haematologica
Journal of the Ferrata Storti Foundation

# Hemophilia A and von Willebrand disease: parallel therapeutic advances in the most common inherited bleeding disorders

*by Omid Seidizadeh, Flora Peyvandi and Pier Mannuccio Mannucci*

*Received: May 29, 2026.*
*Accepted: July 13, 2026.*

*Citation: Omid Seidizadeh, Flora Peyvandi and Pier Mannuccio Mannucci. Hemophilia A and von Willebrand disease: parallel therapeutic advances in the most common inherited bleeding disorders. Haematologica. 2026 July 23. doi: 10.3324/haematol.2026.301336 [Epub ahead of print]*

# Hemophilia A and von Willebrand disease: parallel therapeutic advances in the most common inherited bleeding disorders

Omid Seidizadeh[1], Flora Peyvandi[1, 2] Pier Mannuccio Mannucci[1]

1. Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy
2. Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy

**Correspondence**
Pier Mannuccio Mannucci
Via Pace 9
Email piermannuccio.mannucci@policlinico.mi.it

**Type:** Perspective Review article

**Short Title:** Therapeutic Advances in HA and VWD

## Conflict of interest

OS: has no conflict of interest to declare.
FP: participation in scientific advisory committees for Sanofi, Sobi, Roche, CSL Behring, Novo Nordisk, Biomarin, Regeneron, Metagenomi, Star-Therapeutics, Bayer, Pfizer, Takeda, and TargED; participation in symposia and educational events for Sanofi, Sobi, Biomarin, Kedrion, and Bayer. PMM: speaker fees from Kedrion, Roche and Octapharma.

## Authorship contribution

All authors equally contributed to writing the manuscript. All authors approved the final manuscript.

## Acknowledgements

The Hemostasis & Thrombosis Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is a member of the European Reference Network on Rare Haematological Diseases (ERN-EuroBloodNet, Project ID No. 101157011). ERN-EuroBloodNet is partly co-funded by the European Union under the Fourth EU Health Programme. The Department of Pathophysiology and Transplantation, University of Milan, is funded by the Italian Ministry of University and Research (MUR) through the Dipartimenti di Eccellenza Program 2023–2027. We acknowledge that this work was partially supported by the Italian Ministry of Health – Bando Ricerca Corrente. Figure 1 was created using BioRender (BioRender.com). Figure 2 was generated with assistance from Google NotebookLM. All figure content was reviewed and verified by the authors.

## Abstract

von Willebrand disease (VWD) and hemophilia A (HA) are the most common inherited bleeding disorders, caused by quantitative or qualitative defects of von Willebrand factor (VWF) and coagulation factor VIII (FVIII). Over the past decades, both diseases have undergone a profound therapeutic transformation, evolving from supportive care to highly effective replacement, pharmacological, and prophylactic strategies. This perspective article compares the parallel but distinct trajectories of therapeutic developments in HA and VWD, highlighting shared milestones and disease-specific limitations. In HA, advances in recombinant technology, extended half-life factor concentrates, nonfactor therapies such as FVIII mimetics and emerging gene therapy approaches have established prophylaxis as the standard of care. VWD therapy has evolved more slowly, largely owing to the marked clinical and molecular heterogeneity of this disease, that often causes difficult and delayed diagnosis. Current management is based on desmopressin, plasma-derived products, and recombinant VWF, with limited prophylaxis implementation. Nevertheless, a rapidly expanding pipeline of novel therapies -- including VWF half-life extension strategies, VWF-independent coagulation rebalancing agents, antifibrinolytics, platelet-mimetic technologies, and gene-based approaches -- suggests an imminent shift in VWD management. Collectively, these developments indicate a transition toward more individualized and mechanism-driven therapy, with the potential to fill the therapeutic gap between VWD and HA and improve long-term outcomes and quality of life in patients with these inherited bleeding disorders.

**Keywords:** von Willebrand disease; hemophilia A; prophylaxis; VWD; treatment

## Introduction

von Willebrand disease (VWD) and hemophilia A (HA) are the most common inherited bleeding diseases, with prevalences in the general population of 1 in 1000 for symptomatic cases of VWD and 1 in 10.000 for HA (all degrees of severity).[1,2] VWD is caused by the deficiency or dysfunction of von Willebrand factor (VWF), a large platelet-adhesive glycoprotein essential for primary hemostasis and encoded by a gene on chromosome 12, whereas HA results from X-linked deficiency of coagulation factor VIII (FVIII). [3,4] In the majority of VWD cases FVIII is also deficient, because VWF is the essential endogenous stabilizer of FVIII in plasma.[5] Whilst HA is the epitome of coagulation defects mainly characterized by soft tissue hemorrhages (in joints, muscles, at surgery and after trauma),[2,6] in VWD mucosal tract bleeding owing to the primary hemostasis defect (epistaxis, gastrointestinal bleeding, heavy menstrual bleeding) may be accompanied by soft tissue bleeding (hemarthrosis, post-operative and postpartum bleeding) proportional to the plasma levels of FVIII.[7-9]

The therapy of both rare diseases has witnessed dramatic progress particularly in the last 10-15 years, driven by increased mechanistic knowledge and advances in molecular biology and biotechnology, that prompted evolution from deficient factor replacement with blood derivatives to medications manufactured by recombinant DNA technology, as well as nonfactor products based upon monoclonal antibodies and more recently gene and nucleic acid-based therapies.[10-13] However, differences in diagnostic pathways and healthcare delivery may have contributed to divergent trajectories in disease recognition and management, with VWD more frequently under-recognized or managed outside specialised haemophilia treatment centres compared with HA, particularly for milder phenotypes.[1,2]

This perspective article is focused for general hematologists on the parallel therapeutic advances that materialized first for HA and more recently for VWD. The related trajectory promises a much

more efficacious and feasible secondary prevention of both diseases and their clinical phenotypes, as well as expanded options for personalized medicine.

## Evolution of FVIII- and VWF-directed therapeutics: from replacement to modulation

Figure 1 depicts the timeline of available therapeutics for both HA and VWD and highlights the evolution from such therapies as desmopressin, plasma-derived and recombinant replacement products to nonfactor medications towards gene and nucleic acid-based approaches. Several therapeutic agents originally developed for HA later prompted VWD management because of the physiological interdependence of FVIII and VWF.

