REVIEW ARTICLE

Rebalancing agents in hemophilia: knowns, unknowns, and uncertainties

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Abstract

Treatment options for patients with hemophilia and other bleeding disorders have advanced dramatically over the last few years, not only with the availability of safer factor concentrates, but also with the introduction of factor VIII-mimicking agents. Until recently, there were still areas of hemophilia care that required attention and optimization, including the need for repeated venipuncture, often requiring a central venous access device, and the possible development of inhibitors that limit the efficacy of factor replacement, thereby increasing the complexity and burden of therapy. A new class of rebalancing agents aims to address these remaining issues by inhibiting various natural anticoagulants. Fitusiran is a small interfering RNA agent that reduces antithrombin synthesis in hepatocytes, favoring a procoagulant state. Other promising rebalancing agents are concizumab and marstacimab, which selectively bind to the K2 domain of the tissue factor pathway inhibitor, thus restoring thrombin generation. SerpinPC is a subcutaneous biological inhibitor that blocks the anticoagulant activated protein C pathway, while VGA039 is a monoclonal antibody that targets its cofactor protein S. Although the available clinical data are promising, several important challenges remain. These include the thrombotic risk of rebalancing agents, perioperative and bleeding management, availability in low-income countries, efficacy and factor VIII equivalence compared to existing treatments, ideal target populations, and potential application in other hemostatic disorders. The primary aim of this review is to summarize the best available evidence on these novel rebalancing agents, while highlighting the unknowns, and emphasizing the uncertainties that lie ahead.

Introduction

Hemophilia A (HA) and hemophilia B (HB) are inherited X-linked bleeding disorders caused by a functional deficiency of clotting factors VIII (FVIII) and IX (FIX), respectively, resulting in impaired hemostasis and unwarranted bleeding. Over time, irreversible damage to cartilage and bone occurs, manifesting as chronic arthropathy.[1] For the last two decades, the standard of care for patients with severe hemophilia and non-severe hemophilia with a severe bleeding phenotype has been prophylactic treatment with plasma-derived or recombinant factor concentrates or bypassing agents to minimize the risk of bleeding. However, this requires regular intravenous infusions, a treatment that is particularly burdensome for infants, who often require central venous access, which carries a risk of infection and central venous catheter-related thrombosis.[2] Approximately 30% of patients with HA and up to 10% of patients with HB develop inhibitors, making therapy less effective and patients more prone to severe bleeding.[3,4] Immune tolerance induction, consisting of regular high-dose FVIII or FIX infusions, is the only therapeutic option available to eliminate these inhibitors, with variable efficacy and subsequent high treatment burden and cost. Innovative strategies are being developed to overcome these limitations.

The approval of emicizumab, a humanized bispecific monoclonal antibody against activated FIX (FIXa) and factor X (FX), was a major breakthrough in the treatment of hemophilia with inhibitors.[5-7] This subcutaneous agent has become an established prophylactic regimen for patients with HA, with or without inhibitors. However, while providing effective hemostasis, emicizumab therapy can be challenging due to the need for safe therapeutic modalities to control breakthrough bleeds in inhibitor patients. Due

to its convenient administration, emicizumab has spurred the search for other subcutaneous products, targeting a broader population of patients. As a result, a dynamic portfolio of rebalancing agents is currently undergoing clinical evaluation. These rebalancing strategies are based on the concept that the hemorrhagic phenotype of hemophilia can be significantly improved by shifting the hemostatic balance toward a more procoagulant state and increased thrombin generation. Their major advantage is that they are effective in both HA and HB, with or without inhibitors. The main rebalancing agents currently in various stages of development fall into the three following categories: antithrombin (AT) inhibitors, inhibitors of tissue factor pathway inhibitor (TFPI), and inhibitors of activated protein C (APC) or its cofactor protein S.

Fitusiran, a small interfering RNA therapeutic, aims to restore hemostasis by lowering AT. Concizumab and marstacimab are monoclonal antibodies directed against the Kunitz 2 (K2) domain of TFPI, which have shown promising results in recent phase III trials. SerpinPC, a subcutaneous APC inhibitor, has been shown to safely reduce bleeding episodes in patients with HA and HB. The protein S antibody VGA039 is being investigated for the treatment of bleeding disorders other than hemophilia. The main objective of this review is to summarize the available clinical data on these novel rebalancing approaches, while highlighting some of the unknowns and the major challenges that remain, in particular the potential risk of thrombosis.

