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SUPPLEMENT ARTICLE

Therapeutic and technological advancements in haemophilia care: Quantum leaps forward

Magdalena Lewandowska[1] | Sonia Nasr[2] | Amy D. Shapiro[1]

[1]Indiana Hemophilia & Thrombosis Center, Inc., Indianapolis, Indiana, USA

[2]GLOVAL LLC, Broomfield, Colorado, USA

Correspondence
Amy D. Shapiro, Indiana Hemophilia and Thrombosis Center, Inc. 8326 Naab Road, Indianapolis, IN 46260, USA.
Email: ashapiro@ihtc.org

Abstract

Introduction: Recent technological innovations in haemophilia have advanced at an astounding pace, including gene therapy programmes and bioengineered molecules for prophylaxis, products that reduce treatment burden through half-life extension, unique mechanisms of action, and subcutaneous administration. Additional technological advancements have emerged that are anticipated to further transform haemophilia care.

Aim: Review new and emerging haemophilia therapies, including replacement and bypassing products, digital applications, utilisation of big data, and personalised medicine.

Methods: Data were obtained from peer-reviewed presentations/publications, and ongoing studies in haemophilia, ultrasonography, and artificial intelligence (AI).

Results: Available treatments include new recombinant factors VIII (FVIII) and IX (FIX), extended half-life FVIII/IX products, a new FVIIa product for inhibitor patients, and a FVIIIa-mimetic. Several novel therapeutics are in clinical trials, including FVIIIa mimetics and inhibitors of naturally-occurring anticoagulants. Ongoing gene therapy trials suggest that a single vector infusion using an optimised construct can produce factor activity that reduces bleeding to near zero for years. Today, persons with haemophilia (PwH) approach a lifespan comparable to that of the general population, presenting treatment challenges for age-related co-morbidities. Technological innovations have broadened beyond therapeutics to include large database analyses utilising remote data collection with handheld devices, and to tailor AI applications. Current development efforts include patient-performed ultrasonography, algorithms for scan interpretation, and point-of-care haemostatic testing devices.

Conclusions: We have entered a golden age for haemophilia treatment and care with wide-ranging advancements targeting improved quality of life (QoL). Future-focused efforts by clinical and patient communities may provide equitable access and care for people impacted by haemophilia worldwide.

KEYWORDS
gene therapy, health equity, haemophilia, mimetics, MSKUS, novel therapies, technology

1 | INTRODUCTION

Haemophilia A (HA) and B (HB) are hereditary X-linked recessive disorders caused by deficiency or absence of coagulation factors VIII (FVIII) or IX (FIX), which are encoded by *F8* and *F9*, respectively. Males usually present with bleeding symptoms, while females who carry an altered gene have a varied clinical picture due to non-random inactivation of one X chromosome.

Table 1 summarises the severity and prevalence of HA and HB. The normal range of FVIII and FIX activity levels in the healthy population is broad[1,2], 50–150 IU/dl, while levels in affected persons range from <1 to 40 IU/dl.

The hallmark of haemophilia is spontaneous bleeding into muscles and joints (haemarthrosis). Repeated haemarthroses result in haemophilic arthropathy[3] with approximately 50% of persons with haemophilia (PwH) developing severe arthropathy characterised by chronic joint pain, reduced range of motion, decreased function, and reduced quality of life (QoL).

As late as the 1950s, half of PwH died before the age of 20. By the 1980s, the median lifespan was in the 50s.[4–6] This increase was due to the advent of factor replacement therapy from donated blood. Unfortunately, HIV- and hepatitis-infected blood interrupted the positive trends.[7] The creation of safe and effective replacement therapy with recombinant factor concentrates markedly improved care and set in motion a remarkable evolution in the management and treatment of haemophilia (Figure 1).

Treatment goals have shifted toward improving accessibility for long-term early prophylactic therapy and focusing on prediction, prevention, and treatment of inhibitor development.[8,9] Product expansion with different pharmacokinetics has allowed providers to individualise prophylaxis regimens targeting desired levels and infusion frequency. These patient-specific regimens permit providers to achieve improved outcomes while focusing on patient health needs and life goals, often impeded by a spectrum of challenges. People with bleeding disorders learn to live with their chronic conditions and strive to reach their full potential by preventing or managing bleeding in the context of school, work, and relationships. Psychological and physical challenges complicate disease management and may inhibit or delay the achievement of personal goals.

New factor replacement products, nonfactor therapies, bypassing agents, and gene therapy strategies are advancing at a remarkable pace to bridge the gap between currently available therapies and aspirational goals of achieving a life free of bleeding episodes. Clinical trials to evaluate these new therapies to assess their impact on QoL,[10] and long-term real-world outcomes of licensed therapies are ongoing.

In 2020, bleeding disorders were listed in the Healthy People 2030, a list of measurable national objectives from the United States Department of Health and Human Services. Across the US, individuals, organisations, and communities use Healthy People objectives to establish priorities. Bleeding disorders, despite being rare, have been recognised as a pressing public health issue, alongside prevalent conditions such as cancer, diabetes, and heart disease.

Technologies to improve education, data monitoring, and bedside diagnostics are in development. New technologies enhance communication between patients and care providers and support disease-specific education. Point-of-care tools may allow PwH to not only treat at home but also monitor their levels/haemostatic response and scan for bleeding events.

Additionally, attention is focused on unrecognised biases and health inequities resulting in increased health burden in underserved populations. Patients, caregivers, and community advocates are engaged with medical teams to improve health equity and increase participation for underserved populations in new treatments and technologies on the horizon.

2 | FACTOR AND NONFACTOR THERAPIES

2.1 | HA-specific novel agents

There are currently 12 recombinant factor VIII (rFVIII) products to treat HA in the United States, with several additional therapies currently in development (Table 2). Half-life prolongation utilising pegylation, Fc domain of immunoglobulin G or albumin fusion has resulted in 1.3 to 1.7 fold increase.[11]

TABLE 1 Prevalence and severity of haemophilia A and B

Haemophilia type	Affected gene (protein)	Prevalence per 100,000 males		PwH in each category of severity (concentration of factor) [percentage][68]	
		United States[69,a]	Worldwide[68,b]		
Haemophilia A	F8 (factor VIII)	11	17.1	Severe (<1 IU/dl)	9224/19556 [47%]
				Moderate (1–5 IU/dl)	3455/19556 [18%]
				Mild (6–40 IU/dl)	6877/19556 [35%]
Haemophilia B	F9 (factor IX)	3.7	3.8	Severe (<1 IU/dl)	1690/6188 [27%]
				Moderate (1–5 IU/dl)	2383/6188 [39%]
				Mild (6–40 IU/dl)	2115/6188 [34%]

[a]Surveyed patients at haemophilia treatment centres in the United States.
[b]Australia, Canada, France, Italy, New Zealand, and the United Kingdom.

