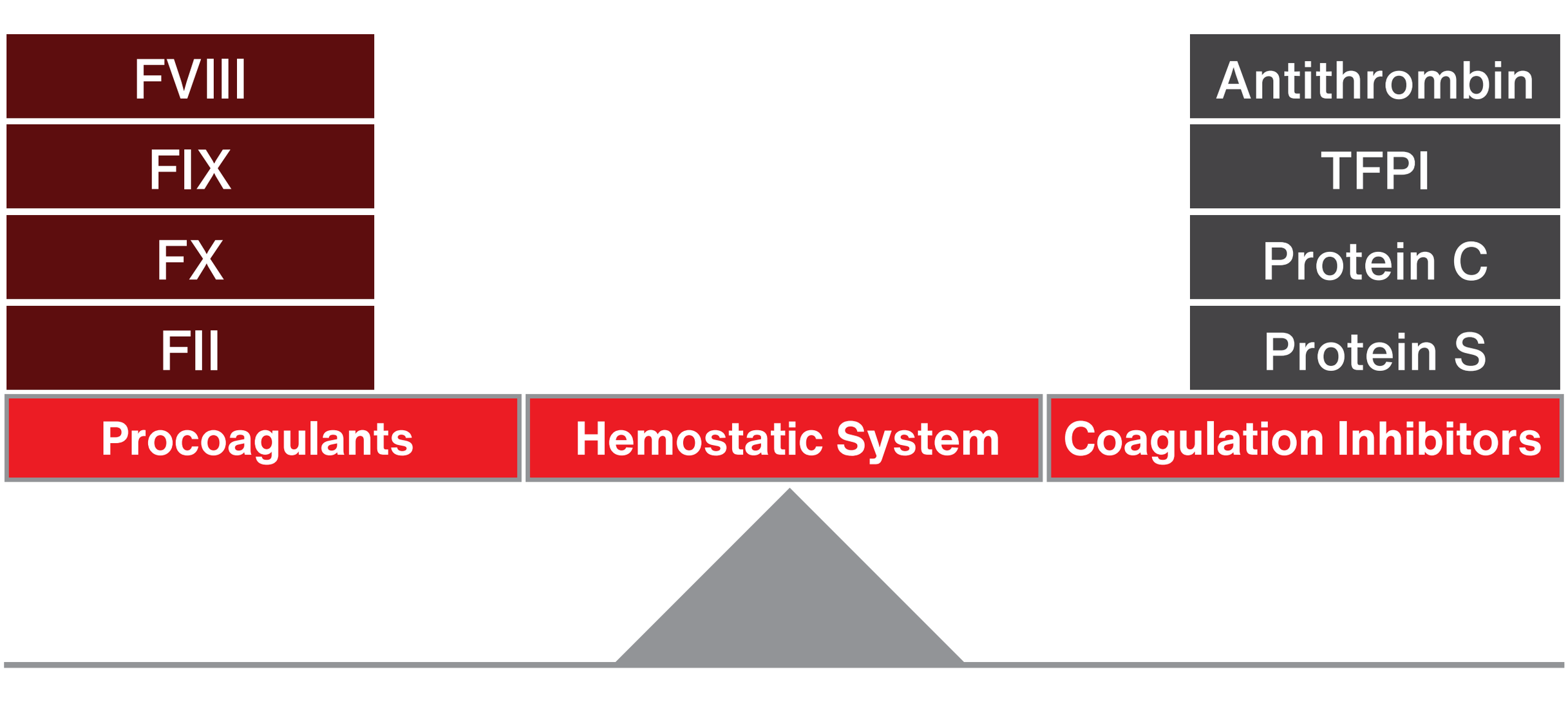


Redefining Strategies for the Management of Hemophilia:

Examining the Clinical Potential of Rebalancing Therapies

Hemostatis is a balancing act.