Thrombin generation

In the traditional model of coagulation,[8] the intrinsic and extrinsic pathways function independently of each other, with little interaction. However, this independence of the coagulation cascade is unlikely to apply to the *in vivo* setting. Therefore, a more contemporary view has emerged, that describes a common set of cell surface-based reactions with three overlapping phases of thrombin generation consisting of initiation, amplification, and propagation.[9] Accordingly, coagulation begins on tissue factor (TF)-exposing cells, relying on the TF/activated factor VII (FVIIa) complex to activate FIX into FIXa and FX into activated FX (FXa), thereby generating trace amounts of thrombin. This initial thrombin burst then activates platelets and stops minor bleeding by adhering to the site of injury and forming a fibrin clot. Next, the proteolytic activity of thrombin generates activated FVIII (FVIIIa).[10,11] FVIIIa acts as a cofactor for FIXa in the propagation phase, resulting in large-scale thrombin generation. In this model, the amplification loop is critical for thrombin generation in tissues with limited expression of TF. It also shows that FVIII and FIX play an important role in amplifying thrombin generation, and thus in clot formation. It is important to note that thrombin generation is controlled by a strict balance between procoagulant and anticoagulant proteins. Therefore, the absence of key proteins is likely to result in either thrombotic or hemorrhagic complications.[9] This revised model highlights that hemophilia should be understood not only as a disorder caused by defective amplification of the coagulation cascade – traditionally treated by replacing the missing FVIII or FIX – but also as a condition characterized by impaired thrombin generation, which can be targeted by alternative therapeutic strategies.

Physiological inhibitors strictly control coagulation

Procoagulant activity is tightly regulated by three major anticoagulant pathways: AT, TFPI, and the APC system. AT is a serine protease that contributes to the removal of thrombin from the circulation; other primary targets include FXa and FIXa.[12] TFPI exerts its effects on the coagulation pathway via three Kunitz-type serine protease inhibitor domains. All of these TFPI inhibitory actions result in extreme inhibition of thrombin generation.[13,14] Next, APC and protein S play a key role in coagulation homeostasis by inactivating activated factor V and FVIIIa.[15] The coagulation cascade culminates in the generation of thrombin, which is key to hemostasis by forming a fibrin network and a stable clot. Accordingly, low thrombin generation is associated with bleeding risks, while high thrombin generation, such as in patients with inherited thrombophilia, increases the risk of venous thrombosis.[16]

Interestingly, hemophilia patients with concomitant inherited prothrombotic factors have a milder bleeding phenotype.[17-20] This provides a proof-of-principle that rebalancing agents are a viable treatment option for hemophilia, which can be conceptualized as a disease of thrombin generation.[21] While factor replacement and bypassing agents work through procoagulant forces, rebalancing agents restore hemostasis by inhibiting natural anticoagulants, thereby increasing thrombin generation. The three main classes of rebalancing agents (Figure 1) are inhibitors of AT, TFPI and the APC/protein S pathway.

Interference with liver synthesis of antithrombin

Fitusiran

Fitusiran is a subcutaneous small interfering RNA therapeutic being developed for bleeding prophylaxis in patients with HA and HB.[22] It works by lowering AT, thus shifting the hemostatic balance toward a more procoagulant state. Unlike other rebalancing agents, fitusiran's mechanism of action is based on natural cellular interference mechanisms designed to cleave AT messenger RNA (mRNA), thereby reducing AT synthesis in the liver.

