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Contemporary Challenges in Hemophilia Care

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Acknowledgements

Lying, thinking
Last night
How to find my soul a home
Where water is not thirsty
And bread loaf is not stone
I came up with one thing
And I don't believe I'm wrong
That nobody,
But nobody
Can make it out here alone.

- from "Alone" by Maya Angelou (1928 – 2014)

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Summary

Contemporary, comprehensive hemophilia care is characterized by its multifaceted nature, involving multiple professions and disciplines to provide holistic care. The increasing complexity of hemophilia care gives rise to new challenges, four of which will be explored in this thesis.

The first challenge involves navigating the evolving treatment landscape for hemophilia, which has witnessed a remarkable revolution in recent years. Those new treatments aim to decrease the treatment burden and to provide highly efficient bleeding protection. In the case of gene therapy, they even represent a potential cure of hemophilia. In this work, we present real-world data exploring patient eligibility for hemophilia gene therapy, as well as data on European healthcare providers' experiences with emicizumab, a new subcutaneously administered treatment for hemophilia A. We also describe outcomes of emicizumab use in obese persons with hemophilia followed at the Cliniques universitaires Saint-Luc. Stemming from the successes of these emerging therapeutic options that allow a dual physical and mental liberation of the disease, this thesis also presents a new ambition and challenge for hemophilia care encapsulated in the concept of achieving a “hemophilia-free mind”.

It is crucial to recognize that modern hemophilia care extends beyond male persons with hemophilia. Heterozygous hemophilia carriers, as well as women and girls with hemophilia, are impacted by hemophilia as well and require appropriate management. Addressing this, we present the original findings of a proactive hemophilia carrier screening study conducted at the Cliniques universitaires Saint-Luc.

Finally, inspired by the necessity to collect structured and digital data, we share our experiences in developing a custom-built hemophilia navigator within the Epic electronic health record system, enabling the integration of several hundreds of variables pertinent to the holistic comprehensive care for persons with hemophilia.

Biography of Evelien Krumb, MD

Evelien Krumb was born in 1992 in Groß-Gerau, Germany. After her medical bachelor (University of Namur, 2011-2014) and master (Université catholique de Louvain, UCLouvain 2014-2018) studies, she obtained her medical degree from UCLouvain in 2018. Subsequently, in the same year, she commenced a specialization program in internal medicine at UCLouvain.

In 2020, she enrolled in a full-time PhD program in medical sciences at UCLouvain in conjunction with her specialization. Upon completion of her doctoral thesis, she intends to conclude her specialization in internal medicine and hematology, with aspirations to further specialize in the field of hemostasis and thrombosis. In addition to her academic pursuits, she has served as the Social Media Editor of the journal *Haemophilia* (John Wiley & Sons Ltd) since 2022.

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Index of Abbreviations

AAV	Adeno-associated Virus
ABR	Annualized Bleeding Rate
ADA	Anti-Drug Antibodies
aPCC	activated Prothrombin Complex Concentrate
BMI	Body Mass Index
COVID-19	Coronavirus disease 2019
CUSL	Cliniques universitaires Saint-Luc
EAHAD	European Association for Haemophilia and Allied Disorders
EHL	Extended Half-life
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FIX	Factor IX
FVIII	Factor VIII
FVIIIa	Activated Factor VIII
HA	Hemophilia A
HB	Hemophilia B
HCV	Hepatitis C Virus
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
HMB	Heavy Menstrual Bleeding
HTC	Hemophilia Treatment Center
IQR	Interquartile Range
ISTH	International Society on Thrombosis and Hemostasis
ITI	Immune Tolerance Induction
LICs	Low-Income Countries
LMICS	Lower-Middle Income Countries
NAbs	Neutralizing Antibodies
PK	Pharmacokinetics
PPH	Postpartum Hemorrhage
PWHs	Persons with Hemophilia

PWHAs	Persons with Hemophilia A
PWHBs	Persons with Hemophilia B
rFIX	recombinant Factor IX
rFVII	recombinant Factor VII
rFVIII	recombinant Factor VIII
RR	Relative Risk
RTB	Reproductive Tract Bleeding
SD	Standard Deviation
SHL	Standard Half-life
TFPI	Tissue Factor Pathway Inhibitor
VWF:Ag	Von Willebrand Factor Antigen
VWF:RCo	Von Willebrand Ristocetin Cofactor Activity
WFH	World Federation of Hemophilia
WGH	Women and Girls with Hemophilia

Introduction

Definition of Hemophilia

Hemophilia A and B are congenital bleeding disorders characterized by a deficiency in coagulation factors VIII (FVIII) (hemophilia A, HA) or IX (FIX) (hemophilia B, HB).[1] They result from a multitude of genetic variants affecting the factor 8 and factor 9 genes located on the long arm of the X chromosome.[2] To date, for each of these genes, there are more than 2000 variants registered in the European Association for Haemophilia and Allied Disorders (EAHAD) coagulation factor variant databases.[3] These variants can either lead to a diminished production or a complete absence of coagulation factors, resulting in varying degrees of hemophilia severity. Hemophilia can manifest as mild (residual clotting factor activity between 5 and less than 40 IU/dL), moderate (between 1 and 5 IU/dL), or severe (less than 1 IU/dL).[4] In some cases, residual clotting factor activity may not align with the observed bleeding phenotype.[5,6] The prevalence at birth of HA and HB has been estimated to be 17.1 per 100 000 male individuals and 3.8 per 100 000 male individuals, respectively.[7]

Without appropriate bleeding prophylaxis, individuals with severe hemophilia will typically suffer from joint hemorrhage or from other, potentially fatal, internal hemorrhage. Recurrent joint bleeding episodes will lead to joint damage and eventually disability. Such joint damage has also been observed in some people with moderate hemophilia, hence bleeding prophylaxis is now also recommended for this group of patients.[8] For those with mild hemophilia, bleeding prophylaxis is primarily required before invasive procedures as there is usually no unprovoked bleeding.[1] Various types of bleeding prophylaxis available to date will be detailed in the following section.

Traditionally perceived as exclusively affecting male individuals due to its X-linked recessive inheritance, hemophilia research in recent decades has revealed that heterozygous female relatives of persons with hemophilia (PWHs) may not only pass on the affected X chromosome to their offspring but also be affected by hemophilia themselves.[9] The subject of hemophilia carriers and women and girls with hemophilia (WGH) will be further examined in Section 3 of this thesis.

The History of Hemophilia Care, Defined by Overcoming Challenges

The evolution of hemophilia care cannot be adequately described without acknowledging the numerous challenges that PWHs, caregivers, and healthcare providers have faced over the years, the first one being **understanding and diagnosing hemophilia**. While the earliest accounts of an abnormal bleeding tendency date back to the second century AD[1,10,11], the term 'hemophilia' and the understanding that HA and HB result from deficiencies in distinct clotting factors did not emerge until the early 19th century and the 1950s, respectively.[1,12] The evolution of modern hemophilia care thus spans the past seven decades.

Prior to the mid-20th century, lacking effective treatment options, PWHs, especially those with a severe bleeding phenotype, were often left to confront a grim fate. The primary challenge during this time revolved around **sustaining the lives of patients**, a task that was often hindered by the limited treatment options available, which primarily consisted of supportive measures and transfusions of whole blood or fresh frozen plasma (FFP).[13] Consequently, those with severe hemophilia frequently succumbed to uncontrollable bleeding at a young age.[1]

In the 1950s, first experiments of purification of FVIII or “antihemophilic factor” and use in persons with hemophilia A (PWHAs) were published by Blombaeck, Kekwick, Soulier and their respective colleagues, enabled by the first assays to measure coagulation factor activity.[11,13–16] Similar works on purification of FIX, or “antihemophilic factor B”, were carried out by Aggeler et al.[17] The discovery of cryoprecipitate by Judith Pool in 1964[18] marked an important step toward effective treatment of bleeds in PWHAs.[10,11] The equivalent for PWHBs was prothrombin complex concentrate (PCC), first marketed in 1953.[11] These products were however not suitable for home treatment, due to their storage and administration requirements.[11,13]

The advent of plasma-derived clotting factor concentrates in the 1960s clearly was a major breakthrough, as it allowed home-treatment for the first time in the 1970s, and also marked the introduction of prophylactic treatment plans as we know them today, aiming to prevent bleeding rather than solely treating acute bleeding episodes.[1,11,13,19] Consequently, a decrease in bleeding frequency, accompanied by reduced pain and disability, translated

into enhanced socio-professional opportunities and an overall improved quality of life for PWHs.[19] **New treatment goals and challenges arose : to make life with hemophilia as "normal" as possible and to provide comprehensive care in specialized centers**.[19]

The "golden era"[13] of hemophilia care in the 1970s was followed by a somber period, overshadowed by the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) epidemics. During that time, plasma-derived coagulation factor replacement products were produced from plasma donor pools, aggregating donations from up to 20 000 donors, and lacking viral inactivation measures.[20] In the 1980s, HIV and HCV spread among PWHs through contaminated blood products, leading to numerous fatalities, PWHs suffering from AIDS and/or liver disease, and psychological trauma in the hemophilia community.[19–22] **Consequently, ensuring the safety of blood products and seeking cures for HIV and HCV infections became paramount**.

Fortunately, in the 1990s, advancements in gene sequencing allowed the production of recombinant clotting factors devoid of infectious risks and viral inactivation procedures were implemented for blood products.[13] Moreover, activated PCC (aPCC) and recombinant FVIIa (rFVIIa), the so-called "bypassing agents", emerged as new treatment options for PWHs who developed inhibitors.[11,13] Additionally, the implementation of immune tolerance induction (ITI) brought new hope for those patients.[13]

The very beginning of the 21st century has been described as a time of "consolidation"[13] and even "stagnation"[19], with regards to innovation in hemophilia care. Still, the first clinical trials for hemophilia gene therapy were started in the early 2000s[23], pegylated interferon in combination with ribavirin and later direct-acting antivirals (DAAs) now offered the possibility of eradicating HCV[13,19,24] and new biomolecular techniques facilitated genetic diagnosis of PWHs and their relatives.[2,25]

In the 2010s, innovation in hemophilia care picked up speed again, **striving for more effective bleeding prevention and reduced treatment burden**: the first clinical trials for hemophilia gene therapy in humans yielded promising early results[26–29], extended half-life (EHL) clotting factors were developed, as well as subcutaneously administered "non-replacement" therapies.[13]

Different types of EHL clotting factors exist, distinguished by the method employed to extend their plasma half-life. These factors are either fused with the fragment crystallizable (Fc) region of Immunoglobulin (Ig) G1 or albumin, or linked with polymer polyethylene glycol (PEG) to prolong their half-life.[13,30] In practice, this translates into a reduction of infusion frequency from three to two times weekly for PWHAs and from twice weekly to once every 10 to 14 days in PWHBs.[31] A further prolongation of FVIII half-life was achieved by linking a rFVIII molecule with a recombinant D'D3 region of VWF and an "XTEN" polypeptide chain. This ultra-long rFVIII molecule (efanesoctocog alfa) allows for a weekly intravenous dosing.[30,32,33]

Non-replacement therapies include bispecific monoclonal antibodies mimicking the action of FVIIIa (emicizumab, Mim-8), a small interfering RNA agent inhibiting antithrombin (Fitusiran), anti-TFPI antibodies (concizumab, marstacimab) and serpin PC, an inhibitor of activated protein C (APC).[13,32] Emicizumab was approved and commercialized in 2018 under the name "Hemlibra".[34,35] All other non-replacement therapies are currently under investigation in clinical trials.

So far in the 2020s, we have witnessed the approval and commercialization of the first gene therapy agents by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These include valoctocogene roxaparvovec (Roctavian) for HA[36] and etranacogene dezaparvovec (Hemgenix) for HB[37]. Additionally, in 2023, the ultra-long rFVIII molecule efanesoctocog alfa, marketed under the name "ALTUVIIIO", received FDA approval for use in children and adults with HA.[33]

Contemporary Challenges in Hemophilia Care

Today, in high-income countries (HICs), hemophilia can be readily diagnosed, life expectancy of PWHs has been drastically improved[1], although not yet fully normalized[7], and safe and highly effective treatments are available. But still, modern hemophilia care is not without challenges, some of which also reflect currently ongoing societal changes.

Now more than ever, our society is defined by **innovation across diverse sectors**, such as technology in general, information technology, and the pharmaceutical industry. In the field of hemophilia, this has resulted in an

unprecedented variety of treatment options for PWHs. While the latter undoubtedly represents a significant advancement in providing PWHs with optimal care, **navigating this new treatment landscape** can be daunting. Shared decision-making approaches for choice of treatment are being studied and adopted in order to foster collaboration between patients, family members and healthcare professionals when treatment decisions are to be made.[38]

The healthcare sector has been deeply impacted by digital advancements or the "digital age".[39] A clear example of this process emerged during the COVID-19 pandemic, with widespread adoption of telehealth services. While digitalization may pose challenges, such as economic factors or accessibility issues, it also presents opportunities. In hemophilia care, for instance, electronic health records (EHRs) hold immense potential for managing the growing complexities of comprehensive care.

The importance of mental health is increasingly recognized in our society, and there is a growing emphasis within healthcare on promoting the mental well-being of both patients and healthcare workers. **This paradigm shift is also evident in hemophilia care**, with certain Hemophilia Treatment Centers (HTCs) already incorporating clinical psychologists into their teams. Furthermore, PWHs' mental health has been recognized as a patient-relevant health outcome.[40,41]

The **gender health gap** that women and girls experience worldwide is increasingly addressed[42], and in parallel, **comprehensive care for hemophilia carriers and WGH** is also receiving greater attention.[43–45]

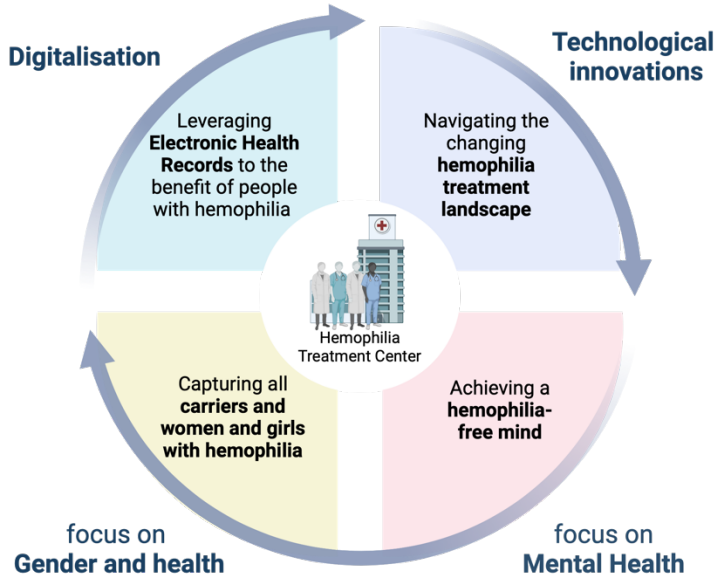

Figure 1 Societal changes resulting in new challenges in hemophilia care.

This thesis examines several contemporary challenges in hemophilia care and aims to provide answers to the following questions:

- *How are innovative treatment options for hemophilia adopted in clinical practice and what are the implications for prophylactic treatment of people with hemophilia?*

- *What determines the psychological ecosystem of the hemophilia patient and how will it be influenced by novel therapies?*

- *How can we effectively screen all female individuals who are potential or obligate carriers of hemophilia?*

- *How can we leverage the electronic health record for the benefit of the hemophilia patient?*

Outline of the Thesis

Section 1: The Impact of the Changing Therapeutic Landscape on the Prophylactic Treatment of Adult Hemophilia Patients

In the first section, real-life experiences with two new therapeutic modalities for hemophilia, namely gene therapy and the bispecific monoclonal antibody emicizumab, were reported.
In **Chapter 1**, we aimed to evaluate how many individuals with severe hemophilia followed at the HTC of the Cliniques universitaires Saint-Luc (CUSL) were realistically eligible for gene therapy, before and after commercialization of gene therapy products. Additionally, we examined the patient characteristics that rendered patients ineligible for gene therapy trials. **Chapter 2** reported results of the 2020 EAHAD survey on real-life experiences with emicizumab, providing a first look into healthcare professionals' experience with emicizumab shortly after the commercialization of the product. We evaluated the overall satisfaction with emicizumab, availability of the product for inhibitor and non-inhibitor patients, safety and efficacy indicators, access to different laboratory monitoring techniques and lastly, experiences with switching to emicizumab during the COVID-19 pandemic. In **Chapter 3** we described our experiences with emicizumab treatment in PWHAs with a Body Mass Index (BMI) greater than 30 kg/m^2, as data on use of emicizumab in this patient group was very scarce at the time of publication.

Section 2: Exploring the Hemophilia Patient's Psychological Ecosystem

The second section features **Chapter 4**, wherein the concept of a "hemophilia-free mind" was proposed as a new ambition of hemophilia care. As previously discussed, recent advancements in therapeutic options have significantly expanded the arsenal for bleeding prevention. These include treatments requiring less frequent injections and, in the case of gene therapy, a single administration, all promising effective prevention of bleeding episodes. With these innovative approaches, patients now have the possibility of being relieved from the relentless cycle of bleeding episodes and resultant disabilities, as well as from the psychological burden imposed by hemophilia on their daily lives.

