Transfusion Medicine and Hemotherapy

Review Article

Transfus Med Hemother
DOI: 10.1159/000552346

Received: December 21, 2025
Accepted: April 14, 2026
Published online: May 5, 2026

Non-Factor Therapies in Haemophilia: The Era of Factor VIII Mimetics and Targeted Rebalancing Agents

Lukas Graf

Centre for Laboratory Medicine, Eastern Switzerland Haemophilia and Haemostasis Centre, St. Gallen, Switzerland

Keywords
Haemophilia · Non-factor therapies · Factor VIII mimetic antibodies · Haemostatic rebalancing

Abstract
Background: Non-factor therapies have substantially reshaped the treatment landscape of haemophilia by restoring effective thrombin generation independently of factor replacement. By targeting key regulatory mechanisms of coagulation, these approaches address limitations of conventional therapy, including intravenous administration, fluctuating factor levels, and inhibitor development. ***Summary:*** Bispecific factor VIII mimetic antibodies enable stable haemostatic protection by functionally substituting the cofactor role of factor VIII, resulting in sustained thrombin amplification with subcutaneous administration. Several years of clinical experience with emicizumab have demonstrated durable efficacy, a favourable safety profile, and broad applicability across patients with haemophilia A with and without inhibitors, establishing factor VIII mimetics as a central component of modern prophylaxis. Next-generation mimetics aim to further optimize potency and haemostatic control. Targeted rebalancing agents enhance coagulation by attenuating endogenous anticoagulants such as tissue factor pathway inhibitor or antithrombin. These approaches provide factor-independent efficacy across haemophilia A and B but introduce distinct safety considerations related to excessive thrombin generation, necessitating dose mitigation and careful monitoring. In acquired haemophilia A, non-factor therapies offer particular advantages by bypassing neutralizing autoantibodies, with prospective data supporting the use of emicizumab for effective bleeding prophylaxis and potential deferral of immunosuppressive therapy in elderly and multimorbid patients. ***Key Messages:*** Non-factor therapies enable convenient haemophilia management through subcutaneous administration and sustained haemostatic control. Continued clinical experience will be essential to define the long-term positioning of rebalancing strategies.

© 2026 The Author(s).
Published by S. Karger AG, Basel

Introduction

The therapeutic landscape of haemophilia has evolved dramatically over the past decade. Although prophylaxis with factor VIII (FVIII) or factor IX (FIX) concentrates remains the global standard of care, even extended-half-life products rarely achieve fully stable haemostatic protection and require regular (typically 1–3 times weekly) intravenous infusions, resulting in clinically relevant peak-trough fluctuations in FVIII/FIX levels and incomplete prevention of subclinical joint bleeding [1]. Persistent arthropathy despite optimized prophylaxis, together with the substantial treatment burden, have driven the development of innovative strategies capable of providing more continuous thrombin generation and simplified treatment administration.

This shift has led to the emergence of non-factor therapies, which restore haemostasis either by mimicking FVIII cofactor activity or by rebalancing the coagulation system through inhibition of natural

karger@karger.com
www.karger.com/tmh

© 2026 The Author(s).
Published by S. Karger AG, Basel

Karger
OPEN ACCESS

This article is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) (https://karger.com/Services/OpenAccessLicense). Usage and distribution for commercial purposes requires written permission.

Correspondence to:
Lukas Graf, lukas.graf@zlmsg.ch

anticoagulants such as antithrombin or tissue factor pathway inhibitor (TFPI) [1, 2]. These agents can be delivered subcutaneously, do not require venous access, and are effective regardless of inhibitor status – features that fundamentally broaden prophylactic options for people with haemophilia A and B.

The clinical impact of this new paradigm was first demonstrated by emicizumab, the initial FVIII mimetic, which produced unprecedented reductions in annualized bleeding rates (ABRs) in patients with and without inhibitors [3, 4]. Next-generation bispecific antibodies such as denecimig (Mim8) and NXT007 aim to further increase potency and achieve thrombin-generation profiles approaching the non-haemophilic range.

In parallel, targeted rebalancing therapies have progressed into late-stage development. Antithrombin lowering with fitusiran resulted in marked bleeding reductions across multiple phase-3 trials and demonstrated sustained efficacy under individualized antithrombin-based dosing [5, 6]. TFPIs such as concizumab and marstacimab amplify extrinsic-pathway thrombin generation and have shown robust prophylactic efficacy in haemophilia A and B.

Clinical Evidence

Factor VIII Mimetics

Mode of Action

Bispecific antibodies that mimic factor VIII are applicable only in haemophilia A and act by functionally replacing activated factor VIII (FVIIIa) rather than restoring the missing protein itself. This concept is applicable because FVIII has no intrinsic enzymatic activity but serves exclusively as a non-enzymatic cofactor within the intrinsic tenase complex. These antibodies simultaneously bind activated factor IX (FIXa) and factor X (FX), thereby spatially approximating the two coagulation factors and enabling efficient FX activation, analogous to the physiological role of FVIIIa. Unlike native FVIII, bispecific antibodies do not require thrombin-mediated activation and are not neutralized by endogenous or alloantibodies against FVIII [7]. Their activity is independent of von Willebrand factor binding and exhibits stable pharmacokinetics, allowing sustained thrombin generation over time even in the presence of FVIII inhibitors. By enhancing FXa generation downstream of FIXa, bispecific antibodies partially restore thrombin amplification and fibrin formation [7, 8]. Key differences between FVIII mimetics are summarized in Table 1.