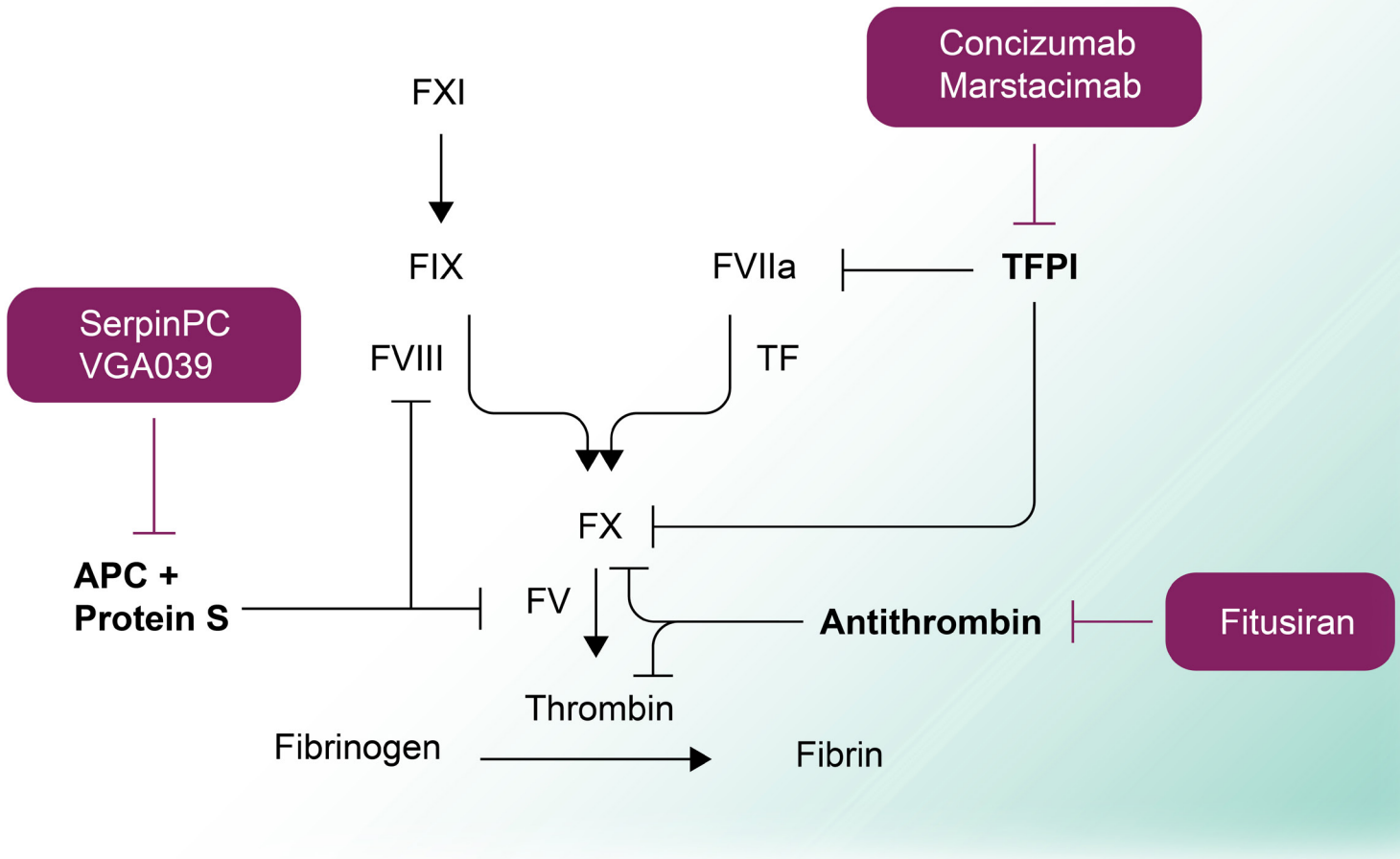

Figure 1. Schematic overview of the position of action of various rebalancing agents within the coagulation cascade. The three different classes of rebalancing agents are shown in red while their respective targets are highlighted in bold: inhibitors of anti-thrombin, inhibitors of tissue pathway factor inhibitor, and inhibitors of activated protein C/protein S. Arrows indicate either activation or inhibition. APC: activated protein C; FVIII: factor VIII; FXI: factor XI; FIX: factor IX; FX: factor X; FV: factor V; TFPI: tissue factor pathway inhibitor; FVIIa: activated factor VII; TF: tissue factor.

In an initial phase I dose-escalation study[22] in healthy volunteers and patients with HA or HB, AT levels were reduced at doses ranging from 0.015 mg/kg weekly to 1.8 mg/kg monthly. When AT levels were reduced by more than 75% from baseline, peak thrombin generation values were at the lower end of the range observed in the healthy volunteers. Of note, in a phase II open-label extension study, a fatal cerebral venous sinus thrombosis occurred after the rapid administration of FVIII concentrate due to an initially misdiagnosed subarachnoid hemorrhage. All fitusiran trials were temporarily halted, but the US Food and Drug Administration subsequently allowed the trials to continue following a protocol amendment to mitigate the risk of thrombosis.[23,24]

Three recently published, phase III open-label studies (ATLAS-INH, ATLAS-A/B, and ATLAS-PPX) evaluated subcutaneous fitusiran prophylaxis in patients with HA or HB, with and without inhibitors.[25-27] The first study (ATLAS-INH)[25] recruited HA and HB patients with inhibitors who had previously received on-demand bypassing agents. They were randomized (2:1) to receive either fitusiran prophylaxis or to continue on-demand bypassing agents. Fitusiran prophylaxis resulted in a 90.8% reduction (95% confidence interval [95% CI]: 80.8-95.6%) in the annualized bleeding rate (ABR), with 25 (66%) participants having zero treated bleeds in the fitusiran group *versus* one (5%) in the on-demand group. In the second study (ATLAS-A/B)[26] in 120 patients with HA or HB without inhibitors, fitusiran prophylaxis was associated with a statistically significant reduction in ABR compared to on-demand clotting factor concentrates, with no bleeding events in approximately half of the participants. In the ATLAS-PPX,[27] fitusiran at a monthly dose of 80 mg in patients with HA or HB, with or without inhibitors, significantly reduced bleeding compared to factor concentrates or bypassing agents (median ABR=0.0; range, 0.0-2.3 *vs*. median ABR=4.4; range, 2.2-10.9), with 63.1% (N=41) of participants experiencing no bleeds.[27] Treatment-emergent adverse events were reported in 12.2% of participants in the ATLAS-INH study, the most common of which were increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, alkaline phosphatase, headache, upper respiratory tract infection and arthralgia. Similar adverse events were reported in the other two phase III trials. Of note, there was a high incidence of cholecystitis and/or cholelithiasis in the fitusiran treatment arms (ATLAS-INH, 14.6%; ATLAS-A/B, 6.3%; ATLAS-PPX, 11.9%).

Table 1. Comparative overview of the phase III trials of the approved rebalancing agents.