Section 3: The Diagnosis and Management of Hemophilia A & B Carriers

In **Chapter 5**, we presented the outcomes of a proactive and systematic hemophilia carrier screening study aimed at screening the largest possible number of female relatives of PWHs receiving care at the HTC of the CUSL. Our goal was to gain a comprehensive understanding of this female population and evaluate how many female individuals still had to undergo genetic testing and how many were affected by a coagulation factor deficiency and/or bleeding symptoms. Additionally, we sought to compare carriers of HA and HB regarding the circumstances of diagnosis, coagulation factor levels, and bleeding symptoms. The study, conducted at the CUSL from May 2021 to April 2023, comprised both a retrospective arm, which examined data from female relatives previously seen at the HTC, and a prospective arm, focused on identifying undiagnosed or insufficiently diagnosed female relatives of probands.

Section 4: Using the Electronic Medical Record for the Benefit of the Hemophilia Patient

As previously discussed in this thesis, the advent of new therapeutic alternatives and a transition from a primarily "joint-bleeding"-centered approach to a more holistic and comprehensive model of hemophilia care has led to increasing complexity in recent years. This complexity presents an opportunity to leverage new digital EHRs, some of which enable customization of their interfaces. Therefore, this fourth and final section consists of **Chapter 6**, detailing the development and implementation of a hemophilia-specific navigator within the Epic EHR at the CUSL.

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SECTION 1

The Impact of the Changing Therapeutic Landscape on the Prophylactic Treatment of Adult Hemophilia Patients

Chapter 1

Patient Selection for Hemophilia Gene Therapy: Real-life Data from a Single Center.

Research and Practice in Thrombosis and Haemostasis. 2021;5(3):390-394. doi:10.1002/rth2.12494

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Summary

Background: While the number of patients with hemophilia who are expected to be or have already been included in gene therapy trials has been regularly reported, the number of unscreened or excluded individuals, in addition to the reasons for exclusion, is mostly not reported.

Methods: We conducted an eligibility assessment of all people with severe hemophilia for gene therapy trials in one large Belgian hemophilia treatment center based on patient selection criteria of gene therapy trials and patients' profiling.

Results: Among 87 adult patients with severe hemophilia A and B, 11 aged ≥65 years and two female individuals were excluded from the analysis. Six patients were excluded because of inhibitor development. One patient exhibited active hepatitis C infection, one had insufficient exposure to FVIII, five had uncontrolled comorbidities, while two were enrolled in other trials and two abused alcohol. Overall, 43 patients were not screened owing to psychosocial factors. Among 14 patients accepting gene therapy, six had adeno-associated virus (AAV) type 5-neutralizing antibodies and one had liver fibrosis. The number of patients who would accept gene therapy in the absence of strict clinical trial requirements was estimated at 36 (41.4%), irrespective of any exclusion criteria.

Conclusion: The majority of individuals with severe hemophilia could not be enrolled in gene therapy trials, almost half of them because of partly modifiable psychosocial reasons (49.4%). The proportion of candidates should substantially increase in the future, as eligibility criteria are likely to change and as more data on long-term efficacy and safety of gene therapy will become available.

Background

Gene therapy is one of the most promising therapeutic innovations in the hemophilia field. Hemophilia is an X-linked recessive bleeding disorder, caused by deficiencies in either coagulation Factor VIII (FVIII) (hemophilia A, HA) or Factor IX (FIX) (hemophilia B, HB), resulting in severe hemorrhagic complications, typically involving joint bleeds, if left untreated. Gene therapy has the potential to provide optimized bleeding protection in HA and HB patients by initiating the production of missing coagulation factors (FVIII and FIX, respectively) in human cells. This new approach can be performed either by delivering functional factor genes to cells or by editing the existing genome. Two options for factor gene delivery are currently studied, the most common being the transfer of F VIII/IX genes into hepatocytes by adeno-associated viruses (AAVs). Another option is gene transfer with lentiviral vectors into the genome of autologous stem cells, which are then delivered intravenously.[1]

The first successful gene therapy trial in hemophilia B was reported by Nathwani et al. in 2011.[2,3] Since then, numerous gene therapy trials have been initiated in both HA and HB populations. To date, 46 gene therapy trials for HA and HB have been registered on clinicaltrials.gov.[4] First results on gene therapy efficacy and safety appear promising.[1] Although Pasi et al. reported in 2020 sustained gene therapy efficacy for HA at 3 years post-injection[5], the U.S. Food and Drug Administration (FDA) delayed its approval of valoctocogene roxaparvovec for hemophilia A in August of the same year, claiming that more data on long-term efficacy and safety are required.[6] Moreover, whether multiple injections of vectors ("redosing") will be needed to sufficiently sustain high factor levels must still be determined.

Current gene therapy trials in the hemophilia field present with numerous well-defined inclusion and exclusion criteria, with only slight variations among protocols.[4] The expected number of patients to be enrolled has generally been reported, whereas the exact number of patients enrolled per hemophilia treatment center (HTC) has mostly not been reported in the context of large-scale international and multicenter studies. The accurate numbers of patients deemed ineligible by the investigators, invited to take part in a gene therapy study, selected for screening, and effectively screened are often left unreported. Some people who are unable to participate in a trial

may still benefit from gene therapy at a later time. This explains why it is difficult to estimate the proportion of people who would likely be eligible for undergoing gene therapy once it has become commercially available.

There are multiple patient characteristics, nonmodifiable, physical factors as well as psychosocial factors, that determine whether a patient is eligible for gene therapy, whether within or outside of a clinical trial. The nonmodifiable parameters include age (patients aged ≥ 65 years are excluded, and current gene therapy trials do not yet include minors), inhibitor status (current presence or past history of inhibitors), liver disease (including fibrosis and active hepatitis C infection), uncontrolled HIV infection, other poorly controlled or severe comorbidities, as well as insufficient FVIII/IX exposure in the past. At present, women with hemophilia are not yet included in trials either.[4,7] The possibly modifiable variables that render the individual unsuitable or unwilling to undergo gene therapy include lack of motivation to participate in a trial, fear, lack of trust in the gene therapy concept, conservatism, geographic factors, socio-economic issues, language barrier and inability or unwillingness to comply with study requirements.

Objectives of the Current Study

This study aimed to estimate the number of individuals with severe hemophilia from a single HTC who have recently been candidates in gene therapy trials or could benefit from gene therapy in the future when it has become commercially available. Additionally, we attempted to identify which modifiable and nonmodifiable patient characteristics recently led to nonscreening for, noninclusion into, or exclusion from gene therapy trials.

Methodology

At the HTC of the Cliniques universitaires Saint-Luc in Brussels, a total of 260 people with hemophilia have been registered and currently, 87 adult patients with severe A and B are actively followed-up. The HTC has previously been selected to recruit patients for two gene therapy trials, focused on HA and HB, respectively.[8,9] All individuals with severe hemophilia had been previously informed on several occasions about gene therapy modalities, including routine follow-up visits, educational meetings, newsletters, surveys, and local patient associations (Belgian Haemophilia

Society/AHVH), in addition to materials provided through the World Federation of Hemophilia (WFH) and European Haemophilia Consortium (EHC).

Eligibility for a gene therapy trial was evaluated individually for each patient, considering the patient selection criteria of current hemophilia gene therapy trials. Patient profiling, that is, assessment of potential participation in a gene therapy trial from a hematologist's perspective, was then performed by two experienced adult hematologists from the HTC, who are this paper's co-authors. Both were actively involved in the care of all enrolled patients and were therefore able to identify psychosocial exclusion criteria for each patient. The opportunity to take part in such a trial was discussed face-to-face with all patients eligible from the hematologists' point of view during review clinics. In addition, attempts were made to estimate the number of patients who would be interested in gene therapy without the burden of a clinical trial. The latter was performed without taking into account a potentially limited access to gene therapy because of clinical, financial, and psychosocial parameters.

Results

A total of 75 adults with severe hemophilia A and 12 adults with severe hemophilia B were considered for this study. Results are displayed in Figure 1. Detailed information on inclusion and exclusion criteria for the two ongoing gene therapy trials for hemophilia at our center can be found on the website of the Belgian Federal agency for medicines and health products.[8,9] As only male patients aged ≥ 18 years are eligible for current gene therapy trials, we first excluded two female patients. Eleven patients aged ≥ 65 years were also excluded. Six patients displayed either a history or current presence of inhibitors against FVIII or FIX, while one patient exhibited active hepatitis C infection and two abused alcohol. None of our patients had uncontrolled HIV infection, which has been defined in most trials as a CD4 count < 200/mm3 or viral load > 20 copies/mL. One of our patients displayed insufficient FVIII exposure; indeed, despite his very mild bleeding phenotype, he was affected by severe hemophilia A. It should be noted that two patients were affected by liver cancer, though both were already among the patients excluded from participation because of their age (≥ 65 years). No further patients were affected by other active cancers. Five patients were excluded because of

uncontrolled comorbidities, such as heart disease, seizures, and Crohn's disease. Two patients who were currently enrolled in other clinical trials were also excluded.

After application of the trial criteria, 57 patients remained. Seven patients were deemed unsuitable to participate in a gene therapy trial by the hematologists and were therefore not approached. Reasons for this were geographic distance (n=4), language barrier (n=3), socioeconomic difficulties (n=2) and major disability rendering participation in a trial too burdensome (n=1). Two or more of these reasons were present in some patients. Of the 50 patients who were informed and interviewed about the possibility of gene therapy, 14 agreed to undergo the screening process, and 29 declined to participate in a gene therapy trial; two of these preferred to receive another investigational therapy. Seven patients were approached by hematologists initially but were later deemed unsuitable to participate in a trial due to cognitive difficulties (n=3), unreliability (n=2), socio-economic difficulties (n=2), geographic distance (n=1) and uncertainty about the patient's willingness and reliability (n=1). There was often more than one reason for exclusion. When adding together patients who refused to participate in a gene therapy trial and those deemed ineligible by their hematologist, 43 patients, or 49.4% of our study cohort, were excluded from participation in a gene therapy trial due to psychosocial factors.

Among the patients accepting gene therapy (n= 14), six were found positive for adeno-associated virus type 5 (AAV5)-neutralizing antibodies (NAbs), and one had a fibrotest and fibroscan compatible with liver fibrosis (F2). Seven patients were thus still eligible for gene therapy trial participation, accounting for 8.0% of the 87 initially assessed patients. Two candidates withdrew their consent because of fear. Two individuals with severe HB have undergone gene therapy, while another HB patient will soon be included in a gene therapy trial.

The number of candidates for gene therapy, if it was widely available, was estimated at 36 (41.4%). For this estimation, all 87 patients were considered, regardless of potential clinical-trial-related exclusion criteria and based on the hypothesis that no particular burden would be associated with follow-up.

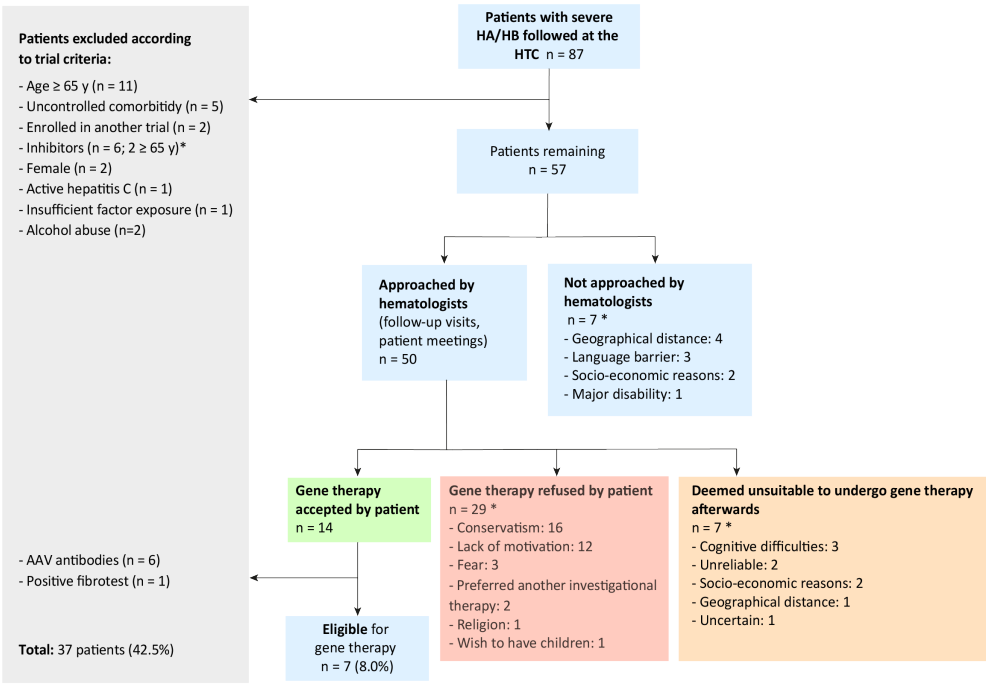

Figure 2 Application of exclusion/nonselection criteria for gene therapy trials at the HTC of the Cliniques universitaires Saint-Luc, Brussels. *Some patients combined two or more of these criteria.

Discussion

Our study demonstrates that in a fairly large cohort of individuals with severe hemophilia less than ten percent were motivated and eligible to participate in a clinical gene therapy study. However, this observation must be further nuanced, given that patients aged ≥ 65 years are not systematically excluded from any clinical trials.

With regard to nonmodifiable patient characteristics, we can easily assume that, in the future, we would be able to treat pediatric patients using gene therapy or those aged ≥ 65 years, in addition to women affected by severe hemophilia. The recent uniQure AMT-061 study using an AAV5 vector containing FIX Padua DNA did not exclude patients with NAbs, yet still obtained good results (FIX activity of 30-54% at 36 weeks post-infusion); hence, gene therapy may be considered for these patients.[1,10]

Of note is that in our study, around 60% of individuals with severe HA and eligible for gene therapy trial participation displayed NAbs, and they were, therefore, excluded from participation.

Several psychosocial and environmental exclusion criteria are directly related to specific constraints, including travel, time spent at the clinic, or psychological stress, which are associated with gene therapy-related study protocols. Despite not being detailed in study protocols, they still play an important role for patient selection.[11] The study protocol for gene therapy consists of a single intravenous injection, yet associated with regular follow-up consultations (weekly at the beginning) with collection of blood, saliva, and semen specimens, thereby rendering study participation time-intensive and burdensome for several patients.[12] Gene therapy administration outside of a clinical study should reduce this burden, thereby increasing the proportion of patients who are likely to receive gene therapy. Regular monitoring, particularly involving liver tests to detect liver damage, will still be essential; these tests, however, can be carried out by a peripheral treatment center close to the patient's home, in strict collaboration with the HTC.

Of the 29 patients who have refused to participate in a trial, three patients reported fear and lack of confidence concerning the gene therapy setting, while 16 patients were not willing to change their usual treatment. This latter observation certainly reflects the need for security and stability. We sincerely hope that strong scientific evidence concerning long-term gene therapy safety and efficacy for the hemophilia indication will be obtained in the future, thus providing answers to several persisting concerns with respect to patient safety, attainable factor levels, durability, and possible re-dosing requirements.[13] In our clinical practice, it appears essential to provide exhaustive information on potential gene therapy risks and benefits, while worries about this new treatment should be taken seriously. We must also pay attention to our patients' expectations regarding gene therapy. It should be made absolutely clear to the candidates that gene therapy neither provides a cure for existing joint damage, nor does it abolish the hereditary nature of hemophilia.[12] The possible need for immunosuppressive therapy during the study should also be discussed with patients. At our HTC, no patient has been excluded on the basis of a refusal to be treated with an immunosuppressive agent or a formal medical contraindication to such treatment.

Lack of motivation to participate in a gene therapy trial was reported by 12 patients, six of whom were excluded because of this sole reason. We expect that most of these patients could be motivated to consider gene therapy outside of a clinical trial setting, providing that they are sufficiently informed and accompanied by their HTC team. Furthermore, based on clinical data, our knowledge of patients, and patients' claims, we anticipated that 36 of our 87 patients with severe hemophilia disease would accept gene therapy, yet outside of a clinical trial, without considering potential exclusionary factors. The PAVING study that was conducted in 2019 and involved a small Belgian patient sample (n=20) demonstrated a more positive attitude of patients with hemophilia toward gene therapy. This study, however, may have been subject to a sampling bias, and thus its participants may not be representative of all Belgian people with hemophilia.[14]

Upon follow-up visits, at patient meetings, and as part of a comprehensive approach to hemophilia care, the hematologists should individually assess gene therapy benefits for each patient and regularly inform them about advances in gene therapy. Scores and algorithms providing guidance for treatment choice in hemophilia must still be developed; these should integrate the main gene therapy efficacy and safety outcomes, which were reported by the core HEM project in 2018.[7,15]

Conclusion

Although the vast majority of individuals with hemophilia with severe disease at our HTC could not be enrolled in gene therapy trials, the proportion of individuals who may actually undergo gene therapy is likely to significantly increase in the future, given that eligibility criteria will change upon commercialization of products. We emphasize that almost half of our patient cohort was excluded primarily due to psychosocial factors, some of which are clearly modifiable, thus constituting leverage points that are able to increase gene therapy adoption. Solid scientific evidence on long-term gene therapy efficacy and safety is urgently needed in order to extend its availability and adoption to a broader population of patients with hemophilia, including women and pediatric patients, as well as those with inhibitors of FVIII/IX or AAV-NAbs.

