# Haemophilia

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**Haemophilia A and B are congenital X-linked bleeding disorders resulting from deficiencies in clotting factors VIII (haemophilia A) and IX (haemophilia B). Patients with severe deficiency, defined as having less than 1% of normal plasma factor activivity, often have spontaneous bleeding within the first few years of life. Those with moderate and mild deficiencies typically present with post-traumatic or post-surgical bleeding later in life. A high index of suspicion and measurement of factor activity in plasma facilitates early diagnosis. In the 21st century, therapeutic advances and comprehensive care have substantially improved both mortality and morbidity associated with these conditions. Management strategies for haemophilia include on-demand treatment for bleeding episodes and all surgeries and regular treatment (ie, prophylaxis) aimed at reducing bleeds, morbidity, and mortality, thereby enhancing quality of life. Treatment options include factor replacement therapy, non-replacement therapies that increase thrombin generation, and gene therapies that facilitate in vivo clotting factor synthesis. The therapies differ in their use for prophylaxis and on-demand treatment, the mode and frequency of administration, duration of treatment effect, degree of haemostatic protection, and side-effects. Monitoring the effectiveness of these prophylactic therapies involves assessing annual bleeding rates and joint damage. Personalised management strategies, which align treatment with individual goals (eg, playing competitive sports), initiated at diagnosis and maintained throughout the lifespan, are crucial for optimal outcomes. These strategies are facilitated by a multidisciplinary team and supported by clinician-led education for both clinicians and patients.**

## Introduction

Haemophilia A and haemophilia B are congenital X-linked bleeding disorders caused by deficiencies in coagulation factors VIII (haemophilia A) and IX (haemophilia B) due to mutations in the *F8* (haemophilia A) or *F9* (haemophilia B) genes on the X chromosome. The prevalence of haemophilia A in males has been traditionally estimated at one in 5000 livebirths, and that of haemophilia B at one in 30 000 livebirths.[1] However, data from 2019 suggest a higher prevalence of one in 4000 male livebirths for haemophilia A and one in 20 000 male livebirths for haemophilia B.[2] Approximately a third of babies born with haemophilia in high-income countries have no family history of the condition.[3] Furthermore, the exact prevalence of female carriers is unknown. However, it is estimated that for every male with haemophilia, there are 1·6 female carriers.[4] A proportion of these carriers have low clotting factor concentrations with symptomatic bleeding.

Deficiencies of FVIII and FIX result in impaired thrombin generation, which is responsible for the bleeding tendencies. Thrombin, the final enzyme of the coagulation cascade, generates an insoluble fibrin mesh from soluble fibrinogen that stabilises the platelet plug (figure 1).[5–7,9–11] FVIII is a predominantly intravascular glycoprotein that acts as a cofactor in the intrinsic tenase complex (figure 1). The mature protein has 2332 amino acids and multiple domains (domain structure A1–A2–B–A3–C1–C2), with the B domain not required for coagulation. It is synthesised and secreted by liver sinusoidal endothelial cells and vascular endothelial cells. Almost all FVIII is found in the intravascular space, where a normal plasma concentration is 0·1 µg/mL; very little FVIII distributes within the extravascular space. FVIII stability and half-life are dependent on non-covalent high-affinity complex formation with von Willebrand factor (VWF). VWF is a multimeric multidomain glycoprotein that also facilitates platelet adhesion to subendothelial collagen. Factors that influence the VWF concentration also influence the FVIII concentration. VWF is primarily synthesised outside the liver by endothelial cells and megakaryocytes. In endothelial cells, VWF and FVIII are stored within Weibel–Palade bodies and are released following stimulation by multiple agonists.

### Search strategy and selection criteria

A literature review was done in PubMed for articles published in English from April 1, 2015, when the previous *Lancet* Seminar on haemophilia was published, to Dec 31, 2023. The focus of the literature review was on treatment options, including novel interventions with the potential to improve control of bleeding tendency. The following search terms were used: (haemophilia[Title/Abstract] OR haemophilia [Title/Abstract]) AND ("therapy" [MeSH Subheading]) AND ("2015/04/01" [Date - Create]: "3000" [Date - Create]) AND (humans[Filter]) NOT (exercise OR physiotherapy OR education) AND (humans[Filter]) NOT ("case reports"[Publication Type]) NOT ("guideline"[Publication Type]). The exception to the guidelines was the third edition of the World Federation of Haemophilia Guidelines on the management of haemophilia. Articles were reviewed on their titles or abstracts. Articles and other key references were chosen in accordance with the focus of the review.
The content was also supplemented by presentations at international meetings in 2022 and 2023, where phase III clinical trial results were presented and have yet to be published in peer-reviewed journals. When multiple relevant papers related to a particular topic were identified, we selected the parent publication wherever possible.