Comparative factor	Fitusiran	Concizumab	Marstacimab
Trial	ATLAS-OLE	explorer7 and 8	BASIS
Target	Antithrombin	TFPI K2	TFPI K2
Mechanism of action	siRNA	Monoclonal antibody	Monoclonal antibody
Number of patients	213	241	116
Frequency	Q2M (AT-DR)	daily	weekly
Dosing	50 mg Q2M (AT-DR)	0.2 mg/kg (1 mg/kg loading dose)	150 mg fixed dose (300 mg loading dose)
Mean ABR (95% CI)	6.4 (5.3-7.7)	explorer7: 1.7 (1.0-2.9) explorer8 HA: 2.7 (1.6-4.6) explorer8 HB: 3.1 (1.9-5.0)	5.08 (3.4-6.8)
Median ABR (IQR)	3.7 (0.0-7.5)	explorer7: 0.0 (0.0-3.3) explorer8 HA: 2.9 (0.0-5.2) explorer8 HB: 1.6 (0.0-4.8)	Not available
Thrombotic events	4	0 (3 prior to revised dosing)	1
Monitoring	Antithrombin levels	Concizumab, TFPI levels	No
Approval	HA/HB with or w/o inhibitors FDA	HA/HB with inhibitors FDA, EMA	HA/HB w/o inhibitors FDA, EMA
Anti-drug antibodies	1.8%	explorer7: 26% explorer8: 14% (HA) and 9% (HB)	20.5%
Adverse events	AST/ALT >3x ULN (3.5%) Cholecystitis, cholelithiasis (3.8%) Injection site reaction (5.6%)	Arthralgia (10%) Injection site reaction (7%) URTI (6%)	Injection site reaction (5.2%)
Co-treatment	FVIII 10 IU/kg, FIX 20 IU/kg aPCC 30 IU/kg, rFVIIa 45 μg/kg	FVIII 20 IU/kg, FIX 30 IU/kg aPCC 50 IU/kg, rFVII 90 μg/kg	Not available

The number of patients includes the total number of patients receiving the rebalancing agent in phase III trials. For fitusiran, 213 patients were exposed to the antithrombin-based regimen in ATLAS-OLE. For concizumab, 114 patients received concizumab in explorer7 (33 patients in group 2, 21 patients in group 3, 60 patients in group 4), and 127 patients in explorer8 (42 patients in group 2, 9 patients in group 3, and 76 patients in group 4). Dosing of fitusiran starts at 50 mg every 2 months, and is subsequently adapted based on the antithrombin levels. The mean annualized bleeding rate (ABR) is shown with the 95% confidence interval between brackets. For fitusiran, the mean overall ABR is shown in ATLAS-OLE. For explorer7, the mean ABR for treated spontaneous and traumatic bleeding episodes in group 2 is shown. For explorer8, the mean estimated ABR for group 2 is shown. For marstacimab, the mean ABR is shown for the active treatment phase *versus* routine prophylaxis. The median observed ABR for fitusiran in ATLAS-OLE is shown with the interquartile range in brackets. For explorer7, the median ABR for treated spontaneous and traumatic bleeding episodes in group 2 is shown. For explorer8, the median ABR for group 2 is shown. For marstacimab, the median ABR is unavailable. For the adverse events with concizumab, the results from explorer7 are shown. Approvals as of June 1, 2025 are indicated. Only approval by the Food and Drug Administration and/or European Medicines Agency is indicated. For co-treatment, the recommended doses of clotting factor concentrate from the respective bleed management guidelines are shown. TFPI K2: tissue factor pathway inhibitor Kunitz 2 domain; siRNA: small interfering RNA; Q2M: every 2 months; AT-DR: antithrombin-based dose regimen; ABR: annualized bleeding rate; 95% CI: 95% confidence interval; IQR: interquartile range; HA: hemophilia A; HB hemophilia B; w/o: without; FDA: Food and Drug Administration; EMA: European Medicines Agency; AST: aspartate transaminase; ALT: alanine transaminase; ULN: upper limit of normal; URTI: upper respiratory tract infection; FVIII: factor VIII; FIX: factor IX; aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII; IU: international units.

In October 2020, the trials were voluntarily halted by the sponsor due to non-fatal thromboembolic events.[28] Following a protocol amendment, dosing resumed in December 2020 with a revised dosing regimen aimed at achieving AT levels between 15 and 35%. This target was chosen because of the increased thrombotic risk observed in patients with AT levels below 10%. The revised dosing regimen consists of a stepwise increase in fitusiran dose, starting at 50 mg every 2 months instead of the previous 80 mg monthly. Patients from the parent phase III studies continued in the open-label extension phase (ATLAS-OLE)[29] on the revised dosing regimen (Table 1). Interim results were recently reported: the AT-based dosing regimen led to a median ABR of 3.7 (interquartile range [IQR], 0.0-7.5). Compared to on-demand bypassing agents and on-demand clotting factor concentrates in the parent studies, the AT-based dosing regimen led to a significant reduction in joint bleeds (72.6% and 71.3% reduction in mean annualized joint bleeding rate, respectively; 95% CI: 47.1-85.8 and 51.6-83.0). However, no significant change was observed *versus* prophylaxis (a 27.7% reduction, 95% CI: -27.9 to 59.1).

Importantly, the AT-based dosing regimen largely mitigated

Table 2. Overview of the strengths and weaknesses of rebalancing agents.