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Chapter 2

Adoption of Emicizumab (Hemlibra) for Hemophilia A in Europe: Data from the 2020 European Association for Haemophilia and Allied Disorders Survey.

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Summary

Background: Emicizumab, a bispecific monoclonal antibody administered subcutaneously, mimicking the action of activated coagulation factor VIII, has been approved in Europe for use in patients with severe hemophilia of all ages.

Aims: To assess availability, acceptance, adverse events, efficacy, laboratory monitoring of emicizumab and the effect of the coronavirus disease 2019 (COVID-19) pandemic on its use.

Methods: Online questionnaire sent to 144 hemophilia treatment centers (November 2020 to January 2021).

Results: Forty-six physicians from 21 countries responded, with a total of 3420 patients with severe hemophilia A under their care. Emicizumab was widely available, for 100% of inhibitor patients and 88% of non-inhibitor patients. No major adverse events were reported. Four reported deaths in patients on emicizumab were not thought to be related to emicizumab. An annualized bleeding rate (ABR) of zero was achieved in 73% of inhibitor patients. Hemostasis was satisfactory in the majority of minor (93.7%) and major (90.7%) surgical procedures performed while on emicizumab. Inhibitor titers were monitored in 78.4% of inhibitor patients on emicizumab, but chromogenic FVIII assay was only available in 73% of centers. The COVID-19 pandemic did not have a major impact on the adoption of emicizumab in most centers (64.9%).

Conclusion: Three years after its rollout in Europe, emicizumab is widely available. Clinical efficacy and safety were evaluated to be very good, keeping in mind the inherent limitations of the study. Unmet needs include establishment of treatment guidelines for surgery and breakthrough bleeding, limited expertise, especially in young children, and availability of laboratory assays.

Background

Hemophilia A (HA) and B (HB) are X-linked recessive bleeding disorders, defined by deficiencies of coagulation factors VIII and IX, respectively. Despite their rarity, we are currently witnessing the emergence of multiple therapeutic innovations for HA and HB, some of which are still under investigation. These innovations include extended half-life recombinant factors, rebalancing agents, gene therapy and non-replacement treatment. Emicizumab (Hemlibra®, Roche) is the only non-replacement treatment that is currently licensed. It is a bispecific monoclonal antibody, developed to treat hemophilia A in both inhibitor and non-inhibitor patients. It mimics the action of activated coagulation factor VIII (FVIIIa) by linking factors IXa and X, leading to activation of factor X. Given its subcutaneous administration and long half-life (27 days), emicizumab reduces treatment burden when compared to factor replacement products. Emicizumab has shown efficacy and safety in phase 3 clinical trials, starting with the HAVEN 1 trial in 2015, followed by the HAVEN 2-5 and STASEY trials; the HAVEN 6 and 7 trials are currently ongoing (Table 1).[1,2,3] Emicizumab significantly reduces the annualized bleeding rate (ABR) in both inhibitor and non-inhibitor patients in the long term and is well tolerated, according to recently published long-term outcomes from the HAVEN 1-4 studies which are highly encouraging.[4] Safety concerns were raised after occurrence of thrombotic microangiopathy and thrombosis in 5 patients with inhibitors receiving concomitant high-dose treatment with activated prothrombin complex concentrates (aPCC, FEIBA®) in the HAVEN 1 study.[1,5] Use of high dose aPCC in patients receiving emicizumab has therefore been discouraged by the manufacturer.[1]

Emicizumab was granted market authorization by the European Medicines Agency (EMA) for HA patients with inhibitors in February 2018 and for severe HA patients without inhibitors in January 2019. In order to assess availability, acceptance, clinical outcomes and laboratory monitoring of emicizumab almost three years after its roll-out in Europe, the European Association for Haemophilia and Allied Disorders (EAHAD) carried out an online survey to hemophilia treatment centers (HTCs) in all of its member countries in November 2020.

Additionally, considering the ongoing coronavirus disease 2019 (COVID-19) pandemic, which has had a significant impact on the functioning of healthcare all over the world, several questions also addressed the potential influence of COVID-19 on the roll-out of emicizumab. In this article, we report and analyze the survey results.

Clinical trial	Start date	Status	Study population	Number of participants
HAVEN 1 [20]	11/2015	Completed	HA patients (any severity) with FVIII inhibitors, > 12 y.o.	109
HAVEN 2 [20]	07/2016	Completed	Pediatric HA patients (any severity) with FVIII inhibitors, < 17 y.o.	88
HAVEN 3 [20]	09/2016	Ongoing	Severe HA patients without FVIII inhibitors, > 12 y.o.	152
HAVEN 4 [20]	01/2017	Ongoing	Severe HA patients with or without FVIII inhibitors, > 12 y.o.	48
HAVEN 5 [20]	04/2018	Ongoing	Severe HA patients with or without FVIII inhibitors, > 12 y.o. and pediatric patients < 12 y.o.	85*
HAVEN 6 [20]	02/2020	Ongoing	Adult and pediatric patients with mild or moderate HA without FVIII inhibitors	70*
HAVEN 7 [20]	02/2021	Ongoing	Severe HA patients without FVIII inhibitors aged <12 months	50*
STASEY [20]	09/2017	Completed	HA patients (any severity) with FVIII inhibitors, > 12 y.o.	195
HOHOEMI [21]	09/2017	Completed	Severe HA patients without inhibitors, < 12 y.o.	13

Table 1 Phase III clinical trials on emicizumab. *estimated enrolment

Methods

An online questionnaire, using SurveyMonkey, comprising 79 questions was sent via email to 144 European Haemophilia Comprehensive Care Centers (EHCCC) and European Haemophilia Treatment Centers (EHTC) in 34 countries. The survey was open from November 17, 2020 to January 31, 2021. Demographics of survey participants were assessed and included country of practice, position, type of center, knowledge about emicizumab and clinical expertise, participation in clinical trials and authorship of original scientific papers on emicizumab.

The surveyed topics included availability of emicizumab in the respondents' countries, use of emicizumab in inhibitor and non-inhibitor patients, satisfaction with and perceptions of emicizumab, laboratory monitoring, adverse events, other considerations and impact of the COVID-19 pandemic on use of emicizumab. Survey results were analyzed using descriptive statistics in SPSS (version 27).

Results

Characteristics of respondents

Of the 144 contacted HTCs, 46 respondents from 21 countries (Fig 1.) completed at least one question, yielding a response rate of 31.9%. The majority were adult hematologists (56.5%; n=26), followed by pediatric hematologists (28.3%; n=13) and other specialists (15.2%; n=7), mostly hematologists working with both adult and pediatric patients. Most respondents (77.8%; n=35) were working in a University medical center, 15.6% (n=7) in other centers, mainly large non-university hospitals, and 6.7% (n=3) in HTCs not embedded in a large hospital.

The vast majority of respondents rated their knowledge of emicizumab as "excellent" (42.2%; n=19) or "good" (40.0%; n=18). Only few reported "average" or "poor" knowledge (respectively 15.6%, n=7, and 2.2%, n=1). Clinical expertise regarding emicizumab was also positively rated: 17.8% (n=8) said they were international experts, 28.9% (n=13) said they were national experts, 26.7% (n=12) reported very good and 22.2% (n=10) basic expertise, and 4.4% (n=2) had no expertise. Out of 44 respondents, 93.2% (n=41) reported that this knowledge was acquired at scientific meetings, 90.9% (n=40) through reading original articles, 65.9% (n=29) through scientific activities organized by Roche (e.g., advisory boards) and 25.0% (n=11) through participation in clinical trials (multiple selections were allowed). Few participants got their knowledge from the Roche website (9.1%; n=4) or other sources (9.1%; n=4). The majority of respondents had never participated in an emicizumab clinical trial (75.0%; n=33), while some had previously worked as a principal investigator (18.2%; n=8) or as a local investigator (6.8%; n=3). In addition, the majority of respondents (74.4%; n=32) reported that they had not yet authored or co-authored scientific articles on emicizumab. The number of patients enrolled in emicizumab trials

in the participating centers ranged from 0 to 33 (median 0, IQR 0-2) in the 28 HTCs that answered the question.

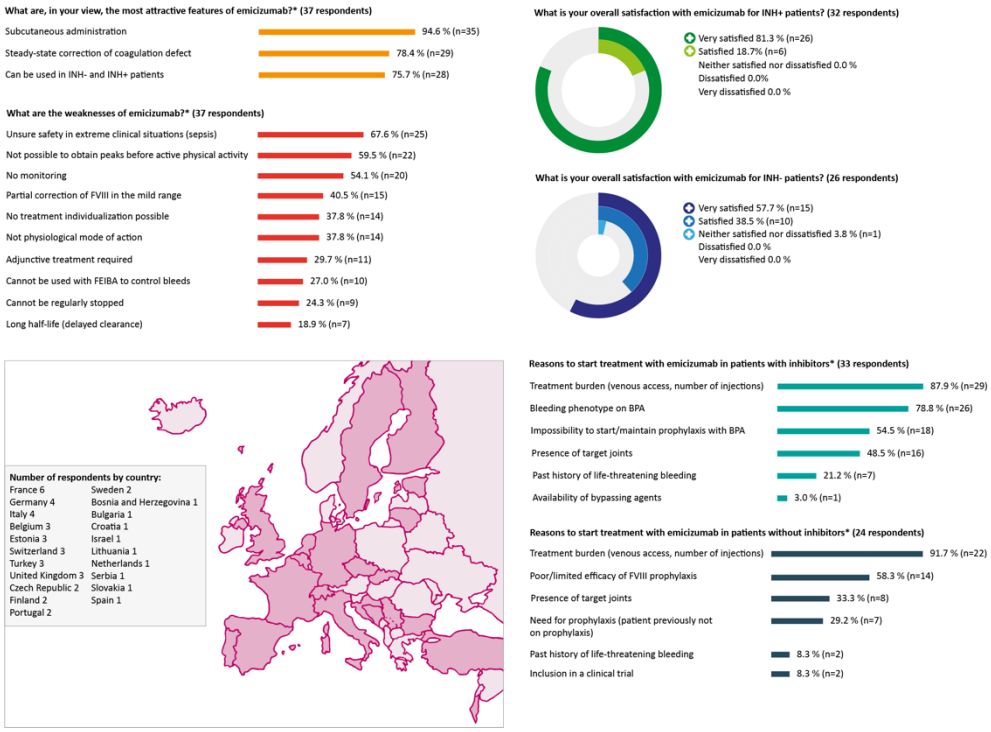

Figure 1 From top left to bottom right: benefits and shortcomings of emicizumab, physicians' satisfaction with emicizumab, number of respondents by country and reasons for switching patients to emicizumab; *multiple selections were allowed.

Availability and pricing of emicizumab

Forty-three participants answered questions about the availability of emicizumab in their countries. Emicizumab was approved in their country for patients with inhibitors. Approval for patients without inhibitors was somewhat less frequent (88.1%; n=37). Among those surveyed, 93.0% (n=40) reported that emicizumab was reimbursed in their country for patients with inhibitors and 71.4% (n=30) reported reimbursement for patients without inhibitors. Compassionate use of emicizumab seemed to be infrequent: 12.2% (n=5) indicated that compassionate access to treatment was available for inhibitor patients and 10% (n=4) for patients without inhibitors.

Most respondents were unaware of the average cost of emicizumab in their country (32.6%; n=14). Furthermore, 34.9% (n=15) indicated a fixed price, 25.6% (n=11) said the price was confidential and 7% (n=3) said it had not yet been fixed. The majority of respondents (95.3%; n=41) did not experience problems with concomitant therapy (FVIII, bypassing agents) in patients on emicizumab. One participant reported a case of severe knee joint bleeding necessitating prolonged concomitant treatment. The other participant who experienced problems with concomitant therapy did not give any further details.

Satisfaction with and perceptions of emicizumab

Satisfaction of physicians with emicizumab was overall very good for patients with and without inhibitors (Fig 1). 64.7% (n=22) of respondents would definitely recommend emicizumab and 35.3% (n=12) would probably recommend it to colleagues. The general quality of the current management of inhibitor patients on emicizumab in the HTCs was rated ‘good’ by 64.7% (n=22) of respondents, ‘perfect’ by 32.4% (n=11) and ‘suboptimal’ by 2.9% (n=1). None of the respondents found the quality to be ‘poor’ or ‘bad’. The most valuable features and most significant weaknesses of emicizumab according to participants are displayed in figure 1. Regarding potential threats to emicizumab in the future, 59.5% (n=22) said they feared misuse of the drug and thrombotic events, 45.9% (n=17) development of antidrug antibodies, 37.8% (n=14) risk of thrombosis and 37.8% (n=14) Roche’s monopoly. Only 5.4% (n=2) of respondents were not concerned about any of these potential risks.

With respect to subcutaneous administration of emicizumab, most of the 34 respondents considered the transition from intravenous infusions to be very easy (51.4%; n=18) or easy (31.4%; n=11). Subcutaneous administration was estimated to be well tolerated in 90-100% of patients according to 85.3% (n=29) of respondents, in 70-90% of patients by 11.8% (n=4) and in 40-70% of patients by 2.9% (n=1) of respondents.

About half (52.8%; n=19) of 36 participants who answered the question stated that they perceived emicizumab as a treatment of choice that should be considered in all patients with severe hemophilia A rather than a “salvage therapy” for patients not currently on prophylaxis (due to poor venous access, poor adherence or imperfect prophylaxis) (33.3%; n=12). In additional

comments, participants described emicizumab as a treatment of choice for prophylaxis in children and young adults with difficult venous access or other compliance issues or with a bleeding phenotype poorly controlled with FVIII, a treatment of choice which may not be considered for all severe HA patients, a treatment for patients with severe arthropathy and difficult venous access, a standard of care for inhibitor patients and an alternative to FVIII replacement therapy in non-inhibitor patients.

Half of the respondents (51.4%; n=19) considered the ultra-long acting FVIII (BIVV001) as the most important alternative to emicizumab in the near future, followed by other non-replacement therapies such as anti-TFPI agents (21.6%; n=8), other FVIII-mimetics (13.5%; n=5), gene therapy (10.8%; n=4) and extended half-life (EHL) FVIII (2.7%; n=1). Respondents estimated adoption of emicizumab for non-inhibitor patients with severe HA in their HTC to be 23.0% after one year, 34.6% after two years and 41.2% after three years.

When asked about the current unmet needs regarding the use of emicizumab (multiple selections were permitted), most respondents (75.7%; n=28) identified laboratory assays in patients on emicizumab as an important issue, followed by limited clinical experience (56.8%; n=21), modalities of cotreatment (bypassing agents or FVIII) (40.5%; n=15), lack of guidelines (27.0%; n=10) and patient education (16.2%; n=6). Other unmet needs cited by the respondents were an affordable price, better (long-term) safety data especially in children less than 2 years of age and elderly patients, data on non-hemostatic effects of emicizumab (e.g., bone health) and individualization of dosing.

Safety of emicizumab

A total of 481 patients (median 5, IQR 2-9), have been treated with emicizumab in 37 centers who answered questions on fatalities in patients on emicizumab. In 35 centers who answered the question, 4 patients who were on emicizumab have died so far. Median age of the patients that died was 53 years with ages ranging from 4 months to 87 years. According to the respondents, these deaths were not related to emicizumab.

Emicizumab in inhibitor patients

Forty participants responded to questions about the use of emicizumab in patients with inhibitors. A total of 3420 patients with severe hemophilia A were registered at these HTCs. The median number of patients with severe HA in each center was 69 (IQR 24-102). A total of 214 patients with a persistent inhibitor (with or without prior ITI) were being followed in HTCs at the time of the survey (median 4, IQR 1-7, min 0, max 28). Reimbursement was granted to 93.4% (n=142) of inhibitor patients on emicizumab and 6.6% (n=10) benefitted from emicizumab in a clinical trial. None of the inhibitor patients were given compassionate access to therapy.

Sixty percent (n=24) of respondents said that prophylaxis with bypassing agents was intended to be the standard of care for patients with a persistent inhibitor in their HTC. In reality, less than a third (median 27.3%, IQR 0.0-63.3%) of inhibitor patients were on prophylaxis with bypassing agents in HTCs before Hemlibra became available. The bypassing agent of choice for prophylaxis in patients with an inhibitor was reported to be a combination of rFVIIa and aPCC (35.1%; n=13) or aPCC alone (35.1%; n=13), followed by rFVIIa alone (29.7%; n=11). Reasons to start emicizumab in patients with and without inhibitors are shown in Figure 1. Data on treatment regimens with bypassing agents before and after the advent of emicizumab are displayed in Figure 2.