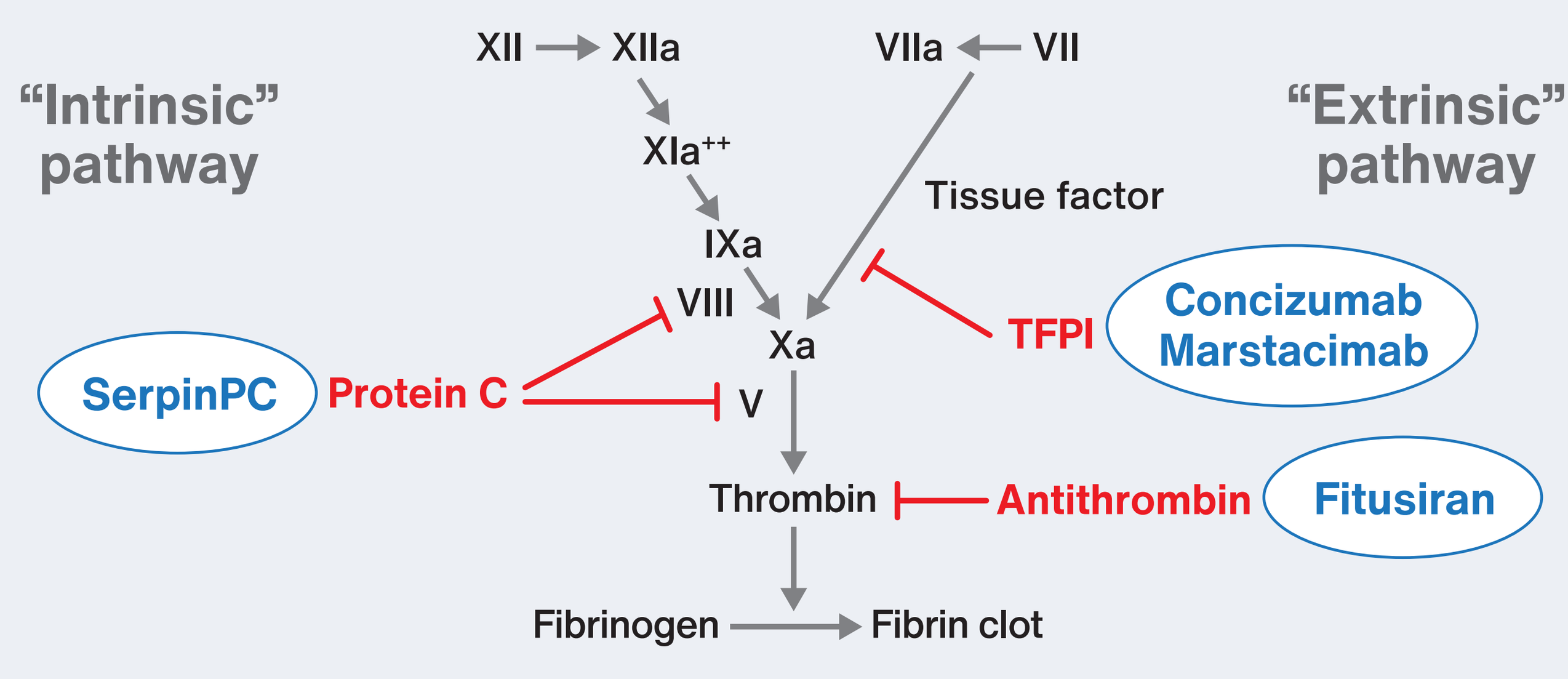
Insufficient procoagulants cause bleeding disorders, while insufficient coagulation inhibitors lead to thrombotic disorders.



Rebalancing is a novel therapeutic approach to hemophilia.

Instead of increasing procoagulant activity of FVIII and FIX, newer treatments silence the natural anticoagulants in the clotting cascade.