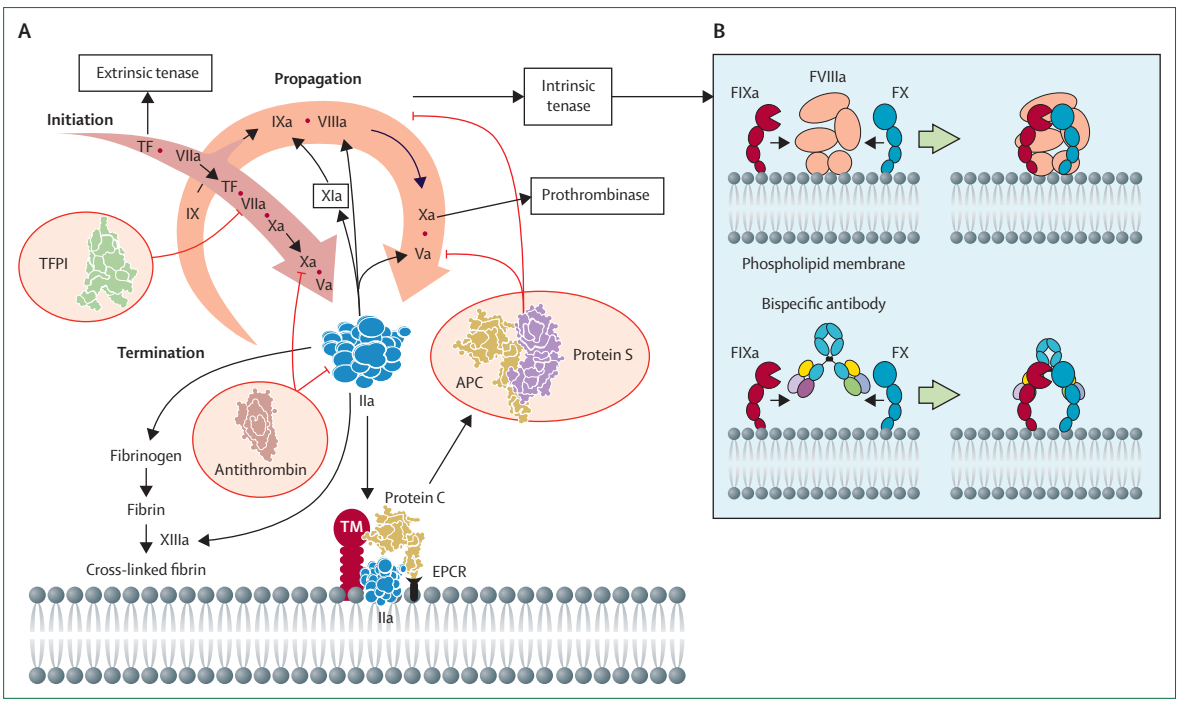


***Figure 1:*** **Overview of normal haemostasis, the intrinsic tenase complex, and its regulation**
Thrombin generation is regulated extensively via multiple pathways. (A) The response to injury, defined as the haemostatic response, includes the rapid formation of a platelet plug (primary haemostasis) stabilised by a fibrin meshwork with thrombin converting soluble fibrinogen to insoluble fibrin mesh (secondary haemostasis) and thus resulting in blood clot formation.[5] A breach of the vessel wall results in subendothelial collagen exposure, which activates primary haemostasis, and tissue factor exposure, which activates secondary haemostasis. Thrombin is the final enzyme of secondary haemostasis or the coagulation cascade.[6,7] A deficiency of thrombin generation is the hallmark of haemophilia A and B, and they are clinically indistinguishable. Thrombin generation is dependent on the formation and regulation of three macromolecular complexes: extrinsic tenase, intrinsic tenase, and prothrombinase complexes on the phospholipid surface of either the injured cell or activated platelets and occurs in three distinct phases: initiation, amplification, and propagation.[8] Three physiological or natural anticoagulant pathways regulate the generation and build-up of thrombin. Extrinsic tenase initiates thrombin generation and is inhibited by TFPI. TFPI is a multivalent K-type serine protease inhibitor with two or three K domains; binding of the K2 domain to FXa results in its inhibition and the subsequent binding of K1 domain to FVIIa in the extrinsic tenase complex stops FXa generation.[9-11] Antithrombin is the principal circulating irreversible inhibitor of active serine proteases, inhibiting thrombin, FIXa, FXa, FXIa, and FXIIa.[11] Thrombin is more sensitive to AT inhibition than FXa and this reaction is increased by heparan sulphate or glycosaminoglycans on the surface of endothelial cells binding to AT. While AT and TFPI inhibit the activated proteases, the protein C pathway (activated protein C [APC] and its cofactor protein S) inactivates cofactors (FVa and FVIIIa) through proteolysis.[12,13] Protein C activation is mediated by thrombin complexed to thrombomodulin, the endothelial cell surface thrombin receptor. The activation of protein C can be augmented by the EPCR, which binds protein C, increasing the affinity of the thrombin–thrombomodulin complex for protein C. The microvasculature has the highest concentration of both glycosaminoglycans and EPCR. (B) The intrinsic tenase complex has FVIIIa as a cofactor for activation of FX by FIXa. The FXa generated here is responsible for the generation of thrombin from prothrombin, with more than 95% of thrombin generated through this complex. FVIIIa mimetics are bispecific IgG antibodies that bind and spatially co-locate the active site of FIXa and the substrate site of FX, with activation of FX to FXa. The development was based on the observation that the distance between two antigen-binding sites of human IgG is similar to the distance between the FIXa and FX binding sites of FVIIIa. APC=activated protein C. EPCR=endothelial protein C receptor. K=Kunitz. TFPI=tissue factor pathway inhibitor. TM=thrombomodulin. Figure adapted from Ten Cate et al[14] with permission from the publisher.

FIX, a serine protease synthesised in hepatocytes, exhibits substantial extravascular distribution. Activated FIX acts on FX with FVIIIa as a cofactor in the intrinsic tenase complex (figure 1). The mature protein has 415 amino acids with no carrier protein and the plasma concentration is 5 µg/mL, which is 50 times higher than that of FVIII.[15] The extravascular pool of FIX is three times larger than the plasma pool, with a large proportion bound to type IV collagen, a substantial component of the subendothelial basement membrane.[16,17]

## Clinical presentation and diagnosis

Bleeding severity is established by the residual plasma activity of the deficient clotting factor. FVIII and FIX concentrations in plasma are routinely measured with activity assays, which are expressed in international units (IU) of activity per mL or dL, or as a percentage of normal activity; 1 IU is the activity of FVIII or FIX in 1 mL of pooled plasma, with normal activity ranging from 50% to 150%. The disorders are categorised as severe, moderate, or mild (figure 2).[18] In severe haemophilia, bleeding complications can present early, including intracranial haemorrhage after birth or bleeding from circumcision. More frequently, symptoms—such as joint and muscle bleeds—appear between ages 6 months and 12 months, aligning with increased mobility and weight-bearing activities on the joints, typically the ankles, knees, elbows, and shoulders. In the absence of treatment, the number of untreated bleeding episodes per year increases during the first 5–6 years of life, up to a maximum of

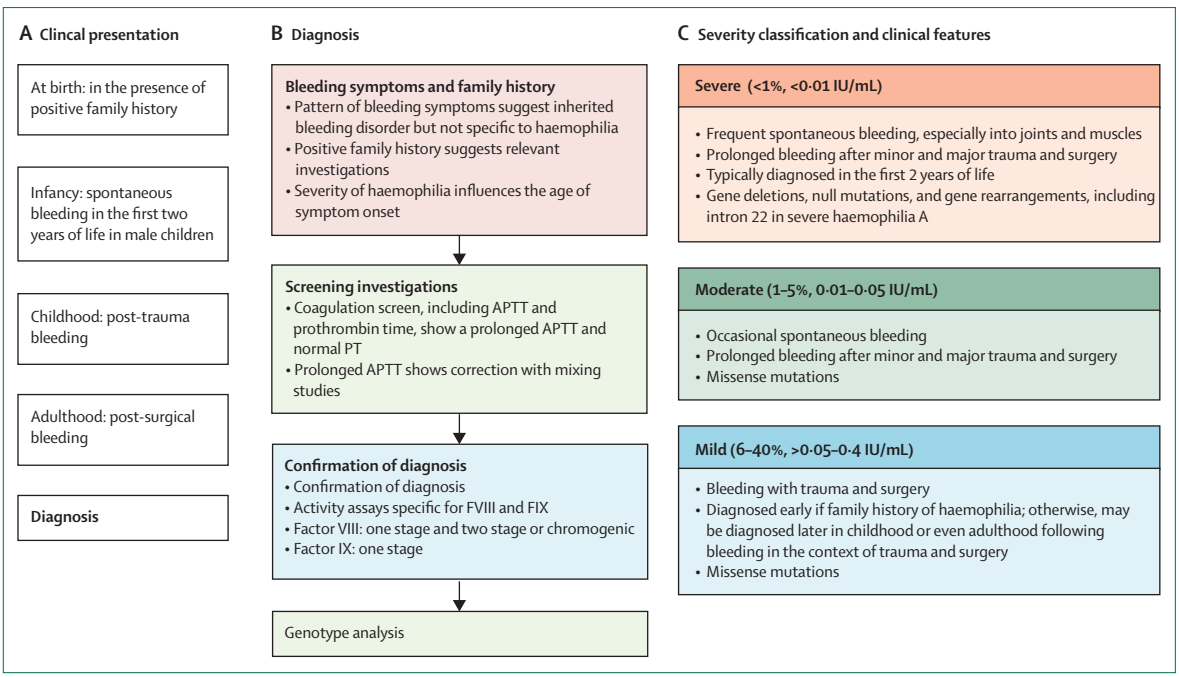


***Figure 2:*** **Clinical presentation and diagnosis**
(A) A high degree of clinical suspicion is crucial for the prompt diagnosis of haemophilia. The severity of the factor deficiency often determines the age at which the condition is identified: those with severe disease are frequently diagnosed within their first few years of life, whereas moderate and mild deficiencies might only become apparent later in life. If there is a known family history, a diagnosis can be made at birth. (B) Following clinical suspicion, the initial investigation typically involves a coagulation screen that reveals a prolonged APTT. Mixing studies—repeating the APTT after combining patient plasma 1:1 with normal plasma—help distinguish a factor deficiency when the prolonged APTT corrects upon the addition of normal plasma. Subsequent specific factor activity assays establish the diagnosis, which is further supported by genotypic analysis. (C) The severity of the deficiency depends on the remaining plasma activity of the affected clotting factor, quantified as either IU/mL (or IU/dL) or expressed as a percentage of normal function. The categorisation of severity to date is based on 2001 guidelines.[14]
APTT=activated partial thromboplastin time. IU=international units.