Emicizumab

Emicizumab has been comprehensively studied within the HAVEN clinical trial program [3, 4, 11–15]. HAVEN 1 demonstrated a significant reduction in ABRs with emicizumab prophylaxis compared with no prophylaxis in inhibitor-positive patients 12 years of age or older with haemophilia A (ABR 2.9 vs. 23.3; 87% reduction; $p < 0.001$; $n = 35$ vs. $n = 18$) [3], representing a true game changer for this vulnerable patient population. These results have also held true in children under 12 years of age with haemophilia A and inhibitors, with 77% experiencing no treated bleeding events in HAVEN 2 under weekly dosing (ABR 0.3; 95% confidence interval [CI], 0.17–0.50; $n = 65$) and an intraindividual reduction in bleeding rates of 99% compared with prior bypassing-agent prophylaxis [12].

In HAVEN 3, emicizumab prophylaxis administered subcutaneously once weekly or every 2 weeks resulted in a significantly lower ABR compared with no prophylaxis in persons ≥12 years of age with severe haemophilia A without inhibitors (ABR 1.5 and 1.3 vs. 38.2; 96–97% reduction; $p < 0.001$); 56% and 60% of participants receiving prophylaxis experienced no treated bleeding events. In an intraindividual comparison ($n = 48$), emicizumab therapy was associated with a 68% lower ABR than previous factor VIII prophylaxis ($p < 0.001$) [4]. Similar findings were observed in HAVEN 4, which evaluated emicizumab administered once every 4 weeks (ABR for treated bleeds 2.4; 95% CI, 1.4–4.3; 56.1% of participants with zero treated bleeds; $n = 41$) [11].

Later in the same study program, HAVEN 6 demonstrated the efficacy and favourable safety profile of emicizumab in individuals with non-severe haemophilia A without FVIII inhibitors who required prophylaxis (ABR for treated bleeds 0.9; 95% CI, 0.55–1.52; 67% with zero treated bleeds; $n = 72$), representing an important advancement for this patient group with previously unmet needs [14].

HAVEN 7 was the first clinical trial dedicated specifically to infants with severe haemophilia A without FVIII inhibitors and demonstrated that subcutaneous emicizumab provides robust prophylactic protection already within the first year of life (ABR for treated bleeds 0.4; 95% CI, 0.30–0.63; $n = 55$). More than half of the infants (54.5%) experienced no treated bleeding events, and no intracranial haemorrhages occurred, underscoring the substantial protective benefit during a particularly vulnerable developmental period. Emicizumab was well tolerated, with only mild injection-site reactions reported (16.4% emicizumab-related adverse events, all grade 1), highlighting its potential to address a critical unmet need by enabling safe and effective early-life prophylaxis [15].

Denecimig (Mim8)

Denecimig (Mim8), an investigational FVIIIa-mimetic bispecific antibody, is being developed within the FRONTIER study program and has shown promising properties already in the phase 1/2 FRONTIER 1 trial [9]. In this partially randomized, multiple-ascending-dose study including 42 participants (9.5%

Table 1. Key characteristics of approved and investigational factor VIII mimetic bispecific antibodies used for non-factor prophylaxis in haemophilia A [7–10]

	Generic name/study identifier		
	Emicizumab	Denecimig/Mim8	NXT007
Brand name	Hemlibra®	Not yet assigned	Not yet assigned
Manufacturer	F. Hoffmann-La Roche Ltd.	Novo Nordisk A/S	Chugai Pharmaceutical Co., Ltd. (in Zusammenarbeit mit F. Hoffmann-La Roche Ltd.)
Regulatory status	Approved; extensive real-world experience	Phase 3 completed, awaiting approval	Early to mid-phase clinical development
Antibody type	Humanized bispecific IgG4 antibody	Human bispecific IgG4 antibody	Humanized bispecific IgG4 antibody
Dependence on von Willebrand factor	No	No	No
Activity in presence of FVIII inhibitors	Yes	Yes	Yes
Relative cofactor potency	Reference	Higher potency suggested vs. emicizumab	Higher potency suggested vs. emicizumab and potentially vs. denecimig (non-clinical data)
Elimination half-life	~25–30 days	~1 month	~10 weeks
Route and frequency of administration	Subcutaneous; weekly to every 4 weeks, dosed by weight	Subcutaneous; weekly to every 4 weeks dosing intervals evaluated/under evaluation in phase 3 trials, weight-band–based dosing	Subcutaneous; dosing interval under evaluation
Additive effect	Additive effects primarily with bypassing agents; no clinically relevant additive effect with FVIII at physiological concentrations	Additive effects with bypassing agents; no clinically relevant additive effect expected with FVIII at physiological concentrations	Additive effects with bypassing agents remain to be fully characterized; no clinically relevant additive effect is expected with FVIII at physiological concentrations

with FVIII inhibitors), Mim8 was well tolerated, with no thrombotic events, no treatment-related serious adverse events, and only one serious adverse event (anxiety-related chest pain) considered unrelated to treatment. Pharmacokinetic and pharmacodynamic data demonstrated dose-proportional exposure and thrombin generation, supporting both once-weekly and once-monthly dosing regimens. Exploratory efficacy signals were encouraging, with only five treated bleeds observed beyond the lowest dose cohort. Overall, FRONTIER 1 provides early evidence that denecimig may offer effective and flexible subcutaneous prophylaxis for people with haemophilia A, including those with inhibitors.