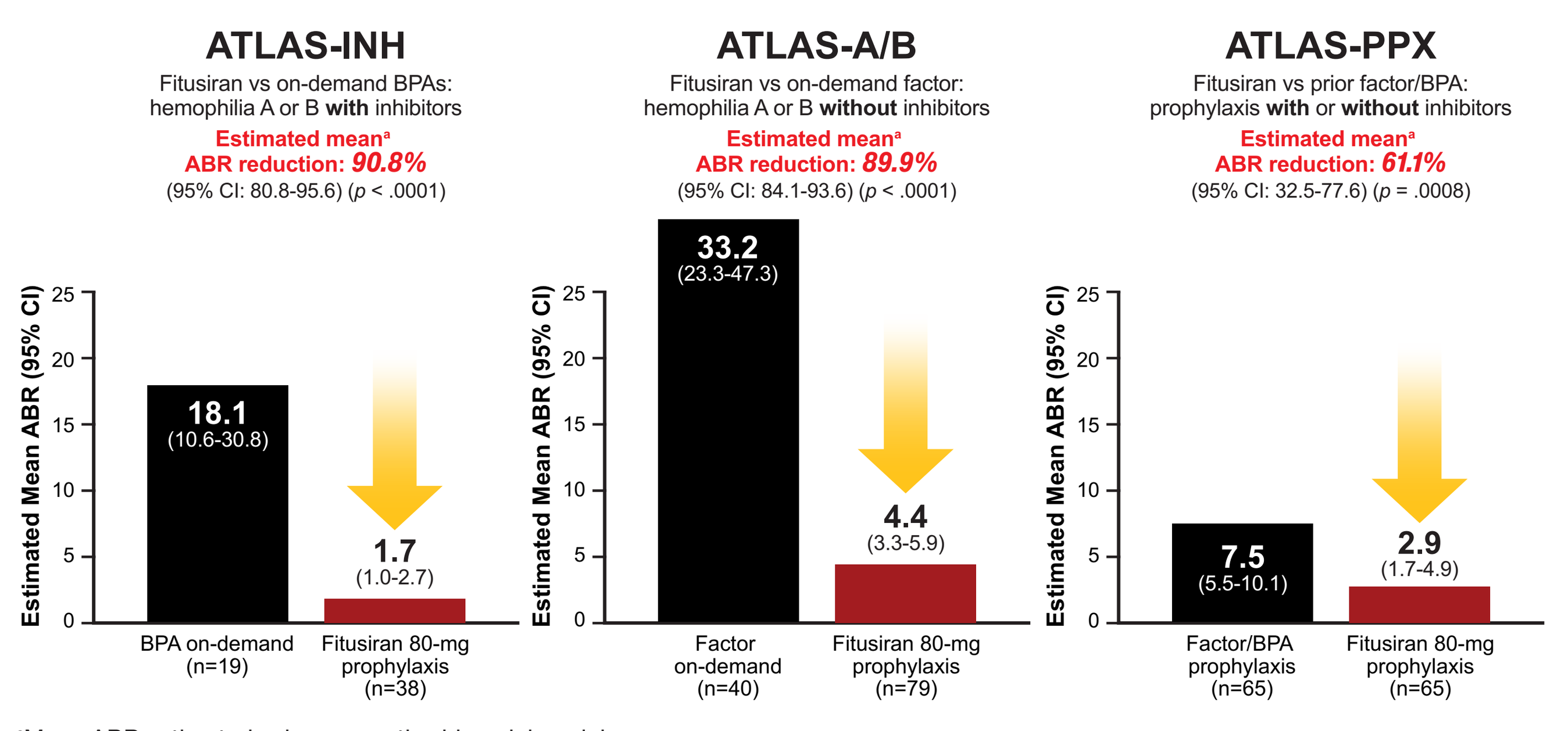
Clotting Cascade



Fitusiran

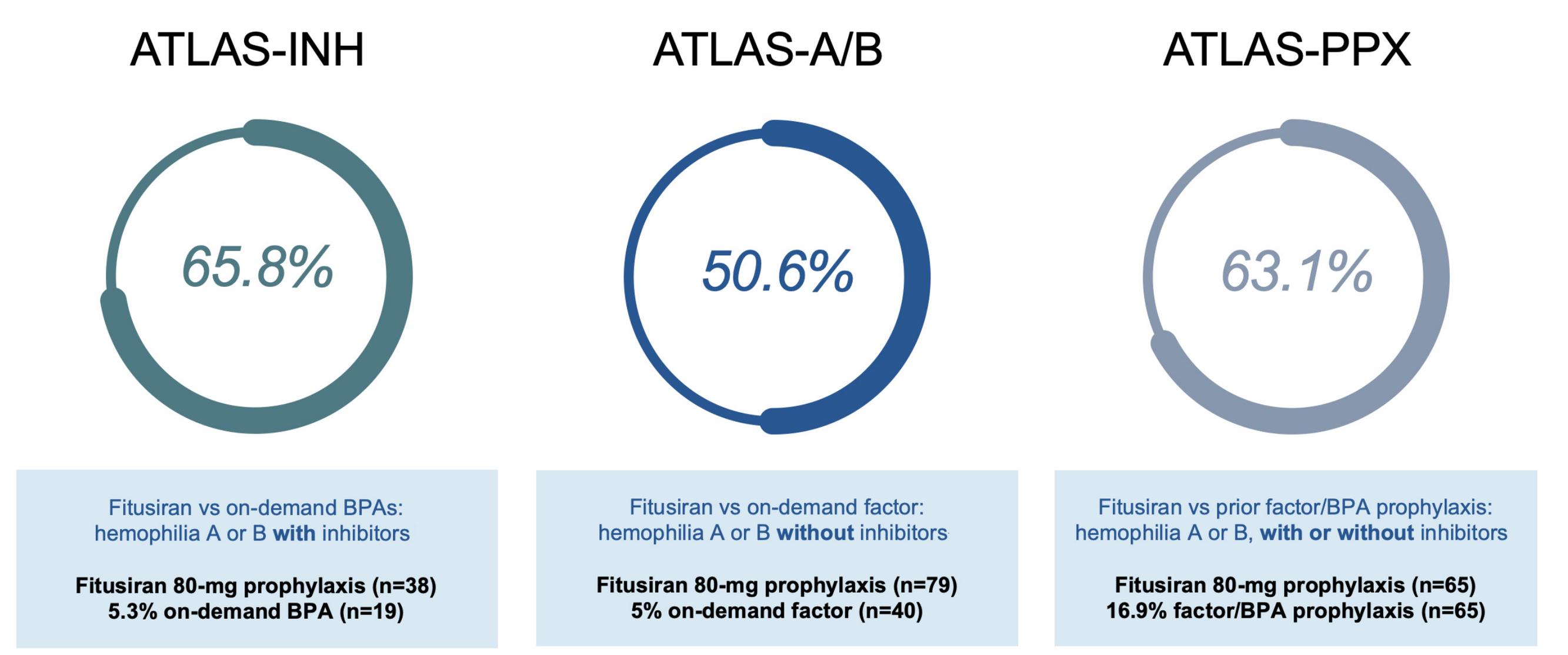
- An siRNA molecule that acts by binding to the mRNA for antithrombin and inhibits its production (and therefore allows thrombin to form)
- Studied in 3 phase 3 clinical trials (in patients aged >12 years with hemophilia A or B; pediatric studies are ongoing):
  - ATLAS-INH trial in patients with inhibitors
  - ATLAS-A/B trial in patients without inhibitors
  - ATLAS-PPX prophylaxis trial in patients with or without inhibitors