20–40 episodes.[19] Before modern treatments, life expectancy was approximately 11 years, with bleeding at any site potentially being fatal. Patients with mild haemophilia might have abnormal bleeding, primarily with trauma or surgery, and patients with moderate haemophilia present with fewer spontaneous bleeds (usually less than 10 per year) in addition to post-traumatic and post-surgical bleeding.

Interindividual variability in bleeding tendency is not uncommon. Several factors influence this, including the type of mutation, co-inheritance of another bleeding disorder, presence of thrombophilic traits that potentially counter bleeding tendency, differences in physical activity, balance of proinflammatory and anti-inflammatory cytokines, and other poorly understood factors.[20–24]

## Diagnosis and laboratory investigations

Diagnosis typically follows the onset of bleeding symptoms in patients for whom de novo mutations are the cause (figure 2). First-line investigations, including a coagulation screen, show a normal prothrombin time and prolonged activated partial thromboplastin time (APTT). Prolonged APTT serves as a surrogate marker for factor deficiency and measurement of factor activity confirms diagnosis and severity. FVIII and FIX activity levels can be measured by two different methods: the one-stage APTT-based clotting assay, which is the most commonly used method worldwide, and the chromogenic assay, which measures the generation of FXa.[25] Specific abnormal FVIII proteins show discrepant results between the two types of assays. Genetic testing for variants is now standard, with more than 3000 *F8* mutations and more than 1000 *F9* mutations identified.[26] The mutation type helps predict disease severity, inhibitor development, and carrier status.

Low FVIII concentrations can be seen in von Willebrand disease, in which VWF concentrations are also low. The primary differential diagnosis for mild haemophilia A is type 2N von Willebrand disease, in which impaired binding of FVIII by VWF causes low FVIII concentrations and is confirmed by genetic testing.[27] Low FVIII concentrations due to specific missense mutations responsible for mild haemophilia A are only identified by chromogenic assays in addition to normal APTT and one-stage assays.[28] Low FIX concentrations usually indicate congenital haemophilia B, but can also occur due to vitamin K deficiency, vitamin K antagonists, liver disease, or rare genetic defects in vitamin K metabolism.[29] FIX concentrations are also low in neonates and substantially

increase during the first year of life, which can result in diagnostic challenges.

### Joint bleeding and haemophilic arthropathy

Recurrent joint and muscle bleeds dominate the clinical presentation of severe and moderate haemophilia and affect treatment strategies. Frequent bleeds contribute to progressive joint damage, including cartilage and underlying bone, culminating in contractures and permanent joint deformities.[3] Indeed, the prevalence of joint damage increases with age; the ankles, knees, elbows, and shoulders are the most affected, with almost no involvement of small joints.[20,30] Patients with mild haemophilia have either no bleeds, or the occasional bleed in a year, but can also have joint damage due to untreated or inadequately treated joint bleeds. Furthermore, there is increasing awareness of the importance of asymptomatic (ie, subclinical) joint bleeds in the development and progression of joint disease.[31]

In adolescents and adults, mild joint bleeds manifest as sensations of fullness, stiffness, and discomfort. Moderate bleeds are accompanied by movement restriction and severe bleeds manifest with substantial swelling, increased warmth, intense pain, and joint immobilisation.[32,33] In children younger than 2–3 years, these symptoms can present as reduced limb mobility.

Regular assessment of joint health is a crucial component of haemophilia care and scoring systems that include clinical assessment of joint damage and functional assessments are valuable in monitoring disease progression.[34] Furthermore, imaging, including plain x-rays, ultrasounds, and MRIs, are increasingly used for monitoring joint health.[35,36] There is active research on the role of biomarkers for the early identification and monitoring of joint disease over time.[37] The sensitivities for joint damage vary for each modality, with distinct advantages and disadvantages, and an overview is provided in figure 3.[34–37]

### Females and haemophilia

Symptomatic haemophilia in females is increasingly recognised as an important clinical issue, moving beyond the traditional view of females as only carriers of the gene. The mechanism underlying low factor activity is inactivation of one of the two X chromosomes during early female embryonic development, in which the maternal and paternal X chromosome have an equal chance of being inactivated. Low activity levels of FVIII or FIX are secondary to inactivation of more maternal X chromosomes with the normal gene. This mechanism often results in factor activity in the mild range, with severe and moderate deficiencies being rare. Mild deficiency, although common, is often missed.[43] Carriers of haemophilia A tend to have more bleeding episodes, such as heavy menstrual bleeding, oral bleeding, and postpartum haemorrhage, compared with females without the condition.[44,45] Studies published in the past 8 years[43,44] highlight the importance of measuring factor activity and evaluating bleeding patterns early in life among potential carriers, ideally before menarche and childbirth. An updated classification for haemophilia in females based on factor activity levels and bleeding tendency has been proposed.[4]

Prenatal testing is available through chorionic villus sampling or amniocentesis, with a 1% risk of miscarriage, and free fetal DNA is increasingly being used to identify the affected fetus.[3] Prenatal diagnosis enables precautionary measures to be taken to prevent perinatal bleeding, such as avoiding vacuum extraction or forceps assistance during delivery, which could increase the risk of both extracranial (eg, subgaleal haemorrhage and cephalohematoma) and intracranial haemorrhage.[3] Atraumatic vaginal delivery is considered safe and avoids the increased maternal morbidity of caesarean section.

## Comprehensive care

Holistic management of haemophilia encompasses not only the correction of bleeding tendencies, but also multidisciplinary care to address short-term and long-term effects of bleeding and its management. Specialised health-care centres known as haemophilia treatment centres have been established to address the physical, psychosocial, and emotional needs of patients with

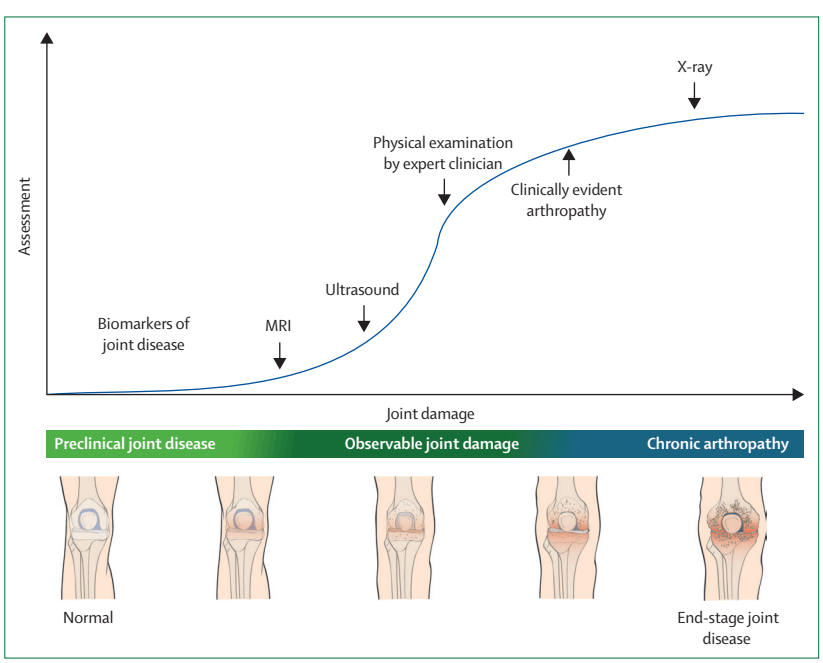


***Figure 3:*** **Monitoring joint disease**
A variety of tools can monitor joint disease, and the aim is to identify bleeding and synovitis (eg, inflammation of the joint lining), joint damage that includes cartilage, bone, and soft tissue damage, and functional limitations. There are several validated clinical scores, including the World Federation of Hemophilia Joint Score (Gilbert score),[38] and the Haemophilia Joint Health Score.[39] Imaging scores include the Pettersson score for plain x-ray,[40] ultrasound scores include the Hemophilia Early Arthropathy Detection with Ultrasound Score,[41] and MRI scoring systems include the International Prophylaxis Study Group MRI scoring system.[42] The role of biomarkers is under investigation, with potential to be used as a screening tool.