An ABR of zero was achieved in 72.9% (n=102) of patients with inhibitors on emicizumab. Among inhibitor patients on emicizumab, 26 (18.3%; n=26) required adjunctive treatment with rFVIIa and none used FEIBA. In the context of adjunctive treatment, two cases of bleeding complications were reported.

A total of 52 inhibitor positive patients in 20 HTCs have undergone invasive procedures (17 major and 45 minor) while on emicizumab. Major surgeries were mainly covered with rFVIIa by 93.3% of HTCs (n=14), while 6.7% (n=1) preferably managed them with emicizumab alone. Minor surgeries were primarily treated with tranexamic acid (57.1%; n=12), followed by treatment with emicizumab alone (23.8%; n=5) and treatment with rFVIIa (19.0%; n=4). Nineteen HTCs answered questions on efficacy of emicizumab during surgery: hemostasis was unsatisfactory in 1 out of 16 (6.3%) major procedures and in 4 out of 43 (9.3%) minor procedures.

The majority of respondents (78.4%; n=29) indicated they monitor the inhibitor titer in inhibitor positive patients on emicizumab. According to survey respondents, 39.7% (n=48) of their inhibitor patients on emicizumab have an inhibitor titer of less than 5 BU. Therefore, they could, at least in theory, be treated with FVIII if needed, although an anamnestic inhibitor rise would be expected to occur subsequently.

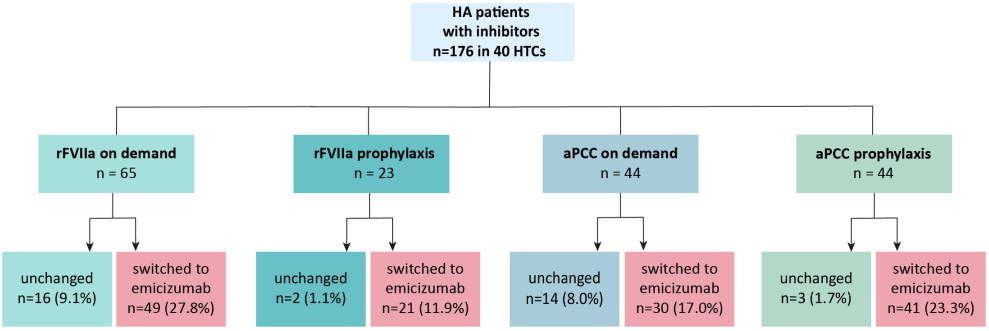

Figure 2 Treatment regimens with bypassing agents in HA patients with inhibitors before and after the advent of emicizumab.

Emicizumab and inhibitor negative patients

For the majority (93.0%; n=291) of patients emicizumab was reimbursed and only a minority (7.0%; n=22) received emicizumab in clinical trials. None of these patients were treated on a compassionate basis. Most of the non-inhibitor patients on emicizumab were aged 18 to 50 years (44.2%; n=150), 7.4% (n=25) were aged less than two years, 27.4 % (n=93) were between 2 and 18 years of age and 20.9% (n=71) were aged more than 50 years. Emicizumab is mostly administered once every two weeks (44.4%; n=12) or weekly (44.4%; n=12). Only few respondents (11.1%; n=4) mostly administer emicizumab every four weeks. The vast majority (93.6%; n=280) of inhibitor negative patients on emicizumab were previously treated with FVIII. Approximately one-quarter of inhibitor-negative pediatric patients (26.6%; n=29) and nearly one-sixth of adult patients (17.6%; n=34) on emicizumab require co-treatment with FVIII for bleeding, trauma or surgery. Only few (n=13) respondents answered the question on frequency of co-treatment with FVIII. FVIII is given less than once per month in most of these HTCs (61.5%; n=8). One third of respondents (30.8%; n=4) reported use of FVIII less than once per year and use of FVIII more than once per month was rare (7.7%; n=1).

Only one of 30 respondents reported 5 cases of switching back to FVIII, for reasons such as patient preference, unspecified personal reasons, bleeding and unspecified side effects. In these 30 HTCs, no patient had so far developed ADAs.

Laboratory monitoring

Thirty-six participants answered questions on laboratory monitoring of emicizumab. Most respondents reported that their laboratories have the expertise to measure FVIII levels (78.4%; n=29) and inhibitor titer (75.7%; n=28) in patients on emicizumab. Chromogenic FVIII assays using bovine reagents, required to measure FVIII in the presence of emicizumab, were available in 70.3% (n=26) of laboratories and chromogenic FVIII assays using human reagents in 57.1% (n=20) of laboratories. Two thirds (67.6%; n=25) of study participants said their laboratory personnel had developed expertise in interpreting assays in patients on emicizumab (no expertise: 27.0%, n=10; unknown: 5.4%, n=2). More than half of the respondents (57.1%; n=20) said that emicizumab levels could not be determined in their laboratories. Detection of anti-drug antibodies (ADAs) was reported to be even less common, with only 2 (5.7%) laboratories detecting ADAs. The majority (59.3%; n=16) of 26 respondents indicated that the activity of emicizumab is measured by a chromogenic FVIII assay using human reagents, while 40.7% (n=11) do not perform such measurements. Eleven out of 23 respondents (47.8%) reported emicizumab activity monitoring once every 6 months, 7 (30.4%) measure activity less frequently and 5 (21.7%) do not measure activity at all.

Emicizumab and COVID-19

Thirty-seven participants answered questions on the impact of the currently ongoing COVID-19 pandemic on use of emicizumab. Almost two thirds (64.9%; n=24) said that the pandemic did not have an impact on adoption of or switch to emicizumab for their patients, yet 24.3% (n=9) found that the switch to emicizumab had been negatively impacted by the pandemic. A small proportion, 5.4% (n=2), said that use of emicizumab was increased by the pandemic and 5.4% (n=2) had no opinion on this particular topic. The COVID-19 pandemic was considered as a reason or motivation to switch patients to emicizumab by 21.6% (n=8) of respondents, versus 70.3% (n=26) who did not perceive this as a reason to switch and 8.1% (n=3) who did not

have an opinion. For the majority of respondents (54.1%; n=20), the pandemic did not have an impact on their patients' acceptance to be switched to emicizumab; still, 29.7% (n=11) could not answer the question and 16.2% (n=6) indicated that there was indeed an impact of the pandemic. In half of the HTCs (48.6%; n=18), hemophilia patients had been infected with COVID-19. In these 18 HTCs, a total of 69 patients treated with FVIII were infected with SARS-Cov-2. Only five patients infected with SARS-Cov-2 in these centers were on emicizumab. The management of COVID-19 in these patients was impacted by emicizumab in only one patient, who had to be treated with low molecular weight heparin.

Discussion

This represents the first multi-national assessment of real-world experiences with emicizumab. Almost three years after market rollout in Europe, the availability of emicizumab is generally very good - slightly better for patients with inhibitors than for patients without inhibitors, probably due to the earlier approval of emicizumab for inhibitor patients and reimbursement issues in some countries. However, price transparency is not assured, and prices remain confidential or unknown in most cases. The main reason to switch patients to emicizumab was treatment burden and/or limited venous access for both inhibitor and non-inhibitor patients. Subcutaneous and infrequent (up to once monthly) administration are indeed key features of emicizumab, which has been shown to reduce treatment burden and improve health related quality of life in adult and pediatric HA patients with and without inhibitors.[6,7,8]

HA patients with inhibitors should have their inhibitor titers monitored at least annually and prior to any surgery[9], but inhibitor monitoring does not appear to be systematic based on our survey results. It must be kept in mind that patients on emicizumab should be considered as mild HA patients, which implies a lower but still present risk of bleeding. Carcao et al. recommend that all patients with inhibitors should have at least one attempt at ITI.[10,11] This may be done in combination with emicizumab, although concerns about safety of emicizumab in this context have been raised by the UK Haemophilia Centre Doctors' Organisation (UKHCDO) in their 2018 interim guidance due to lack of data on the subject.[12]

Another aspect in which our results deviate from the European principles of inhibitor management is patient participation in research and innovation[9]: only very few inhibitor patients have received emicizumab in a clinical trial. In addition, although most respondents work in academic centers, the majority of them have not (yet) participated in clinical trials on emicizumab and have not published on the subject. We encourage all of them to participate in research protocols in the future and to publish their clinical experiences with emicizumab, particularly in areas where there is currently only limited data available. For example, data on management of inhibitor and non-inhibitor patients on emicizumab undergoing surgery is currently scarce and no guidelines on a European or global level, only proposals and recommendations on a national level, are available so far.[12,13,14] Results of the EAHAD survey are mostly in line with these recommendations and with published data from the HAVEN studies and two HTCs in the US.[15,16,17] Regarding bypassing agents, rFVIIa is the treatment of choice for patients with inhibitors on emicizumab.[10,11,13,14,16] Survey results are consistent with this recommendation.

Previously, we had estimated that the COVID-19 pandemic could have a positive impact on the adoption of emicizumab, as it provides a more stable anticoagulant level and reduces bleeding frequency, thus reducing the need for (urgent) medical care and hospital visits.[18] However, in the surveyed HTCs, there is a trend toward a decline in switch to emicizumab during the pandemic and the majority of clinicians do not see the pandemic as an additional motivation to proceed to treatment changes. The COVID-19 pandemic did not seem to have had a negative impact on patients' acceptance to be switched to emicizumab.

In the surveyed HTCs, there is still room for improvement regarding availability of laboratory assays, especially availability of chromogenic FVIII assay using bovine reagents, which is the only FVIII assay to date that does not suffer from interference with emicizumab. This method is also preferable for measurement of FVIII inhibitors during treatment with emicizumab.[19]

Clinician knowledge and expertise regarding emicizumab appear to be good and, interestingly, scientific meetings are the primary source of knowledge about this new therapeutic agent. This re-emphasizes the importance of international meetings such as the annual EAHAD congress and the

importance of keeping them alive during the COVID-19 pandemic by organizing virtual meetings.

Limitations

Only 46 of 144 contacted HTCs answered our questionnaire. This relatively low response rate may have been, at least partly, due to the increased workload associated with the COVID-19 pandemic. Half of the respondents were national or international experts, which may limit the potential for generalizing our findings to European HTCs with less clinical expertise on emicizumab. In addition, although clinical efficacy and safety were assessed in this survey, the significance of these data is limited by the study design.

Conclusion

This study is the first to report data on real-life experiences, acceptance and availability of emicizumab in Europe, gathered through surveying a large number of HTCs. Satisfaction with emicizumab was generally very good and most clinicians would recommend emicizumab to their colleagues. Certain unmet needs persist and should be addressed by future research on safety and efficacy of emicizumab in the long-term and in particular clinical contexts. International treatment guidelines must be established, especially for surgical procedures and breakthrough bleeds. Laboratory assays in patients on emicizumab must be made available in a larger number of HTCs. While adoption of emicizumab in European HTCs is likely to increase in the coming years, other promising treatments are currently under investigation and could prove to be equally attractive. Decision-making tools will be needed in order to allow clinicians to personalize treatment for each patient.

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Chapter 3

Emicizumab Dose Capping in Obese Patients with Hemophilia A: Early Outcomes at a Single Center.

Haemophilia. 2022;28(6):e245-e247. doi:10.1111/hae.14644

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Dear Editor,

During phase 3 clinical trials and since its commercialization, emicizumab (Hemlibra®), a bispecific monoclonal antibody acting as a substitute for activated coagulation factor VIII (FVIII), has proven effective for bleeding prevention in people with hemophilia A (PWHA) with and without inhibitors. It is administered subcutaneously, requires less frequent injections compared to intravenously administered factor replacement products and thereby reduces the treatment burden.[1] For all these reasons, emicizumab is a potentially life-changing treatment option for PWHA, especially those with inhibitors. Safety concerns include thrombotic microangiopathy and thrombosis after concomitant use of activated prothrombin complex concentrate (aPCC) and occurrence of anti-drug antibodies (ADA).[1]

Emicizumab can be administered following different maintenance dosing regimens, after a loading dose of 3 mg/kg once a week during four weeks: 1.5mg/kg once weekly (Q1W), 3 mg/kg every two weeks (Q2W) or 6 mg/kg every four weeks (Q4W). After the loading dose period, plasma concentrations of emicizumab will remain stable over time, in contrast to conventional factor replacement products, whose pharmacokinetics are marked by peaks and troughs. The total body weight-based dosing scheme currently used in clinical trials and clinical practice, and which applies to pediatric and adult patients with or without inhibitors, is supported by population pharmacokinetic analysis.[2,3] However, little is known about emicizumab dosing strategies in obese patients (i.e. individuals with a BMI greater than 30 kg/m2 as per the WHO definition[4]). Considering that the prevalence of overweight and obesity in PWH is approaching that of the general population[5], this is an important issue. The impact of obesity on pharmacokinetics and usage of coagulation factor concentrate has been previously discussed in the literature[5,6] and adds to other potential problems associated with obesity in PWH such as cardiovascular disease and musculoskeletal and psychological health.

Apart from a post-hoc analysis of the HAVEN 1, 3 and 4 studies by Recht et al. presented at the ISTH 2021 congress[7], there is no data available on efficacy of emicizumab in overweight and obese PWHA. The authors concluded that emicizumab was as efficacious in obese PWHA as in non-obese PWHA, which is shown by annual bleeding rates (ABRs) that are not significantly different and therapeutic plasma concentrations (>30 µg/mL)

achieved in both groups. In the reviewed HAVEN studies, emicizumab dosing was based on total body weight, but information on the highest amount of emicizumab administered or on individual pharmacokinetic profiles is not publicly available.

On its website, emicizumab manufacturer Roche provides a dosing guide for body weights of up to 150 kg.[8] For an individual with HA weighing 150 kg, this would require for example four-weekly injections of 900 mg of emicizumab on a Q4W dosing scheme, which is supposed to be associated with the lowest treatment burden. Importantly, such high doses of emicizumab represent relatively high injection volumes for subcutaneous administration: an injection of 900 mg of emicizumab would equal a total injection volume of 6 mL, requiring three separate injections per administration. According to the manufacturer's recommendations, volumes greater than 2 mL should be subdivided into multiple injections[9], since larger injection volumes may cause injection site pain and increase the risk of injection site reactions.[10]

In a simulation study on the pharmacokinetic implications of dosing emicizumab based on vial size, the authors mention that emicizumab dose may be calculated based on ideal weight in obese patients, in analogy to factor VIII replacement therapy, where ideal weight may be the adequate reference for dose calculation.[11,12] The latter is due to the relatively small increase in plasma volume in relation to adipose tissue with increasing body weight and thus an increased in vivo recovery of FVIII in obese patients. Dosing based on ideal weight may avoid overtreatment of patients and would also be more beneficial from an economic point of view.[11] In our view, in the case of emicizumab, dose adaptation should also aim to reduce the number of subcutaneous injections per administration to reduce the "injection burden" associated with treatment and, in theory, improve treatment adherence.

We therefore adopted a dose capping approach to treatment of obese PWHA with emicizumab at our hemophilia treatment center (HTC) at the Cliniques universitaires Saint-Luc, Brussels. Among 86 adults with moderate or severe hemophilia A currently followed at the HTC, 45 are treated with emicizumab. Among the emicizumab-treated PWHA, 16 are overweight (defined by a BMI greater than 25 kg/m2 [4]) and five have a BMI ≥ 30 kg/m2, therefore considered obese. Ages of these PWHA range from 31 to 49 years and they

have been treated with emicizumab for 17, 20, 23, 29 and 30 months now. All had received prophylaxis with standard or extended half-life recombinant FVIII before switching to emicizumab. One of them had undergone successful immune tolerance induction (ITI) for eradication of a FVIII inhibitor during childhood. Details of the obese PWHA are presented in Table 1.

Case	Age (y)	Body weight (kg)	BMI (kg/m^2)	Treatment duration (m)	Maintenance dosing regimen	Adverse events	Bleeding episodes since initiation of emicizumab	aPTT after switching to emicizumab (seconds)
1	44	101	31,9	30	300 mg Q2W	Moderate injection site reaction	0	23,9
2	49	120	37,0	29	600 mg Q4W	None	0	23,5
3	31	123	38,0	23	600 mg Q4W	None	0	22,2
4	34	101	33,4	20	600 mg Q4W	None	0	21,3
5	35	106	33,5	17	600 mg Q4W	None	0	27,3

Table 1 Characteristics of PWHA with a BMI above 30 kg/m^2 treated with emicizumab at the Cliniques universitaires Saint-Luc, Brussels.

After completion of the loading dose period, patients were put on an emicizumab maintenance dosing regimen of 600 mg Q4W (dose capped for a weight of 100 kg) in order to reduce the treatment burden as much as possible. One of them had to be switched to 300 mg Q2W, which was motivated by the occurrence of joint pain on the days before injection when he was on a 600 mg Q4W regimen. To date, all patients tolerate emicizumab well and no major adverse events such as thrombosis or ADAs have occurred. One patient had a moderate injection site reaction upon treatment initiation. Since the switch to emicizumab, none of them has experienced any provoked or spontaneous bleeding. Activated partial thromboplastin time (aPTT) is in the normal range in all patients. We did not perform measurements of plasma emicizumab concentration or global coagulation assays in these patients.