In the meantime, the phase 3 clinical trial program for denecimig (Mim8) has largely been completed, with the 26-week main phase of the FRONTIER2 study demonstrating superiority of once-weekly and once-monthly prophylaxis in reducing ABRs compared with prior clotting factor concentrate prophylaxis (estimated mean ABR 2.32 and 1.79 under prior prophylaxis vs. 1.28 and 1.54 during the extension phase), and sustained bleed control over 52 weeks, with up to 70% of participants experiencing zero treated bleeds and a median ABR of 0; however, full peer-reviewed results have not yet been fully published [16].

NXT007

NXT007 is a next-generation FVIIIa-mimetic bispecific antibody engineered from emicizumab to achieve substantially higher cofactor activity and improved pharmacokinetics. In preclinical studies, NXT007 generated thrombin generation levels comparable to 100 IU/dL FVIII, thereby reaching the non-haemophilic range of coagulation potential [10]. In vivo, NXT007 exerted potent haemostatic activity at ~30-fold lower plasma concentrations than emicizumab, suggesting increased biologic potency [17]. This enhanced potency suggests

Table 2. Comparison of tissue factor pathway inhibitor inhibitors used as rebalancing agents, including dosing, pharmacologic properties, and clinical development status [22–24]

	Generic name	
	Concizumab	Marstacimab
Brand name	Alhemo®	Hympavzi®
Manufacturer	Novo Nordisk A/S	Pfizer Inc.
Regulatory status	Approved, currently for patients with haemophilia A/B with and without inhibitors	Approved, currently for patients with haemophilia A/B without inhibitors
Antibody type	Humanized monoclonal IgG4 antibody	Human monoclonal IgG1 antibody
Primary target	TFPI Kunitz-2 domain	TFPI Kunitz-2 domain
Mechanism of action	Releases inhibition of FXa and TF-FVIIa initiation complex; enhances extrinsic pathway initiation and thrombin generation	Releases inhibition of FXa and TF-FVIIa initiation complex; enhances extrinsic pathway initiation and thrombin generation
Route and frequency of administration	Subcutaneous; daily dosing	Subcutaneous; weekly dosing
Dose mitigation strategy	Individualized dose based on concizumab plasma concentration and weight	Fixed/flat dose, weight independent
Functional half-life	Shorter functional half-life, 39–195 h	Longer functional half-life, 16–18 days
Additive effect	Potential additive procoagulant effects with factor concentrates or bypassing agents; requires cautious concomitant use	Potential additive procoagulant effects with factor concentrates or bypassing agents; clinical relevance remains to be fully characterized

that NXT007 may enable effective prophylaxis at lower exposure levels and with less frequent dosing, potentially including monthly administration. Whether this translates into improved haemostatic protection and reduced breakthrough bleeding remains to be established in clinical studies. Overall, NXT007 may represent a step toward prophylaxis that more closely approximates physiological FVIII function and may contribute to narrowing the remaining efficacy gap observed under current non-factor therapies [10, 17].

Rebalancing Agents

Unified Rationale

Rebalancing agents are designed to restore haemostatic competence by modulating endogenous anticoagulant pathways rather than replacing the deficient coagulation factor. The central rationale is that insufficient thrombin generation, rather than the absence of a specific factor, is the primary determinant of bleeding risk [18]. Because this strategy enhances downstream thrombin generation, it is mechanistically independent of whether the underlying deficiency involves factor VIII or factor IX. Consequently, rebalancing agents are effective across different forms of haemophilia, including haemophilia A and B, and remain active in the presence of inhibitory antibodies [19]. By shifting the balance toward controlled procoagulant activity, these therapies establish a rebalanced, rather than normalized, haemostatic state [18, 20].

Tissue Factor Pathway Inhibitors

Mode of action: TFPIs act by neutralizing tissue factor pathway inhibitor, a key regulator of the initiation phase of coagulation. TFPI normally suppresses thrombin generation by inhibiting factor Xa and the tissue factor-factor VIIa complex. By blocking TFPI, primarily its Kunitz-2 domain, TFPIs release this brake on the extrinsic pathway, allowing enhanced FXa generation. Increased FXa formation leads to amplified thrombin generation downstream, partially compensating for the intrinsic pathway defect in haemophilia [21]. This mechanism restores early thrombin burst and supports subsequent propagation of coagulation independent of FVIII or FIX activity and irrespective of inhibitor status. As a consequence, TFPI inhibition rebalances haemostasis but requires careful dosing to avoid excessive thrombin generation and thrombotic risk [22]. A comparison of TFPIs is provided in Table 2.

Concizumab: concizumab is a subcutaneously administered, anti-tissue factor pathway inhibitor monoclonal antibody developed to enhance thrombin generation independently of FVIII or FIX and thereby provide bleed protection across all haemophilia subtypes. Early clinical trials demonstrated proof of concept: concizumab showed a favourable safety profile, with no serious adverse events or anti-drug antibodies observed in 24 participants, predictable pharmacokinetics consistent with target-mediated drug disposition, and a dose-dependent reduction in unbound TFPI accompanied by increased thrombin generation [23].