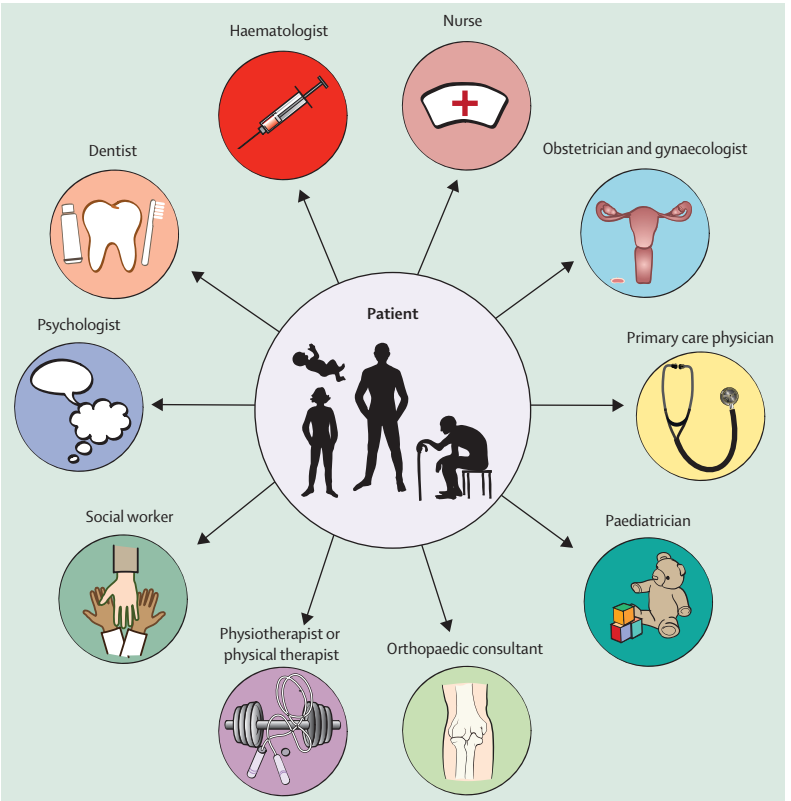


***Figure 4:*** **Multidisciplinary care for haemophilia**
Multidisciplinary care forms the cornerstone of comprehensive haemophilia care. The range of health-care professionals involved varies according to the patient's age, bleeding control, treatment burden, and the degree of joint damage and functional limitations. Comprehensive haemophilia care, while supporting self-management, aims to address the physical, social, and psychological needs of patients in the context of the long-term effects of bleeding and its treatment. Ultimately, the goal is to foster autonomy and improve overall outcomes for individuals living with haemophilia.

haemophilia.[46] The multiprofessional comprehensive care (figure 4) provided by haemophilia treatment centres, along with the availability of home treatments, has greatly reduced mortality from bleeding complications, even before the introduction of prophylactic therapy.[47,48] Similar to other patients managing chronic conditions, patients with haemophilia must navigate a fragmented health-care system and cope with symptoms and their emotional effects. Patients must also understand complex medication regimens, make difficult lifestyle changes, and address health-care demands on their physical, psychological, and social aspects of their life.[49]

## Management principles and treatment options

Haemophilia has several effective therapies that control bleeding and can be categorised based on their mechanism of action (panel). These therapies include factor replacement therapies, which replace the missing clotting factor, non-replacement therapies, which increase thrombin generation through unique mechanisms, and gene therapy, which seeks to restore the endogenous synthesis of the deficient factor. Adjunctive therapies also decrease the risk of bleeding and rebleeding.

On-demand treatment refers to the use of replacement therapy in response to a bleed or immediate threat of a bleed (eg, surgery). Most patients with severe haemophilia and some with moderate or mild haemophilia will have frequent bleeding, which, if not prevented, leads to long-term joint damage. As such, prophylaxis, which is the use of treatments that prevent bleeds, has become the standard of care.[3] Prophylaxis has resulted in a near normal lifespan due to a reduction in fatal bleeding and has also decreased joint damage and morbidity.[33,50,51] Prophylaxis can be achieved with replacement therapy, non-replacement therapies, and gene therapy.

## Replacement therapies and clotting factor concentrates

Replacement therapy has been the mainstay of haemophilia care for more than half a century. Until the 1970s, plasma was the source of FIX, and cryoprecipitate was the primary source of FVIII. Plasma-derived clotting factor concentrates (CFCs) were first developed in the 1970s and are derived from pooled human plasma. By comparison, recombinant CFCs were first developed in the 1990s and are produced using genetically engineered cells and recombinant technology.[52]

### Extended half-life clotting factor concentrate

The half-lives of unmodified FVIII (8–12 h) and FIX (18–24 h) necessitates frequent intravenous administration for effective prophylaxis. Two leading technologies have been used to improve the half-life of FVIII and FIX. In Fc or albumin fusion technology, the recombinant fusion proteins generated with either the Fc region of immunoglobulin or albumin have a longer half-life because they benefit from the endothelial neonatal Fc receptor recycling pathway responsible for the long half-life of immunoglobulins and albumin.[53–56] By contrast with PEGylation, the covalent attachment of inert polyethylene glycol (PEG) polymers to CFCs[57] increases the hydrodynamic volume of the molecule through the adsorption of water, increasing its size by five to ten times, with reduced renal filtration, receptor binding, and clearance.[58,59]

FVIII half-life extension has been achieved with Fc fusion and PEGylation and FIX half-life extension has been achieved with Fc fusion, albumin fusion, and PEGylation.[3] Since the introduction of extended half-life CFCs, unmodified CFCs are now referred to as standard half-life CFCs. Extended half-life FIX products have a median half-life extension three to five times higher than standard half-life CFCs, with substantial heterogeneity regarding the extent of extravascular distribution.[60] PEGylated FIX and albumin fusion FIX have reduced extravascular distribution compared with Fc fusion FIX. The variable extravascular distribution might affect the dose and plasma FIX concentrations required for effective bleed prevention.[60,61]

Extended half-life FVIIIs show a median half-life prolongation 1·5–2 times higher than standard half-life FVIIIs; this restricted prolongation is due to the high-affinity VWF–FVIII interaction that limits the increase in FVIII half-life extension beyond that of VWF's half-life.[62] The development of the fusion rFVIIIFc-VWF-XTEN (efanesoctocog alfa) addresses this shortcoming by covalently linking FVIII to a recombinant D'D3 fragment of VWF, which stabilises FVIII and prevents binding to endogenous VWF, uncoupling it from VWF-mediated clearance.[62] XTENs are hydrophilic sequences of natural amino acids that shield the molecule from proteolytic degradation and reduce renal clearance, with two XTEN peptides increasing the half-life.[62] The net result is a four-fold increase in half-life with normal to near-normal FVIII plasma activity levels (>40 IU/dL until day 4 and approximately 10 IU/dL on day 7) on weekly dosing.[63] Although efanesoctocog alfa is only available in some jurisdictions to date, this is increasing.