These data suggest that a total monthly emicizumab dose of 6 mg/kg, limited to a maximum of 600 mg, may be effective in obese PWHA, but they are limited by the small size of the cohort and lacking pharmacokinetic data. Emicizumab and factor concentrates differ in their route of administration, pharmacokinetics and pharmacodynamics, therefore emicizumab dosing in obese PWHA cannot be extrapolated from experience with factor concentrates alone and our observations need further validation through assessment of clinical efficacy and collection of pharmacokinetic data. Of

note, in the phase 1 emicizumab dose-escalation study in a small cohort, emicizumab was shown to reduce ABR effectively when administered at a dose of 1 mg/kg/week, which is less than the dose we used in the described obese PWHA.[13] Furthermore, dosing regimens of the phase III clinical trials, which are now used in clinical practice, were initially obtained through pharmacometric analysis and modeling based on the early clinical studies.[3,14] These standard dosing regimens are intended to cover much of the high interindividual variability in emicizumab pharmacokinetics, and hence individual dose reductions may be an option in the future, not only in obese PWHA.[14] Personalized pharmacokinetic models and tools, similar to the WAPPS-Hemo project, could be used to tailor emicizumab dosing more precisely, but accurate determination of emicizumab plasma concentrations is currently expensive and not widely available. This approach could decrease the risk of over-treating obese PWHA on emicizumab and considerably reduce the number of vials and injections needed, thereby reducing treatment burden. It would also be beneficial from a financial point of view. Regular follow-up of obese patients on a capped dosing scheme is however necessary.

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SECTION 2

Exploring the Hemophilia Patient's Psychological Ecosystem

Chapter 4

Living with a « Hemophilia-free Mind » - The New Ambition of Hemophilia Care?

Research and Practice in Thrombosis and Haemostasis. 2021;5(5):e12567. doi:10.1002/rth2.12567

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Summary

Despite the numerous and ground-breaking therapeutic advances made in the field of hemophilia over the past decades and particularly in recent years, hemophilia remains a disease that has a major impact on the daily lives of our patients, through the multiple complications and burdensome treatments it imposes. The disease burden is not only physical, but also psychological and is difficult to evaluate solely by questionnaires and scores. In this article, we propose to examine the absence of psychological burden and of permanent thoughts about the disease and its complications in people with hemophilia as a new ambition that should guide hemophilia care and research in the future.

Hemophilia is a hereditary bleeding disorder with multiple complications. Health care professionals specialized in hemophilia are confronted with the reality of this disease during regular consultations with each of their patients. These review clinics deliver an important opportunity to ensure the best management of the disease and to assess its diverse consequences. For most people with hemophilia, especially those with moderate and severe hemophilia, their physical and mental wellbeing are constantly at stake, as the disease impacts their daily activities. This is beautifully summarized in a famous book by Peter Jones entitled "Living with Hemophilia" that was originally published in 1974.[1]

Ground-breaking therapeutic advances in hemophilia have been achieved during these last decades; biotechnological advances have allowed the development of more secure (recombinant factor products) and effective (recombinant factors with extended half-life) therapies for hemophilia[2] in addition to the establishment of multidisciplinary care in hemophilia reference centers.[3] The development of less burdensome treatments (i.e., non-replacement therapy) is nonetheless very recent and is only beginning to be available to larger numbers of patients in developed countries. Currently, the available treatments - including the most recent ones - cannot cure the disease as they only compensate partially the disease's effects, either in a steady state (emicizumab) or fluctuating mode (factor concentrates). Such treatments are not completely exempt of limitations as they require repetitive intravenous or subcutaneous administrations. Although their effectiveness has been proven, they do not prevent all bleeding events and do not ease the pains and disabilities, particularly of the joints, which have developed progressively as a result of frequent hemorrhages in the past.

The efficacy of hemophilia treatments is typically determined by measuring the frequency of bleeding events, including those occurring in target joints, by assessing painful symptoms through standardized tools and by assessing joint status clinically or by radiological imaging. To measure the overall impact of hemophilia and treatment efficacy in people with hemophilia, many other approaches have been integrated and validated. Such approaches attempt to quantify physical activity, evaluate quality of life and determine the patients' own representations of the disease.[4-7]

The evaluation is mainly based on questionnaires that seek to explore each patient's mental ecosystem and to determine the multiple consequences of hemophilia on their daily life, a task that is both difficult and ambitious.

Although these questionnaires and tools for assessing quality of life are of major interest, they are not free from limitations.[8] Their routine implementation is often tedious and time-consuming. In this context, having a simple indicator that could integrate the multiple physical and psychological impacts of hemophilia and its management would be a critical step.

The only biological difference between people with and people without hemophilia is a deficiency in one of the clotting factors that results from the presence of a genetic variant at the end of the X chromosome. The consequences of this apparently small difference are substantially enormous, as it influences and shapes the whole life of a person with hemophilia. Every morning, the "hemophilic disease", through its constraining treatments and complications, reminds patients of their vulnerabilities.

Although hemophilia is a hematologic disease with mainly muscular and skeletal consequences, it does not spare each patient's mind. In other words, the hemophilia patient, even if well treated with current treatment options, rarely has his mind free of hemophilia. The different dimensions of this mental burden, depending on treatment modalities, are summarized in Figure 1.

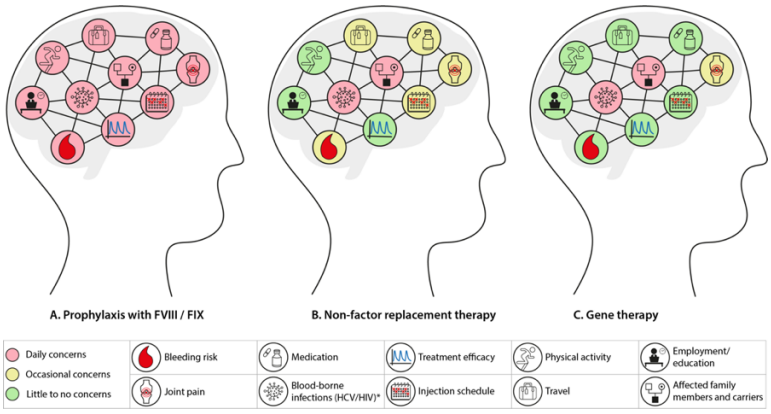

Figure 1 Concerns of people with moderate or severe hemophilia according to different treatment modalities. FVIII, coagulation factor VIII; FIX, coagulation factor IX. * In patients born before 1990

Indeed, people affected by moderate or severe hemophilia are continually confronted with multiple questions which impact their behavior and lead them to adopt more or less automatic coping strategies that they have acquired over the years. Some of these questions are detailed below:

1. Should I treat myself today? When was my previous treatment? When will my next treatment be?
2. Which activities will likely cause pain today? How can I avoid or control the pain?
3. What is the bleeding risk for me today? Will the activity I am considering be dangerous?
4. What will I not be able to do today that I would like to do?
5. Will the fact that I have hemophilia make me feel different from people who are not affected by hemophilia?
6. What skills will I develop and use to cope with the disease today?
7. Will I be able to cope by myself or will I need help and support?

Drug treatment of hemophilia, optimized management and ideally a cure should replace these questions with another reality, described in the statements below:

1. I do not have to treat myself today, tomorrow or the day after tomorrow. I do not have to consider my last treatment.
2. I am not in pain and should not fear pain.
3. I do not have to worry about being exposed to any particular risk of bleeding.
4. I can do what I want without any real restrictions.
5. I do not have to feel different from people who are not affected by hemophilia.
6. I do not have to find skills and strategies to cope with the disease.
7. I do not need more help or support than another person.
8. I do not even have to consider and ask myself the above questions.

In this hypothesis, the treatment of hemophilia with its pains, fears, frustrations, coping strategies, perceived differences with other people without hemophilia and frequent lack of independence disappear and no longer engage the patients' mind and mental energy. A day without hemophilia on their minds, a day without considering themselves as

“bleeders”, as opposed to healthy people, is surely the prime aspiration of these people. To free them as much as possible from the biological, physical, and especially mental grasp of hemophilia is what ideal treatments should aim for. This is a difficult goal to achieve, but ideally it should inspire and motivate caregivers and future research.

In routine clinical practice, asking people if they currently experience days when their minds are not preoccupied by hemophilia could be a first step in this process. In our own experience, such "hemophilia-free days" are now possible for some of our patients treated with long half-life factor IX concentrates or emicizumab. Some of these patients, for several days a month, seem to be able to live without suffering actively from hemophilia both physically and mentally. This is also true for patients who have been treated with gene therapy, at least for those who, several months after the factor infusion, have achieved sufficient endogenous FIX or FVIII levels (ideally almost in the normal range) and who are no longer burdened by the gene therapy study protocols.

Lately, we were inspired by the words of a man with hemophilia B who benefited from gene therapy in November 2019 at our hemophilia treatment center in Brussels. He responded very favorably to the treatment and reported feeling free from hemophilia’s shackles as his fears and anxiety disappeared from his daily life. Apart from being “bleed free” since the administration of gene therapy and feeling less joint pain, he also felt his mind to be absolved from the constant psychological distress. Whereas before gene therapy, his thoughts had constantly revolved around the disease, the next injection, and the risk of bleeding between two injections, he felt that these days were now mostly over. This case is consistent with observations made by W. Miesbach and R. Klamroth during interviews of three gene therapy study participants in Germany.[9]

Asking the patient if life is currently granting them "hemophilia-free days" is a simple, empathetic, and informative question. It allows us to appreciate the overall impact of hemophilia therapies on each patient and their relatives. It also allows us to explore how we can further help our patients on ultimately finding the path of "living without hemophilia".

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SECTION 3

The Diagnosis and Management of Hemophilia A & B Carriers

Chapter 5

Proactive Systematic Hemophilia Carrier Screening: A Step Toward Gender Equity in Hemophilia Care.

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Summary

Despite numerous efforts to raise awareness, many hemophilia carriers and female persons with hemophilia (PWHs) remain undiagnosed. Between May 2021 and April 2023, we identified potential and obligate carriers of hemophilia A (HA) and B (HB) by updating pedigrees of all PWHs followed at the Cliniques universitaires Saint-Luc, Brussels. Retrospective data on previously screened females were collected, including bleeding history, coagulation factor levels, and testing for the proband's pathogenic variant. Additionally, a proactive approach involved sending 125 invitation letters to unscreened or incompletely screened individuals, through related PWHs. In pedigrees of 287 male PWHs (226 HA, 61 HB) and 7 female index patients from 236 families (184 HA, 52 HB), a total of 900 female individuals were identified. Of those, 454 were obligate and/or genetically proven carriers, and 118 were noncarriers. Genetic testing was conducted in 133 obligate, 237 potential, and 4 sporadic carriers, with 190 obligate and 328 potential carriers remaining untested. Among carriers with known factor levels (261/454), 42 (23.0%) HA and 23 (29.5%) HB carriers, had a factor level below 40 IU/dL. Carriers with a factor deficiency were screened on average 6 years earlier than other females (p=0.034). This study represents the first systematic effort to identify potential carriers among families of all PWHs within a single center, emphasizing the challenges in comprehensive screening for female individuals genetically linked to one or more PWHs. Such initiatives are vital for achieving equitable access to hemophilia care for all potentially affected individuals, irrespective of gender.

Introduction

The first explicit report of female carriership of hemophilia dates back to 1803, by John Conrad Otto[1], who described a family lineage of several decades earlier, wherein only males were affected by an often-fatal bleeding disorder, later named 'hemophilia' by Hopff[2] and Schoenlein[3], and which we now know is marked by a deficiency of coagulation factor VIII (FVIII) (hemophilia A, HA) or IX (FIX) (hemophilia B, HB). The disease was passed down through generations by female ancestors who appeared to show no symptoms themselves. Thomas Hunt Morgan's discovery of X-linked recessive inheritance in 1910 further elucidated the inheritance pattern described by Otto[4]. At the beginning of the 20th century, anecdotal reports of hemophilia carriers experiencing abnormal bleeding surfaced[5] and gradually accumulated[6–12], yet research on carriers was mainly focused on the genetic transmission of the disease and not on the potential bleeding consequences. Bleeding symptoms in hemophilia carriers and, thanks to new biomolecular techniques, the diagnosis of carriers, gained increasing interest by the end of the 20th century.[13] However, it took until 2021 – 218 years after Otto's report – for the term "Women and Girls with Hemophilia" (WGH) to be officially defined by the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH).[14] Several underlying mechanisms explaining why hemophilia carriers may exhibit low factor levels have been identified, with skewed X-chromosome inactivation being the most commonly described.[15-17] Importantly, not only carriers with a factor deficiency may experience abnormal bleeding; it has been reported that a quarter of those with factor levels above 50 IU/dL may also suffer from abnormal bleeding symptoms.[14]

Research on hemophilia carriers and WGH has progressed slower compared to research focusing on male persons with hemophilia (PWHs) and gender inequities persist in the diagnosis, care, and treatment of hemophilia, and bleeding disorders in general [18,19] (Figure 1). Many female relatives of PWHs remain unaware of their carrier status or experience diagnostic delay and their coagulation factor levels are not systematically measured.[18–20] In contrast to male PWHs, WGH and carriers often do not benefit from specialized care.[18,21]

Care gaps for carriers and WGH are even bigger in countries with limited resources[22,23], but even in high-resource countries systemic barriers and political decisions may limit access to care for WGH.[24] Despite advancements in hemophilia therapies, including gene therapy and non-replacement therapies, access for WGH has been limited and they have been excluded from most clinical trials for these new therapeutic agents.[14] Additionally, the impact of caregiving for affected males on predominantly female caregivers has been largely overlooked.[25]

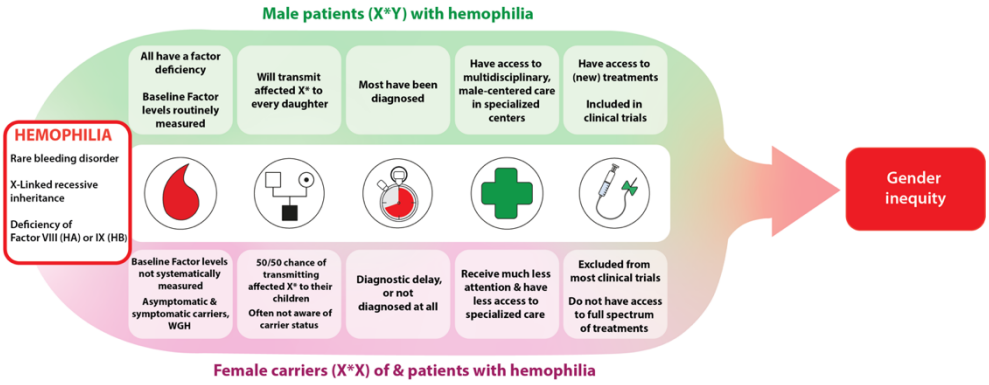

Figure 1 Gender inequities in hemophilia care.

At the hemophilia treatment center (HTC) of the Cliniques universitaires Saint-Luc in Brussels, the screening of female relatives of PWHs and the care for WGH and symptomatic carriers have been integral parts of the clinical routine for the past two decades. However, prior to this study, we lacked precise information about the number of carriers and potential carriers within the families of PWHs followed at the center, and the effectiveness of our approach. Moreover, despite the increasing interest in hemophilia carriers within the scientific community, concrete strategies for systematic hemophilia carrier screening have been lacking.

In this report, we present the outcomes of a proactive and systematic hemophilia carrier screening study, where the primary objectives were to screen the highest possible number of potential and obligate hemophilia carriers within a single HTC and to assess the effectiveness of our approach. Furthermore, we aimed to compare carriers of HA and HB, examining circumstances of diagnosis, coagulation factor levels, bleeding symptoms, and hemostatic treatment requirements.

Methods

The study was conducted at the Cliniques universitaires Saint-Luc, Brussels, Belgium, from May 2021 until April 2023 and was approved by the local Ethics Committee. It was registered on Clinical.Trials.gov under the identifier NCT05217992. The study consisted of both a retrospective and a prospective arm.

While conducting a retrospective data analysis of electronic medical records, we utilized data acquired through routine carrier screening of female relatives of PWHs. These data included FVIII and FIX levels, genetic testing results, bleeding history, hemostatic treatment history, and family pedigrees. Only data from female individuals presumed to be alive at the start of the study were included in the analysis.

In addition to this retrospective analysis and to further enhance the screening of female relatives of PWHs, we adopted a proactive and systematic approach to reach out to previously unscreened or incompletely screened individuals. During personal contacts with PWHs regularly followed at the HTC (referred to as “probands” hereafter), either during clinical follow-up visits or telephone interviews, pedigrees of probands were analyzed and unscreened potential and obligate carriers of hemophilia were identified, complementing the pedigree information gathered during the retrospective part of the study. Probands were provided with a total of 125 invitation letters to our study, either in paper or electronic form, and were asked to forward these to the unscreened female individuals in their families.

Respondents to the invitation were seen at the clinic, where their general medical and bleeding history were taken, individual bleeding risk was determined, and coagulation factor levels (FVIII, VWF:Ag and VWF:RCo for HA; FIX for HB) were assessed. Coagulation factor levels were measured using either a one-stage assay, a chromogenic assay, or both. For the statistical analysis, the lowest level recorded for each patient was used, regardless of the assay method employed. With the informed consent of the participant, genetic testing for the proband’s pathogenic variant was performed.