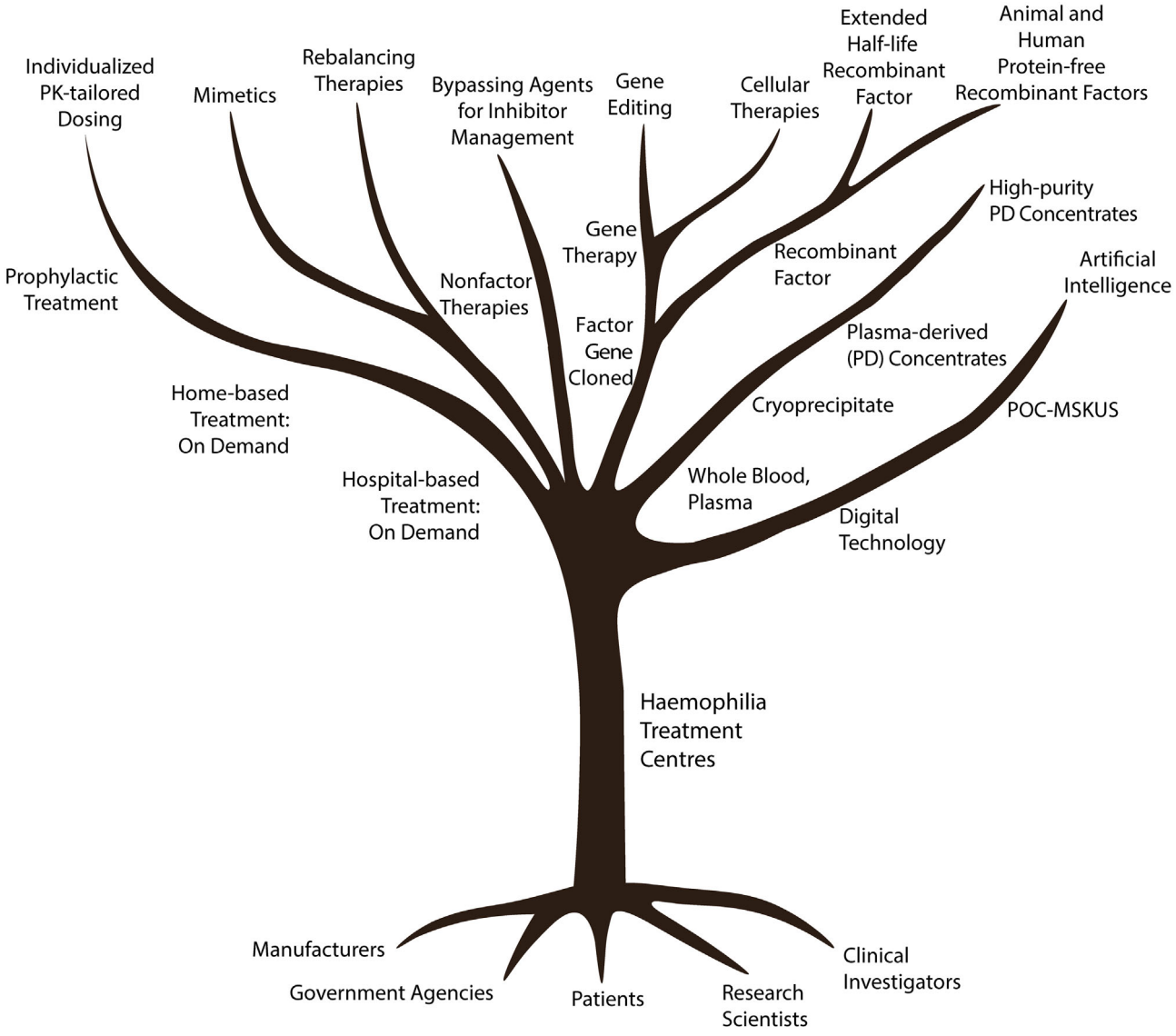

FIGURE 1 Schematic depiction of the evolution of haemophilia treatment

The successful development of FVIII mimetic therapy using humanised bispecific monoclonal antibodies that substitute for the scaffold effect of FVIIIa by bridging factors IXa and X has revolutionised the treatment of HA. Emicizumab is a FVIII mimetic currently licensed for persons with haemophilia A (PwHA) with or without inhibitors.[12,13] Subcutaneous delivery, reduced treatment frequency, and stable haemostatic levels have resulted in improved treatment adherence, bleeding rate, and QoL. Mim8, another FVIIIa mimetic, showed 15-fold increased potency compared with emicizumab in animal models and is currently in early-phase clinical trials.[14]

FVIII is dependent on its noncovalent complex with von Willebrand factor (VWF) to prevent its rapid clearance, which presents a therapeutic challenge to extend its half-life. Recent approaches uncoupling this ceiling effect are in development. The molecule most advanced in clinical trials is BIVV001 (efanesoctocog alfa, rFVIIIFc-vWF-XTEN), a B domain-deleted, Fc fusion recombinant FVIII protein with a VWF-stabilising D′D3 domain that prevents endogenous VWF binding; two biodegradable polypeptides (XTENs) further extend half-life through steric shielding. As a result, the half-life of BIVV001 is 3 to 4 times longer than that of rFVIII.

Gene and cellular therapies for the treatment of PwHA are in various stages of development. The use of adeno-associated virus (AAV) vectors allows for hepatic tropism, non-pathogenicity, and the ability to transduce dividing and non-dividing cells. Gene editing technologies such as zinc-finger nucleases (ZFNs), clustered interspaced short palindromic repeats (CRISPR) with associated protein 9 (Cas9), and transcription-activator-like effector nucleases (TALENS) are progressing. Cellular therapy is also being explored, where cells are transduced ex vivo and transplanted into the host.