### Principles of clotting factor use for surgery and bleeds

The treatment of bleeds and prevention of surgical bleeding requires rapid restoration of thrombin generation by increasing factor concentrations into the normal range (50–150% of normal). Prompt treatment of bleeds expedites the resorption of blood and reduces risks of complications. Rapid treatment of intracranial haemorrhage can be lifesaving, with reduced morbidity.

The pharmacokinetics of clotting factors are crucial in establishing the dose and frequency of factor infusions when treating bleeds.[64,65] The dose of CFCs is based on the desired factor activity levels, namely the peak level and its expected incremental recovery (the rise in factor activity following the administration of a unit of factor per kg of body weight). Trough activity levels—the lowest activity level between infusions—are affected by the frequency of infusion and half-life of the factor. Trough levels influence the risk of rebleeding as the clot undergoes turnover during tissue repair. Recommended factor activity levels for different types of bleeds and surgical procedures are detailed in the latest World Federation of Haemophilia guidelines (appendix p 1) and the aim is to increase activity levels to the lower end of normal for minor bleeds and the upper end of normal for major bleeds and major surgery.[3]

The duration of treatment is dictated by the bleed severity and nature of surgery. For major bleeds (eg, intracranial haemorrhage) or major surgeries (eg, joint replacement), 10–14 days of full factor coverage (defined as regaining close to normal factor activity levels) might be required. For less severe bleeds or minor surgeries (eg, circumcision), 1–3 days of full factor coverage usually suffice. Fewer doses can be used with extended half-life factors, particularly extended half-life FIXs.[3] The effectiveness of rapid factor replacement therapy in the management of spontaneous and traumatic bleeds is enhanced through homecare programmes, in which patients and their families are trained to administer factors at the first symptom of a bleed. Haemophilia treatment centres have historically played a pivotal role in educating patients and families, enabling many, including children older than 3 years, to have treatment at home.[3] However, the insertion of central venous access

***Panel:*** **Therapeutic interventions in haemophilia A and B**

**Factor replacement therapies (clotting factor concentrates)**
- Plasma-derived
- Recombinant, standard half-life factors
- Recombinant, extended half-life factors*

**Non-replacement therapies (non-factor therapies and bypassing agents)†**

*FVIIIa mimetics and inhibitors of physiological anticoagulants*
- Haemophilia A only
  - Emicizumab
  - Mim8/NXT-007

*Inhibitors of physiological anticoagulants*
- Monoclonal antibodies against tissue factor pathway inhibitor
  - Concizumab
  - Marsticimab
- Antithrombin knockdown
  - Fitusiran
- Inhibition of activated protein C
  - Serpin PC
  - SR604
- Inhibition of Protein S

*Bypass agents*
- Activated recombinant factor VII
- Activated prothrombin complex concentrates

**Gene therapies**

*Adeno-associated viral vector*
- Etranacogene dezaparvovec (haemophilia B)
- Valoctocogene roxaparvovec (haemophilia A)
- Fidanacogene elaparvovec (haemophilia B)

*Clinical trials*
- Cellular therapies
- Lentiviral
- Gene editing

**Adjunctive therapies**
- Desmopressin
- Antifibrinolytic agents (Lysine analogues)
  - Tranexamic acid
  - Epsilon aminocaproic acid
- Fibrin glue

*The extension (*vs* standard half-life factors) is approximately 1·5 times higher for extended half-life FVIII (excluding efanesoctocog alfa, which is 4 times higher) and 3–5 times higher for extended half-life FIX. †In this group, as of 2023, only emicizumab has a worldwide licence; the others are in various phases of clinical trials or regulatory approvals.

See Online for appendix

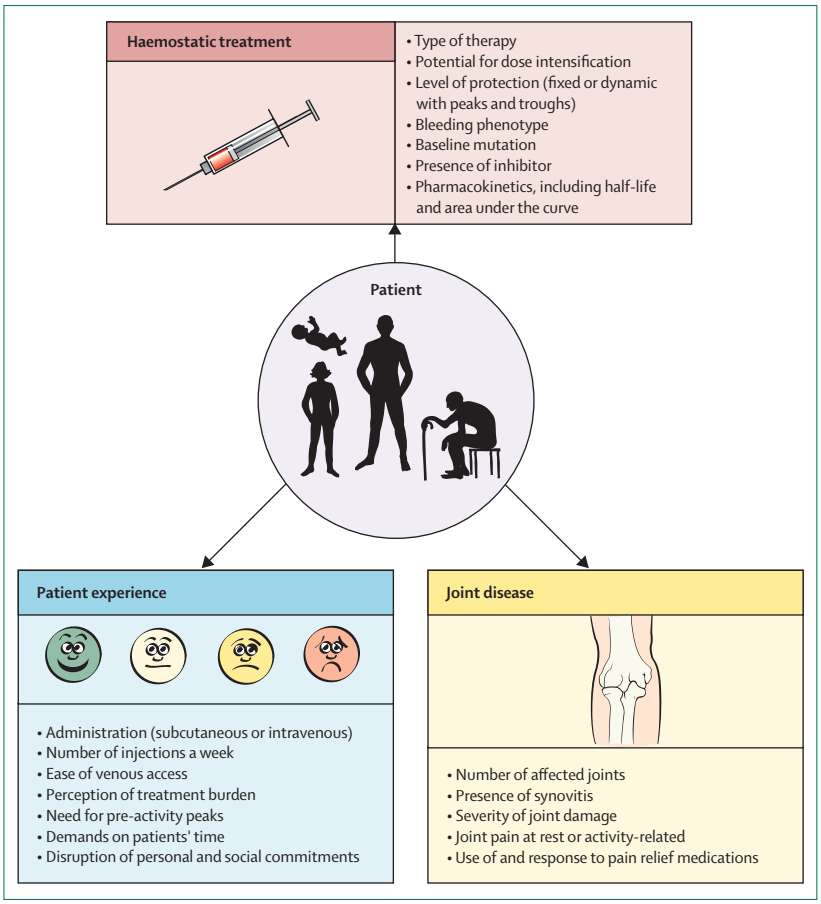


***Figure 5:*** **Personalised prophylaxis**
Personalised prophylaxis has three key elements: the haemostatic treatment regimen, patient experience and quality of life, and the presence of joint disease. In clinical practice, these elements entail tailoring the treatment regimen to accommodate individual genetic, physiological, and social factors; unique responses to therapy; and disease-related or treatment-related complications, such as joint disease or the development of inhibitors. Patient preferences, aspirations, and quality of life are also integral to this approach. However, because joint disease is primarily irreversible and typically less amenable to changes in haemostatic treatment, such as pain relief medications and surgical interventions, it often necessitates additional or alternative interventions.[61,71,72]

devices in the chest might be necessary for many children with poor venous access to administer therapies.