Concurrently with both the retrospective and the prospective components of the study, family pedigrees of all PWHs followed at the HTC were updated and digitalized. Anonymized pedigrees were created using PhenoTips, and later in Epic when this feature became available at the clinic. In the proactive recruitment arm of the study, only females aged >12 years and <75 years were included. No age limit was applied for retrospective data collection. Statistical analysis of the data was performed using SPSS version 27.

Results

Study population

At the time of the analysis, 287 male PWHs (226 HA, 61 HB) were regularly followed at the HTC and causative genetic variants were known in all of them. Additionally, seven female PWHs were considered as probands (3 HA, 4 HB), meaning they were the first individuals to be diagnosed in their respective families. In total, 236 families (184 HA, 52 HB) were registered at the HTC. Twenty appointments at the bleeding disorders clinic were scheduled following the proactive outreach to unscreened potential and obligate carriers. Through retrospective and prospective data collection, 900 presumably alive female individuals could be identified.

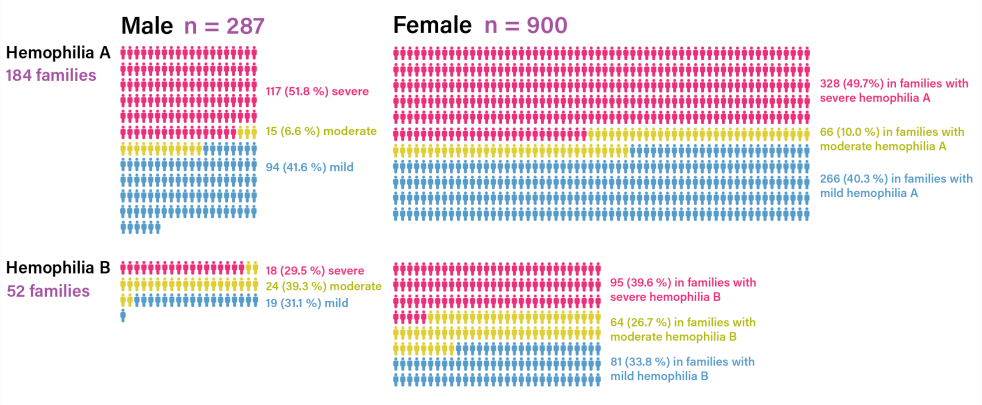

Figure 2 Overview of the study cohort, comprising 236 families. In these families, there were approximately three times as many female individuals who were potential or obligate carriers of hemophilia, based on their position in the family pedigree, compared to male probands. The severities of hemophilia affecting the families are depicted in red (severe), green (moderate), and blue (mild).

An overview of the study population according to sex and hemophilia type and severity is shown in Figure 2. Mean age of male individuals was 39.9 years (range 1-97) (HA) and 40.2 years (range 3-80) (HB), with 81.9% (n=235) aged 18 years or older. Mean age of female individuals was 44.1 years (range 1-99) (families with HA) and 44.4 years (range 5-101) (families with HB), with 90.2% (n=450) aged 18 years or older. Date of birth was not known in 44.6% (n=401) of female individuals. At least 64 females (7.1%) were living abroad.

Female individuals were categorized into four priority groups based on their proximity to the nearest hemophilia patient in the pedigree (Table 1). Group 1 comprised mothers, sisters, half-sisters (on the mother's side), daughters and sporadic carriers (i.e., carriers with no other known relatives affected by hemophilia), group 2 maternal aunts, nieces and grand-daughters, group 3 maternal grandmothers and cousins and group 4 maternal grandaunts and grand-cousins. Nine females could not be assigned to a specific priority group.

Diagnosis of carriers

Of 900 females, 454 (50.4%) were found to be obligate and/or genetically proven carriers of hemophilia (329 HA, 125 HB) and 118 could be identified as non-carriers (Figure 3). In eight of these non-carriers, carriership was ruled out because of genetic testing results confirming non-carrier status in their mothers. Carrier status has been confirmed through genetic testing in 131 obligate carriers, 126 potential carriers, and 7 index cases. Genetic testing is yet to be conducted for 328 potential carriers and 190 obligate carriers.

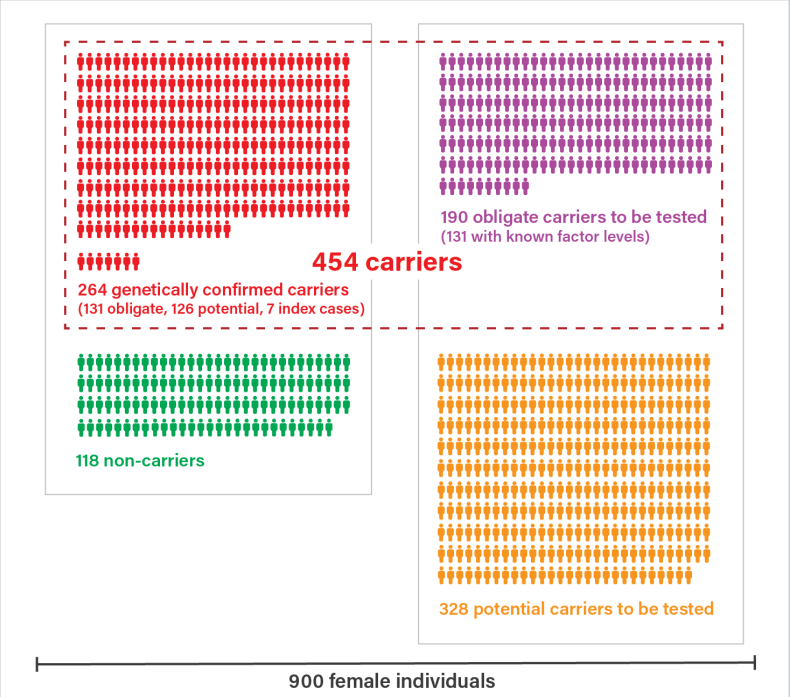

Figure 3 Carrier status of female individuals.

Mean age at diagnosis of carriership or non-carriership of female individuals for whom this exact age could be determined was 30.7 years (range 1-82) in families with HA and 30.1 years (range 0.5-93) in families with HB (p=0.809). In families with severe, moderate and mild hemophilia, mean age at diagnosis of females was, respectively, 29.7 (range 1.0-76.0), 29.6 (range 0.5-77.0) and 32.1 years (range 1.0-93.0) (p=0.535). Mean age at diagnosis of females with a FVIII or FIX deficiency (lowest factor level below 40 IU/dL) was 25.8 years (SD 18.4, range 1.0-63.0) compared to 31.8 years (SD 19.1, range 0.5-82.0) for those without a factor deficiency (p=0.034). Since the exact age at diagnosis could not be determined in the two females with severe hemophilia and there were no females with moderate hemophilia, the reported mean age at diagnosis of females with a factor deficiency equals the mean age at diagnosis of females with mild hemophilia in our cohort.

		Genetic testing performed	Genetic testing not yet performed	Total n (100%)	p-value
Hemophilia A					
Severity in family	Severe	129 (39.3 %)	199 (60.7 %)	328	
	Moderate	19 (28.8 %)	47 (71.2 %)	66	
	Mild	93 (35.0 %)	173 (65.0 %)	266	
					0.213
Hemophilia B					
Severity in family	Severe	31 (32.6 %)	64 (67.4 %)	95	
	Moderate	38 (59.4 %)	26 (40.6 %)	64	
	Mild	25 (30.9 %)	56 (69.1 %)	81	
					0.001
Hemophilia A					
	Priority group 1	167 (43.0 %)	221 (57.0 %)	388	
	Priority group 2	43 (26.4 %)	120 (73.6 %)	163	
	Priority group 3	25 (30.9 %)	56 (69.1 %)	81	
	Priority group 4	1 (5.3 %)	18 (94.7 %)	19	
					< 0.001
Hemophilia B					
	Priority group 1	69 (44.5 %)	86 (55.5 %)	155	
	Priority group 2	13 (21.7 %)	47 (78.3 %)	60	
	Priority group 3	11 (45.8 %)	13 (54.2 %)	24	
	Priority group 4	1 (100.0 %)	0 (0.0 %)	1	
					0.009

Table 2 Prevalence of genetic testing according to hemophilia type, severity and priority group.

In families with HA, the proportion of female individuals who have had genetic testing was 39.3%, 28.8% and 35.0% in families with severe, moderate and mild hemophilia, respectively (p=0.132). In families with HB, female individuals were more likely to be tested in families with moderate hemophilia (59.4%) compared to those with severe (32.6%) and mild (30.9%) hemophilia (p=0.01); this difference can however be attributed to the presence of one large family comprising 6 male persons with moderate HB and 22 female individuals, of whom most (n=18, 82%) have had genetic testing.

The prevalence of genetic testing according to priority group is shown in Table 1.

Coagulation factor levels

Frequencies of different coagulation factor level ranges in carriers and non-carriers are shown in Table 2. Coagulation factor levels had been measured at least once in 57.5% of carriers. Among carriers with known factor levels, 23.0% (n=42) and 29.5% (n=23) of HA and HB carriers, respectively, had a factor deficiency below 40 IU/dL (p=0.264), and 35.5 % (n=65) and 41.0% (n=32) had a factor level below 50 IU/dL (p=0.399). Carriers with a factor deficiency most often had mild hemophilia. One HA carrier and one HB carrier were regularly followed for severe hemophilia. One third of HA carriers (33.3%) and about one fourth of HB carriers (24.4%) had borderline factor levels, ranging between 40 and 60 IU/dL.

Mean minimum FVIII and FIX levels were significantly lower in carriers of HA and HB than in non-carriers (Table 2). No statistically significant difference was observed between the mean minimum FVIII level in HA carriers and the mean minimum FIX level in HB carriers (p=0.597). Carriers of HA with blood group O had significantly lower FVIII, VWF:Ag and VWF:RCo levels than carriers of HA with blood group non-O (Table 3). In both HA and HB carriers, the proportion of carriers with a factor level below 40 IU/dL did not significantly differ between families with severe, moderate and mild hemophilia (Table 4), neither did mean coagulation factor levels in carriers with a factor deficiency in these groups (26.2, 30.4 and 27.1 IU/dL in families with severe, moderate and mild HA and HB, p=0.344).

	HA Carriers	HA Non-carriers	Total	p-value
FVIII min. level				
Mean, IU/dL (SD)	61.42 (28.20)	117.93 (35.32)		< 0.001
< 1 IU/dL, n (%)	1 (0.5)	0 (0.0)	1 (0.4)	
1-5 IU/dL, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
6-15 IU/dL, n (%)	3 (1.6)	0 (0.0)	3 (1.3)	
16-39 IU/dL, n (%)	38 (20.8)	0 (0.0)	38 (15.8)	
40-60 IU/dL, n (%)	61 (33.3)	1 (1.8)	62 (25.8)	
≥ 61 IU/dL, n (%)	80 (43.7)	56 (98.2)	136 (56.7)	
Total, n	183	57	240	
VWF:Ag min. level				
Mean, IU/dL (SD)	111.19 (45.04)	112.54 (38.10)		0.853
VWF:RCo min. level				
Mean, IU/dL (SD)	107.80 (42.79)	116.80 (44.56)		0.221
	HB Carriers	**HB Non-carriers**	**Total**	**p-value**
FIX min. level				
Mean, IU/dL (SD)	59.36 (29.90)	103.09 (30.40)		< 0.001
< 1 IU/dL, n (%)	1 (1.3)	0 (0.0)	1 (1.0)	
1-5 IU/dL, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
6-15 IU/dL, n (%)	1 (1.3)	0 (0.0)	1 (1.0)	
16-39 IU/dL, n (%)	21 (26.9)	0 (0.0)	21 (21.0)	
40-60 IU/dL, n (%)	19 (24.4)	2 (9.1)	21 (21.0)	
≥ 61 IU/dL, n (%)	36 (46.2)	20 (90.9)	56 (56.0)	
Total, n	78	22	100	

Table 2 Mean minimum coagulation factor levels and frequencies of different coagulation factor level ranges in carriers and non-carriers.

Hemophilia A carriers	**Blood group O**	**Blood group non-O**	**p-value**
FVIII minimum level	n = 44	n = 46	
Mean, IU/dL (SD)	49.07 (22.45)	62.00 (24.88)	0.011
VWF:Ag minimum level	n = 40	n = 37	
Mean, IU/dL (SD)	88.03 (32.50)	118.38 (30.35)	< 0.001
VWF:RCo minimum level	n = 40	n = 36	
Mean, IU/dL (SD)	84.40 (32.40)	117.72 (37.58)	< 0.001

Table 3 FVIII and VWF levels according to blood group O or non-O in HA carriers

		Hemophilia A	Hemophilia B	p-value
Minimum factor level < 40 IU/dL				
Severity in family	**Carriers**	42 / 183 (23.0 %)	23 / 78 (29.5 %)	
	Severe	20 / 97 (20.6 %)	8 / 27 (29.6 %)	
	Moderate	5 / 18 (27.8 %)	12 / 31 (38.7 %)	
	Mild	17 / 68 (25.0 %)	3 / 20 (15.0 %)	
		p = 0.706	p = 0.193	
	Non-carriers	0 / 57 (0.0 %)	0 / 22 (0.0 %)	
	p-value	< 0.001	0.004	0.264
Minimum factor level < 50 IU/dL				
Severity in family	**Carriers**	65 / 183 (35.5 %)	32 / 78 (41.0 %)	
	Severe	34 / 97 (35.1 %)	11 / 27 (40.7 %)	
	Moderate	7 / 18 (38.9 %)	15 / 31 (48.4 %)	
	Mild	24 / 68 (35.3 %)	6 / 20 (30.0 %)	
		p = 0.951	p = 0.427	
	Non-carriers	1 / 57 (1.8%)	1 / 22 (4.5 %)	
	p-value	< 0.001	0.001	0.399

Table 4 Prevalence of coagulation factor deficiency and low coagulation factor levels according to hemophilia type and severity.

Bleeding symptoms

Relative risks of different bleeding symptoms in HA and HB carriers according to minimum coagulation factor levels are listed in Table 5. Heavy menstrual bleeding (HMB) was the most frequent bleeding symptom in both adult HA and adult HB carriers, affecting 30.5% and 28.7% of them, respectively (p=0.200). Carriers of HA with a factor deficiency had a more than two-fold risk of experiencing HMB than non-carriers of HA (RR 2.39, CI95 1.46-3.92) and a two-fold risk compared to HA carriers with normal FVIII levels (RR 1.96, CI95 1.12-3.42). Carriers of HA with borderline factor levels had an increased risk of HMB (n=20, 41.7%) compared to non-carriers (n=7, 20.0 %) (p=0.037) (RR 1.48, CI95 1.05-2.09), but were not found to have an increased risk compared to HA carriers with normal levels (p=0.626) (RR 1.11, CI95 0.73-1.71). While HA carriers with a FVIII deficiency experienced HMB more often than those with borderline factor levels, this difference was not statistically significant (p=0.057).

Carriers of HB with a FIX deficiency experienced HMB more often (n=8, 44.4%) than non-carriers of HB (n=4, 28.6%) (RR 1.33, CI95 0.74-2.41) and carriers of HB with normal factor levels (n=10, 34.5%) (RR 1.29, CI95 0.63-2.65), yet these differences were not statistically significant (p=0.358 and p=0.495, respectively). There was also no significant difference regarding occurrence of HMB in carriers of HB with borderline FIX levels (n=5, 31.3%) compared to non-carriers of HB (n=4, 28.6%) (p=1.000) (RR 1.33, CI95 0.737-2.41) or carriers of HB with normal factor levels (p=0.826) (RR 0.91, CI95 0.39-2.14). The observed difference in frequency of HMB between carriers of HB with a FIX deficiency and those with borderline factor levels was not statistically significant (p=0.429).

Overall, carriers with blood group O had a higher rate of HMB compared to carriers with non-O blood groups (55.6% vs 29.1%, p=0.005) and a higher relative risk of HMB (RR 1.7, CI95 1.2-2.5). Among carriers of HA, the difference in HMB frequency (51.2% vs 32.5%, p=0.085) and RR (1.4, CI95 1.0-2.2) did not reach statistical significance. However, carriers of HB with blood group O experienced HMB significantly more frequently than those with non-O blood groups (72.7% vs 20.0%, p=0.007; RR 3.6, CI95 1.2-10.7).