Incorporating gene therapy into clinical practice brings challenges to maximise benefit while minimising risk. These challenges include selecting the appropriate patients, screening for pre-existing AAV capsid antibodies, monitoring for short- and long-term adverse events, and monitoring factor levels/liver enzymes to ensure sustainable/durable

TABLE 2 Approved and investigational therapeutics for haemophilia A

FVIII replacement products for haemophilia A		
Product	**Status/clinical trial number**	**Approximate half-life (hours)[a]**
Standard half-life rFVIII (HA without inhibitor)		
Recombinate[70]	FDA approved	Adults: 14.6
Kogenate FS[71]	FDA approved	Adults: 13.7–14.6
		Peds: 7.8–15.3
Advate[72]	FDA approved	Adults: 12.0
		Peds: 8.7–11.2
Novoeight[73]	FDA approved	Adults: 10.8–12.0
		Peds: 7.7–10.0
Xyntha[74]	FDA approved	Adults: 11.2–16.7
		Peds: 8.3
Kovaltry[75]	FDA approved	Adults: 14.2–14.4
		Peds: 9.6–12.2
Nuwiq[76]	FDA approved	Adults: 17.1
		Peds: 11.9–13.1
Extended half-life rFVIII (HA without inhibitor)		
Eloctate[77] (IgG-1 Fc-domain fusion)	FDA approved	Adults: 16.4–19.7
		Peds: 12.7–14.9
Adynovate[78] (PEGylation)	FDA approved	Adults: 13.4–14.7
		Peds: 11.8–12.4
Afstyla[79] (single chain technology)	FDA approved	Adults: 14.2–14.3
		Peds: 10.2–10.4
Jivi[80] (PEGylation)	FDA approved	Adults: 17.9–18.6
Esperoct[81] (O-glycoPEGylation)	FDA approved	Adults: 17.4–21.7
		Peds: 13.8–14.7
Investigational extended half-life rFVIII uncoupled from VWF dependence (HA without inhibitor)[82]		
BIVV001[83], Efanesoctocog alfa,rFVIIIFc-VWF-XTEN (Fc, VWF D'D3, XTEN polypeptides)	Phase 1: NCT05042440 (Completed)	Adults: 37.6–42.5
	Phase 1/2: NCT03205163 (Completed)	
	Phase 3: NCT04644575, NCT04759131 (Recruiting)	
OCTA101[84], human-cl rhFVIII (Nuwiq) and recombinant human VWF fragment dimer	Phase 1/2: NCT04046848 (Not recruiting; on hold Dec 2021)	Not yet reported
CSL 626[85], rD'D3-FP albumin fusion to extend half-life of vWF fragment, co-administered with rFVIII Single Chain	Preclinical development	Not yet reported
FVIIIa mimetic bispecific antibodies (HA with or without inhibitor)		
Emicizumab[86] (Subcutaneous: 1 × per week, 1 × every 2 weeks, or 1 × every 4 weeks)	FDA approved	Adults, adolescents, & children: 26.9 ± 9.1 days
Mim8[14] (subcutaneous: 1 × per week or 1 × per month)	Phase 2: NCT04204408 (Active, not recruiting)[82]	Preclinical (Cynomolgus monkeys): 14.0 (range 10–17) days

(Continues)

TABLE 2 (Continued)

Investigational gene and cell therapy for haemophilia A			
Product	**Status/clinical trial number**[82]	**Vector**	**Sponsor**
Giroctocogene Fitelparvovec (SB-525)[87]	Phase 3: NCT03587116 (Recruiting)	AAV 2/6	Pfizer/Sangamo
	Phase 3: NCT04370054 (On hold, Nov 2021)		
	Phase 2: NCT03061201 (Active, not recruiting)		
Auto CD34+PBSC	Phase 1: NCT03818763 (Recruiting)	Lentiviral vector, Pleightlet (MUT6)	Medical College of Wisconsin
AAV2/8-HLP-FVIII-V3	Phase 1: NCT03001830 (Recruiting)	AAV 2/8	University College, London
SPK-8011	Phase 1/2: NCT03003533 (Recruiting)	AAV-LK03	Spark therapeutics
SPK-8016[88]	Phase 1/2: NCT03734588 (Active, not recruiting) HA with inhibitor	AAV5	Spark therapeutics
Valoctocogene roxaparvovec[89]	Phase 1/2: NCT04684940 (Recruiting)	AAV5	BioMarin pharmaceutical
	Phase 3: NCT04323098 (Recruiting)		
	Phase 1/2: NCT02576795 (Active, not recruiting)		
	Phase 3: NCT03370913, NCT03392974 (Active, not recruiting)		
BAY 2599023	Phase 1/2: NCT03588299 (Recruiting)	AAVhu37	Bayer
YUVA-GT-F801	Phase 1: NCT 03217032 (Not yet recruiting)	FVIII-Lentivector	Shenzhen Geno-Immune Medical Institute
SIG-001	Phase 1/2: NCT04541628 (On hold, Jul 2021)	Encapsulated cell therapy	Sigilon therapeutics

Abbreviations: FVIII, factor VIII: rFVIII, recombinant factor VIII; HA, haemophilia A; VWF, von Willebrand Factor.
[a]Half-life for each of these products was derived from published data and is provided as clinical reference for treatment decisions. No head-to-head data exist for comparison.

FVIII expression. Additional opportunities for research include treating children, re-treatment if needed over time, and addressing the short- and long-term toxicity of the vector on the target organ.

2.2 | Haemophilia B-specific novel agents

Six recombinant factor IX (rFIX) concentrates are licensed to treat HB, three of which are extended half-life products (Table 3). Half-life prolongation utilising pegylation, Fc domain of immunoglobulin G or albumin fusion has resulted in four- to six-fold increase.[11] These products are administered as infrequently as every 2 weeks with a half-life of 65–104 h. Recent research efforts have focused on subcutaneous delivery, achieved by adding XTEN polymers to rFIXFc *Padua* variant molecule (BIVV002)[15] or using a FIX variant with three amino acid substitutions resulting in increased potency compared to endogenous FIX.[16]

Several gene therapy trials with AAV vectors in patients with haemophilia B (PwHB) using the FIX Padua transgene[17] are ongoing and have demonstrated an eight-fold higher FIX activity level than achieved with wild type FIX.