Significant reductions in ABR, even when comparing 2 prophylactic strategies (ATLAS-PPX):



[a]Mean ABR estimated using a negative binomial model.
Information presented here is intended as a summary of these studies only—direct comparisons cannot be made between the studies.

High numbers of patients with zero bleeds in the trial efficacy period

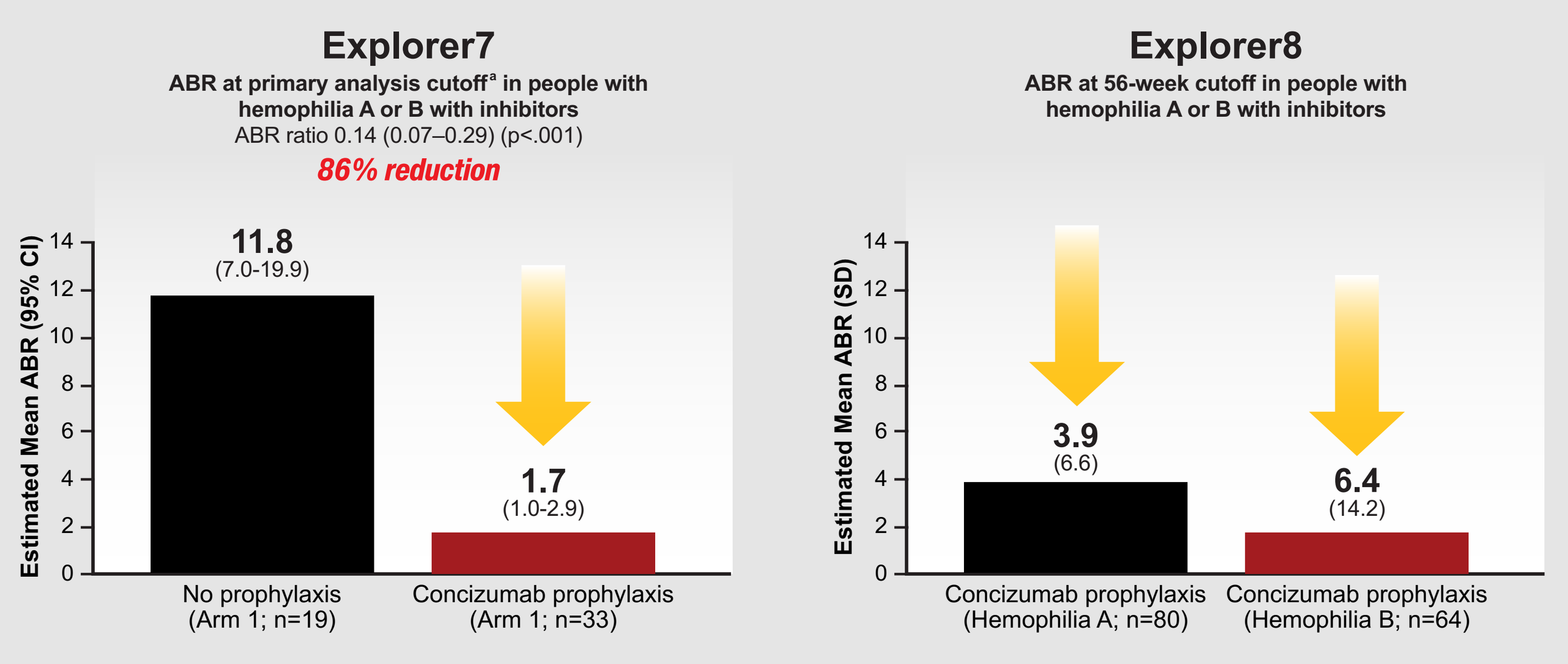


- **Common AEs across trials:** Liver enzyme elevations, URTI, headache, nasopharyngitis, and abdominal pain
- **Special AEs of interest:** Elevated liver enzymes (>3x ULN), cholecystitis, and cholelithiasis; thromboembolic events (rare)
- **Reported TEAEs leading to discontinuation:** Spinal vascular disorder and suspected spinal vessel thrombosis in 1 patient (ATLAS-INH); cholecystitis in 1 patient and increased alanine aminotransferase concentrations in 1 patient (ATLAS-A/B)
- **No treatment-related deaths reported**