**Early replacement therapies: cryoprecipitate and plasma-derived concentrates**

An efficacious therapy for both HA and VWD first materialized in the 1960s with the availability of cryoprecipitate, a blood product that contains both FVIII and VWF. Its discovery by Judith Graham Pool represented a landmark advance that transformed both HA and VWD from conditions managed primarily with supportive care into treatable diseases.[14] Practical limitations for its production by blood banks and storage issues led to the commercial manufacturing of lyophilized plasma-derived concentrates containing both FVIII and VWF in varying relative proportions. Originally produced for HA, they were subsequently employed and licensed also for VWD, first with a product characterized by a high relative proportion of VWF to FVIII activities and then with others with more balanced proportions of the two related moieties.[10,15-17] In VWD, this type of replacement therapy was planned to restore both FVIII levels and the primary hemostasis functions of VWF. The clinical use of these products purified from large plasma pools was jeopardized in the 1980s by the transmission of bloodborne viral infections as hepatitis and HIV, subsequently tackled with the adoption in the

manufacturing process of such virucidal procedures as heating, filtration and solvent detergent,[18,19] that markedly improved product safety.

**Desmopressin: the first pharmacological therapy for inherited bleeding disorders**

The shadow of bloodborne infections but also the relatively limited availability and costs of these products prompted in the 1970s the search of pharmacological treatments for both HA and VWD that led to the development of desmopressin, a vasopressin derivative listed by WHO among essential drugs.[20] It is efficacious in mild HA, in the most frequent VWD type 1 plus in selected cases of type 2 by transiently raising the plasma levels of FVIII and VWF through the release of these endogenous moieties from vascular endothelial cells.[21] Notably, desmopressin was the first therapy for inherited bleeding disorders that could be administered by the subcutaneous and intranasal routes, at variance with the venous access needed for plasma-derived products. Overall, it is estimated that this medication has the potential to manage globally more than 220,000 bleeding episodes annually, underscoring its substantial clinical value plus cost-effectiveness.[22]

**Recombinant technologies and the emergence of prophylaxis**

In the 1980s cloning of genes encoding VWF and FVIII led to novel use of recombinant DNA technology for manufacturing FVIII and VWF.[23] Recombinant products also avoided the risk of pathogen transmission associated with plasma-derived therapies. In the 1990s the safety and successful clinical adoption of recombinant of FVIII fostered, at least in higher-income countries, the more widespread implementation of prophylaxis regimens as the preferred management of HA that, pioneered in Sweden, became state-of-the art in the decade.[23-25] The transition from episodic treatment to preventive care transformed HA from a disabling disease characterized by recurrent hemarthroses and related arthropathy into a condition compatible at least in high income settings with near-normal quality of life and life expectancy.[26]

It took a few more years to produce by recombinant technology such as huge and complex protein as VWF and it is a monument of ingenuity that a commercial product was first employed in 2013 in patients with the most severe form of VWD (type 3) and subsequently in other types, providing the first plasma-free replacement option.[27] The advantages of recombinant VWF are a plasma half-life longer than that of plasma-derived products and an intact multimeric pattern, although the product is more expensive for prophylaxis and is not reimbursed in several countries.[28]

**Extended half-life factor concentrates**

Notwithstanding that prophylaxis became the paradigm of management of HA since the 1990s, its implementation was hampered by the need of frequent intravenous injections owing to the short plasma half-life of FVIII. These challenges highlighted the unmet need to improve patients' treatment adherence and quality of life by reducing the infusion frequency burden. A first step was the production of a new class of antihemophilic drugs endowed with a more extended plasma half-life by means of the recombinant fusion of coagulation factors with such proteins as albumin and IgG Fc or their conjugation with a chemical such as polyethylene glycol.[10,29,30] First-generation extended half-life FVIII products prolonged the half-life by roughly 1.3–1.5-fold compared with standard products, allowing to reduce prophylaxis frequency from three times weekly to twice weekly, or from every other day to every 3 days, depending on individual pharmacokinetics.[31-34] More recently, further progress in biotechnology allowed the manufacturing of a product with such a more extended plasma half-life that can be administered once weekly by overcoming the VWF-imposed FVIII half-life ceiling.[35,36]

**The nonfactor revolution**

In the frame of this evolving scenario, a spectacular milestone was the development and clinical use for prophylaxis of HA of the first nonfactor replacement medication, namely emicizumab. This

bispecific monoclonal antibody, when administered subcutaneous, mimics in plasma activated FVIII by putting together in optimal configuration the enzymatic activities of factors IXa and Xa.[37,38] This truly innovative drug, licensed on the basis of the largest clinical number of patients ever used for the clinical approval of a hemostatic drug, is efficacious in HA patients of all ages with and without coagulation FVIII inhibitors and is currently being used at various dosages globally in approximately 40.0000 cases with all degrees of severity.[37-42] Its use has been associated with profound reductions in annualized bleeding rates and a major improvement in quality of life owing to the shift to subcutaneous and infrequent administrations. Nevertheless, breakthrough bleeding still occurs, and factor replacement remains necessary in clinical settings such as major surgery or trauma.[43] The strategy of activated FVIII mimicking is being more recently pursued by means of at least two other products, such as Mim8 and NXT007, which differ from emicizumab for being more favorable in terms of FVIIIa mimicking potency as well as for a longer plasma half-life that allows much more spaced subcutaneous injections.[44-47]

**Rebalancing therapies targeting natural anticoagulants**

Emicizumab as the first nonfactor replacement agent for HA paved the way to other compounds acting through distinct mechanisms of action. Defective thrombin generation is rebalanced in HA (but at a variance with emicizumab, also in hemophilia B) by products that quench the naturally occurring anticoagulant activity of antithrombin and tissue factor pathway inhibitor (TFPI).[48,49] This goal is attained through different mechanisms: fitusiran is based on RNA liver silencing of antithrombin,[48,49] whereas concizumab[50] and marstacimab[51] are monoclonal antibodies that inhibit TFPI activity in plasma. These compounds -- that can be administered subcutaneously at intervals ranging from daily (concizumab) to weekly (marstacimab) and up to every two months (fitusiran) -- offer an ample choice for personalized therapy in both the hemophilias.[48-51] At variance with

emicizumab, their approval was obtained recently, so that real world experience is still limited. This snag is particularly relevant pertaining to the potential risk of thrombosis related to thrombin rebalancing and its uncontrolled production.