In phase 2 studies (explorer4 and explorer5), once-daily concizumab prophylaxis demonstrated proof of concept for bleeding reduction in people with haemophilia A or B with and without inhibitors, with ABRs of 3.0–5.9 in patients with inhibitors and 7.0 in patients with haemophilia A without inhibitors in the main phase and 4.8 and 6.4, respectively, during the extension; most adverse events were mild, and no thromboembolic events were observed [25, 26]. These findings were confirmed in the phase 3 explorer7 trial, where concizumab prophylaxis resulted in a markedly lower ABR compared with no prophylaxis in patients with haemophilia A or B with inhibitors (mean ABR 1.7 vs. 11.8; 95% CI, 0.07–0.29; $p < 0.001$), with a median ABR of 0 under treatment and no thromboembolic events reported after trial restart with dose mitigation [27]. Similarly, in the phase 3 explorer8 trial, concizumab significantly reduced spontaneous and traumatic bleeding episodes compared with no prophylaxis in patients with haemophilia A and B without inhibitors (ABR ratio 0.14 [95% CI, 0.07–0.29; $p < 0.0001$] in haemophilia A and 0.21 [95% CI, 0.10–0.45; $p < 0.0001$] in haemophilia B). An initial safety signal of thromboembolic events, with three non-fatal events reported across the concizumab clinical program (including two in explorer8), led to a temporary treatment pause and implementation of dose mitigation measures; no thromboembolic events were reported after trial restart [20].

Marstacimab: marstacimab is a subcutaneously administered monoclonal antibody targeting TFPI, designed to restore haemostatic balance independently of FVIII or FIX. In the phase 3 BASIS trial, once-weekly marstacimab reduced bleeding rates in people with severe haemophilia A or moderately severe to severe haemophilia B without inhibitors: mean ABRs decreased from 39.86 (95% CI, 33.05–48.07) under prior on-demand therapy to 3.20 (95% CI, 2.10–4.88; ABR ratio 0.080; $p < 0.0001$), and from 7.90 (95% CI, 5.14–10.66) under prior factor prophylaxis to 5.09 (95% CI, 3.40–6.78; difference −2.81; $p = 0.0349$), demonstrating superiority over both treatment strategies. Marstacimab was generally well tolerated, with no deaths or thromboembolic events reported; adverse events were mostly mild, and no unexpected safety signals were observed [24].

Antithrombin Suppression

Mode of action: antithrombin suppression restores haemostasis by reducing the activity of antithrombin, a key endogenous inhibitor of thrombin and factor Xa, thereby enhancing downstream thrombin generation. By increasing overall thrombin generation irrespective of the initiating defect, this strategy compensates for impaired haemostatic balance across a range of bleeding disorders but necessitates careful pharmacodynamic control to prevent excessive procoagulant activity [28].

Fitusiran: fitusiran is a subcutaneously administered small interfering RNA therapeutic that lowers antithrombin to rebalance haemostasis independently of FVIII or FIX. In the phase 3 ATLAS-INH trial in patients with haemophilia A or B with inhibitors, once-monthly prophylaxis significantly reduced ABRs compared with on demand by passing agents (1.7 vs. 18.1 events per year; 90.8% reduction; $p < 0.0001$), with 66% of participants experiencing no treated bleeds [6]. Similar efficacy was observed in patients with haemophilia without inhibitors in ATLAS-A/B, where the median ABR was 0.0 (IQR, 0.0–3.4) with fitusiran prophylaxis compared with 21.8 (8.4–41.0) under on-demand treatment, and 51% of participants experienced no treated bleeding events. [5]. The ATLAS-PPX head-to-head study further demonstrated that switching from prior factor-based prophylaxis to fitusiran was associated with fewer bleeding events (median ABR 6.5/4.4 vs. 0.0) and a higher proportion of patients with no treated bleeds (63.1% vs. 16.9%), supporting its potential as an effective prophylactic option [29]. Safety findings included asymptomatic elevations of ALT/AST >3× the upper limit of normal in 3.5% of participants (exposure-adjusted incidence rate 2.06 per 100 patient-years), which were transient and resolved spontaneously without evidence of clinically relevant liver injury, as well as infrequent thromboembolic events (1.4%; 0.82 per 100 patient-years). In ATLAS-OLE, an individualized antithrombin-based dose regimen targeting antithrombin activity levels of 15%–35% was associated with an improved safety profile while maintaining clinically meaningful bleed protection, with a median ABR of 3.7 (IQR, 0.0–7.5); 78% of participants were treated with regimens administered once every 2 months, corresponding to as few as six injections per year [30].

Non-Factor Therapies: Emerging Role in AHA

Non-factor therapies represent an attractive conceptual strategy for acquired haemophilia A (AHA) as they bypass the neutralizing autoantibodies directed against factor VIII (FVIII) and aim to restore effective thrombin generation. From a mechanistic perspective, all currently available non-factor therapies, including FVIII mimetics and rebalancing agents targeting natural anticoagulants, would be expected to exert haemostatic activity in AHA as they do not rely on endogenous FVIII function. However, the clinical translation of rebalancing agents such as TFPIs or antithrombin suppression in AHA remains uncertain, particularly with regard to thrombotic risk. Patients with AHA are typically elderly, multimorbid, and frequently exhibit cardiovascular comorbidities, rendering them especially vulnerable to excessive thrombin generation [31]. In this context, the risk-benefit balance of potent rebalancing agents has not yet been defined, and prospective data in AHA are lacking.