Strengths	Risks or Limitations
Subcutaneous administration	Risk of thrombosis
Thrombin generation independent of FVIII/FIX	Not detectable or measurable with routine clotting factor assays; specialized assays required
Rapid onset of action	Inability to detect activity in acute settings (e.g., emergency department) with routine clotting assays
No cross-reactivity with FVIII/FIX inhibitors	Need for monitoring for some agents (e.g., AT/TFPI levels)
Use in patients with inhibitors	Requirement for individualized treatment regimens
Long half-life (allowing infrequent dosing) for some agents	Complex and unvalidated management of patients with inhibitors (modality of ITI and co-treatment with bypassing agents)
Potential to convert severe hemophilia A/B into a mild phenotype	Risk of anti-drug antibody development (detection and management modalities not standardized)
Availability of several therapeutic agents targeting different pathways	Complex mechanisms of action
Attractive option for patients with hemophilia B (with or without inhibitors)	Limited dosing flexibility; fixed treatment regimens
Potential normalization of blood coagulation (currently unknown)	Limited clinical data in women and girls with hemophilia A/B
Potential applicability in other rare bleeding disorders	Hemostatic efficacy: non-inferiority to current prophylaxis not demonstrated for some agents
Potential use in low-income countries (especially agents requiring minimal monitoring and infrequent dosing)	Competitive and evolving marketing environment; future adoption uncertain
Convenient storage conditions for some compounds	Complexity of shared decision-making

The strengths are shown on the left, and the risks or limitations on the right. FVIII: factor VIII; FIX: factor IX; AT: antithrombin; TFPI: tissue factor pathway inhibitor; ITI: immune tolerance induction.

the adverse effects of the original dosing regimen. The risk of thrombotic events was significantly reduced with an exposure-adjusted incidence rate of 0.82/100 patient-years *versus* 2.28/100 patient-years for the original dose regimen. Three out of four thrombotic events during ATLAS-OLE were considered unrelated to fitusiran: an old cerebral infarction and embolic stroke of unknown origin both in a patient with additional cardiovascular risk factors, and a postoperative catheter-related deep vein thrombosis after administration of excessive doses of activated prothrombin complex concentrate (aPCC). The thrombosis that was considered to be related to fitusiran occurred after surgery, with doses of clotting factor concentrate exceeding the recommended doses. In addition, there was a lower rate of AST/ALT elevations and cholecystitis/cholelithiasis per 100 patient-years with the AT-based dosing regimen compared to the original dose regimen (2.06/2.26 *vs*. 18.25/14.67).

Compared to on-demand bypassing agents, fitusiran had a positive but insignificant effect on the quality of life as assessed by the Haemophilia Quality of Life Questionnaire for Adults transformed physical health score, and led to a significant improvement *versus* previous on-demand clotting factor concentrates.[29] However, there was no improvement compared to previous prophylaxis. Immunogenicity was low with four patients (1.8%) developing anti-drug antibodies during the extension study. These did not have an effect on the pharmacodynamics of fitusiran. Ten major surgical operations were performed while patients where on fitusiran during the phase II study.[30] In six out of ten cases, the hemostatic efficacy was rated as excellent. No hemostatic efficacy was reported in the other four cases. Treatment with fitusiran was paused before two operations.

Overall, fitusiran prophylaxis was effective in both HA and HB, and therefore has the potential to be transformative in the management of all people with hemophilia.[31] The AT-based dosing regimen improved the safety of fitusiran treatment, albeit at the expense of a higher ABR. The single-arm ATLAS-NEO trial (NCT05662319) will further evaluate whether the AT-based dosing regimen reduces the frequency of treated bleeds in fitusiran-naïve patients.

Tissue factor pathway inhibition by antibodies

Concizumab

This humanized IgG4 monoclonal antibody binds to the Kunitz 2 domain of TFPI, and acts independently of FVIII and FIX. This agent prevents TFPI from blocking FXa, favoring a procoagulant state.[32-34] When the inhibitory activity of

TFPI is reduced, sufficient FXa is generated via the FVIIa/TF complex to attain hemostasis.

In the recently published explorer7 phase III study, patients with HA or HB with inhibitors were randomized (1:2 ratio) to receive either no prophylaxis for at least 24 weeks (group 1) or concizumab prophylaxis for at least 32 weeks (group 2), or were nonrandomized to receive concizumab prophylaxis for at least 24 weeks (groups 3 and 4).[35] A parallel phase III trial was conducted in 148 patients with HA or HB, without inhibitors (explorer8) (Table 1).[36] The studies were halted in March 2020 due to non-fatal thrombotic events in three enrolled patients.[37] With new mitigating safety measures and guidelines in place, the study hold was lifted and concizumab therapy was restarted with a loading dose of 1 mg/kg/day, followed by 0.2 mg/kg/day and subsequent dosing could be adjusted based on the concizumab plasma concentration at week 4. No new thromboembolic events were reported after the resumption of concizumab therapy. The study analysis showed that the overall median ABR for patients with inhibitors on concizumab therapy (groups 2, 3, and 4) was zero episodes. Adverse events included arthralgia (10%), injection site erythema (7%) and upper respiratory tract infection (6%). During explorer7, two patients experienced hypersensitivity-type reactions, after which both patients permanently discontinued the study treatment.