Concizumab

- An anti-TFPI antibody, which restores FXa production
- Studied in 2 phase 2 trials and several phase 3 trial (some of which are ongoing), in patients aged >12 years with hemophilia A or B with or without inhibitors

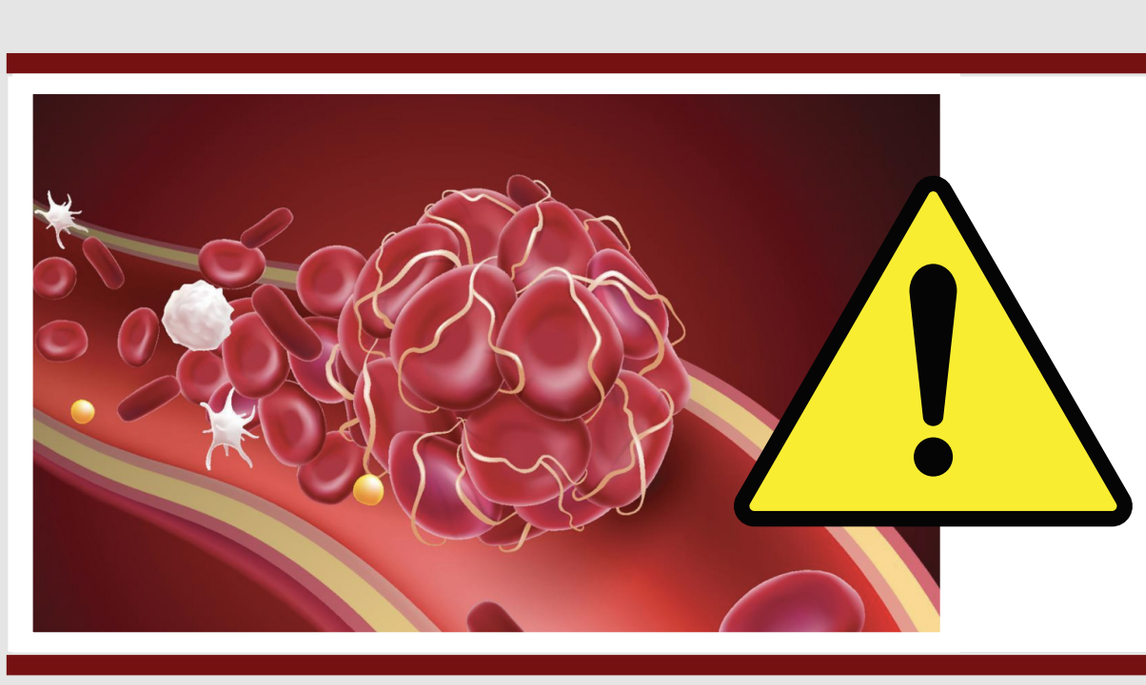
Showed significant reductions in ABR, even when comparing 2 prophylactic strategies



[a]Includes participants previously on-demand that were randomized to receive concizumab prophylaxis (Arm 2; n=33), participants that transferred from the Explorer4 trial, and an additional group of participants that were on prior prophylaxis or on-demand (Arms 3 and 4, respectively; n=81).
Images adapted for educational purposes only from Matsushita T, et al. *N Engl J Med*. 2023 and Astermark J, et al. *Blood*. 2023.

Concizumab had an overall favorable safety profile in phase 3 clinical trials:

- **Common AEs:** Arthralgia, injection-site erythema, URTI, and elevation of prothrombin fragments 1 and 2
- **Special AEs of interest:** Thromboembolic events (rare) and increase in D-dimer