In contrast, emicizumab is currently supported by the most robust clinical evidence among non-factor

therapies in AHA. Its FVIII-mimetic mechanism directly compensates for the functional deficit caused by FVIII autoantibodies and is unaffected by inhibitor presence. The prospective, multicentre phase 2 GTH-AHA-EMI trial (n = 47) demonstrated that emicizumab prophylaxis was associated with a very low clinically relevant bleeding rate (0.04 bleeds per patient-week; upper 97.5%, CI 0.06) during the first 12 weeks after diagnosis, even in the absence of immunosuppressive therapy. Importantly, 33 of 47 (70%) patients experienced no bleeding events. Thromboembolic events were infrequent (stroke n = 1), and overall safety findings were acceptable (with four deaths reported, including two due to bleeding, one due to COVID-19, and one due to cardiac arrest, none considered related to emicizumab) in this predominantly elderly population [32]. These findings were corroborated by data from the Japanese AGEHA study (n = 14, including patients eligible and ineligible for immunosuppression), which demonstrated effective bleed prevention with no major bleeds after treatment initiation, safe perioperative management (23 surgeries without bleeding), and feasibility of long-term prophylaxis; anti-emicizumab antibodies were observed in 2 patients, with accelerated drug clearance in 1 case but without an apparent impact on overall clinical efficacy [33]. Furthermore, a propensity score-matched comparison of emicizumab prophylaxis versus immunosuppressive therapy demonstrated lower bleeding rates (incident rate ratio 0.325; 95% CI, 0.182–0.581), fewer fatal infections (0% vs. 11%), and improved overall survival at 24 weeks (90% vs. 76%; hazard ratio 0.44; 95% CI, 0.24–0.81) with emicizumab during the early disease phase [34]. Based on these data and subsequent expert consensus recommendations, emicizumab can now be considered the preferred non-factor option for bleeding prophylaxis in AHA, enabling deferral or individualization of immunosuppressive therapy while providing effective and predictable haemostatic protection [35].

Safety Concerns: Thrombosis Risk and Immunogenicity

Non-factor replacement therapies substantially alter the haemostatic balance and therefore raise specific safety concerns, particularly with regard to thrombotic risk and immunogenicity. Unlike conventional factor replacement, these agents do not restore physiological regulation of coagulation but instead induce a rebalanced procoagulant state by bypassing or attenuating endogenous control mechanisms. As a consequence, excessive thrombin generation represents the central mechanistic risk across all non-factor approaches. Thrombotic events have been reported with several non-factor therapies, most prominently during early clinical development phases [1, 36].

For FVIII mimetics such as emicizumab, thrombotic complications and thrombotic microangiopathy were initially observed predominantly in the context of concomitant high-dose activated prothrombin complex concentrate (aPCC), particularly at cumulative doses exceeding 100 U/kg/day and prolonged exposure (>24–48 h). In the HAVEN 1 trial, 3 cases of thrombotic microangiopathy and 2 thrombotic events occurred under such conditions. Following the implementation of mitigation strategies (limiting aPCC to ≤100 U/kg/day and preferring recombinant activated factor VII [rFVIIa]), no thrombotic microangiopathy or thrombotic events were observed with lower-dose aPCC in both clinical trials and real-world data [37].

Rebalancing agents targeting anticoagulant pathways appear to carry a more intrinsic thrombotic risk as they directly suppress physiological inhibitors of coagulation. In clinical studies with TFPIs, including concizumab, thrombotic events were observed, leading to temporary trial pauses and subsequent protocol amendments with dose adjustments and risk mitigation strategies. For example, in the phase 3 explorer7 and explorer8 trials, treatment was temporarily halted following non-fatal thromboembolic events. Development of earlier-generation TFPIs such as befovacimab was discontinued due to drug-related thrombotic serious adverse events observed during the study phase. [38]. Subsequent dose-mitigation strategies, individualized dosing algorithms, and enhanced pharmacodynamic monitoring were introduced to limit peak thrombin generation and improve safety [2]. While these measures have reduced thrombotic signals, long-term real-world data remain limited, and particular caution is warranted in patients with a high thromboembolic risk [21].

Antithrombin suppression with fitusiran was also associated with thrombotic events during early development, which led to refinement of dosing strategies. In subsequent studies, an antithrombin-based dose regimen targeting antithrombin activity levels of 15%–35% was implemented to improve the safety profile; under this approach, thrombotic events were infrequent (4/286 participants [1.4%]; exposure-adjusted incidence rate 0.82 per 100 patient-years) in ATLAS-OLE, with all events occurring in the presence of predisposing risk factors and three of four events assessed as unrelated to fitusiran [30].

Immunogenicity represents an additional concern, although its clinical relevance appears limited for most non-factor therapies [39]. Neutralizing anti-drug antibodies against emicizumab are uncommon, occurring in 18 of 668 patients (2.7%), and are only rarely associated with reduced drug exposure (0.6%) or loss of efficacy leading to treatment discontinuation (0.1%) [40]. Anti-drug antibodies have been reported with some TFPIs, reaching incidences of up to approximately 25% in phase 2 studies, although these were typically low-titre and transient and were not associated with a consistent

impact on pharmacokinetics, efficacy, or safety [23, 41]. Overall, while non-factor therapies have demonstrated favourable benefit-risk profiles, their safe use depends on structured dose mitigation, avoidance of high-risk drug combinations, and vigilant clinical and laboratory surveillance to prevent excessive procoagulant activity.

Future Perspectives

Factor VIII mimetics, most notably emicizumab, are established as a standard prophylactic option in haemophilia A with inhibitors, based on phase 3 data demonstrating marked reductions in ABRs and a high proportion of patients without treated bleeds. In haemophilia A without inhibitors, they represent an effective alternative to factor replacement, particularly in patients with poor venous access, including infants, or in those who prefer subcutaneous over intravenous treatment [42].