Similarly, in patients without inhibitors (explorer8),[36] the ABR was lower with concizumab than with no prophylaxis, with an estimated mean ABR ratio of 0.14 (95% CI: 0.07-0.29; *P*<0.0001) for patients with HA, and 0.21 (95% CI: 0.10-0.45; *P*<0.0001) for patients with HB. Interestingly, a non-randomized intra-patient comparison with previous prophylaxis was also performed. However, non-inferiority over prior prophylaxis was not established. These results may have been biased by three outlier patients. The median ABR was comparable between those receiving concizumab and those with prior prophylaxis both in HA (2.3; IQR, 0.0-4.7 for concizumab *vs*. 2.2; IQR, 0.8-6.2 for prophylaxis) and HB (1.4; IQR, 0.0-8.1 for concizumab *vs*. 2.1; IQR, 0.9-4.2 for prophylaxis). The most common adverse events were infection by severe acute respiratory syndrome coronavirus-2 (13%), D-dimer increase (8%) and upper respiratory tract infection (7%) in patients receiving concizumab. Injection-site reactions were observed in 15% of patients, leading to treatment discontinuation in one patient. No hypersensitivity-type reactions were reported.

Marstacimab

Marstacimab is a fully human monoclonal IgG1 antibody targeting the Kunitz 2 domain of TFPI.[38] It can be administered intravenously or subcutaneously. In the phase III BASIS trial,[39] 116 patients with hemophilia were treated with marstacimab for 12 months compared to prophylaxis and on-demand intravenous regimens with FVIII or FIX concentrates, after a 6-month observation period (Table 1). Marstacimab reduced the mean ABR for treated bleeds by 91.6% compared to on-demand therapy (*P*<0.0001), and demonstrated superiority (*P*=0.0376) over prophylaxis, with a 35.2% reduction in ABR. The treatment was generally well tolerated. However, a first thromboembolic event was reported at the last study update (Matino *et al*., Oral Presentation at EAHAD 2025).

Recently, both concizumab and marstacimab were approved by the European Medicines Agency for patients with HA and HB with antibodies (concizumab)[40] and without antibodies (marstacimab),[41] respectively.

Blocking the activated protein C pathway

The protein C pathway is one of the major anticoagulant mechanisms in blood vessels.[15] APC resistance due to factor V Leiden, which is the most common risk factor for deep vein thrombosis, has been associated with milder hemophilia.[18] This suggests that the bleeding severity of hemophilia may be reduced by inhibiting the APC pathway. Accordingly, several compounds targeting protein C and protein S are under investigation.

SerpinPC

SerpinPC is a small molecule inhibitor that prolongs prothrombinase activity by reducing APC activity, thereby increasing thrombin generation. In a first-in-human, open-label, adaptive-design study,[42] the safety, tolerability, and pharmacokinetics of subcutaneous SerpinPC dosing were evaluated in participants with HA or HB. Preliminary results from the AP-0101 study indicated that SerpinPC was well tolerated and showed evidence of activity in hemophilia patients with an 88% reduction in self-reported all-bleed ABR. However, Centessa terminated the development of SerpinPC as a treatment for hemophilia.[43] This was a strategic decision following the approval of marstacimab.

VGA039

VGA039 is a fully human IgG4 monoclonal antibody directed against protein S, targeting not only the APC pathway, but also TFPIα, whose cofactor is protein S. VGA039 is thus able to modulate both the initiation phase and propagation phases of coagulation. Unlike most other rebalancing agents, VGA039 is being studied in diseases other than hemophilia. For example, VGA039 has been shown to be effective in restoring thrombin generation in the plasma of patients with a variety of coagulation factor deficiencies.[44] VIVID2 (NCT05776069) is a phase Ia single-ascending dose study in patients with von Willebrand disease.[45] A total of seven patients have been dosed as of October 23, 2024, including patients with type 1, type 2 and type 3 von Willebrand disease. VGA039 was well tolerated in these patients, and showed promising, albeit very preliminary efficacy.

Other targets

In addition to AT, TFPI and protein C/protein S, other targets are being investigated. Protein Z-dependent protease inhibitor (ZPI) disrupts the assembly of the prothrombinase complex by inhibiting FXa in the presence of protein Z.[46] It also inhibits activated FXI. A single-domain antibody directed against ZPI (ZPI-sdAb2) increased thrombin generation in the plasma of patients with severe HA and factor XI deficiency.[47] In addition, ETX-148 is a ZPI-targeting small interfering RNA that induced sustained knockdown of the protein in non-human primates, supporting injection every 3 months in patients. In a mouse model of HA and HB, mETX-148 significantly improved joint health.[48] Finally, protease nexin-1 is an inhibitor of thrombin, found in the α-granules of platelets.[49] In mice, blocking protease nexin-1 resulted in increased thrombin production. In plasma from patients treated with emicizumab, an increased rate of thrombin generation was observed.[50]

Challenges with rebalancing agents

The available clinical data on rebalancing drugs are likely to have a positive impact on the future of hemophilia management, but it must be emphasized that several important challenges remain. First, rebalancing agents do not eliminate all bleeding events. In addition, a major concern when modulating hemostasis toward a more procoagulant state is the risk of uncontrolled thrombin generation, which ultimately leads to thrombotic complications. When it comes to these novel therapies, it would be very useful to know the "FVIII or FIX equivalence", as a better understanding of this parameter would be required before patients on novel therapies undergo surgery or experience major bleeding. Another issue worth mentioning is that these novel therapies interfere with many standard coagulation assays. Furthermore, questions remain on their cost-effectiveness, the impact on shared-decision making, long-term follow-up, pediatric data, real-world adherence and the use of rebalancing agents in other bleeding disorders.