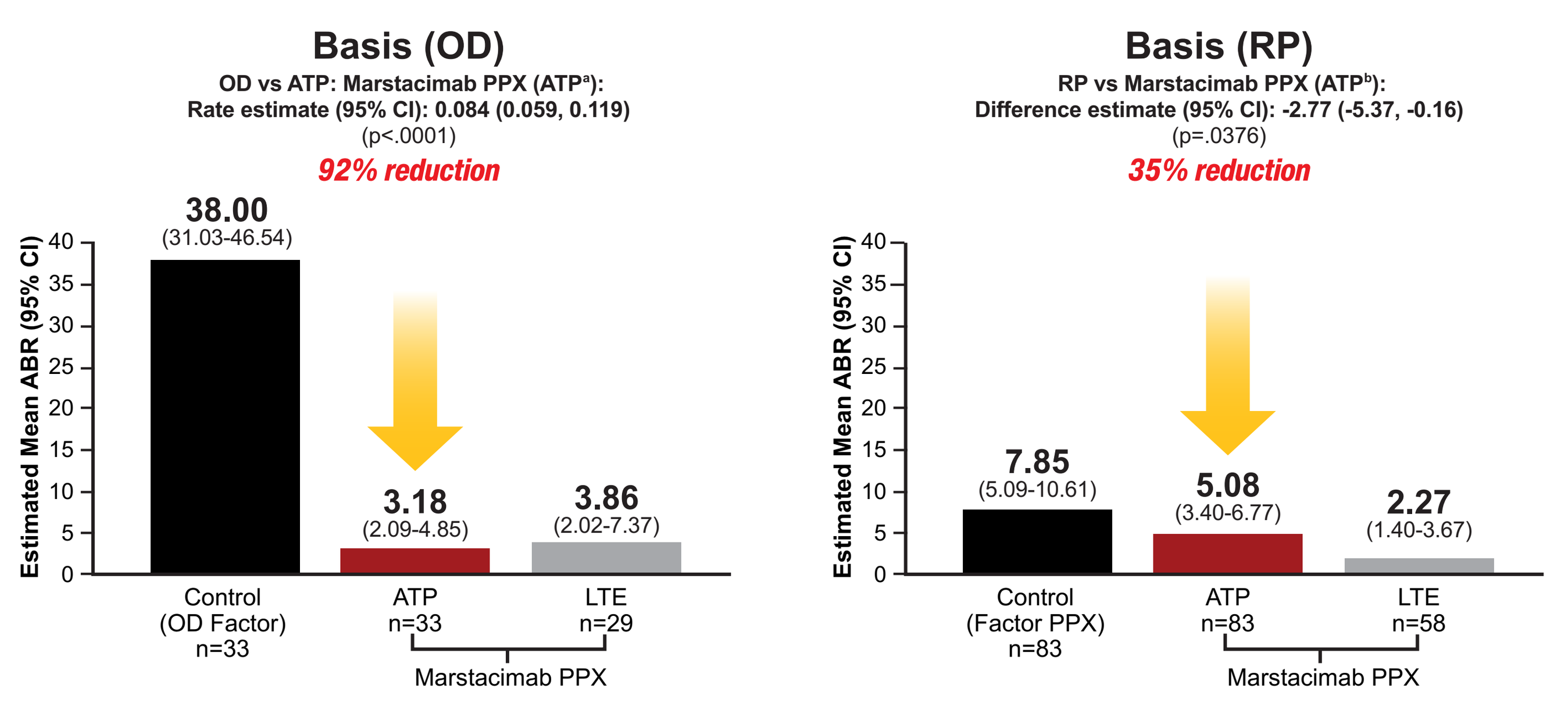
Both fitusiran and concizumab carry a potential risk of thromboembolic events.

Agent	Clinical Trial	Thromboembolic Events
Fitusiran	ATLAS-INH	4 TEAEs of special interest, suspected/confirmed VTE in 2 (5%) patients: ▪ DVT (non-serious), subclavian vein thrombosis (serious), superficial thrombophlebitis (non-serious) ▪ Antithrombin activity before onset: 11.9% and 7.8%-11.6%
	ATLAS-A/B	No suspected/confirmed thromboembolism
	ATLAS-PPX	2 suspected/confirmed thromboembolic events in 2 (3%) patients: ▪ Cerebrovascular accident and thrombosis (suspected thrombosis on papilla of left eye) ▪ After treatment restart, no thromboembolic events were reported
Concizumab	Explorer7	During "on-treatment" period[a]: ▪ Groups 1-4: 1 event in 1 (1%) patient (renal infarction; non-fatal) During "on-treatment, without data on initial regimen" period[b]: 0 events
	Explorer8	4 thromboembolic events in 2 (1.3%) patients ▪ DVT, pulmonary embolism, superficial vein thrombosis in 1 patient and acute myocardial infarction in 1 patient; all non-fatal

In phase 3 clinical trials, a small number of patients receiving fitusiran or concizumab experienced thromboembolic events, leading to implementation of risk mitigation strategies.
[a]The period during which patients were exposed to on-demand treatment with bypassing agents or concizumab treatment.
[b]The period during which patients were exposed to on-demand treatment with bypassing agents or concizumab treatment, with the exclusion of the data on the initial concizumab regimen.