However, targeted rebalancing agents, such as TFPI inhibition and antithrombin suppression, are emerging as complementary rather than competitive strategies, particularly for patient populations not optimally served by current options. These include patients with haemophilia B with inhibitors, for whom effective prophylactic strategies have historically been limited; patients with haemophilia A or B without inhibitors who prefer or require subcutaneous treatment, and patients with haemophilia A who seek subcutaneous prophylaxis but are not optimally controlled with currently available FVIII mimetic therapies. [1, 36]. Increasing evidence suggests that future treatment algorithms may gradually move beyond static factor activity measurements toward pharmacodynamic biomarkers that more comprehensively reflect global thrombin generation and overall clot-forming capacity, particularly in the context of non-factor therapies that cannot be adequately monitored using conventional factor activity assays [43, 44].

Beyond currently approved agents, several novel targets within the anticoagulant regulatory network are under active investigation, including inhibition of activated protein C and modulation of key endogenous anticoagulant mechanisms governing thrombin generation [36]. Early clinical data support the feasibility of these approaches. For example, the APC inhibitor SerpinPC has demonstrated sustained bleed reduction in persons with severe haemophilia in a first-in-human study with subcutaneous dosing every 2–4 weeks and no unexplained chronic elevations in D-dimer observed over prolonged follow-up [45]. Similarly, VGA039, a novel investigational agent evaluated in patients with von Willebrand disease, increased thrombin generation in a dose-dependent manner without clinically relevant D-dimer elevations or thromboembolic events in early-phase studies ($n = 6$), supporting the concept of controlled haemostatic rebalancing [46].

Conclusion

Non-factor therapies have profoundly expanded and are expected to further expand the therapeutic landscape of haemophilia, offering a broad range of mechanistically distinct options that extend far beyond traditional factor replacement [1]. Factor VIII mimetics, rebalancing agents targeting TFPI or antithrombin, and emerging approaches acting on additional anticoagulant pathways provide unprecedented flexibility to tailor prophylaxis to individual patient needs [36]. A key advantage shared by all non-factor therapies is subcutaneous administration, which represents a major clinical benefit for patients with poor venous access and substantially reduces treatment burden across all age groups [47].

Among these strategies, FVIII mimetics, most notably emicizumab, are supported by several years of robust clinical trial and real-world experience, demonstrating durable efficacy, favourable safety, and broad applicability across inhibitor and non-inhibitor populations. In contrast, targeted rebalancing agents represent a highly promising but less mature class, with comparatively limited long-term clinical experience and a narrower evidence base to date [48]. Early thrombotic signals observed during development have underscored the importance of careful dose mitigation and pharmacodynamic guidance for these agents [1].

As the number of non-factor options continues to grow, optimal therapy selection will increasingly rely on an integrated understanding of mechanism of action, patient-specific risk factors, and laboratory monitoring beyond conventional factor assays [49]. Collectively, non-factor therapies mark a paradigm shift toward more stable haemostasis, simplified administration, and individualized care, while ongoing clinical experience will be essential to define the long-term positioning of rebalancing agents within this evolving treatment landscape.

Conflict of Interest Statement

L.G. has received speaker's fees from Novo Nordisk, Roche, and Sobi and honoraria from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, and Sobi.

Funding Sources

L.G. has received grant funding from Sobi and Roche.

Author Contributions

L.G. conceived and designed the review and drafted and critically revised the manuscript. L.G. approved the final version of the manuscript and agrees to be accountable for all aspects of the work.

References

1 Mancuso ME, Croteau SE, Klamroth R. Benefits and risks of non-factor therapies: redefining haemophilia treatment goals in the era of new technologies. Haemophilia. 2024;30(Suppl 3):39–44. https://doi.org/10.1111/hae.14976

2 Nogami K, Shima M. Current and future therapies for haemophilia-beyond factor replacement therapies. Br J Haematol. 2023;200(1):23–34. https://doi.org/10.1111/bjh.18379

3 Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in Hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809–18. https://doi.org/10.1056/NEJMoa1703068

4 Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have Hemophilia A without inhibitors. N Engl J Med. 2018;379(9):811–22. https://doi.org/10.1056/NEJMoa1803550

5 Srivastava A, Rangarajan S, Kavakli K, Klamroth R, Kenet G, Khoo L, et al. Fitusiran prophylaxis in people with severe Haemophilia A or Haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023;10(5):e322. https://doi.org/10.1016/S2352-3026(23)00037-6

6 Young G, Srivastava A, Kavakli K, Ross C, Sathar J, You CW, et al. Efficacy and safety of fitusiran prophylaxis in people with Haemophilia A or Haemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial. Lancet. 2023;401(10386):1427–37. https://doi.org/10.1016/S0140-6736(23)00284-2

7 Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood. 2017;130(23):2463–8. https://doi.org/10.1182/blood-2017-08-801662

8 Kitazawa T, Shima M. Emicizumab, a humanized bispecific antibody to coagulation factors IXa and X with a factor VIIIa-cofactor activity. Int J Hematol. 2020;111(1):20–30. https://doi.org/10.1007/s12185-018-2545-9

9 Lentz SR, Chowdary P, Gil L, Lopez-Jaime FJ, Mahlangu J, Matytsina I, et al. Frontier1: a partially randomized phase 2 study assessing the safety, pharmacokinetics, and pharmacodynamics of Mim8, a factor VIIIa mimetic. J Thromb Haemost. 2024;22(4):990–1000. https://doi.org/10.1016/j.jtha.2023.12.016

10 Teranishi-Ikawa Y, Soeda T, Koga H, Yamaguchi K, Kato K, Esaki K, et al. A bispecific antibody NXT007 exerts a hemostatic activity in Hemophilia A monkeys enough to keep a nonhemophilic state. J Thromb Haemost. 2024;22(2):430–40. https://doi.org/10.1016/j.jtha.2023.09.034