## Optimisation of prophylaxis with CFCs

Although the benefits of prophylaxis were well documented in the 1990s and early 2000s, prophylaxis had variable uptake globally, with a rapid increase following the demonstration of its benefits in children in a randomised controlled study.[31] Prophylaxis that is implemented early is now accepted as the standard of care across all age groups in patients with severe haemophilia and patients with moderate or mild haemophilia with a severe phenotype.[3] The reduction in mortality and joint damage has become evident from longitudinal studies.[66]

Several post hoc analyses and clinical trials have shown a correlation between the number of bleeds in a year and the time spent at low factor activity levels (ie, trough activity levels, especially activity less than 1% of normal).[67–69] World Federation of Haemophilia guidelines recommend intensification of the CFC prophylaxis regimen targeting trough activity levels of around 3–5%.[3] This intensification requires a higher dose, frequency, or both, and optimisation is facilitated by dosing applications that determine dose and frequency based on the patient's calculated half-life, pharmacokinetic profile, and desired trough activity levels.[3,64,70] Although the principles are broadly applicable to FIX, the factors that contribute to bleeding in haemophilia B are less clear. The clearance of FVIII and FIX is faster in children; consequently, children might require more frequent prophylactic infusions.[64]

Over the past few decades, an improved understanding of factors that predispose to joint bleeds has established the concept of personalised prophylaxis.[61,71] Personalised prophylaxis customises treatment to an individual's likelihood of bleeding, optimising protection while minimising costs and effort (figure 5).[72,73] Delayed and missed doses often contribute to increased bleeds, which are often due to difficult venous access in young and older patients, and non-adherence in young adults. Decreasing the frequency of infusions by switching to extended half-life CFCs to lessen treatment burden enhances adherence and therefore patient outcomes.[74]

## Adjunctive treatments

Effective management of joint bleeds extends beyond haemostatic support and includes specific measures, such as joint rest, ice application, compression, and elevation (the RICE protocol), along with analgesia followed by graduated physiotherapy in the recovery phase.[32] In specific cases, joint aspiration for large haemarthroses can be beneficial. Antifibrinolytic agents, tranexamic acid, and ε-aminocaproic acid, given orally or intravenously, are crucial for managing bleeds at mucosal sites characterised by high fibrinolytic activity, such as the oropharynx, nose, gastrointestinal tract, and uterus.[3] However, their use is contraindicated in cases of upper urinary tract bleeding as it can result in clot obstruction.[3]

Desmopressin is a synthetic vasopressin analogue that stimulates the release of endogenous VWF and FVIII from Weibel–Palade bodies in vascular endothelial cells, enhances platelet adhesiveness, and has antidiuretic and vasodilatory effects.[75] In most mild and some moderate cases of haemophilia A, desmopressin can be sufficient to raise the activity levels of FVIII to stop or prevent bleeding. Desmopressin can be administered intravenously over 30 min, subcutaneously, or intranasally, with no difference in half-life or peak effect seen between the intravenous and subcutaneous route. However, the intranasal route is less effective.[76] Peak response is seen between 60 min and 90 min after the start of infusion.[77] A therapeutic trial is recommended for evaluating treatment response, with factor activity levels measured pre-dose and at 1 h, 2 h, and 4–6 h post-administration. The most important side-effect is related to fluid retention due to its

antidiuretic effect, which can cause hyponatraemia and seizures, particularly in young children (<3 years) or those with excessive fluid intake. Effectiveness diminishes with repeated use due to depletion of endogenous VWF or FVIII reserves (tachyphylaxis). Fluid restriction to less than 1·5 L per day is essential. Generally, it is not used more than once per day for up to 3 days; fluid restriction and monitoring sodium concentrations are essential, particularly when more than one dose is administered.[76] Caution is advised in patients with risk factors for coronary or cerebral artery thrombosis or uncontrolled hypertension.

## Complications of therapy: transfusion-transmitted infection

Two substantial complications of factor replacement are the historical issues of infection with blood-borne viruses through contaminated blood and blood products and the development of antibodies to FVIII and FIX. During the early 1980s, a large proportion of people with severe haemophilia (60–70%) contracted HIV, with larger numbers having contracted hepatitis C virus due to exposure to contaminated plasma-derived products.[78] Many either succumbed to these diseases or continue to live with associated health burdens.[79] For the past 30 or more years, the application of viral inactivation processes for plasma-derived CFCs has enhanced their safety.[3] Apprehension regarding the potential transmission of new or unidentified pathogens, such as prions causing Creutzfeldt–Jakob disease through blood and its derivatives, steered the medical community towards predominantly using recombinant CFC to eliminate this risk.[80]

## Complications of therapy: inhibitors

Inhibitors are alloantibodies that neutralise the administered FVIII or FIX factors secondary to the immune system, recognising them as non-self antigens. Inhibitors develop in approximately 20–35% of individuals with severe haemophilia A and around 10% of those with severe haemophilia B.[81,82] Typically emerging within the first 10–20 exposure days, inhibitors are more common in young children with severe haemophilia.[3] However, they may also arise in older patients who did not have early access to CFCs or in those with moderate or mild haemophilia who only reach the threshold number of exposure days later in life.

The development of inhibitors complicates bleed management and renders FVIII or FIX replacement therapies ineffective, with increased bleeding leading to increased mortality (up to 70% higher odds of death), severe disability, and reduced health-related quality of life.[83–85] A unique feature of inhibitors to FIX is the occasional presentation with anaphylactic reactions with or without nephrotic syndrome.[3] Inhibitor development is multifactorial and influenced by both genetic and acquired factors. Genetic risk factors include family history, Black or Hispanic ethnicity, specific mutations in the *F8* gene, and polymorphisms in immune regulatory genes.[82,85] Acquired risk factors include the intensity of exposure to factor replacement and the context of such exposure, particularly in the presence of concomitant danger signals—such as another infection—to the immune system.[86] Furthermore, a lower inhibitor incidence was shown in patients treated with VWF-containing plasma-derived FVIII compared with those receiving recombinant FVIII in the randomised SIPPET study.[81] Other studies refute this finding, and the SIPPET trial did not include the new recombinant standard half-life and extended half-life FVIII products.[87,88]

Inhibitors are measured using the Nijmegen–Bethesda assay, which shows the inhibitory capacity of the patient's plasma to neutralise the clotting factor in normal plasma and is expressed quantitatively in Bethesda units (BU). An inhibitor is first considered to be present (≥0·6–0·7 BU) and is then categorised as high-tire (≥5·0 BU) or low-titre (<5 BU).[81] Bleed management in the presence of inhibitors includes the use of bypassing agents, but some bleeds in patients with low-titre inhibitors can be managed with increased doses of FVIII or FIX. Bypassing agents, including activated prothrombin complex concentrate (APCC) and recombinant activated FVII (rFVIIa eptacog alfa and eptacog-beta), generate thrombin independently of FIX or FVIII, with all showing similar efficacy in the management of joint bleeds.[89,90] For patients with haemophilia A and inhibitors (not on emicizumab), either APCC or rFVIIa can be used for bleed treatment. In patients with haemophilia B and inhibitors, rFVIIa is recommended over APCC, as the latter contains FIX and can exacerbate allergic reactions.[3] Although bypassing agents have been used prophylactically, the effectiveness is less than that of FVIII or FIX replacement therapy in patients without inhibitors and much lower than that seen with emicizumab in patients with inhibitors.[81]

### *Inhibitor eradication*

Inhibitors can be eradicated with immune tolerance induction, which involves frequent (usually daily) injections of FVIII or FIX over months to years.[84,91,92] This approach eradicates inhibitors in about 50–70% of patients with high-titre inhibitors to FVIII, although it is less successful for inhibitors to FIX.[91] Consequently, immune tolerance induction has been attempted in most patients with haemophilia A and inhibitors; its use in patients with haemophilia B with inhibitors is less prevalent and immunosuppressive agents are often added to increase immune tolerance induction success.[84] Although immune tolerance induction dates back to the 1970s, the most effective regimen is still under investigation.[92] Furthermore, the role of immune tolerance reduction is actively debated, with many not considering it obligatory as the introduction of non-replacement therapies has resulted in more effective prophylaxis for patients with haemophilia A both with and without inhibitors in the past decade.