**Gene therapy and future curative strategies**

Following the outstanding success of emicizumab and other nonfactor products, the second decade of this century witnessed the advent of gene therapy, endowed with the potential to address the management of HA toward cure. Valoctocogene roxaparvovec was developed by a Californian company. Notwithstanding some limitations relative to the varied and unpredictable expression of the transgene, progressive diminution of the FVIII plasma levels and the issue of hepatotoxicity, the results of clinical trials of this first attempt of gene therapy in adults with severe HA showed substantial clinical benefits epitomized by the elimination or marked reduction of the need of prophylaxis with factor or nonfactor therapeutics.[52,53] More recently, the manufacturer has taken the unexpected decision to discontinue commercialization, in spite of the fact that more than 50 patients have bene treated in real world situations in the USA, Germany and Italy. Gene editing technologies such as CRISPR/Cas9 are still in their infancy in HA, perhaps for the predominance in severe disease of a null gene variant such as the intron 22 inversion that is a formidable challenge for editing.[54-56] Nevertheless, preclinical studies are ongoing with attempts of editing platelets, hepatocytes and hemopoietic stem cells.[57-58] The myth of oral therapy for HA unsuccessfully pursued for many years is becoming promising with the current phase 1 evaluation of a FVIIIa mimicking antibody engineered to make it orally absorbable and circulation available.[59]

Despite their promise, emerging technologies raise important safety considerations. Rebalancing therapies may increase the thrombotic risk due to excessive thrombin generation, whereas gene therapy approaches are associated with concerns regarding hepatotoxicity, variability and durability

of FVIII expression, and long-term safety. Similar considerations will need careful evaluation as comparable technologies enter clinical development for VWD.

## Translating therapeutic advances to von Willebrand disease

With this background of an almost miraculous progress in HA, what is the corresponding scenario for VWD, the most frequent inherited bleeding disorder? Which are the novelties after the formidable development and availability of recombinant VWF? Notably, the VWF structural complexity, endothelial storage, shear dependence, and VWD phenotypic heterogeneity makes therapeutic targeting challenging in VWD and prevents it from being simply confined to protein replacement or modulation, at variance with HA. In addition to plasma-derived VWF-FVIII concentrates, desmopressin, and recombinant VWF which still are the cornerstone of therapy for all forms of VWD, several innovative therapeutic strategies are now emerging.[12,13] Although most of them are in preclinical stages or are in the very early-phase of clinical development, these strategies reflect a growing effort to translate to the management of VWD the therapeutic advances achieved in HA.

It should be emphasized upfront that these approaches are mainly aimed at prophylaxis rather than the episodic management of acute episodes of bleeding, and none is currently licensed for clinical use. Nevertheless, several candidates are in the pipeline and can be differentiated according to their mechanisms of action and their potential personalized and precision-based application to different VWD types and predominant clinical manifestations (Table 1). Some of them aim to extend the plasma half-life of VWF and FVIII, others rebalance thrombin generation without directly targeting VWF, others modulate fibrinolysis, which plays a key role in the onset of bleeding in mucosal tracts, particularly heavy menstrual bleeding. Collectively, these developments may substantially expand the therapeutic landscape of VWD in the coming years, particularly but not exclusively for patients

with severe disease or those requiring long-term prophylaxis. In this perspective article, we discuss these emerging agents according to their mechanisms of action.

**Increasing endogenous VWF-FVIII levels**

A first group of investigational therapies aims to enhance endogenous VWF levels and prolong the persistence in plasma of both VWF and its companion FVIII. KB-V13A12 is a bispecific single-domain antibody that bridges circulating VWF to albumin, thereby exploiting FcRn-mediated recycling in order to prolong the plasma half-life of both VWF and FVIII without interfering with VWF function or ADAMTS13-mediated proteolysis.[60] A single subcutaneous dose of KB-V13A12 in VWD1 mice produced a 2-fold increase in VWF and FVIII for up to 10 days, improved multimer pattern and corrected the bleeding defect using the saphenous vein puncture model.[61] Similarly, HMB-002 is a monovalent antibody directed against the VWF CK domain whose engineered Fc portion enhances FcRn-dependent recycling and increases circulating VWF/FVIII levels.[62] In nonhuman primates, HMB-002 doubled endogenous VWF and FVIII levels preserving VWF multimer pattern.[62] This project has now entered clinical development and is being evaluated in an ongoing phase 1/2 first-in-human trial (Velora Pioneer; NCT06754852) in patients with VWD, with the first participant dosed in 2025. Another innovative approach is BT200/rondoraptivon pegol, a pegylated RNA aptamer derived from ARC1779 that targets the VWF A1 domain and inhibits VWF–GPIbα interaction.[63] It reduces platelet adhesion at higher doses, yet low doses paradoxically increase VWF and FVIII levels, improve multimer pattern, and raise platelet counts by modulating VWF clearance, its peri-procedural clinical use being already reported in type 2B VWD.[63,64]

**VWF-independent strategies: FVIII mimicry and thrombin rebalancing**

In parallel with strategies aimed at increasing endogenous VWF and FVIII, additional agents attempt to rebalance coagulation independently of VWF replacement and to restore hemostasis by enhancing thrombin generation and mimicking FVIII activity. As described earlier, emicizumab restores thrombin generation and its off-label use in type 3 VWD, particularly in cases with anti-VWF alloantibodies, demonstrated hemostatic efficacy and improved quality of life.[65,66] Ongoing studies, such as the phase 3 WILL-EMI (NCT06998524) or the phase 1 BCDI-XII (NCT05500807), aim to establish safety and efficacy as an alternative to replacement products.[13,67] Efanesoctocog alfa, originally developed for hemophilia A, may be of utility in selected VWD subtypes, including type 2N and type 3, by providing VWF-independent and sustained FVIII levels.[68-70]

A separate class of investigational agents enhances thrombin generation through the modulation of naturally occurring anticoagulant systems. VGA039 is a monoclonal antibody that inhibits protein S cofactor activity toward activated protein C and tissue factor pathway inhibitor, thereby enhancing thrombin generation.[71] It is currently being evaluated in a phase 3 multicenter, open-label, crossover study in all VWD types: NCT07115004 investigates safety and efficacy of subcutaneous VGA039 for bleeding prevention.

**Genetic and molecular strategies**

In contrast to protein- and antibody-based therapies, emerging genetic approaches seek potentially durable correction of the underlying molecular defect. Allele-selective, small interfering RNA strategies aim to silence dominant-negative VWF gene variants while preserving expression from the normal allele,[72,73] whereas CRISPR/Cas9-based editing technologies attempt the direct correction of pathogenic variants.[74] Parallel efforts in gene therapy have explored lentiviral and adeno-associated viral approaches for endothelial expression of VWF, although challenges remain because

of the large size of the VWF cDNA and the physiological complexity of multimer assembly.[74] Additional approaches focus on preventing excessive VWF degradation, particularly in type 2A VWD and the acquired von Willebrand syndrome, through monoclonal antibodies targeting VWF-ADAMTS13 interactions or directly inhibiting ADAMTS13 activity.[75] A new non-*VWF* genetic approach has recently emerged for VWD by targeting fibrinolysis. ALN-6400 is an investigational RNAi therapeutic that inhibits liver plasminogen production to reduce fibrinolysis and enhance hemostasis.[76] It is currently being evaluated in a phase 1/2 trial (NCT06659640) assessing safety and efficacy of the subcutaneous administration in healthy volunteers and patients with hereditary hemorrhagic telangiectasia.[77] In addition, HMBeacon is a phase 2 study meant to evaluate ALN-6400 in adult VWD women with heavy menstrual bleeding (NCT07575308).