2.3 | Coagulation rebalancing agents

Strategies to rebalance haemostasis by targeting naturally occurring inhibitors of coagulation are under development (Figure 2). These therapeutic agents offset decreased or absent procoagulants, are

TABLE 3 Approved and investigational therapeutics for haemophilia B

FIX replacement products for haemophilia B without inhibitor		
Product	**Status/clinical trial number**	**Approximate half-life (hours)[a]**
	Standard half-life rFIX	
BeneFIX[90]	FDA approved	Adults: 22.4–23.8
		Peds: 15.6–16.7
Rixubis[91]	FDA approved	Adults: 25.7
		Peds: 23.2–27.7
Ixinity[92]	FDA approved	Adults: 24.0
	Extended half-life rFIX	
Alprolix[93] (IgG-1 Fc-domain fusion protein)	FDA approved	Adults: 80.0–97.0
		Peds: 68.0–72.0
Idelvion[94] (rAlbumin fusion protein)	FDA approved	Adults: 87.0–118.0
		Peds: 90.0–93.0
Rebinyn[95] (GlycoPEGylated)	FDA approved	Adults: 83.0–89.4
		Peds: 69.6–76.3
	Investigational extended half-life rFIX	
BIVV002,[15,96] rFIXFc-XTEN (XTEN polymers added to rFIX Fc Padua variant) subcutaneous	Preclinical development	Not yet reported
Dalcinonacog alfa[16,97] (rFIX with three amino acid substitutions) subcutaneous or intravenous	Phase 1/2: NCT03186677 (Completed; Development halted Nov 2021)	Adults; subcutaneous: 53.9–106.9
		Adults; intravenous: 27.0 ± 2.2

Investigational gene and cell therapy for haemophilia B without inhibitor			
Product	**Status/clinical trial number[82]**	**Vector**	**Sponsor**
AAV5-hFIXco-Padua (etranacogene dezaparvovec, AMT-061)	Phase 2: NCT03489291 (Active, not recruiting)	FIX Padua-AAV5	CSL Behring/UniQure
	Phase 3: NCT03569891 (Active, not recruiting)		
PF-06838435 (fidanacogene elaparvovec, SPK-9001)	Phase 1/2: NCT02484092 (Completed)	FIX Padua-AAV-Spark100	Pfizer (Spark)
	Phase 2: NCT03307980 (Recruiting)		
	Phase 3: NCT03861273 (Recruiting)		
AAV5-hFIX (AMT-060)	Phase 1/2: NCT02396342 (Completed)	WT FIX-AAV5	UniQure
BAX 335 (AskBio009)	Phase 1/2: NCT01687608 (Active, not recruiting)	FIX Padua-AAV8	Baxalta (Shire)
YUVA-GT-F901	Phase 1: NCT03961243 (Not yet recruiting)	FIX-Lentivector	Shenzhen Geno- Immune Medical Institute
BBM-H901	Phase 1: NCT04135300 (Active, not recruiting)	FIX-recombinant AAV capsid	Institute of Haematology & Blood Diseases Hospital; East China University of Science and Technology
scAAV 2/8-LP1-hFIXco	Phase 1: NCT00979238 (Active, not recruiting)	FIX-AAV 2/8	St. Jude Children's Research Hospital

Abbreviation: rFIX, recombinant factor IX.

[a]Half-life for each of these products was derived from published data and is provided as clinical reference for treatment decisions. No head-to-head data exist for comparison.

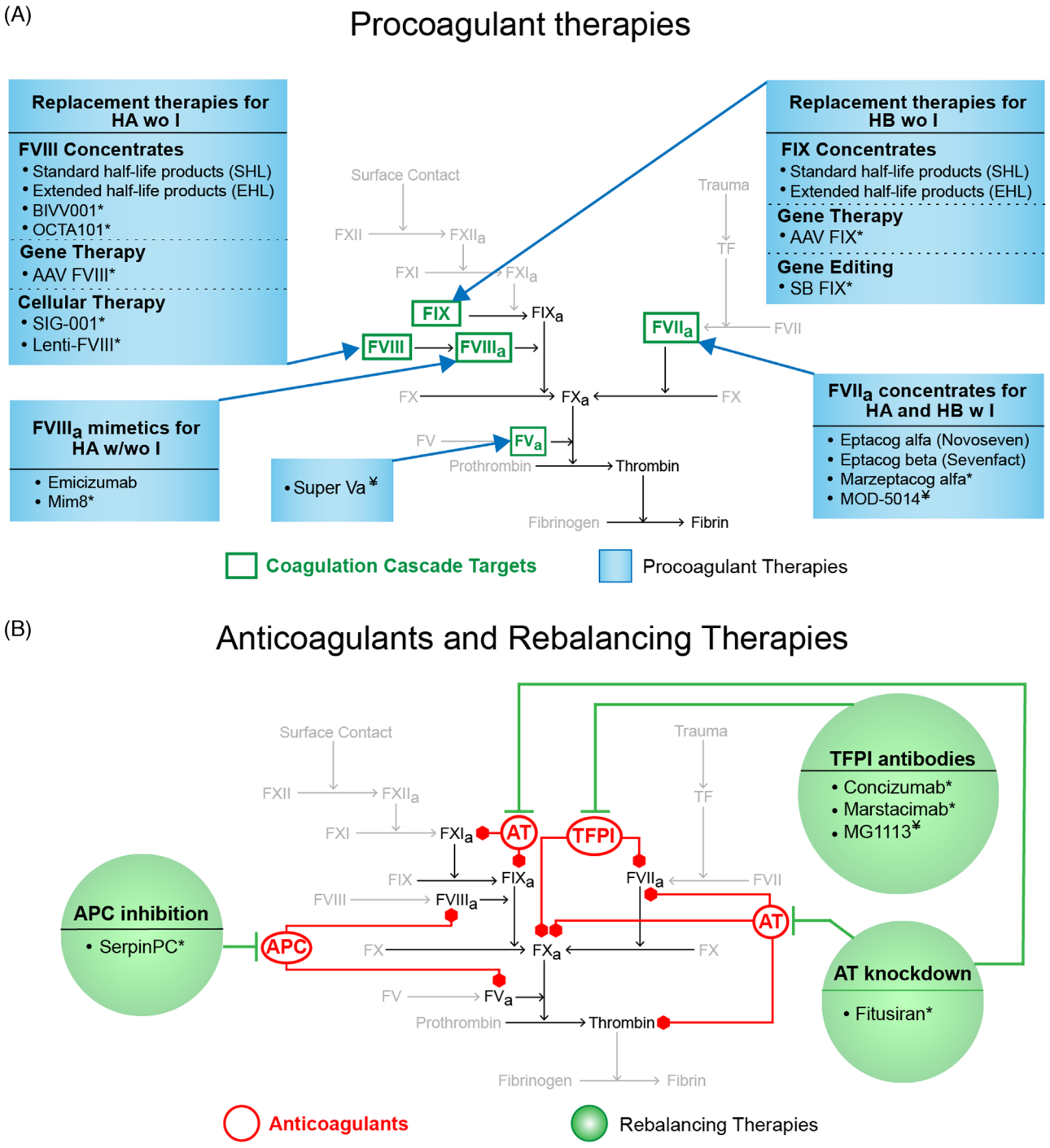

FIGURE 2 A simplified illustration of the intervention targets in the coagulation cascade for traditional and novel therapies in haemophilia A and B. Panel A depicts procoagulant therapies. Panel B shows products that target anticoagulants. HA, haemophilia A; HB, haemophilia B; w I, with inhibitor; wo I, without inhibitor; w/wo I, with or without inhibitor; *investigational therapies, ¥ agents in preclinical development; TFPI, tissue factor pathway inhibitor; APC, activated protein C; AT, antithrombin

administered subcutaneously, and may be used to treat HA or HB with or without inhibitors (Table 4).