11 Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with Haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019;6(6):e295–305. https://doi.org/10.1016/S2352-3026(19)30054-7

12 Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, Jiménez-Yuste V, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with Hemophilia A with inhibitors. Blood. 2019;134(24):2127–38. https://doi.org/10.1182/blood.2019001869

13 Yang R, Wang S, Wang X, Sun J, Chuansumrit A, Zhou J, et al. Prophylactic emicizumab for Hemophilia A in the Asia-Pacific region: a randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6(2):e12670. https://doi.org/10.1002/rth2.12670

14 Négrier C, Mahlangu J, Lehle M, Chowdary P, Catalani O, Bernardi RJ, et al. Emicizumab in people with moderate or mild Haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematol. 2023;10(3):e168–77. https://doi.org/10.1016/S2352-3026(22)00377-5

15 Pipe SW, Collins P, Dhalluin C, Kenet G, Schmitt C, Buri M, et al. Emicizumab prophylaxis in infants with Hemophilia A (HAVEN 7): primary analysis of a phase 3b open-label trial. Blood. 2024;143(14):1355–64. https://doi.org/10.1182/blood.2023021832

16 Lentz SR, Abraham A, Ay C, Chan AKC, Jiménez Yuste V, Oldenburg J, et al. Mim8 prophylaxis in adults and adolescents with Hemophilia A: 52-week efficacy and safety outcomes from the phase 3 Frontier2 study. Blood. 2025;146(Suppl 1):537–8. https://doi.org/10.1182/blood-2025-537

17 Yamaguchi K, Haraya K, Koga H, Nishimura K, Inaba K, Muraoka M, et al. NXT007 enhances in vitro coagulation potential in the coexistence of emicizumab in Hemophilia A through distinct complex formation. Res Pract Thromb Haemost. 2025;9(8):103236. https://doi.org/10.1016/j.rpth.2025.103236

18 Van Thillo Q, Hermans C. Rebalancing agents in Hemophilia: knowns, unknowns, and uncertainties. Haematologica. 2025;110(12):2902–12. https://doi.org/10.3324/haematol.2025.288245

19 Jiménez-Yuste V. Non-factor therapies for Hemophilia: achievements and perspectives. Semin Thromb Hemost. 2025;51(1):23–7. https://doi.org/10.1055/s-0044-1796651

20 Chowdary P, Angchaisuksiri P, Apte S, Astermark J, Benson G, Chan AKC, et al. Concizumab prophylaxis in people with Haemophilia A or Haemophilia B without inhibitors (explorer8): a prospective, multicentre, open-label, randomised, phase 3a trial. Lancet Haematol. 2024;11(12):e891–904. https://doi.org/10.1016/S2352-3026(24)00307-7

21 Mahlangu JN. Progress in the development of anti-tissue factor pathway inhibitors for Haemophilia management. Front Med. 2021;8:670526. https://doi.org/10.3389/fmed.2021.670526

22 Chowdary P. Anti-tissue factor pathway inhibitor (TFPI) therapy: a novel approach to the treatment of Haemophilia. Int J Hematol. 2020;111(1):42–50. https://doi.org/10.1007/s12185-018-2548-6

23 Eichler H, Angchaisuksiri P, Kavakli K, Knoebl P, Windyga J, Jiménez-Yuste V, et al. A randomized trial of safety, pharmacokinetics and pharmacodynamics of concizumab in people with Hemophilia A. J Thromb Haemost. 2018;16(11):2184–95. https://doi.org/10.1111/jth.14272

24 Matino D, Palladino A, Taylor CT, Hwang E, Raje S, Nayak S, et al. Marstacimab prophylaxis in Hemophilia A/B without inhibitors: results from the phase 3 BASIS trial. Blood. 2025;146(14):1654–63. https://doi.org/10.1182/blood.2024027468

25 Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Chowdary P, et al. Subcutaneous concizumab prophylaxis in Hemophilia A and Hemophilia A/B with inhibitors: phase 2 trial results. Blood. 2019;134(22):1973–82. https://doi.org/10.1182/blood.2019001542

26 Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Eichler H, et al. Long-term efficacy and safety of subcutaneous concizumab prophylaxis in Hemophilia A and Hemophilia A/B with inhibitors. Blood Adv. 2022;6(11):3422–32. https://doi.org/10.1182/bloodadvances.2021006403

27 Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, et al. Phase 3 trial of concizumab in Hemophilia with inhibitors. N Engl J Med. 2023;389(9):783–94. https://doi.org/10.1056/NEJMoa2216455

28 Young G, Lenting PJ, Croteau SE, Nolan B, Srivastava A. Antithrombin lowering in hemophilia: a closer look at fitusiran. Res Pract Thromb Haemost. 2023;7(4):100179. https://doi.org/10.1016/j.rpth.2023.100179

29 Kenet G, Nolan B, Zulfikar B, Antmen B, Kampmann P, Matsushita T, et al. Fitusiran prophylaxis in people with Hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024;143(22):2256–69. https://doi.org/10.1182/blood.2023021864

30 Young G, Kavakli K, Klamroth R, Matsushita T, Peyvandi F, Pipe SW, et al. Safety and efficacy of a fitusiran antithrombin-based dose regimen in people with Hemophilia A or B: the ATLAS-OLE study. Blood. 2025;145(25):2966–77. https://doi.org/10.1182/blood.2024027008