**Other new approaches**

Beyond targeted modulation of VWF and coagulation pathways, more general hemostatic approaches are also under development. Synthetic platelet nanoparticles (SynthoPlate) are peptide-coated lipid vesicles that mimic platelet adhesion and aggregation by binding VWF, collagen, and activate platelet receptors at injury sites, thereby enhancing primary hemostasis independently of the native platelet function.[78]

Taken together, these developments suggest that VWD therapeutics may progressively follow the trajectory observed in HA, albeit with greater complexity and need for more individualized approaches because of the broader heterogeneity of VWD phenotypes and clinical severity.

## Prophylaxis in hemophilia A and VWD: similarities and differences

Even though prophylaxis represents a cornerstone of management in both HA and VWD, its role, implementation and clinical impact differ substantially between the two disorders. If one compares

the annual bleeding rate in patients managed episodically rather than prophylactically, median values are in most cases 20–30 or more in HA versus 5–6 in VWD cases except for the more severe forms (Figure 2). A key difference between the two disorders lies in the bleeding phenotype.[1,2] In HA, spontaneous joint bleeding is a defining feature, making continuous prophylaxis highly effective in altering the disease trajectory. In VWD, bleeding is often mucocutaneous, intermittent, and highly variable in onset and severity between and within patients, which complicates the identification of candidates benefitting from long-term prophylaxis. In HA, prophylaxis is the standard of care, aiming to prevent spontaneous joint and soft tissue bleeding and thereby preserve long-term musculoskeletal function. This strategy is supported by the high annual bleeding rate in patients treated episodically and the well-established link between recurrent hemarthroses and arthropathy (Figure 2).[79] Importantly, women and girls with HA and symptomatic carriers may experience clinically relevant bleeding, including heavy menstrual bleeding, epistaxis, and joint bleeds.[80]

On the other hand, at variance with HA, prophylaxis regimens are not necessarily required in all VWD cases and until now their adoption has largely been restricted to those with a history of more severe and frequent bleeding.[81] This situation was experienced by us when attempting to enroll VWD cases in the only randomized study showing the superiority of twice-weekly prophylaxis over episodic therapy with a plasma-derived FVIII-VWF concentrate. We managed to enroll only 19 patients in the two study arms because many potentially eligible cases stated during screening interviews that their bleeding episodes were not frequent or severe enough to justify the burden of twice-weekly intravenous injections.[82] However, recurrent minor mucosal bleeds significantly affect disease burden and quality of life, indicating that treatment decisions should not solely rely on major bleeding frequency.

Prophylaxis is warranted in several clinical situations in VWD. Epistaxis occurs frequently in children and is often associated with considerable anxiety in families despite limited severity. Gastrointestinal bleeding is a threatening and difficult-to-control complication in older patients owing to the development of angiodysplastic lesions in the gastrointestinal tract in types 2A, 2B, and 3 VWD. Recurrent joint bleeding may lead to severe and disabling arthropathy in type 3 VWD. Furthermore, heavy menstrual bleeding in adult women and girls with VWD is associated with markedly impaired health status and quality of life and is frequently jeopardized by a delayed diagnosis.[83,84] Thus, despite the efficacy of currently available therapies, important unmet needs remain, because a number of persons with VWD continue to experience physical and psychosocial limitations as well as the burden of intravenous injections, in contrast to the subcutaneous therapies now available for HA. These unmet needs are especially cogent in women with VWD, who often relied on hormonal therapy rather than prophylaxis in order to control heavy menstrual bleeding, with variable efficacy and notable side effects.

Despite these differences, both diseases share a growing need for more focused and personalized prophylaxis strategies that reduce treatment burden and improve quality of life.[79] The advent of extended half-life products and nonfactor therapies, particularly subcutaneous agents, is progressively reshaping the prophylaxis paradigm in HA. With the emergence of easier-to-administer and more global hemostasis-modulating therapies, there is an increasing option to reconsider which VWD patients may benefit from prophylactic strategies.

## Conclusions

The therapeutic trajectories of HA and VWD illustrate two parallel yet distinctly paced revolutions in inherited bleeding disorders. Both have evolved from conditions managed mainly with supportive care into treatable and, in many cases, preventable disorders through prophylaxis. As the two most

common inherited bleeding disorders, they have experienced different paces of advances, clinical attention, and innovation of treatment strategies. HA has undergone a particularly rapid transformation, driven by a relatively homogeneous pathophysiology and the clear success of factor replacement, extended half-life products, nonfactor therapies, and gene-based approaches. These advances have established prophylaxis as the standard of care and enabled many patients to achieve near-normal life expectancy and daily functioning. In contrast, despite being the most common inherited bleeding disorder, VWD witnessed a slower and more complex pace of therapeutic evolution, largely reflecting its marked molecular and clinical heterogeneity as well as difficult and often delayed diagnosis, notwithstanding the central regulatory role of VWF in primary hemostasis and FVIII stabilization. However, this gap is now narrowing, driven by advances in pathophysiology-based and precision-targeted therapeutic strategies. Several novel treatment options for VWD are expected to become available in the near future, with the potential to substantially reshape the management paradigm.