Among adult carriers with a factor deficiency, reproductive tract bleeding other than HMB (RTB) (mostly post-partum hemorrhage (PPH), 19/27, 70.4%) was significantly more frequent in adult HB carriers than in adult HA carriers (p=0.002). In adult HA carriers with a factor deficiency, the proportion of carriers affected by RTB was exactly the same (n=2, 5.7%) as in non-carriers of HA (n=2, 5.7%) (p=1.000) and lower than in HA carriers with normal FVIII levels (n=7, 11.3%) (p=0.363). In adult HA carriers with borderline FVIII levels, the proportion of carriers with RTB was higher (n=5, 10.4%) than in non-carriers (p=0.693) and was lower than in HA carriers with normal FVIII levels (p=0.884), although not significantly in both cases. Adult HB carriers with a FIX deficiency had a more than two-fold risk of RTB compared to HB carriers with normal FIX levels (RR 2.36, CI95 1.24-4.47). In adult HB carriers with borderline FIX levels, RTB did not occur significantly more often (n=2, 12.5%) than in non-carriers of HB (n=1, 7.1%) (p=1.000) or HB carriers with normal FIX levels (n=3, 10.3%) (p=1.000). Although reproductive tract bleeding (RTB) was more frequent in HB carriers with a FIX deficiency compared to those with borderline FIX levels, this difference

was not statistically significant (p=0.125), possibly due to the limited number of observations.

Easy bruising was more frequent in HA carriers with a factor deficiency (n=16, 42.1%) than in HB carriers with a factor deficiency (n=5, 22.7%), yet this difference was not statistically significant (p=0.129). Both HA and HB carriers with a factor deficiency did not experience easy bruising significantly more often than non-carriers (p=0.147 and p=0.419, respectively). Similar frequencies of easy bruising were observed between HA carriers with a FVIII deficiency and those with borderline FVIII levels (p=0.842), as well as between HB carriers with a FIX deficiency and those with borderline FIX levels (p=0.790).

Epistaxis was more frequent in HA carriers with a FVIII deficiency (n=8, 21.1%) than in HB carriers with a FIX deficiency (n=3, 13.6%), although not significantly (p=0.474). HA carriers with a FVIII deficiency had an increased risk of epistaxis compared to those with normal FVIII levels (RR 1.58, CI95 0.91-2.76), yet this was not statistically significant (p=0.144). In HB carriers, the frequency of epistaxis was similar between those with a FIX deficiency and those with normal FIX levels (RR 1.06, CI95 0.42-2.67, p=1.000). Additionally, there were similar frequencies of epistaxis observed between HA carriers with a FVIII deficiency and those with borderline FVIII levels (p=0.915), as well as between HB carriers with a FIX deficiency and those with borderline FIX levels (p=1.000).

HA carriers with a FVIII deficiency had a more than two-fold risk of developing anemia (RR 2.38, CI95 1.53-3.71) and iron deficiency (RR 2.30, CI95 1.46-3.61) compared to HA carriers with normal factor levels. Similar figures were observed in HB carriers, with an RR for anemia of 2.18 (CI95 1.23-3.86) and an RR for iron deficiency of 2.69 (CI95 1.88-3.83) compared to HB carriers with normal factor levels. HA carriers who experienced HMB had a three-fold risk of being anemic (RR 3.13, CI95 1.03-9.55) compared to those who did not experience HMB. Such an increased risk could not be demonstrated for HB carriers (RR 1.19, CI95 0.37-3.78).

	FVIII level			FIX level		
	< 40 IU/dL	40-60 IU/dL	> 60 IU/dL	< 40 IU/dL	40-60 IU/dL	> 60 IU/dL
Heavy menstrual bleeding*						
Frequency, n (%)	22/35 (62.9)	20/48 (41.7)	23/62 (37.1)	8/18 (44.4)	5/16 (31.3)	10/29 (34.5)
RR (CI95)	1.96 (1.12-3.42)	1.11 (0.73-1.71)	1	1.29 (0.63-2.65)	0.91 (0.39-2.14)	1
Reproductive tract bleeding*, **						
Frequency, n (%)	2/35 (5.7)	5/48 (10.4)	7/62 (11.3)	7/18 (38.9)	2/16 (12.5)	3/29 (10.3)
RR (CI95)	0.59 (0.17-2.07)	0.95 (0.47-1.92)	1	2.36 (1.24-4.47)	1.14 (0.36-3.62)	1
Easy bruising						
Frequency, n (%)	16/38 (42.1)	20/50 (40.0)	17/66 (25.8)	5/22 (22.7)	3/18 (16.7)	6/32 (18.8)
RR (CI95)	1.57 (0.96-2.57)	1.42 (0.95-2.14)	1	1.15 (0.55-2.42)	0.91 (0.33-2.50)	1
Epistaxis						
Frequency, n (%)	8/38 (21.1)	11/50 (22.0)	7/66 (10.6)	3/22 (13.6)	2/18 (11.1)	4/32 (12.5)
RR (CI95)	1.58 (0.91-2.76)	1.54 (0.99-2.39)	1	1.06 (0.42-2.67)	0.92 (0.28-3.04)	1
Hematomas						
Frequency, n (%)	4/38 (10.5)	2/50 (4.0)	1/66 (1.5)	2/22 (9.1)	0/18 (0.0)	1/32 (3.1)
RR (CI95)	2.33 (1.39-3.91)	1.57 (0.69-3.60)	1	1.70 (0.71-4.06)	-	1
Bleeding after dental procedures						
Frequency, n (%)	5/38 (13.2)	2/50 (4.0)	5/66 (7.6)	5/22 (22.7)	0/18 (0.0)	2/32 (6.3)
RR (CI95)	1.42 (0.72-2.81)	0.65 (0.20-2.13)	1	1.98 (1.08-3.61)	-	1
Perioperative bleeding						
Frequency, n (%)	5/38 (13.2)	2/50 (4.0)	8/66 (12.1)	5/22 (22.7)	1/18 (5.6)	2/32 (6.3)
RR (CI95)	1.06 (0.51-2.22)	0.44 (0.13-1.55)	1	1.98 (1.08-3.61)	0.92 (0.18-4.77)	1
Mucosal bleeding						
Frequency, n (%)	5/38 (13.2)	10/50 (20.0)	5/66 (7.6)	2/22 (9.1)	1/18 (5.6)	3/32 (9.4)
RR (CI95)	1.42 (0.72-2.81)	1.68 (1.10-2.59)	1	0.98 (0.32-3.02)	0.68 (0.12-3.85)	1
Bleeding requiring transfusion						
Frequency, n (%)	0/38 (0.0)	0/50 (0.0)	6/66 (9.1)	3/22 (13.6)	1/18 (5.6)	0/32 (0.0)
RR (CI95)	-	-	1	2.68 (1.88-3.83)	2.88 (1.96-4.23)	1
Abnormal bleeding after trauma						
Frequency, n (%)	5/38 (13.2)	2/50 (4.0)	2/66 (3.0)	2/22 (9.1)	0/18 (0.0)	0/32 (0.0)
RR (CI95)	2.10 (1.22-3.62)	1.17 (0.43-3.18)	1	2.60 (1.84-3.67)	-	1
Hemarthrosis						
Frequency, n (%)	4/38 (10.5)	0/50 (0.0)	0/66 (0.0)	1/22 (4.5)	0/18 (0.0)	0/32 (0.0)
RR (CI95)	2.94 (2.24-3.87)	-	1	2.52 (1.81-3.52)	-	1
Other bleeding						
Frequency, n (%)	1/38 (2.6)	0/50 (0.0)	0/66 (0.0)	0/22 (0.0)	0/18 (0.0)	0/32 (0.0)
RR (CI95)	2.78 (2.15-3.60)	-	1	-	-	1
Anemia						
Frequency, n (%)	9/38 (23.7)	3/50 (6.0)	3/66 (4.5)	4/22 (18.2)	4/18 (22.2)	1/32 (3.1)
RR (CI95)	2.38 (1.53-3.71)	1.17 (0.51-2.68)	1	2.18 (1.23-3.86)	2.57 (1.39-4.77)	1
Iron deficiency						
Frequency, n (%)	10/38 (26.3)	4/50 (8.0)	4/66 (6.1)	3/22 (13.6)	2/18 (11.1)	0/32 (0.0)
RR (CI95)	2.30 (1.46-3.61)	1.17 (0.57-2.43)	1	2.68 (1.88-3.83)	3.00 (2.01-4.48)	1

Table 5 Bleeding symptoms in HA and HB carriers according to minimum coagulation factor levels (*in women ≥ 18 years old; **other than HMB).

Hemostatic Treatment

In carriers for whom information on hemostatic treatment use was available, 26.6% (n=37) of HA carriers and 40.3% (n=27) of HB carriers (p=0.047) have had to receive a hemostatic treatment at least once in their lifetime at the time of the study. The most frequently used agent in both HA and HB carriers was tranexamic acid, used in 22.3% (n=31) and 34.3% (n=23), respectively (p=0.066) (Figure 4). The second most-used agent was DDAVP (14.4%, n=20) in HA carriers and recombinant FIX products (29.9%, n=20) in HB

carriers. In HA carriers, coagulation factor replacement products were less commonly used, explained by the fact that DDAVP is available as an alternative in these patients. Two HA carriers were treated with regular emicizumab prophylaxis, and one HB carrier was on regular prophylaxis with an EHL rFIX product.

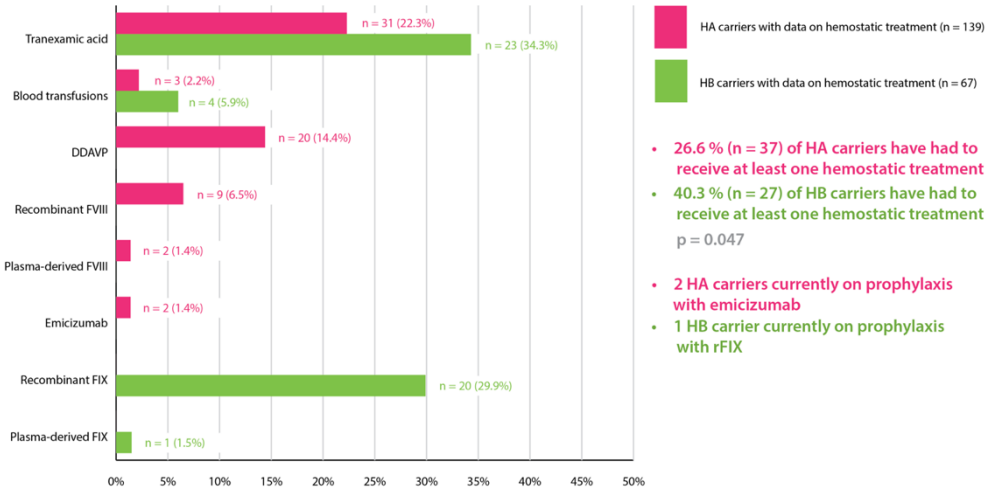

Figure 4 Hemostatic treatments administered at least once in carriers.

Discussion

Establishing and regularly updating family pedigrees of PWHs is a fundamental yet often underutilized clinical practice in bleeding disorder care and marks the initial stride toward ending gender disparities in hemophilia care. Its primary goal is to ensure that all female and male relatives of PWH, even the more distant ones in the pedigree, receive timely diagnosis and appropriate bleeding prophylaxis. While the establishment of family pedigrees for genetic counseling and testing purposes figures in the 2020 WFH guidelines for the management of hemophilia and multiple reports of carrier diagnosis in PWH's families do exist[22,26–34], concrete strategies for systematic carrier screening, aiming to screen all potential and obligate carriers genetically linked to a PWH, have not yet been described. Moreover, to the best of our knowledge, such reports are also absent for other X-linked recessive disorders, such as Duchenne and Becker muscular dystrophies, Adrenoleukodystrophy or X-linked retinal diseases.

In a survey of 150 carriers of different X-linked disorders by Choi et al., most participants (54%) declared that they had been diagnosed as a carrier only after giving birth to an affected boy.[35] This finding might seem logical if all carriers were entirely asymptomatic. However, cases of symptomatic carriers of X-linked disorders have been described and may be more frequent than expected.[36] Symptomatic hemophilia carriers and WGH may go undiagnosed because their abnormal bleeding symptoms are overlooked or mistaken as normal, especially in families where HMB is common among women carrying hemophilia.[37,38]

This study represents the first attempt to comprehensively identify all carriers and potential carriers in a HTC's patient cohort and to reach out to unscreened individuals. It allowed us to obtain a precise inventory of known carriers, potential carriers yet to be tested and non-carriers in our HA and HB patient cohort. It revealed that at least more than half of the 900 female individuals within our cohort were carriers. However, a significant number of potential carriers (328, as depicted in Figure 3) have yet to undergo genetic testing. Additionally, 59 obligate carriers have not had their factor levels tested. These statistics underscore the challenges of comprehensively screening all female relatives, despite our proactive efforts.

Several factors contributed to the difficulty in reaching PWHs' relatives for testing. Firstly, some undiagnosed potential carriers fell into age brackets that were excluded from the prospective arm of our study: among undiagnosed potential carriers with known age, 8.1% (6/74) were below the age of 12 years, while 14.9% (11/74) were above the age of 75 years. Furthermore, given the cosmopolitan nature of Brussels, where our HTC is located, it is unsurprising that at least 64 female individuals resided abroad, making outreach and obtaining testing results more complex. Moreover, our study started during the Covid-19 pandemic, which further complicated matters by making non-urgent hospital visits less feasible and appealing for potential participants. It also made the organization of patient information events impossible. These events, which had been regularly held before the pandemic, would have provided a valuable opportunity to explain the rationale behind carrier screening to PWHs and their female relatives during face-to-face meetings. They would have also facilitated the exchange of experiences among symptomatic carriers and WGH.

The success of any carrier screening initiative relies significantly on the awareness and proactivity of hematologists, as well as the motivation and health literacy of the probands. These probands act as intermediaries between their relatives and healthcare professionals during the initial contact. Unfortunately, various factors can disrupt this communication channel, including family conflicts and the stigma surrounding PWHs, as well as stigma surrounding menstruation and reproduction within certain families or cultures.[39,40] In our study, we provided verbal information about the implications of hemophilia carriership, as well as written materials in the form of informational brochures. However, we faced a challenge in monitoring whether and how effectively this information was relayed to the female relatives. It is noteworthy that, prior to the commencement of the study, repeatedly raising awareness among male PWHs about the importance of carrier screening was already part of the clinical routine at our HTC. An additional explanation for why many female relatives of PWHs remain unscreened, despite proactive efforts by hematologists, may be that the most motivated and health-literate relatives of probands have likely already been screened. Those remaining unscreened may be harder to reach or motivate to attend the clinic. Furthermore, we hypothesize that individuals with abnormal bleeding are more likely to seek specialized care or respond to clinic invitations than those who are asymptomatic, leading to a certain selection bias when reporting bleeding symptoms in a population of female relatives of PWHs.

In addition to screening the highest possible number of potential carriers in our cohort, our study's second objective was to compare carriers of HA and HB in various aspects. We observed similarities in the circumstances of diagnosis, with both groups having a similar proportion of carriers having had genetic testing and an average age at diagnosis of around 30 years. Within our cohort, female individuals with mild hemophilia were diagnosed, on average, seven years later than their male counterparts with mild hemophilia (mean age at diagnosis of 18.2 years), highlighting the diagnostic delays frequently experienced by women with bleeding disorders. Considering the significant implications of carrier status for family planning, there is evidently a need for earlier detection of carriers. The ideal timing of genetic testing is debated and influenced by local legal frameworks, especially regarding testing minors.[41,42] Authors of the European principles of care for women and girls with inherited bleeding disorders advise to perform genetic testing in

adolescence or early adulthood and in certain cases it may be envisaged in children.[21] Ideally, the genetic status should be known before pregnancy to enable informed reproductive choices.[41,43,44] Today, hemophilia carriers have various reproductive choices, including preimplantation and prenatal diagnostics. These options empower them to make informed decisions regarding pregnancies, enabling them to prevent or choose to terminate a pregnancy if it is found that the child may have hemophilia, or to simply be prepared for precautionary measures that will be taken during delivery and for a life with a hemophilic child.

Our findings regarding mean coagulation factor levels in carriers versus non-carriers are in line with central tendency measures of coagulation factor levels previously reported in the literature for both groups.[34,45–49] The correlation between the severity of hemophilia in a family and the coagulation factor levels in HA and HB carriers remains uncertain. At this time, the prevailing evidence suggests that there is more support for the absence of such a correlation[26,47,50–52], as observed in our cohort, rather than its existence.[53] There were no significant differences in the proportion of carriers with a factor deficiency and in mean coagulation factor levels between HA and HB carriers. As in a previous report by James et al.[54], HMB was the most frequently reported bleeding symptom experienced by HA and HB carriers, without a significant difference in occurrence in both groups. The incidence of HMB noted within our cohort of HA carriers with a factor deficiency closely aligns with findings reported by Plug et al. in carriers (both HA and HB, predominantly HA) with a deficiency.[45] Furthermore, when compared to the Dutch cohort from 2006, we identified a comparable relative risk of anemia and iron deficiency among carriers with a factor deficiency in contrast to carriers exhibiting normal levels.[45]

It is interesting to note that RTB/PPH was significantly more frequent in HB carriers, although absolute numbers were low. This discrepancy between HA and HB carriers might be attributed to the fact that, unlike in HA carriers in whom FVIII levels physiologically rise during pregnancy due to hormonal changes, FIX levels in HB carriers do not show a similar increase, potentially rendering HB carriers more vulnerable to PPH without adequate hemostatic cover. Given the low number of carriers in our cohort who experienced hemarthrosis it is difficult to make assumptions about possible differences between HA and HB carriers. Nevertheless, it is important to acknowledge

the possibility of underrecognized joint microbleeds and damage in carriers, underscoring the need for further research attention to musculoskeletal issues.[37,55,56] In general, future research should gather more detailed data on bleeding symptoms and treatment of bleeding episodes in hemophilia carriers, as well as on the bleeding phenotypes of carriers with borderline factor levels.