Hemostatic efficacy

Many patients who are treated with rebalancing agents continue to experience bleeding episodes. This is reflected by the ABR and the proportion of patients who do not achieve a zero-bleed status. The goals of hemophilia management (universal access to prophylaxis, which is greatly facilitated by the subcutaneous administration of rebalancing agents in patients with HA or HB, with or without inhibitors; attainment of a "zero-bleed" state for all patients, which remains elusive with these therapies; and normalization or near normalization of hemostasis, which remains difficult to assess with these agents) are unlikely to be fully achieved with the current generation of rebalancing therapies. In addition, it is important to emphasize the complex trade-off that is inherent to the use of rebalancing agents: achieving improved hemostatic effectiveness while cautiously limiting the risk of thrombosis, which is closely linked to their mode of action and dosing strategies.

Thrombotic risk

Rebalancing agents seem to carry an inherent risk of thrombosis, since thrombotic events have been reported under treatment with all three products that have received regulatory approval. It should be noted that the thrombotic events reported in the fitusiran and concizumab studies were associated with other thrombotic risk factors, including the use of bypassing agents and excessive factor concentrates, as well as an unknown pre-existing deep vein thrombosis. Despite the improved safety following the implementation of a revised bleed management plan and revised dosing for fitusiran and concizumab, these drugs must be used with extreme caution, particularly given the highly selective patient populations in the clinical trials. Patients with a history of arterial or venous thromboembolism, ischemic disease or impaired renal or hepatic function were excluded. In the ATLAS-OLE and explorer trials, the presence of thrombophilia and recent malignancy were exclusion criteria. In the BASIS trial (NCT03938792), patients could not be included if they were over 74 years of age. More real-world data are needed to ensure the safety of these drugs in patients with additional thrombotic risk factors and in thrombotic risk situations, such as urgent surgery, trauma and sepsis. Conversely, for patients without additional thrombotic risk factors who continue to experience bleeding, intensifying the treatment despite the increased thrombotic risk may be an acceptable option. In the case of fitusiran, the dosage can be increased to achieve AT levels close to, or even below, 15%. It is currently unclear whether treatment with TFPI inhibitors can be intensified.

Factor VIII equivalence and laboratory monitoring

It should be noted that these promising new agents are not able to normalize thrombin generation to the levels found in subjects without hemophilia. As a result, it is likely that patients on rebalancing agents will still require factor supplementation in the event of bleeding or following traumatic events or surgery. Not surprisingly, it would be helpful to know the "FVIII or FIX equivalence" parameter in such circumstances. Animal models have provided some insight into FVIII equivalence for fitusiran and concizumab.[51] A quantitative systems pharmacology model estimated that AT levels of 15-35% result in peak thrombin levels similar to 20-40% FVIII equivalence.[52] However, further research is needed, taking into account additional factors such as changes in laboratory monitoring practices.

There are other practical dilemmas regarding laboratory testing. First and foremost, standard coagulation assays, including prothrombin time and activated partial throm-

boplastin time, only provide information about the clotting time during the initiation phase of coagulation.[9] In contrast, global coagulation assays should turn out to be valuable monitoring tools before, during, and after the administration of rebalancing agents.[51] These include thrombin generation assays, which continuously measure the level of active thrombin in the sample, and rotational thromboelastometry, which has evolved from thromboelastography, and allows visual assessment of blood coagulation from clot formation, through propagation and stabilization, to clot dissolution.

Treatment of bleeding and perioperative management

While rebalancing therapies significantly reduce ABR compared with standard prophylaxis, it must be emphasized that bleeding events still occur. For breakthrough bleeding and invasive procedures, adjunctive therapy is required because rebalancing agents do not fully correct coagulation, but the optimal management of these bleeding events has not been fully established. In the phase II fitusiran study,[53] 107 bleeding events were reported in 14 patients. The study protocol included guidelines for bleeding management consisting of specified reduced doses of FVIII, FIX, aPCC and rFVIIa (10 IU/kg, 20 IU/kg, 30 IU/kg, and ≤45 μg/kg, respectively). While satisfactory hemostasis was achieved in 60% of cases with a single reduced dose of a factor or bypassing agent, significant variability was observed between patient subtypes. Little evidence is available to better guide the management of bleeding episodes in patients receiving concizumab or marstacimab. Similarly, there is a paucity of evidence regarding the perioperative management of patients receiving rebalancing agents. During the fitusiran clinical program, a total of 60 major surgical procedures were performed according to the bleeding management guidelines with reduced dosing or frequency of coagulation factor concentrate. Good hemostatic control was achieved in the majority of cases. In seven operations, AT concentrate was used to reverse the pharmacodynamic effect of fitusiran with good hemostatic outcome.[54] In the explorer7 and explorer8 studies, 44 surgical procedures including six major operations were performed.[55] Thirty bleeding episodes were reported. Dental surgical procedures were the most frequent cause for surgery-related bleeding. In case of major surgery, a concizumab pause is recommended, followed by standard perioperative management. For marstacimab, data regarding the management of bleeding and surgery are scarce.