2.4 | Bypassing agents

There are two recombinant factor VIIa products (NovoSevenRT and SevenFACT), and one human plasma-derived activated prothrombin complex concentrate (FEIBA) licensed to treat bleeding episodes in patients with HA or HB with inhibitors (Table 5). Marzeptacog alfa is an investigational modified rFVIIa with four amino acid substitutions engineered to increase potency nine-fold and half-life up to 13.1 h, and designed for subcutaneous administration;[18] however, the manufacturer halted their clinical development programme in November 2021.

TABLE 4 Investigational rebalancing agents for haemophilia A and B

Nonfactor prophylactic therapies for haemophilia A and B with or without inhibitor		
Product	**Status/clinical trial number**	**Approximate half-life (hours)[a]**
	siRNA-AT	
Fitusiran[56,98] (subcutaneous: 1 × every other month, may switch to 1 × per month based on AT levels)	Phase 3: NCT03549871 (Active, not recruiting)	Adults: 2.6–5.3
	Phase 3: NCT03754790 (Recruiting)	Investigational rebalancing agents for haemophilia A and B
	Phase 3: NCT03417245, NCT03417102 (Completed)	
	Phase 2/3: NCT03974113 (Recruiting)	
	Phase 1/2: (Active, not recruiting)	
	Anti-TFPI monoclonal antibodies	
Concizumab[57,99] (subcutaneous: daily)	Phase 3: NCT05135559 (Not yet recruiting)	Adults: 31.1–74.2
	Phase 3: NCT04083781 (Active, not recruiting)	
	Phase 3: NCT04082429 (Recruiting)	
	Phase 2: NCT03196284, NCT03196297 (Completed)	
	Phase 1: NCT02490787 (Completed)	
PF-06741086, Marstacimab[100] (subcutaneous: 1 × per week)	Phase 3: NCT03938792, NCT05145127 (Recruiting)	Adults: 33.3–65.8
	Phase 2: NCT03363321, NCT02974855 (Completed)	
	Phase 1: NCT04878731, NCT02531815, NCT04832139 (Completed)	
MG1113[101] (subcutaneous)	Phase 1: NCT03855696 (Completed)	Not yet reported
	Anti-APC	
SerpinPC[102] (subcutaneous: 1 × per month)	Phase 1/2: NCT04073498 (Active, not recruiting)	Adults: 4–5 days
	Gain-of-function engineered factor	
Super FVa[103]	Preclinical development	Not yet reported

Abbreviations: APC, activated protein C; siRNA-AT, small interfering RNA targeting antithrombin; TFPI, tissue factor pathway inhibitor.
[a]Half-life for each of these agents was derived from published data and is provided as clinical reference for treatment decisions. No head-to-head data exist for comparison. Half-life of rebalancing agents does not directly correlate with haemostatic efficacy.

3 | TECHNOLOGICAL ADVANCES IN CARE

3.1 | Musculoskeletal ultrasonography

Haemophilic arthropathy represents significant morbidity and financial burden for PwH, even with early adoption of prophylaxis. Prompt and accurate diagnosis using clinical and imaging scoring tools[3] is required to identify joint bleeding to prevent or slow subsequent damage and progression. These empiric tools are essential as patient/physician perception of bleeding as the cause of painful musculoskeletal episodes is inaccurate in more than half of cases.[4]

Additionally, care of persons with mild haemophilia is often complicated by a delayed and complex presentation of bleeding episodes; this may also apply to PwH with more severe disease on novel therapies if they are inexperienced in recognising a bleeding event. There is a gap in the evaluation of clinically asymptomatic or nearly asymptomatic joints of young PwH in whom joint disease may be missed or underestimated because of barriers to obtain baseline magnetic resonance imaging.[19] Musculoskeletal ultrasound (MSKUS), specifically point-of-care MSKUS (POC-MSKUS), has emerged as a promising tool to meet this need with good correlation of MSKUS scores with clinical constructs and an association between MSKUS findings and functional joint status.[4,20] Further clinical evidence is needed to determine if MSKUS-detectable findings in haemophilic arthropathy are sensitive to prophylactic therapy changes in children or adults.

POC-MSKUS adoption and implementation rates by care providers in haemophilia treatment centres (HTCs) are rising globally,[4,21] and

TABLE 5 Approved and investigational bypassing agents

Bypassing agents for HA or HB with inhibitor			
Product	**Status/clinical trial number**	**Approximate half-life (hours)[a]**	**Mode and frequency of administration**
	Recombinant FVIIa		
NovoSeven RT, eptacog alfa[104]	FDA approved	Adults: 3.2	Intravenous: 90 mcg/kg every 2 h
		Peds: 1.9–3.0	
SevenFACT, eptacog beta[105]	FDA approved	Adults; 75 mcg/kg: 1.7	Intravenous; two initial dose regimens:
		Adults; 225 mcg/kg: 1.4	75 mcg/kg every 3 h; or
			Initial dose of 225 mcg/kg. If haemostasis is not achieved within 9 h, additional 75 mcg/kg doses may be administered every 3 h as needed
	Investigational recombinant FVIIa		
MarzAA, marzeptacog alfa[18] (four engineered amino acid substitutions)	Phase 3: NCT04489537 (Development halted, Nov 2021)	Adults: 13.1	Subcutaneous; daily Dosing not yet reported
	Phase 1/2: NCT04548791 (Development halted, Nov 2021)		
	Phase 2: NCT03407651 (Completed)		
	Phase 1: NCT04072237 (Completed)		
	Plasma-derived activated prothrombin complex concentrate		
FEIBA[106,107]	FDA approved	Adults: 4–7	Intravenous; 50–100 units/kg, every 6–12 h for bleed treatment

Abbreviations: HA, haemophilia A; HB, haemophilia B; FVIIa, activated factor VII.