## Non-replacement and non-factor therapies

The advent of non-replacement non-factor therapies in the past decade has resulted in a shift in haemophilia treatment. Non-replacement therapies increase thrombin generation through various mechanisms; some mimic the cofactor function of activated FVIII and others inhibit physiological anticoagulants or facilitate thrombin generation (figure 1) via alternative pathways. Non-replacement therapies include bypass agents used for bleed management and non-factor therapies, which are solely used for prophylaxis, with the latter categorised by the mechanism of action.

### Bispecific antibodies as FVIIIa mimetics

Emicizumab is a humanised bispecific monoclonal antibody that mimics the cofactor function of FVIIIa to act as a bridge between FIXa and FX, with subsequent activation of FX by FIXa.[93] This unique mechanism is not affected by the presence of inhibitors and the FIXa–FX complex preferentially binds FVIII over emicizumab when both are present.[93] As an IgG antibody, emicizumab can be administered subcutaneously with a long half-life of approximately 29 days, enabling fewer injections over the treatment course compared with replacement therapy with clotting factors.[94–98] Clinical trials and real-world data have shown the effectiveness of emicizumab in bleed prevention in children and adults of all ages when administered every 1–4 weeks, regardless of inhibitors, with more than two-thirds of patients having no bleeds in a year.[95–103] Pre-clinical data indicate that patients on emicizumab have protection equivalent to baseline FVIII activity within the range of 10–20 IU/dL.[104,105]

Bleeds in patients on emicizumab require additional intravenous haemostatic therapies (FVIII or bypassing agents, depending on inhibitor status). Concurrent administration of FVIII concentrate is safe, but FVIII monitoring is challenging as emicizumab interferes with standard clot-based (one stage) and some chromogenic assays.[106] Alternative assays (eg, bovine chromogenic assays) are increasingly available.[106] For patients with inhibitors on emicizumab, APCC is not recommended due to reported cases of thrombosis and thrombotic microangiopathy.[95] Thrombosis and thrombotic microangiopathy has been noted when APCC was given for more than 24 h at doses greater than 100 IU/kg. These events were due to the accumulation of FIXa and FX, the substrates for emicizumab, contributing to drug–drug interaction.[95] In the presence of emicizumab, coagulation is regulated by the low levels of circulating FIXa and inhibition of the prothrombinase complex.[107] Thrombosis and thrombotic microangiopathy were not seen with rFVIIa and it is considered safe.[108] Emicizumab alone has an extremely low rate of thrombotic complications. However, there have been a few cases of thrombosis in patients treated solely with emicizumab in the presence of other risk factors.[109]

Patients on emicizumab can also undergo minor surgeries, such as the removal of central venous access devices, without the need for additional haemostatic coverage. However, many clinicians still elect to administer an extra dose of replacement FVIII or a bypassing agent as a precautionary measure.[110] Minor limitations include injection site reactions, characterised by localised pain and swelling (more pronounced with higher volumes), and a very low rate (<1%) of neutralising anti-drug antibodies.[96] Overall, emicizumab is less burdensome than replacement FVIII prophylaxis and much more effective than bypassing agent prophylaxis for people with haemophilia with inhibitors.[99] In countries where emcizumab is available, approximately between half and two thirds of patients prefer it over other options. It is also the preferred option in young children, even in the absence of inhibitors.[111] Low-dose (25–75% reduction in dose) emicizumab prophylaxis appears to be efficacious at reducing bleeds.[111–114] Other FVIII mimetics (Mim8; NXT-007) are undergoing clinical investigation and appear similarly effective at lower drug concentrations than emicizumab.[115–117]

## Inhibitors of physiological anticoagulants

The observation that a minority of patients with severe factor deficiencies have a non-severe phenotype, potentially explained by inherited deficiencies of natural anticoagulants, has led to the investigation of the clinical effect of improved thrombin generation through the inhibition of physiological anticoagulants.[22,23,118] The principal anticoagulants include antithrombin, a serine protease inhibitor that inhibits predominantly thrombin and FXa; tissue factor pathway inhibitor (TFPI), the dominant inhibitor of the initiation pathway; protein C, which inhibits cofactors FVa and FVIIIa; and protein S, a cofactor for protein C.

### Antithrombin knockdown

Fitusiran is a small interfering RNA designed to reduce hepatic antithrombin production through the degradation of its mRNA.[119] Phase 1 studies showed a correlation between peak thrombin concentrations and decreased antithrombin activity, with peak thrombin at the lower end of the normal range when antithrombin activity was decreased by greater than or equal to 75%.[120] Pivotal phase 3 clinical trials involving patients with and without inhibitors showed a significant reduction in annualised bleed rates with monthly subcutaneous administration of fitusiran.[121,122]

However, the use of fitusiran has been complicated by elevated liver enzymes, unexplained cholecystitis, and thrombosis, related to the drug and its effects. Five patients were reported to have thrombosis in the clinical trials; two had antithrombin concentrations between 10% and 20% of normal but received other haemostatic therapies, and the other three patients had antithrombin concentrations less than 10% without concurrent

haemostatic treatment.[123] To mitigate the risk of thrombosis, it is now recommended to use very low doses of FVIII, FIX, or bypassing agents (when additional haemostatic protection is needed) and to adjust fitusiran doses to target antithrombin concentrations of 15–35% of normal.[123] Moreover, lower fitusiran dosing is thought to reduce liver toxicity.[123]

### Monoclonal antibodies against TFPI

TFPI suppresses the initiation pathway of coagulation by inhibiting tissue factor–FVIIa complexes and FXa.[10] Consequently, inhibiting TFPI can enhance thrombin generation. Although four molecules targeting TFPI have been developed, only two (monoclonal antibodies concizumab and marstacimab) have progressed to phase 3 trials, with both targeting the Kunitz (K)2 domain of TFPI.[124–126] The development of befovacimab, the third monoclonal antibody against K1 and K2 domains, was halted due to the occurrence of thrombotic events without concomitant CFCs or bypassing agents.[127] Similarly, concizumab phase 3 studies had to be paused due to thrombotic events in the context of concomitant haemostatic therapy.[124,128] These events led to a new dosing regimen and a strategy that suggested the use of CFCs and bypassing agents at the lowest recommended dose for bleed management.[124,125] Concizumab clinical trials in patients with and without inhibitorss showed clinical efficacy, but did not show superiority to previous CFC prophylaxis.[124,125] Marstacimab showed efficacy in patients without inhibitors and superiority over previous CFC prophylaxis, but the pre-study annualised bleed rates were high and subgroup analysis is awaited.[126]

### Activated protein C and protein S inhibition

Preclinical and in vitro studies have shown that inhibition of activated protein C restores clot formation and decreases bleeding.[129] Serpin protein C is an engineered serine protease inhibitor engineered from α1-anti-trypsin with three substitution mutations to confer selective inhibition of activated protein C.[129] Early clinical trials have shown promising clinical effects.[130] Monoclonal antibodies against protein S are also in clinical development.[131]

## Non-factor therapies versus replacement therapy

Non-factor therapies offer several advantages over traditional CFCs, as they are effective even in the presence of inhibitors, and some can be used for both haemophilia A and haemophilia B.[132] These therapies reduce treatment burden with increased convenience of subcutaneous administration, and the long half-lives allow infrequent dosing.[111,132] In addition, non-factor therapies provide consistent haemostatic protection without the peaks and troughs of replacement therapy, and their flexible administration timing is less disruptive to patients' daily lives than the typically morning-administered clotting factor replacement therapies.