Cost-effectiveness and accessibility

Many patients in low-income countries do not have access to innovative hemophilia therapies.[56] The introduction of a new class of drugs could increase competition among hemophilia treatments, which would subsequently reduce costs in the long term. Furthermore, the dosing frequency of fitusiran could provide an opportunity to treat patients in areas with limited access to medication. In contrast, TFPI inhibitors do not require monitoring, facilitating treatment in areas without laboratory expertise. Further research is required to evaluate the efficacy of reduced doses or extended treatment intervals, which could potentially reduce treatment costs. To date, no reports on the cost-effectiveness of rebalancing agents in high-income countries have been published.

Shared decision-making in the era of rebalancing agents

Shared decision-making has become a cornerstone of hemophilia clinical practice. However, this process has been challenged by the advent of rebalancing agents with inherently complex mechanisms of action. The increasing number of these agents, each with different properties and clinical profiles, adds further complexity to treatment decisions. It is therefore essential that the strengths and limitations of each therapeutic option are carefully discussed with patients and that patients are helped to gain a clear understanding of these aspects (Table 2).

Other unknowns and uncertainties

The potential use of rebalancing agents in children with hemophilia remains uncertain. ATLAS-PEDS is evaluating the use of fitusiran in children under 12 years old (NCT03974113), while explorer10 (NCT05135559) and BASIS KIDS (NCT05611801) are evaluating TFPI inhibitors in children under 12 and 18, respectively. Furthermore, data on the long-term safety and efficacy are limited. In a phase II open-label extension study,[30] patients who had received fitusiran for a median period of 4.1 years continued to experience stable bleeding control. The hitherto reported exposure time to TFPI inhibitors is shorter: at least 76 weeks for concizumab,[57] and no further follow-up is available for marstacimab. Finally, questions remain regarding adherence to rebalancing agents in the real world. Treatment frequency varies from daily injections to injections every 2 months. Therefore, it is expected that adherence to fitusiran would be greater due to its dosing frequency, although this has yet to be studied in practice.

Positioning rebalancing agents in the therapeutic algorithm of hemophilia

Many new hemophilia treatments have entered the market, and many more are in clinical development. The key question is how this new class of medications will fit into the increasingly competitive therapeutic landscape. While phase III trial results are encouraging, particularly for the treatment of HB with inhibitors, the general hemostatic efficacy appears to be lower than that of emicizumab and the newest clotting factor concentrates.[5,58-60] Identifying the ideal candidates for treatment with rebalancing agents will be challenging. Important factors include the efficacy of the patients' current treatment, their preference for subcutaneous *versus* intravenous administration, and the presence of thrombotic risk factors. Patients who are not well controlled by current therapies focusing solely on re-

placing or mimicking FVIII or FIX may benefit from increased thrombin generation through other routes, as generated by rebalancing agents. Future studies will need to clarify the role of rebalancing agents in relation to existing treatments.

Rebalancing agents in other hemostatic disorders

The mechanism of action of rebalancing agents is independent of FVIII and FIX. Therefore, these agents are potentially effective in other bleeding disorders. Fitusiran reduced bleeding in a mouse model of severe FX deficiency.[61] In addition, concizumab improved hemostasis in plasma from patients with Glanzmann thrombasthenia,[62] and marstacimab increased thrombin generation in plasma from patients with selected coagulation factor deficiencies and von Willebrand disease.[63] As previously discussed, VGA039 has been evaluated *ex vivo* in a variety of coagulation factor deficiencies,[44] and is now being developed primarily as a treatment for von Willebrand disease (NCT05776069).

Conclusions and perspectives

Rebalancing agents are an exciting new class of hemophilia treatment. Several drugs have received regulatory approval based on promising clinical results showing a significant reduction in ABR compared with standard prophylaxis. However, the hurdles encountered in the clinical evaluation of these novel therapeutics clearly highlight the need for great caution. Despite the reduction in ABR, bleeding is still common, and its management is likely to be more complicated due to the novel therapeutics involved. In addition, the reduction of bleeding is offset by what appears to be an inherent risk of thrombosis. More real-world data are needed to better identify the optimal patient candidates with a low risk of thrombosis or a positive benefit-risk ratio, bearing in mind that other excellent hemophilia treatments are currently available, each with their own strengths and limitations. In addition, as hemophilia therapy continues to evolve, there is a concurrent need to determine how to measure clinical efficacy. Similarly, patient-reported outcomes and quality-of-life measures are critical components of trials that should be considered to further improve outcomes for patients with HA or HB. Finally, due to their mechanism of action, rebalancing agents may provide an alternative treatment for other bleeding disorders, for which options are more limited.

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Contributions

QVT conceptualized and wrote the manuscript. CH conceptualized, wrote and supervised the writing of the manuscript.

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Artificial intelligence

Artificial intelligence was used for linguistic editing of the submitted manuscript.

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