[a]Half-life for each bypassing agent was derived from published data and is provided as clinical reference for treatment decisions. No head-to-head data exist for comparison. There are no data correlating half-life with haemostatic efficacy.

point-of-care imaging is now part of the medical student curriculum. The percentage of HTCs adopting this method varies by region (Table 6). A recent global HTC survey reported about 50% using POC-MSKUS. Perceived barriers to implementation revealed by a survey from the Prophylaxis Study Group were lack of personnel trained to deliver POC-MSKUS (69.2%; 74/107), closely followed by the time commitment for study performance (68.2%; 73/107).[21]

In addition to supporting the clinical evaluation of acute bleeding and/or painful musculoskeletal episodes,[4] POC-MSKUS has the potential to follow joints longitudinally and provide insight into disease activity (joint effusion, synovial proliferation) and, to a lesser extent, osteochondral derangement.[4,19,20,22] Several protocols and scoring systems have been proposed with varying degrees of validation, adoption, and implementation by HTCs.[23–25]

There remain knowledge gaps that need to be addressed as MSKUS is increasingly used to support clinical decision making and is incorporated into research and clinical trials.[19,20,26,27] A standardised and harmonised scoring system that builds in complexity yet allows for comparison should be developed and adopted to address these issues. Future research should focus on how ultrasound protocols can be standardised, validated, and implemented across various clinical and research settings.

3.2 | Near-patient and individualised care

Handheld and pocket POC-MSKUS probes are within patients' reach;[28] establishing a solid foundation for clinical implementation and understanding the appropriate application and limitations of this tool are critical to support personalised and patient-centred care.[19,29]

In 2010, proof of concept was demonstrated for the feasibility of at-home diagnosis of joint bleeding in PwHA treated with prophylaxis.[30] The next step in the evolution of near-patient care is to train patients to image their joints when a bleed is suspected. An ongoing clinical trial (NCT04131920) assesses the feasibility and utility of a patient handheld home ultrasound (HHUS) to determine if joint pain is caused by bleeding. Telehealth and image transmission support PwH to assess bleeds at home with this modality. Recently, 10 PwH were trained

TABLE 6 Use of musculoskeletal ultrasonography: results from the global survey of HTCs[4]

HTCs and ultrasound use	Number (%)	Regions using ultrasonography [number (%)]	
Routinely use MSKUS	42/76 (55%)	Unknown	
Routinely use POC-MSKUS	40/76 (53%)	European HTCs	22/37 (60%)
		Other	7/15 (47%)
		North American HTCs	25/57 (44%)

Abbreviations: HTC, haemophilia treatment centre; MSKUS, musculoskeletal ultrasonography; POC-MSKUS, point-of-care musculoskeletal ultrasonography.

to use HHUS to image views for haemarthrosis detection in ankles, elbows, and knees. Three months after training, with guidance, participants were comfortable with the technology and could acquire the correct image with near-perfect quality in minutes. Providers felt that it was easy to guide the participants and believed that participants would learn and improve their HHUS skills even with infrequent use.[31]

Currently, PwH travel to a healthcare provider or laboratory for haemostatic assays. The provision of at-home coagulation testing would increase convenience, reduce laboratory variability, allow for resource conservation, and potentially improve access to medical care. It may enable the monitoring of novel agents depending on the assay system. ENZYPAD, which comprises a blood sampling device, a microfluidic cartridge, a processor, and a mobile phone application, is being developed for commercial use (enzyre.org). This product may support at-home blood coagulation analysis, instantly sending results to the healthcare provider.

3.3 | Use of pharmacokinetics for individualised care

Prophylactic therapy with factor replacement is costly and challenging due to the need for frequent intravenous infusions. The implementation of personalised prophylaxis in PwHA without inhibitors was evaluated in a longitudinal, multicentre, prospective feasibility study of 15 children and adults. Participants used the Web Accessible Population Pharmacokinetic Service -Haemophilia (WAPPS-Hemo.org) to generate pharmacokinetic (PK) profiles.[32] Currently, WAPPS-Hemo is a global network comprising 591 centres and over 10,000 patients. This site provides myWAPPS to enable a view of real-time estimates of factor levels (Figure 3), ideally resulting in improved patient education and informed adjustment of the patient's treatment plan.

3.4 | Artificial intelligence in haemophilia care

The use of information and communication technology in health care, E-health, is an important approach to improve access and quality of care for patients living with chronic diseases;[33] this technology supports care advancement, especially in resource-constrained countries.[34,35] AI in health care is an overarching term used to describe the use of machine-learning algorithms and software to simulate human reasoning in analysis and interpretation of complex medical and health care data. AI has been proposed to improve access to health care professionals and aid in diagnoses for PwH.

AI development fostered fast market penetration of innovative messaging platforms and health chatbots.[36,37] Recently, a chatbot was designed to address identified disease knowledge gaps among PwH in Senegal.[38] This unique chatbot is designed to recognize voices speaking in French and Wolof (a common language in Senegal), providing text answers in both languages through a user-friendly interface integrated into both Android and Apple iOS devices.[39] A multidisciplinary team of blood disorder specialists, data scientists in Switzerland, Senegal, and Denmark, and a cohort of PwH living in Senegal are currently involved in the latest technical project development phase. The AI chatbot will be implemented in several African countries, including Gambia and Ivory Coast. The comprehensive educational content adapted to the local needs of PwH coupled with the AI digital platform might also act as a catalyst to empower PwH and other blood disorders in Africa and beyond. The usability and impact of the AI chatbot will be assessed through Patient-Reported Outcomes Measurement tools.

Advances in AI further support streamlined patient care; Klara is a secure conversational patient engagement platform that improves patient experience and operational efficiency by up to 30% by streamlining inbound and outbound patient communication. Klara may be used for telehealth as well as for HIPAA-compliant texting that is then automated using smart workflow tools and AI.