31 Burgmann CH, Sachs UJ, Trautmann-Grill K, Pfrepper C, Knöbl P, Greil R, et al. Comorbidity and adverse events in acquired Hemophilia A: data from the GTH-AHA-EMI study. Res Pract Thromb Haemost. 2024;8(7):102565. https://doi.org/10.1016/j.rpth.2024.102565

32 Tiede A, Hart C, Knöbl P, Greil R, Oldenburg J, Sachs UJ, et al. Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHA-EMI): an open-label, single-arm, multicentre, phase 2 study. Lancet Haematol. 2023;10(11):e913–21. https://doi.org/10.1016/S2352-3026(23)00280-6

33 Shima M, Suzuki N, Nishikii H, Amano K, Ogawa Y, Kobayashi R, et al. Final analysis results from the AGEHA Study: emicizumab prophylaxis for acquired Hemophilia A with or without immunosuppressive therapy. Thromb Haemost. 2025;125(5):449–59. https://doi.org/10.1055/a-2384-3585
34 Hart C, Klamroth R, Sachs UJ, Greil R, Knoebl P, Oldenburg J, et al. Emicizumab versus immunosuppressive therapy for the management of acquired Hemophilia A. J Thromb Haemost. 2024;22(10):2692–701. https://doi.org/10.1016/j.jtha.2024.06.010
35 Pfrepper C, Klamroth R, Oldenburg J, Holstein K, Eichler H, Hart C, et al. Emicizumab for the treatment of acquired Hemophilia A: consensus recommendations from the GTH-AHA Working Group. Hamostaseologie. 2024;44(6):466–71. https://doi.org/10.1055/a-2197-9738
36 Peyvandi F, Seidizadeh O, Mohsenian S, Garagiola I. Exploring nonreplacement therapies' impact on Hemophilia and other rare bleeding disorders. Res Pract Thromb Haemost. 2024;8(4):102434. https://doi.org/10.1016/j.rpth.2024.102434
37 Sidonio RF Jr, Young G, Escuriola Ettingshausen C, Mahlangu J, Ozelo MC, Srivastava A, et al. Activated prothrombin complex concentrate in patients receiving emicizumab prophylaxis: from evidence to clinical practice. Res Pract Thromb Haemost. 2025;9(4):102926. https://doi.org/10.1016/j.rpth.2025.102926
38 Mancuso ME, Ingham SJM, Kunze M. Befovacimab, an anti-tissue factor pathway inhibitor antibody: early termination of the multiple-dose, dose-escalating phase 2 study due to thrombosis. Haemophilia. 2022;28(5):702–12. https://doi.org/10.1111/hae.14595
39 Prezotti ANL, Frade-Guanaes JO, Yamaguti-Hayakawa GG, Ozelo MC. Immunogenicity of current and new therapies for Hemophilia A. Pharmaceuticals. 2022;15(8):911. https://doi.org/10.3390/ph15080911
40 Schmitt C, Emrich T, Chebon S, Fernandez E, Petry C, Yoneyama K, et al. Low immunogenicity of emicizumab in persons with haemophilia A. Haemophilia. 2021;27(6):984–92. https://doi.org/10.1111/hae.14398
41 Mahlangu J. Anti-tissue factor pathway inhibitors for hemophilia: are these treatments the answer to overcoming current treatment limitations? Expert Rev Hematol. 2025;18(7):521–7. https://doi.org/10.1080/17474086.2025.2519002
42 Hermans C, Pierce GF. Bispecific antibodies mimicking factor VIII in hemophilia A: converting innovation to an essential medicine. Res Pract Thromb Haemost. 2023;7(4):100173. https://doi.org/10.1016/j.rpth.2023.100173
43 Sidonio RF Jr, Hoffman M, Kenet G, Dargaud Y. Thrombin generation and implications for hemophilia therapies: a narrative review. Res Pract Thromb Haemost. 2023;7(1):100018. https://doi.org/10.1016/j.rpth.2022.100018
44 Josset L, Rezigue H, Dargaud Y. Thrombin generation assay to support hematologists in the era of new Hemophilia therapies. Int J Lab Hematol. 2025;47(2):212–20. https://doi.org/10.1111/ijlh.14406
45 Baglin T, Huntington JA, Koch A, Mocanu I, Makhaldiani L. Serpin-PC in persons with severe hemophilia (PwH): updated results from a multicenter multi-part, first-in-human study. Blood. 2023;142(Suppl 1):2619. https://doi.org/10.1182/blood-2023-179969
46 Millar CM, Raheja P, Wheeler AP, Kshirsagar S, Schoergenhofer C, Machin NC, et al. A Phase Ia study of VGA039, a Protein S-targeting monoclonal antibody, in individuals with Von Willebrand disease demonstrates concentration-dependent increases in thrombin generation for reducing bleeding. Blood. 2024;144(Suppl 1):3981. https://doi.org/10.1182/blood-2024-208020
47 Dargaud Y, Janbain M. Clinical utility of subcutaneous factor VIII replacement therapies in hemophilia A: a review of the evidence. J Blood Med. 2021;12:1031–6. https://doi.org/10.2147/JBM.S260923
48 Alcedo Andrade PE, Mannucci PM, Kessler CM. Emicizumab: the hemophilia A game-changer. Haematologica. 2024;109(5):1334–47. https://doi.org/10.3324/haematol.2022.282099
49 Garcia VC, Mansfield C, Pierce A, Leach C, Smith JC, Afonso M. Patient and caregiver preferences for haemophilia treatments: a discrete-choice experiment. Haemophilia. 2024;30(2):375–87. https://doi.org/10.1111/hae.14928