## References


1. Seidizadeh O, Eikenboom JC, Denis CV, et al. von Willebrand disease. Nat Rev Dis Primers. 2024;10(1):51.
2. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. Nat Rev Dis Primers. 2021;7(1):45.
3. Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4(10):2103-2114.
4. Oldenburg J, Ananyeva NM, Saenko EL. Molecular basis of haemophilia A. Haemophilia. 2004;10:133-139.
5. Pipe SW, Montgomery RR, Pratt KP, Lenting PJ, Lillicrap D. Life in the shadow of a dominant partner: the FVIII-VWF association and its clinical implications for hemophilia A. Blood. 2016;128(16):2007-2016.
6. Mannucci PM, Kessler CM, Germini F, et al. Bleeding events in people with congenital haemophilia A without factor VIII inhibitors receiving prophylactic factor VIII treatment: a systematic literature review. Haemophilia. 2023;29(4):954-962.
7. Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375(21):2067-2080.
8. Federici AB, Bucciarelli P, Castaman G, et al. Management of inherited von Willebrand disease in Italy: results from the retrospective study on 1234 patients. Semin Thromb Hemost. 2011;37(5):511-521.
9. Tosetto A, Badiee Z, Baghaipour MR, et al. Bleeding symptoms in patients diagnosed as type 3 von Willebrand disease: results from 3WINTERS-IPS, an international and collaborative cross-sectional study. J Thromb Haemost. 2020;18(9):2145-2154.
10. Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Haemost. 2023;21(3):403-412.
11. Butterfield JS, Hege KM, Herzog RW, Kaczmarek R. A molecular revolution in the treatment of hemophilia. Mol Ther. 2020;28(4):997-1015.
12. Denis CV, Susen S, Lenting PJ. von Willebrand disease: what does the future hold? Blood. 2021;137(17):2299-2306.
13. Casari C, Leebeek FW, Peyvandi F. Historical, current and future treatments for von Willebrand disease. Haematologica. 2026;111(1):54-66.
14. Pool JG, Shannon AE. Production of high-potency concentrates of antihemophilic globulin in a closed-bag system: Assay in vitro and in vivo. N Engl J Med. 1965;273(27):1443-1447.
15. Bennett E, Dormandy K. Pool's cryoprecipitate and exhausted plasma in the treatment of von Willebrand's disease and factor-XI deficiency. Lancet. 1966;2(7466):731-732.
16. Mannucci PM, Tenconi PM, Castaman G, Rodeghiero F. Comparison of four virus-inactivated plasma concentrates for treatment of severe von Willebrand disease: a cross-over randomized trial. Blood. 1992;79(12):3130-3137.
17. Federici AB, Castaman G, Franchini M, et al. Clinical use of Haemate P in inherited von Willebrand's disease: a cohort study on 100 Italian patients. Haematologica. 2007;92(7):944-951.

18. Evatt BL. The tragic history of AIDS in the hemophilia population, 1982-1984. J Thromb Haemost. 2006;4(11):2295-2301.
19. McClure CP, Kean K, Reid K, et al. Reconstruction of the historic time course of blood-borne virus contamination of clotting factor concentrates, 1974-1992. J Med Virol. 2024;96(7):e29774.
20. Mannucci PM, Pareti FI, Ruggeri ZM, Capitanio A. 1-Deamino-8-D-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrand's disease. Lancet. 1977;309(8017):869-872.
21. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. Blood. 1997;90(7):2515-2521.
22. Gringeri A, Mannucci PM, Gringeri M, Castaman G, Peyvandi F. Global estimation of the bleeding episodes treatable with desmopressin in von Willebrand disease and hemophilia A. Haematologica. 2025;110(8):1710-1722.
23. White GC, McMillan CW, Kingdon HS, Shoemaker CB. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. N Engl J Med. 1989;320(3):166-170.
24. Nilsson IM. Experience with prophylaxis in Sweden. Semin Hematol. 1993;30(3 Suppl 2):16-19.
25. Moreno MM, Cuesta-Barriuso R. A history of prophylaxis in haemophilia. Blood Coagul Fibrinolysis. 2019;30(2):55-57.
26. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535-544.
27. Mannucci PM, Kempton C, Millar C, et al. rVWF Ad Hoc Study Group. Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. Blood. 2013;122(5):648-657.
28. Peyvandi F, Kouides P, Turecek PL, Dow E, Berntorp E. Evolution of replacement therapy for von Willebrand disease: from plasma fraction to recombinant von Willebrand factor. Blood Rev. 2019;38:100572.
29. Schulte S. Innovative coagulation factors: albumin fusion technology and recombinant single-chain factor VIII. Thromb Res. 2013;131 Suppl 2:S2-6.
30. Ivens IA, Baumann A, McDonald TA, Humphries TJ, Michaels LA, Mathew P. PEG ylated therapeutic proteins for haemophilia treatment: a review for haemophilia caregivers. Haemophilia. 2013;19(1):11-20.
31. Powell JS, Josephson NC, Quon D. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. Blood. 2012;119(13):3031-3037.
32. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015;126(9):1078-1085.
33. Mannucci PM. Benefits and limitations of extended plasma half-life factor VIII products in hemophilia A. Expert Opin Investig Drugs. 2020;29(3):303-309.

34. Collins P, Chalmers E, Chowdary P, et al. The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. Haemophilia. 2016;22(4):487-498.
35. Konkle BA, Shapiro AD, Quon DV, et al. BIVV001 fusion protein as factor VIII replacement therapy for hemophilia A. N Engl J Med. 2020;383(11):1018-1027.
36. Von Drygalski A, Chowdary P, Kulkarni R, et al. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. N Engl J Med. 2023;388(4):310-318.
37. Shima M, Hanabusa H, Taki M, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. Blood Adv. 2017;1(22):1891-1899.
38. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809-818.
39. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379(9):811-822.
40. Pipe SW, Shima M, Lehle M, 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.
41. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2021;137(16):2231-2242.
42. Howard M, McKinley D, Sanabria F, Ko RH, Nissen F. Evaluation of the safety of emicizumab prophylaxis in persons with hemophilia A: an updated summary of thrombotic events and thrombotic microangiopathies. Blood. 2021;138(Supplement 1):3186.
43. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. Haemophilia. 2022;28 Suppl 4(Suppl 4):103-110.
44. Voorberg J, Postmus T, Schols S. Next generation FVIII mimetic bispecific antibody for hemophilia A. J Thromb Haemost. 2022;20(6):1301-1305.
45. Persson P, Amstrup AB, Coester HV, Matytsina I, Bas S. Mim8, a novel factor VIIIa mimetic bispecific antibody, shows favorable safety and pharmacokinetics in healthy adults. Res Pract Thromb Haemost. 2023;7(6):102181.
46. Sambe T, Miwa T, Yoneyama K, Ishida T, Yamazaki T, Shima M. A first-in-human study of NXT007, a next-generation, activated factor VIII-mimetic bispecific antibody, in healthy participants. J Thromb Haemost. 2025;23(10):3098-3110.
47. Mancuso ME, Chan AK, Shanmukhaiah C, et al. Mim8 bispecific antibody prophylaxis in hemophilia A with or without inhibitors. N Engl J Med. 2026;394(17):1696-1709.
48. Srivastava A, Rangarajan S, Kavakli K, 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-e332.
49. Young G, Srivastava A, Kavakli K, 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):1427-1437.