AI can also potentially improve at-home POC-MSKUS by overcoming access to care barriers, including distance from the HTC or reduced mobility. Combining AI with currently available HHUS will allow accurate recognition of joint bleeds. An international expert group in data science, ultrasonography, and haemophilia care is developing an algorithm that was trained by viewing over 50,000 images of the knee from community controls and over 1,000 images of the knee from PwH. Expert review of images for distended synovial recess and blood confirmed that reliable detection of distended synovial recesses using AI was possible. The results from this pilot study serve as proof of concept to develop an algorithm to detect synovial recess distension as an indirect indication of bleeding. Because the algorithm requires more training with PwH images to differentiate blood from synovial fluid, a clinical HTC validation study is planned. In parallel, developers are creating a tool to guide transducer positioning to support the use of ultrasound by a patient or caregiver at home.[40]

AI, as a self-learning program that mimics human cognition, requires data input that is then integrated, analysed, and used for the machine

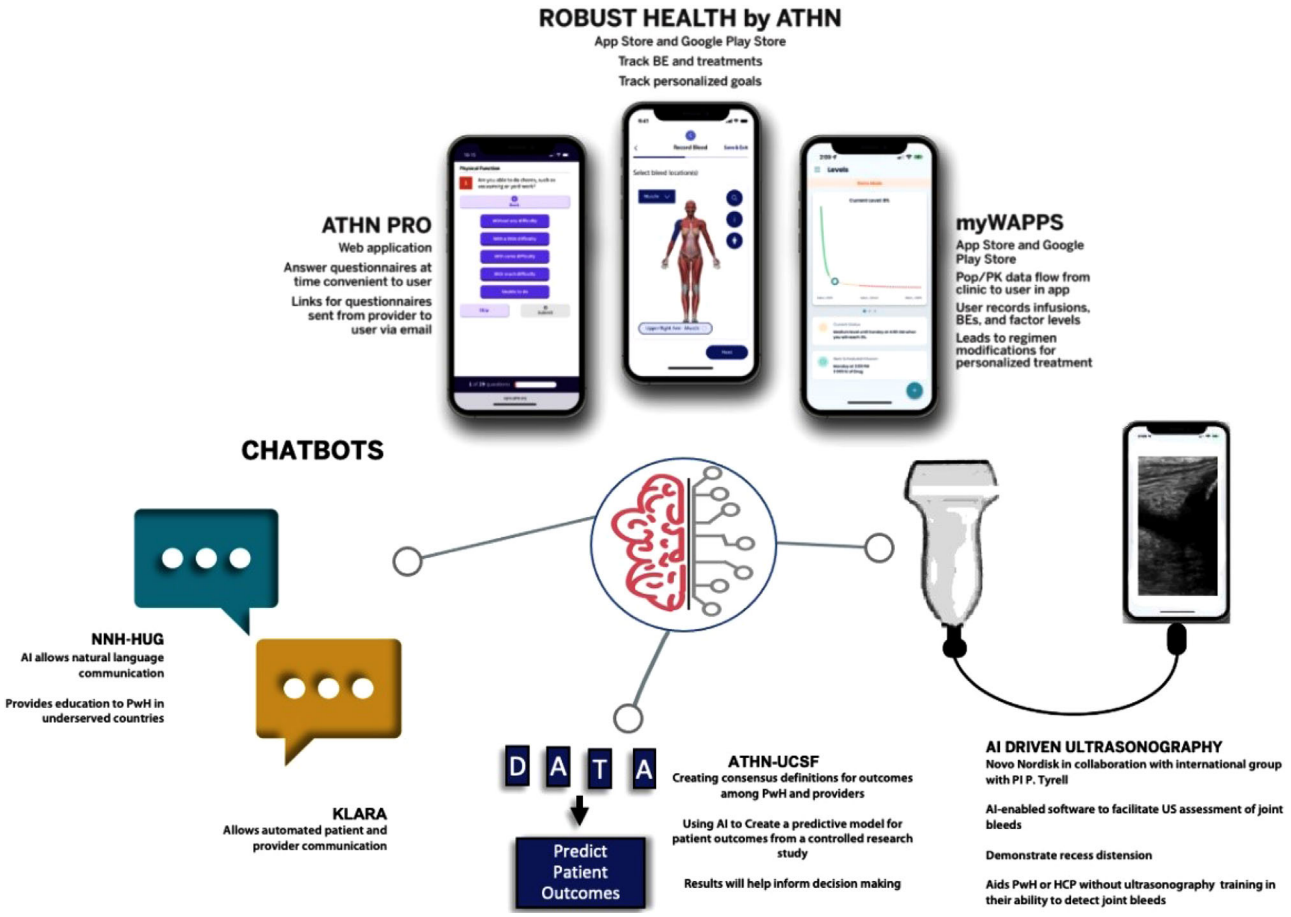

FIGURE 3 Current innovations in application development and artificial intelligence (AI) projects to educate, communicate, and improve the lives of PwH. Top panel summarizes American Thrombosis and Hemostasis Network-led applications: ATHN PRO, ROBUST HEALTH, and myWAPPS. Bottom panel lists current AI and machine learning projects: chatbots, integrated messaging and telehealth platform, data-driven predictive model for outcomes, and AI-enabled software to assist ultrasonographic visualisations of joints. BE, bleeding event; Pop/PK, population pharmacokinetics; PwH, people with haemophilia

to evolve and refine decision making. The availability of large data systems is critical for deep learning. Researchers and clinicians are making steady progress to develop technological solutions for patients who input clinical data into web-based or mobile applications. A recent focus has been to expand data collection to include outcome measures related to individuals' QoL and goals, targeting functional cures, and enabling PwH to live as normal a life as possible.

Multiple systems for data collection within the haemophilia community exist worldwide. Digital diaries and mobile applications ease the burden to record data and outcomes. The American Thrombosis and Hemostasis Network (ATHN) has an affiliate network of over 145 US based HTCs that provide services to patients with coagulation disorders; ATHN routinely collects anonymised demographic, clinical, and genetic data from thousands of US patients into a national database (ATHNdataset). ATHN's goal is to secure data, advance knowledge, transform care—and ultimately improve the lives of people with bleeding and clotting disorders.[41] In partnership with research groups, ATHN created several smartphone apps that patients can use to assist treatment reporting and management (Figure 3).

A recent ATHN initiative in collaboration with the Center for Digital Health Innovation at the University of California, San Francisco focuses on AI and machine learning.[42] This group is training algorithms to evaluate large, anonymised datasets from PwH to determine how markers are associated with defined patient outcomes. AI algorithms will further be trained based on ATHN studies and information from the ATHNdataset used to validate findings. As part of this initiative, funded by a Pfizer Global Medical Grant, ATHN partnered with the National Hemophilia Foundation to develop consensus definitions of poor outcomes for PwH. The ultimate goal is to create a predictive model to identify PwH at risk for poor outcomes to assist providers to design interventions that improve care.

4 | CHALLENGES IN PATIENT MANAGEMENT

The role of HTCs to guide personalised care delivery for optimal outcomes is critical as treatment options expand. Novel therapeutics require increased pharmacovigilance for possible adverse events; an organised national network with centralised data collection is required

to advance care. HTCs also remain at the forefront of managing several preventative care areas, including monitoring bone health, identification, and risk mitigation of those at high risk of cardiovascular disease (CVD), thrombosis risk mitigation, prophylaxis optimisation, and perioperative management. HTC multidisciplinary teams have expanded their focus to address these and other emerging issues, such as programme design and implementation to meet the needs of special populations, including but not limited to the diagnosis and treatment of women, newborns, and those racially or ethnically diverse.