However, there are limitations to non-factor therapies. For example, we believe they exhibit a ceiling effect, in which higher doses offer no additional benefit and potentially increase the risk of thrombotic complications. In addition, they cannot boost haemostatic potential in response to haemostatic insults, which poses a low but present risk of bleeding in individuals participating in high-impact sports or activities.[101–103,132] Most non-factor therapies are unsuitable for treating active bleeding episodes or surgical procedures that require additional CFCs or bypassing agents, which can lead to undesirable interactions, including thrombosis, as described above.[95] The absence of long-term outcome studies raises questions about their long-term efficacy. Furthermore, there are considerable regional differences in access.

## Gene therapy

Eligibility to gene therapy is restricted to adults with severe haemophilia. Gene therapy encompasses a range of strategies designed to provide endogenous, potentially perpetual clotting factor production. Interventions include the provision of functioning genes, editing of dysfunctional genes, or cellular therapies. Gene therapy offers the potential to achieve a steady-state measurable factor activity levels with the potential for preventing all or most bleeds following a single treatment intervention. After more than three decades of research, the platform to date with the best risk:benefit ratio is in vivo gene addition by an adeno-associated viral (AAV) vector-based liver-directed approach, despite some previous failures.[133–137] A functional copy of the *F8* or *F9* gene is packaged inside AAV vectors that are devoid of propagative viral gene elements, but have the genetic elements necessary for efficient expression and secretion of FVIII or FIX protein into the plasma (appendix p 2). Administration is through a single outpatient intravenous infusion that lasts between 1 h and 3 h. There are several challenges to achieving effective outcomes, including the presence of neutralising antibodies to AAV in 25–40% of patients secondary to previous exposure to wild type AAVs that might impede liver uptake.[134] The primary adverse event is elevation in liver transaminases secondary to an immune response to gene therapy. This immune response is occasionally linked to partial or complete loss of transgene expression.[133] The exact pathophysiological mechanism behind these transaminase elevations remains elusive. Hypotheses include capsid-specific cytotoxic T-cell responses against vector-transduced cells, intrinsic hepatocyte dysfunction, or innate immune responses.[134] Clinically, this response has been managed with steroids, with the treatment duration ranging from 3 weeks to 18 months, depending on the gene therapy.[133]

Etranacogene dezaparvovec, an AAV5-based liver-directed gene therapy that incorporates the highly active Padua FIX transgene, has been approved for adults with severe to moderately severe haemophilia B. In the phase 3 study involving 54 participants, more than 90% had near-normal FIX activity after 2 years, significantly

reducing bleeding episodes.[138] Outcomes were consistent, even in participants with pre-existing neutralising antibodies, except for one individual with exceptionally high antibody concentrations with no response to treatment. Only nine participants had transaminase elevation, which was effectively managed with oral corticosteroids and stable FIX expression was seen within 6 months post-treatment.[138]

Valoctocogene roxaparvovec, also an AAV5 vector carrying a B domain-deleted FVIII transgene, is approved for adults with severe haemophilia A. In a phase 3 trial involving 134 participants who were negative for AAV5 neutralising antibodies, 88% had FVIII activity levels in the mild to normal range 1 year post-treatment, with a significant reduction of bleeding episodes.[139] Although 88% of participants required immunosuppression for transaminase elevation, most were successfully weaned off corticosteroids within 1 year. An observation seen with FVIII gene therapy trial is the decline in FVIII activity with time.[140,141] Long-term data and modelling suggest continued expression in the mild haemophilia range for at least 5 years after treatment.[140] Despite challenges, studies indicate that a single infusion of liver-directed AAV-based gene therapy is generally effective, with manageable immune responses.[139–141] This therapy, which delivers *F8* or *F9* cDNA with liver-specific promoter elements, can achieve protein expression levels for years, allowing for the cessation of prophylaxis and reduced bleeding compared with conventional treatments, with improved quality of life.[142] However, there are limitations, including the variability and long-term stability of factor concentrations, particularly for FVIII expression.[143,144] Additionally, there is an unresolved question regarding the potential genotoxicity risks associated with the low percentage of chromosomal integration events of the delivered genetic material.[145] It is also not indicated in children or patients with inhibitors. To address these issues and enhance our understanding of the safety and efficacy of this therapeutic approach, ongoing data collection from both national and global registries of gene therapy recipients is imperative.[146] As we progress, newer cellular-based therapies are being trialled, including stem cell transplants with ex vivo manipulated stem cells, CRISPR-Cas9-based editing of the *F9* gene (NCT06379789), and endogenous production of clotting factors through other novel techniques, although most are pre-clinical at the time of writing of this Seminar.

## Challenges and future directions

Despite substantial improvements, treatments to date for haemophilia have limitations. From a clinical perspective, there is increasing appreciation of rationalised non-adherence, in which a patient makes an active decision not to follow instructions provided by health-care professionals due to constraints of time and resources.[61,147,148] Non-factor therapies have addressed the treatment burden with improved disease control, but still require occasional use of replacement therapy for bleeding episodes. This shift means that children and their parents might not develop the skills to manage bleeds, leading to a wait-and-watch approach rather than the previous strategy of if in doubt, treat. This shift has unknown effects on disease outcomes.

Future innovations aim to minimise patient burden and normalise haemostasis. Criteria for switching between treatments need discussion, as a third of patients in clinical trials continue to have bleeds. It is also essential to appreciate that correcting haemostatic tendencies does not reverse existing joint damage, a substantial unmet need. New therapies raise questions about the long-term outcomes with modified FVIII and FIX molecules, the effects of non-replacement therapies on joint health in active patients, and the role of gene therapy in children younger than 12 years. There are also concerns about interactions with comorbidities and the potential loss of protection against thrombosis.

Additionally, cost-effectiveness assessments are crucial, especially given global variations in access. Local pathways should address patient needs, particularly in low-income and middle-income countries where the high cost of therapies limits their use. The influx of new treatment options challenges patients and clinicians in selecting appropriate therapies and adequate consideration of individual goals and needs is essential. Additionally, the role of haemophilia treatment centres is likely to shift from teaching self-administration of factors to monitoring non-factor therapies and integrating gene therapy into care protocols.

## Conclusion

Haemophilia A and B are the most prevalent severe bleeding disorders and their management has transformed over the past 15 years, driven by breakthroughs in biotechnology and a deeper understanding of coagulation mechanisms. The introduction of new therapies has not only reduced mortality rates, but also substantially decreased morbidity and the overall treatment burden. These advancements place greater responsibility on clinicians and patient organisations to provide comprehensive education, ensuring patients are well informed and actively involved in making health-care decisions. There is also an increasing role for advocacy to ensure that access is not restricted to a few patients.

**Contributors**

All authors contributed equally to the manuscript, participating in the drafting, reviewing of various versions, and approving the final version. SWP completed the second draft. PC did a PubMed literature review. Subsequent drafts were reviewed and edited by all co-authors before final submission. During the preparation of this work, the authors used ChatGPT (version 4.0) to harmonise the English writing style. The authors have reviewed and edited the final version and take full responsibility for the content of the publication.

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