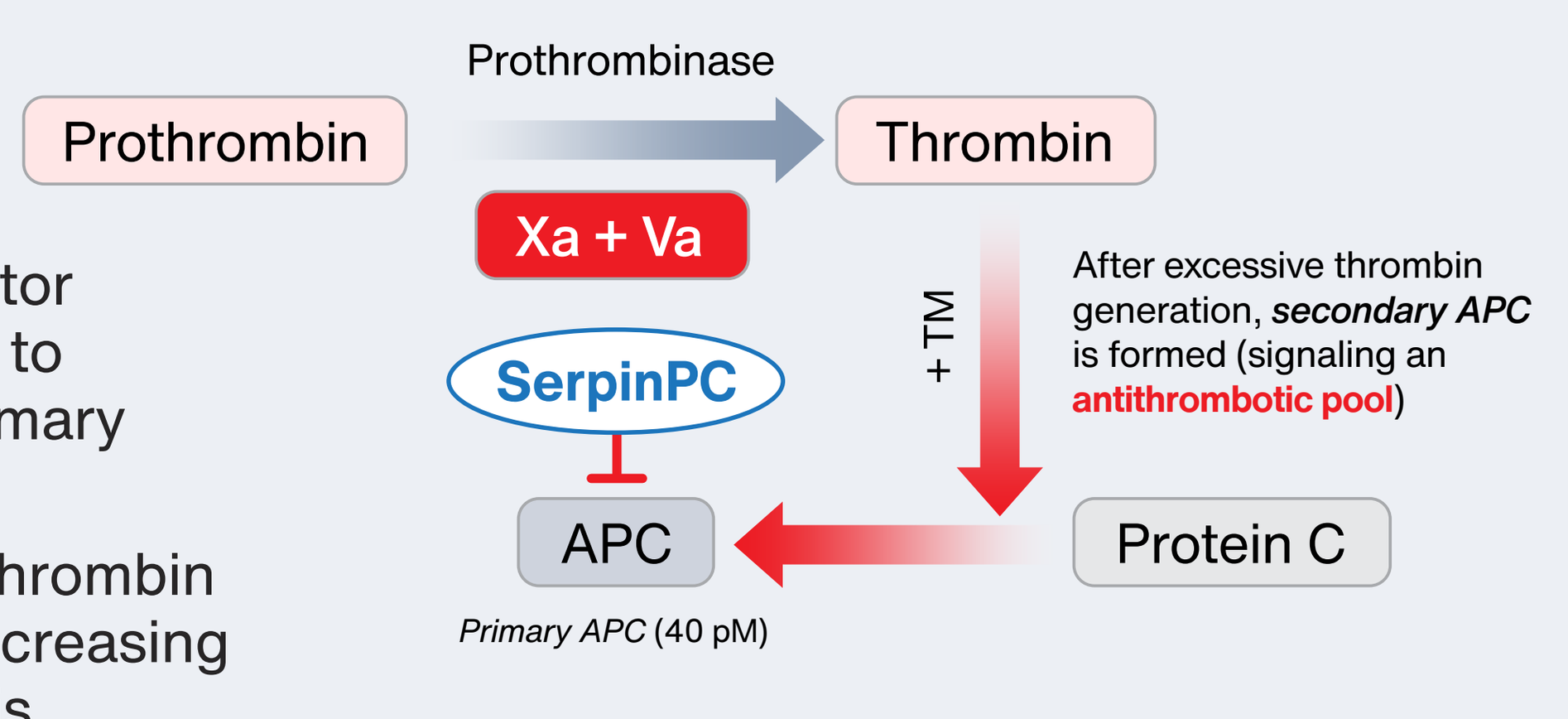
Marstacimab

- An anti-TFPI antibody, with the same mechanism of action as concizumab
- Currently under investigation in several phase 3 clinical trials in adults and children with hemophilia A or B with or without inhibitors with an LTE of 1 study
- Initial analyses show significant reductions in ABR compared with both on-demand and prophylaxis study groups, which have continued into the LTE



[a]Mean (range) duration of marstacimab treatment: 12.1 (11.5-13.1) months.
[b]Mean (range) duration of marstacimab treatment: 11.6 (0.9-12.8) months.