4.1 | Bone health

Reduced bone marrow density was observed in children and adult PwH. The role of FVIII in human bone metabolism is not entirely elucidated. In mice and in vitro assays, FVIII–VWF complex has a direct role in bone remodelling. FVIII–VWF binds to osteoprotegerin and receptor activator of NF-kappa B ligand (RANKL), enhancing the inhibitory effect of both RANKL and osteoprotegerin-induced osteoclastogenesis.[43]

Emicizumab's ability to support bone metabolism in PwHA was recently evaluated in a study comparing PwHA on rFVIII or emicizumab therapy and healthy controls. Researchers found that bone biomarkers in PwHA on emicizumab were comparable to those from patients on FVIII prophylaxis.[44]

4.2 | Cardiovascular disease

Cardiovascular disease is the leading cause of mortality in the US and is responsible for nearly 1 in 4 deaths.[45,46] Near-normal lifespans of PwH in conjunction with improved haemostatic levels have led to an increased need to manage age-related comorbidities. Historically, the bleeding risk in PwH precluded antithrombotic therapy; now sustained haemostasis with current prophylaxis regimens allows antithrombotic therapy in selected individuals.[47]

Hypertension is a strong risk factor for mortality and CVD.[48] Several historical studies suggested a higher prevalence of hypertension in PwH, the pathophysiology of which is poorly defined. A recent systematic review revealed a higher prevalence of hypertension in PwH, with an odds ratio of 1.45 compared to the general population, that was independent of usual cardiovascular risk factors, such as obesity,[49] diabetes, and smoking.[50] Epidemiological data from CDC's Community Counts suggest that the prevalence of obesity in registry participants 20 years of age and older was 34%, compared with 19% of the national population. Aggressive CVD risk factor stratification and mitigation should be integrated into the comprehensive care of PwH.[51]

4.3 | Thrombotic risk

Thrombotic risk in PwH is mitigated by clotting factor deficiency, with rare cases reported mostly in the setting of known risk factors, such as orthopaedic surgery, use of bypassing agents, and inherited or acquired hypercoagulable disorders.[52–54] Achieving consistent haemostatic factor levels in PwH will necessitate individualized thrombotic risk assessment with appropriate thromboprophylaxis as needed to ensure optimal patient outcomes. Rebalancing agents represent an important advance for fragile populations such as PwHB with inhibitors, who have limited therapeutic options and inadequate bleed prophylaxis. Patients receiving rebalancing agents require close monitoring due to increased thrombotic risk. The long half-life of nonfactor therapies needs to be considered, especially when the need for additional haemostatic therapy arises.[55] Risk mitigation strategies have been implemented for agents that have been linked to unanticipated thrombotic events.[56,57] Continued diligence with monitoring and reporting of real-world data will be important post approval of novel agents.

4.4 | Treatment of newborns

WFH guidelines recommend early prophylaxis with clotting factor concentrates or other haemostatic agents before the onset of joint bleeding, ideally before age three.[58]

As emicizumab abrogates the need for venous access, a significant challenge in infants and children, earlier prophylaxis initiation is now feasible. Further investigation is needed to determine the ideal timing of prophylaxis initiation with emicizumab as well as the ultimate impact of delayed exogenous factor exposure on inhibitor development.

4.5 | Striving toward health equity

Inequitable healthcare access by disadvantaged populations leads to an increased preventable disease burden. Identifying care barriers, including gender inequity, financial challenges, education, race, language, and cultural diversity/ethnicity is crucial to advance health equity in haemophilia care.

4.5.1 | Women and girls with haemophilia

The X-linked inheritance pattern of haemophilia has introduced a bias against women, historically labelled carriers, and presumed asymptomatic.[59] This bias has often led to suboptimal clinical care and precluded women and girls with haemophilia (WGH) from clinical trial participation. Community Counts, the US surveillance database for bleeding disorders, reported that 0.5% of severe, 1.4% of moderate, and ~20% of mild PwHA were female.[60]

Recently, a new haemophilia female nomenclature was established by the International Society on Thrombosis and Haemostasis, considering FVIII and FIX plasma levels and bleeding phenotype. Consistent with males with haemophilia, females with low FVIII or FIX plasma levels of <0.01, 0.01–0.05, and >0.05–< 0.4 IU/ml were defined as having severe, moderate, and mild haemophilia, respectively.[61] In patients whose FVIII/FIX plasma levels are ≥0.4 IU/ml, the bleeding phenotype

differentiates between symptomatic and asymptomatic carriers. This nomenclature change was driven by identifying the need to increase earlier diagnosis, improve access to care, and expand clinical trial participation in women.

4.5.2 | Racial inequity

A literature review reveals sparse data on health disparities among minorities with bleeding disorders, consistent with scientific underrepresentation and significant knowledge gaps. Treatment challenges include delay in diagnosis, socioeconomic disparities, and educational barriers.[62] Non-white adolescent PwHA are five times more likely to report high levels of chronic pain despite no difference in adherence to recommended clotting factor treatment regimens. Data reveal that the inhibitor prevalence amongst PwH is highest among Black and Hispanic communities.[63–65] In addition, a retrospective single-centre analysis suggested a significantly lower ITI success rate among African Americans (58% vs. 92% in Caucasians).[66] In contrast, the North American Immune Tolerance Registry found no difference in success rates. Further studies are needed to determine whether the initiation of ITI is the same in racially diverse groups and if the success rate is indeed lower in these high-risk populations.[67] In 2021, the Hemophilia Federation of America established the Bleeding Disorders Health Disparities Council to help identify and address issues faced by the bleeding disorder community.

5 | CONCLUSION

In summary, there have been wide-ranging advances in haemophilia therapeutics and in management innovations that together support improved outcomes and QoL for all living with bleeding disorders. Questions remain for both new and standard therapies. Opportunities continue to improve treatment, address issues across the life span, and identify and address disparities due to gender, race, ethnicity, and other areas of inequality. New therapies are gradually becoming accessible to the global bleeding disorder community. Implementing these advances to improve the health and outcomes of all patients requires further work. As advances in care accelerate at an unprecedented pace, our work as care providers has expanded and we as a community must strive to meet these new challenges together.

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AUTHOR CONTRIBUTIONS

Magdalena Lewandowska, Sonia Nasr, and Amy D. Shapiro contributed equally to this work. All authors reviewed and approved the manuscript.

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