50. Matsushita T, Shapiro A, Abraham A, et al. Phase 3 trial of concizumab in hemophilia with inhibitors. N Engl J Med. 2023;389(9):783-794.
51. Mahlangu JN, Lamas JL, Morales JC, et al. A phase 1b/2 clinical study of marstacimab, targeting human tissue factor pathway inhibitor, in haemophilia. Br J Haematol. 2023;200(2):229-239.
52. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med. 2022;386(11):1013-1025.
53. Madan B, Ozelo MC, Raheja P, et al. Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A. J Thromb Haemost. 2024;22(7):1880-1893.
54. Pinotti M, Newby GA, Selvaraj S, Pipe SW. Gene editing for haemophilia-the next frontier. Haemophilia. 2026 Apr 16. doi:10.1111/hae.70238. [Epub ahead of print]
55. Park CY, Lee DR, Sung JJ, Kim DW. Genome-editing technologies for gene correction of hemophilia. Hum Genet. 2016;135(9):977-981.
56. Pipe SW, Selvaraj SR. Gene editing in hemophilia: a “CRISPR” choice? Blood. 2019;133(26):2733-2734.
57. Mátrai J, Chuah MK, VandenDriessche T. Preclinical and clinical progress in hemophilia gene therapy. Curr Opin Hematol. 2010;17(5):387-392.
58. Srivastava A, Abraham A, Aboobacker F, et al. Lentiviral gene therapy for hemophilia A using CD34+ hematopoietic cells. N Engl J Med. 2025;392(5):450-457.
59. Matsushita T, Nogami K, Shanmukhaiah C. FVIIIa Mimetics: New Approaches and Next-Generation Initiatives. Haemophilia. 2026 Apr 16. doi:10.1111/hae.70231. [Epub ahead of Print]
60. McCluskey G, Heestermans M, Peyron I. A fully humanized von Willebrand disease type 1 mouse model as unique platform to investigate novel therapeutic options. Haematologica. 2025;110(4):923-937.
61. Peyron I, Casari C, McCluskey G, et al. A bispecific nanobody for the treatment of von Willebrand disease type 1. Blood. 2025;146(21):2597-2607.
62. Häger M, Zivkovic M, Gandhi PS, et al. HMB-002: a monovalent antibody that elevates circulating VWF and FVIII levels for treatment of Von Willebrand Disease. Blood Adv. 2026;10(7):2551-2562.
63. Ay C, Pabinger I, Kovacevic KD. The VWF binding aptamer rondoraptivon pegol increases platelet counts and VWF/FVIII in type 2B von Willebrand disease. Blood Adv. 2022;6(18):5467-5476.
64. Moser M, Ay C, Schoergenhofer C, Gilbert JC, Zhu S, Jilma B. Rondaptivon pegol (BT200) to correct thrombocytopenia in a peri-interventional setting in type 2B von Willebrand disease (VWD). Blood. 2024;144(Supplement 1):3984.
65. Weyand AC, Flood VH, Shavit JA, Pipe SW. Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies. Blood Adv. 2019;3(18):2748-2750.
66. Giuffrida AC, Siboni SM, Baronciani L, Poli G, Gandini G, Peyvandi F. Emicizumab in type 3 von Willebrand Disease: report of a case with an alloantibody and literature review. Semin Thromb Hemost. 2025;51(1):73-80.

67. Roberts J, Chien M, Gupta S, et al. Emicizumab for severe von willebrand disease (VWD): The (EmiVWD) study enrollment 2025. Blood. 2025;146(Supplement 1):1315.
68. Ryu JH, Bauer KA, Schulman S. Periprocedural management of type 2N von Willebrand disease with efanesoctocog alfa. J Thromb Haemost. 2023;21(12):3508-3510.
69. Castaman G, Mannucci PM. Treating von Willebrand disease without von Willebrand factor. J Thromb Haemost. 2026;24(1):47-48.
70. Susen S, Trossaërt M, Zilberstein M, et al. A phase 1, open-label study to assess the pharmacokinetics, safety, and tolerability of a single intravenous injection of efanesoctocog alfa in adults with type 2N or type 3 von Willebrand disease. J Thromb Haemost. 2026;24(1):79-87.
71. Millar CM, Raheja P, Wheeler AP, 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(Supplement 1):3981.
72. Casari C, Pinotti M, Lancellotti S. The dominant-negative von Willebrand factor gene deletion p.P1127_C1948delinsR: molecular mechanism and modulation. Blood. 2010;116(24):5371-5376.
73. Campioni M, Legendre P, Loubiere C. In vivo modulation of a dominant-negative variant in mouse models of von Willebrand disease type 2A. J Thromb Haemost. 2021;19(1):139-146.
74. Barraclough A, D'Amico A, Leite de Oliveira R. Restoration of VWF in von Willebrand disease type 3 canine ECFCs through CRISPR-Cas9 mediated gene editing. Res Pract Thromb Haemost. 2022;6(Suppl 1):601-602.
75. Barraclough A, Bär I, Van Duijl T, et al. Rewriting the script: gene therapy and genome editing for von Willebrand Disease. Front Genome Ed. 2025;7:1620438.
76. Rauch A, Legendre P, Christophe OD. Antibody-based prevention of von Willebrand factor degradation mediated by circulatory assist devices. Thromb Haemost. 2014;112(5):1014-1023.
77. Cevasco C, Ivanciu L, Gansner J, Camire R, Slingsby ML. Hepatic plasminogen lowering with a galnac-conjugated siRNA reduces plasmin generation and fibrinolysis but has no effect on thrombin generation in rats and mice. Blood. 2025;146(Supplement 1):3058.
78. Roullet S, Luc N, Rayes J. Efficacy of platelet-inspired hemostatic nanoparticles on bleeding in von Willebrand disease murine models. Blood. 2023;141(23):2891-2900.
79. Miesbach W, Berntorp E. Translating the success of prophylaxis in haemophilia to von Willebrand disease. Thromb Res. 2021;199:67-74.
80. Hermans C, Johnsen JM, Curry N. Women and girls with inherited bleeding disorders: Focus on haemophilia carriers and heavy menstrual bleeding. Haemophilia. 2024;30 Suppl 3:45-51.
81. Federici AB. Prophylaxis in patients with von Willebrand disease: who, when, how? J Thromb Haemost. 2015;13(9):1581-1584.
82. Peyvandi F, Castaman G, Gresele P, et al. A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease. Blood Transfus. 2019;17(5):391-398.

83. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-325.
84. Franchini M, Seidizadeh O, Mannucci PM. Prophylactic management of patients with von Willebrand disease. Ther Adv Hematol. 2021;12:20406207211064064

**Table 1. Emerging therapeutic approaches for von Willebrand disease, grouped by mechanism of action.**

| Mechanism of Action | Agent | Drug Class | Mechanism | Development Stage |
|---|---|---|---|---|
| Increasing Endogenous VWF-FVIII Levels | ***KB-V13A12*** | Bispecific single-domain antibody | Bridges VWF to albumin; exploits FcRn-mediated recycling to prolong VWF and FVIII half-life without impairing VWF function or ADAMTS13 proteolysis | Preclinical (VWD1 murine model) |
| | ***HMB-002*** | Monovalent antibody (engineered Fc) | Targets VWF CK domain; enhanced FcRn-dependent recycling increases circulating VWF and FVIII levels while preserving multimer pattern | Phase 1/2 (NCT06754852; Velora Pioneer; first-in-human, 2025) |
| | ***BT200 / Rondoraptivon pegol*** | Pegylated RNA aptamer | Targets VWF A1 domain; low doses modulate VWF clearance, paradoxically increasing VWF and FVIII levels and improving multimer pattern | Peri-procedural use reported in type 2B VWD (clinical) |
| FVIII Mimicry | ***Emicizumab*** | Bispecific monoclonal antibody | Mimics activated FVIII by bridging FIXa and FX; restores thrombin generation independently of VWF | Approved for HA; off-label use in type 3 VWD; Phase 3 (WILL-EMI, NCT06998524); Phase 1 (BCDI-XII, NCT05500807) |
| | ***Efanesoctocog alfa*** | Extended half-life recombinant FVIII | VWF-independent, sustained FVIII replacement; bypasses VWF-imposed half-life ceiling | Approved for HA; under evaluation in type 2N and type 3 VWD |
| Thrombin Generation Rebalancing | ***VGA039*** | Monoclonal antibody | Inhibits protein S cofactor activity toward activated protein C and TFPI, enhancing thrombin generation across all VWD types | Phase 3 (NCT07115004; multicenter, open-label, crossover; all VWD types) |
| Fibrinolysis Modulation | ***ALN-6400*** | RNAi therapeutic (siRNA) | Inhibits hepatic plasminogen production, reducing fibrinolysis and enhancing hemostasis; non-VWF approach targeting mucosal bleeding | Phase 1/2 (NCT06659640; healthy volunteers and HHT patients); Phase 2 (HMBeacon, |

| Mechanism of Action | Agent | Drug Class | Mechanism | Development Stage |
|---|---|---|---|---|
| | | | | NCT07575308; VWD women with HMB) |
| | ***Tranexamic acid / antifibrinolytics*** | Lysine analogue | Inhibits plasminogen activation; adjunct to reduce mucosal bleeding, particularly heavy menstrual bleeding | Established adjunct therapy (guideline-recommended) |
| **Genetic and Molecular Strategies** | ***Allele-selective siRNA*** | RNA interference | Silences dominant-negative VWF variants while preserving expression from the normal allele (relevant in type 2 and type 3 VWD) | Preclinical |
| | ***CRISPR/Cas9 gene editing*** | Gene editing | Direct correction of pathogenic VWF variants; potential durable molecular correction | Preclinical |
| | ***Viral vector gene therapy (lentiviral / AAV)*** | Gene therapy | Endothelial expression of VWF; challenges include large VWF cDNA size and multimer assembly complexity | Preclinical |
| **Prevention of Excessive VWF Degradation** | ***Anti-ADAMTS13 monoclonal antibodies*** | Monoclonal antibody | Inhibit ADAMTS13-mediated VWF proteolysis; preserve high-molecular-weight multimers (relevant in type 2A VWD and acquired VWS) | Preclinical |
| **Novel Hemostatic Agents** | ***SynthoPlate (synthetic platelet nanoparticles)*** | Peptide-coated lipid nanoparticle | Mimics platelet adhesion and aggregation by binding VWF, collagen, and activating platelet receptors at injury sites; enhances primary hemostasis independently of native platelet function | Preclinical |

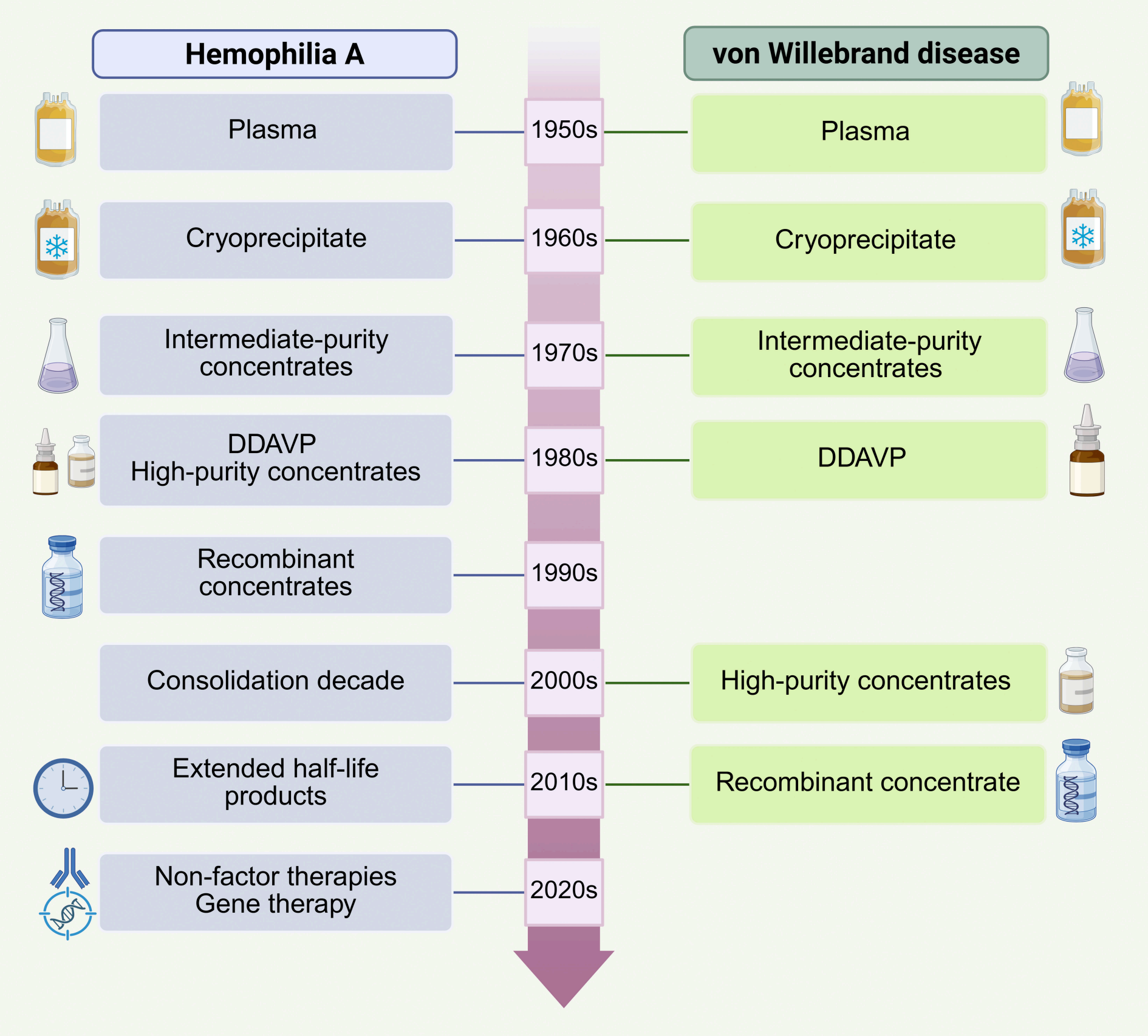
Abbreviations: AAV, adeno-associated virus; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs 13; FVIII, factor VIII; FIXa, activated factor IX; FX, factor X; FcRn, neonatal Fc receptor; HA, hemophilia A; HHT, hereditary hemorrhagic telangiectasia; HMB, heavy menstrual bleeding; RNAi, RNA interference; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor; VWD, von Willebrand disease; VWF, von Willebrand factor; VWS, von Willebrand syndrome.