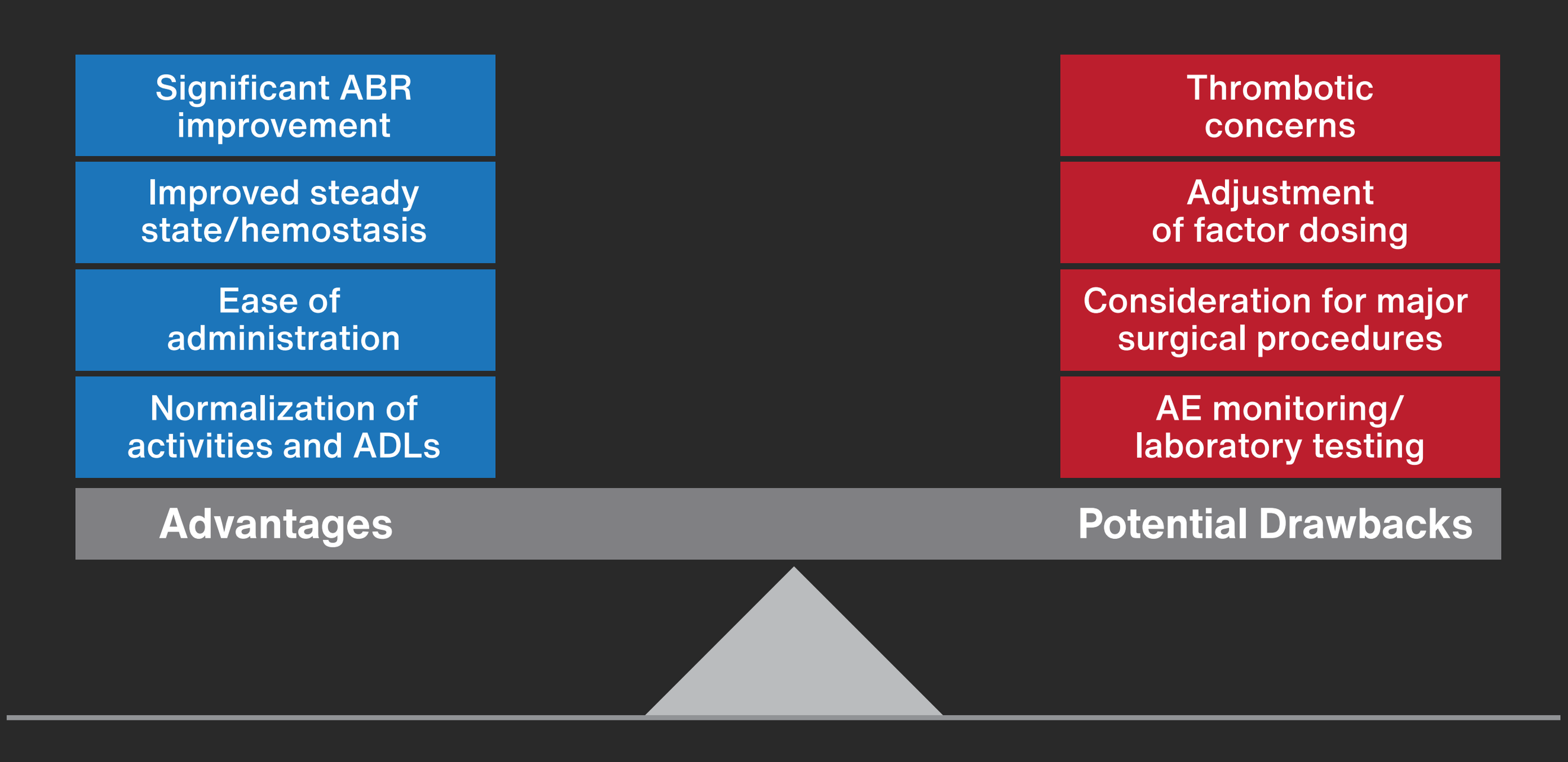
SerpinPC



- An investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit primary (circulating) APC
- Designed to restore thrombin generation without increasing the risk for thrombosis
- Inhibition of primary APC allows early prothrombinase (initiation stage) more time to make thrombin, but there is no further bleeding reduction by inhibiting secondary APC
- Currently being evaluated in an ongoing first-in-human, open-label multicenter study using an adaptive design, in subjects with severe hemophilia A and B
- Phase 2 study with 3 years of extension data has shown low ABR (n=20); all bleed ABR reported as 1.0 (96% reduction from baseline)

Summary

Rebalancing agents are an important development in hemophilia A/B treatment, but questions and concerns remain:



Advantages:

- ABRs were improved compared with on-demand and factor prophylaxis; however, bleeding rates were higher than ideal (ABR 1.3-6.4)
- ADL is no longer the goal for patients, especially younger patients, with hemophilia
  - Rebalancing agents allow increased physical activity, but how much activity is too much? When should activities still be discouraged?
- Patients have greater ability to undergo minor procedures

Potential Drawbacks/Considerations:

- Adjustment of factor dosing will be necessary to address the small but important thrombotic risk, which will be an important educational change for patients and providers
- Major surgical procedures will require time to either discontinue prophylactic product or cotreat with factor products and adjust rebalancing agents
- Monitoring AEs with laboratory testing will be recommended to address expected abnormalities that could affect medical evaluation for other concerns (eg, elevated LFTs with fitusiran; elevated D-dimer with concizumab)

Abbreviations

ABR: annualized bleeding rate
ADL: activities of daily living
AE: adverse event
APC: activated protein C
ATP: active treatment phase
BPA: bypassing agent
DVT: deep vein thrombosis
FII: factor II
FIX: factor IX
FVIII: factor VIII
FX: factor X
FXa: activated factor X
LFT: liver function test
LTE: long-term extension
mRNA: messenger RNA
OD: on-demand
RP: routine prophylaxis
siRNA: small-interfering RNA
TEAE: treatment-emergent adverse event
TFPI: tissue factor pathway inhibitor
ULN: upper limit of normal
URTI: upper respiratory tract infection
VTE: venous thromboembolism

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