**Figures legend**

**Figure 1. Parallel treatment evolution of hemophilia A and von Willebrand disease.** The timeline illustrates the historical development of therapeutic approaches for hemophilia A (left, blue) and von Willebrand disease (VWD, right, green) from the 1950s to the present. Both conditions initially relied on whole plasma and cryoprecipitate, followed by intermediate- and high-purity plasma-derived concentrates. The 1980s introduced desmopressin (DDAVP), the first non-plasma-derived pharmacological therapy for both disorders. From the 1990s onward, the two conditions diverged: hemophilia A rapidly adopted recombinant concentrates, prophylaxis, and subsequently extended half-life products, whereas VWD management continued to evolve more gradually, with high-purity concentrates and recombinant VWF becoming available in the 2000s–2010s. The current decade represents a transformative era for hemophilia A, with nonfactor therapies and gene therapy entering clinical practice, while multiple analogous innovative approaches are now emerging for VWD. The arrow indicates the direction of ongoing therapeutic progress for both conditions.

**Figure 2. Prophylaxis paradigms in hemophilia A and von Willebrand disease.** The figure compares prophylaxis implementation in hemophilia A and von Willebrand disease. In hemophilia A, prophylaxis is the standard of care, supported by high annualized bleeding rates under episodic treatment (typically ≥20–30 episodes) and the well-established link between recurrent hemarthroses and arthropathy. In VWD, bleeding rates are generally lower (5–6 episodes), predominantly mucocutaneous and intermittent, and long-term prophylaxis has been reserved for more severe cases, including recurrent epistaxis, gastrointestinal bleeding, joint bleeds in type 3, and heavy menstrual bleeding. A major remaining disparity is the continued reliance on intravenous administration in VWD, in contrast to the subcutaneous nonfactor therapies now reshaping the

prophylaxis landscape in hemophilia A. Importantly, bleeding in hemophilia A also affects women and girls, including symptomatic carriers with FVIII <40 IU/dL, in whom heavy menstrual bleeding and joint bleeding may be under-recognized within current prophylaxis frameworks.

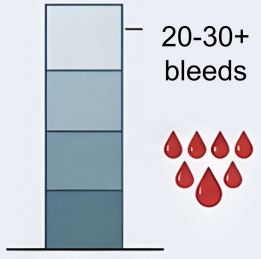

Hemophilia A
von Willebrand disease
Plasma
1950s
Plasma
Cryoprecipitate
1960s
Cryoprecipitate
Intermediate-purity concentrates
1970s
Intermediate-purity concentrates
DDAVP
High-purity concentrates
1980s
DDAVP
Recombinant concentrates
1990s
Consolidation decade
2000s
High-purity concentrates
Extended half-life products
2010s
Recombinant concentrate
Non-factor therapies
Gene therapy
2020s

# Prophylaxis paradigms: Hemophilia A vs. von Willebrand disease

## Clinical baseline

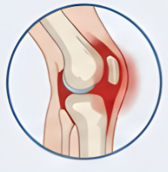
### Hemophilia A

**Median annual bleeding rates**

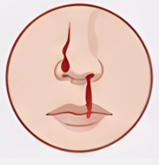



Episodic management

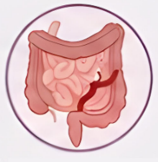
**Primary bleeding requiring prophylaxis**



Joint bleeding and arthropathy



Mucocutaneous bleeding

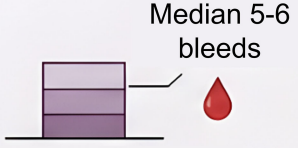


GI bleeding

Heavy menstrual bleeding

### von Willebrand disease

**Median annual bleeding rates**




Many cases (excluding severe)

## Prophylaxis implementation

### Hemophilia A

**Strategic approach to care**

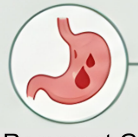
Maintaining Musculoskeletal Health

### von Willebrand disease

**Strategic approach to care**

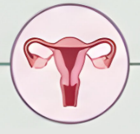
Targeted/selective based on the individual history

**von Willebrand disease high-risk indicators**

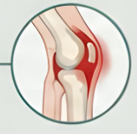


Recurrent GI bleeding (Types 2A, 2B, 3)

Severe childhood epistaxis

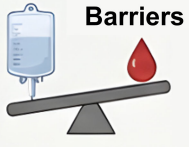


Heavy menstrual bleeding



Joint bleeding (Types 3, 2N)

**Barriers to von Willebrand disease prophylaxis**



Many patients decline prophylaxis due to the burden of frequent IV infusions

## The evolving treatment landscape

### Hemophilia A

**Current treatment burden**

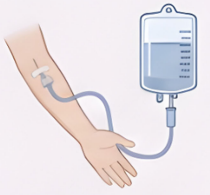
Transitioned toward subcutaneous and non-factor therapies

**Future outlook**

Extended half-life and subcutaneous therapies are reshaping care

### von Willebrand disease

**Current treatment burden**



Remains reliant on plasma-derived IV injections

**Future outlook**

Extending Hemophilia A advances to selected von Willebrand disease cases

**Shared clinical objectives:** Improve quality of life and reduce overall treatment burden through effective and individualized prophylaxis.