As emphasized by Gregory et al. in 2007[39], ongoing screening efforts regarding hemophilia carriers and WGH are crucial, particularly amidst the diminishing frequency and shortening of patient-healthcare professional interactions thanks to novel therapeutics for hemophilia. The imperative to continually update pedigrees remains essential, since even groundbreaking treatments like gene therapy do not alter the hereditary nature of hemophilia. Additionally, the transition of PWHs from pediatric to adult care marks a vulnerable phase where keeping track of the patient's relatives becomes challenging.[41] Furthermore, girls who underwent coagulation factor level assessments during childhood still require genetic testing later in life and should not be overlooked.[41] Identified carriers, especially those experiencing abnormal bleeding, should benefit from regular follow-up at the HTC.

To conclude, this study represents the first reported initiative to systematically identify and screen (potential) hemophilia carriers among families of all PWHs followed at a single HTC. We have gained new insights into practical aspects of carrier diagnostics, while also identifying persistent challenges in providing comprehensive screening to relatives of PWHs. Initiatives similar to our study should be replicated by other HTCs internationally, as they would represent a crucial step toward ensuring equitable access to hemophilia diagnosis and care for all potentially affected individuals, regardless of sex and gender.

Limitations

The main limitation of our study lies in the mostly retrospective nature of our data. Bleeding and hemostatic treatment data were coded as binary variables and no data on specific bleeding or treatment episodes was collected. Abnormal bleeding data were aggregated from patient-reported bleeding symptoms rather than using bleeding scores like the ISTH-BAT. Moreover, as mentioned earlier, we assume that individuals experiencing abnormal bleeding are more likely to seek specialized medical care, leading

to selection bias in the reporting of bleeding symptom frequency in female relatives of PWHs. Only the lowest coagulation factor levels of each individual were considered for the analysis, and no adjustment was made for use of estrogen and/or progesterone treatments for contraceptive or substitutive purposes and for age. Coagulation factor levels measured during pregnancy were not taken into account. Establishing family pedigrees heavily relies on patient reports, and a certain degree of imprecision, particularly in large families, cannot be entirely eliminated.

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SECTION 4

Using the Electronic Health Record for the Benefit of the Hemophilia Patient

Chapter 6

Building a Hemophilia-specific Navigator in Epic® Electronic Health Records: Single-center Preliminary Experience.

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Summary

Background: With the increasing complexity of hemophilia care and the advent of numerous therapeutic innovations, there is an unmet need for documentation and data collection tools tailored to people with hemophilia (PWH). To date, no fully integrated hemophilia-specific electronic health record (EHR) has been described in the literature.

Aim: To evaluate the feasibility of integrating a hemophilia-specific navigator into the Epic EHR.

Methods: Based on clinical experience and registry datasets, we identified key variables describing both PWH and carriers of hemophilia. These were then incorporated into a REDCap database, which served as a starting point for the development of a comprehensive hemophilia flowsheet. We built a dedicated hemophilia navigator within Epic that includes a flowsheet featuring up to 212 variables, as well as customized note templates and patient lists integrating data from the hemophilia flowsheet.

Results: It was feasible to develop a hemophilia navigator within Epic over the course of 12 months. The navigator's flowsheet enables systematic and comprehensive clinical assessment of PWH and carriers, while customized patient lists provide a quick summary of each patient's profile to the hemophilia treatment center staff and highlight issues that require an intervention. In our clinical practice, patients actively participated in the new documentation process and responded positively to the navigator.

Conclusion: Adapting EHRs to the needs of PWH and carriers promotes holistic care for this population and provides an opportunity for patient empowerment. Such hemophilia-specific EHRs are expected to promote standardization of care and facilitate the collection of registry data on a national and international level.

Introduction

Hemophilia, an X-linked recessive bleeding disorder caused by deficiencies in coagulation factor VIII (hemophilia HA, HA) or IX (hemophilia B, HB), impacts the lives of individuals living with the disease in multiple ways, not only physically as a result of joint and muscle bleeds but also socially, professionally and mentally. In recent decades, the treatment paradigms for hemophilia have moved away from exclusively preventing and treating bleeds to a more comprehensive approach that considers each person as a distinct individual with their own clinical history, socioeconomic circumstances, and mental ecosystem. Furthermore, bleeding prophylaxis and treatment have evolved dramatically, as reflected by a revolution in hemophilia treatment in recent years, with the introduction of extended half-life factor concentrates, non-replacement therapies and gene therapy.[1]

Choosing the optimal treatment for a given patient has become a difficult task, since patient populations are highly heterogenous. Patients differ in their clinical history, increasingly marked by various comorbidities as hemophilia patients' life expectancy increases, their treatment preferences and quality of life expectations. In addition, caregivers are important stakeholders in the hemophilia patient journey and their involvement should be valued more than ever.

While the key elements of a follow-up consultation in the haemophilia clinic and of the hemophilia patient's care pathway have been established[2,3] and while their increasing consideration undoubtedly improves the quality of hemophilia care, there is still an unmet need for multidimensional, multidisciplinary and collaborative tools that integrate all variables defining each unique hemophilia patient. Such tools should foster appropriate (therapeutic) decision-making and a rigorous patient follow-up.

The tools currently available (paper notes, generic current electronic health records (EHRs)) are not sufficient to fulfill these ambitious objectives. At the haemophilia treatment center (HTC) of the Cliniques universitaires Saint-Luc (CUSL) in Brussels, Belgium, we aimed to evaluate the feasibility of integrating a hemophilia-specific navigator into the Epic (Epic Systems) EHR in order to fill this need. To date, Epic Systems' EHR is mainly used in the United States and has been rolled out in several other countries (Netherlands, Switzerland, Denmark, Saudi Arabia, Australia, Canada,

Lebanon).[4] At our clinic, Epic was implemented in November 2020 to replace outdated software. The CUSL were the first clinic to adopt Epic in Belgium and the first worldwide to use it in French.[5]

Epic is designed as an "all-in-one" EHR, which allows in- and outpatient medical documentation, drug prescriptions and scheduling of treatment plans, the arrangement of appointments, display of biological test and imaging results and billing. Furthermore, at our hospital, patient data from the four Belgian health networks, which are used for electronic communication between all Belgian hospitals and general practitioners, can be accessed directly through the Epic user interface. Patients can access part of their health record through the "MyChart" patient portal (called "Mon Saint-Luc" in our institution). The Epic EHR supports more than 40 different medical specialties and may be further customized.[6] Data input forms and data handling tools may be built in Epic according to the specific needs of each medical specialty. For example, it is possible to create note templates, containing custom lists ("SmartLists"), text blocks ("SmartTexts" and "SmartPhrases") and data from EPIC flowsheets. These elements are not exclusively built by the hospital's IT specialists but also by specifically trained staff members called "SmartToolBuilders" or "physician builders", although they may not necessarily be physicians.[7]

Several ways in which Epic's customizable data recording tools can be of use in clinical practice have been described[8–18], such as integrating disease-specific monitoring and screening tools[9,11,13,17,18], streamlining documentation and patient handoffs[8], developing a prescription tool for online educational material[10], integrating third-party health technology software and hardware[12,14] as well as implementing disease-specific structured data handling tools.[15,16] However, to our knowledge, there has not been any attempt so far to implement a hemophilia-specific navigator in Epic.

Methods

Our project was started in July 2021, when Epic had already been operational for nine months in our clinic and several issues that occurred in the beginning had been fixed. We started by identifying all variables defining hemophilia patients and carriers (such as hemophilia type and severity, inhibitor status and bleeding phenotype). This was done by four hematologists and one physiotherapist, all with experience in the field of

hemophilia, and a physician builder. The variables were based on our clinical experience and hemophilia registry datasets such as the World Bleeding Disorders Registry (WBDR)[19] and the Pediatric Network on hemophilia management registry (PedNet).[20]

The variables of this first draft were then integrated in a REDCap database, containing 206 items, and later coded into a structured EPIC flowsheet. In regular meetings of the development team, the structure of the flowsheet was optimized, and some elements were added or removed. Simultaneously, note templates for hemophilia patients and carriers that can import data from the hemophilia flowsheet were built. In addition, the hemophilia-specific flowsheet injects data into specifically built patient lists (only accessible to hemophilia specialists in our institution). The items featured in these lists are shown in Figure 1. Several items, such as annual bleeding rate (ABR) and annual joint bleeding rate (AJBR), are displayed as icons or bullets of different colors. The date of the last hematology consultation is automatically shown for each patient on the list, even if the hemophilia flowsheet has not been completed yet. The flowsheet's structure is illustrated in Figure 2.

Results

Over a 12-month period, it was possible to create a hemophilia-specific navigator within Epic that included a flowsheet, note templates, and patient lists specific to the disease. All staff members who participated in the project did so alongside their regular clinical responsibilities. The navigator was implemented in routine clinical practice in June 2022 and to date, the hemophilia flowsheet, containing up to 212 variables for hemophilia patients and 36 for hemophilia carriers, has been completed for 75 patients with HA and 18 patients with HB at our HTC. During the first 10 months of using the navigator, we have noted several benefits and identified remaining challenges.

We observed that filling out the flowsheet for the first time during consultations was more time consuming than traditional note taking. However, once the hemophilia flowsheet had been filled out, clinicians were able to get a quick overview about the patient's history and status through the flowsheet itself and the above-mentioned patient lists. In addition to this overview, the visual indicators contained in the patient lists made abnormal parameters stand out and thus made it possible to identify patients for whom

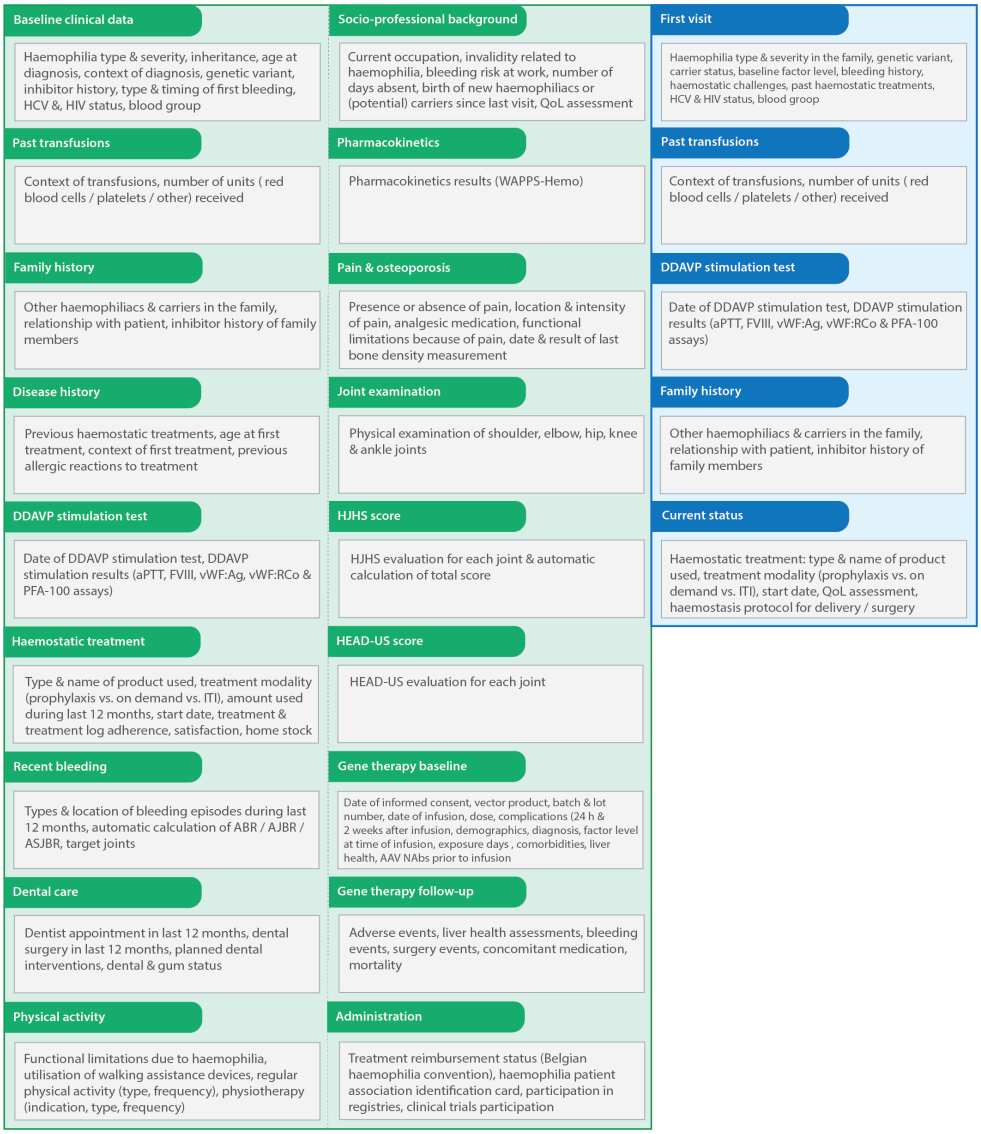
an intervention was required. In that manner, we were for example able to identify patients who experienced pain causing functional limitations or who had a high ABR. Furthermore, by visualizing the last date of consultation in hematology for every patient we could readily identify patients who required a follow-up consultation and promptly reach out to them.

The flowsheet also prompted clinicians to document elements that are at risk of being overlooked in a routine follow-up consultation, one example being the systematic updating of the family history. A family history section already exists in Epic, but, from our experience, clinicians tend to forget to update this section during follow-up consultations once it has been filled out. The hemophilia flowsheet however incites clinicians to investigate whether any new hemophilia patients have been born in the family or if there are any potential hemophilia carriers who have not yet been screened. We are presently using this feature in our recruitment process for an ongoing carrier screening project.[21]

Certain functionalities of Epic have been adapted to hemophilia patient care in our HTC, without being part of the hemophilia navigator as such. As per the request of the HTC staff, alerts for individuals with severe bleeding disorders were implemented in Epic immediately after the “Go Live”. These alerts are constantly visible in the left sidebar, and by clicking on them, users can access information about the type and severity of the bleeding disorder, current hemostatic treatment, and contact details of the treating bleeding disorder specialists. Additionally, hemophilia treaters receive pop-up alerts in case of hospital admissions and pre-admissions of patients with bleeding disorders.

Although we did not explicitly collect data on patient satisfaction, we can say that in our clinical practice the hemophilia navigator was generally well received by the patients who actively participated in filling out the flowsheet. Regarding the development process, building hemophilia-specific note templates that integrate data from the flowsheet in a narrative document was a particularly challenging task, notably because the data entered in the flowsheet needed to be integrated into complete and coherent sentences in the note template.

Figure 1 How hemophilia patients engage with their medical records according to the different types of documentation in health care.



AAV-NAbs: adeno-associated virus neutralising antibodies, ABR: annualised bleeding rate, AJBR: annualised joint bleeding rate, aPTT: activated partial thromboplastin time, ASJBR: annualised spontaneous joint bleeding rate, DDAVP: desmopressin, FVIII: coagulation factor VIII, HCV: hepatitis C virus, HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound, HIV: human immunodeficiency virus, HJHS: Hemophilia Joint Health Score, ITI: immune tolerance induction, PFA: platelet function analyser 100, QoL: quality of life, vWF:Ag : von Willebrand factor antigen, vWF:RCo : von Willebrand factor ristocetin cofactor activity, WAPPS-Hemo: Web-Accessible Population Pharmacokinetic Service – Hemophilia.

Figure 2 Content of the hemophilia flowsheet by category. First two columns from left to right (in green): general flowsheet for PWH in general. Third column (in blue): flowsheet for hemophilia carriers.

Discussion

From the increasing adoption of EHRs in healthcare facilities arise not only challenges, but also a variety of opportunities for customization and data handling that would have been highly time-consuming or even impossible with traditional paper records. We developed a hemophilia-specific navigator in Epic to help clinicians systematically cover all domains that are relevant for assessment and follow-up of hemophilia patients, as recommended by the European Haemophilia Standardisation Board in 2011[2] and of which some, such as dental care or social participation, are at risk to be forgotten in the rush of a busy and tightly scheduled consultation. On the other hand, information that is already encoded in other parts of the Epic EHR (such as vital parameters) is not supposed to be duplicated in our navigator.

As healthcare providers face increasing pressure to work efficiently, with busy schedules and staff shortages, utilizing a standardized flowsheet to cover all domains of the hemophilia workup can help ensure comprehensive care for all patients, promoting health equity. Additionally, these tools facilitate the assessment of hemophilia-specific elements for clinicians who are not hemophilia specialists, as the flowsheet guides them through every step of history taking. This is particularly valuable in situations where staff turnover is high, such as during rotations of trainee physicians in internal medicine. Likewise, some patients visit the clinic less regularly (e.g., patients with mild hemophilia and a mild bleeding phenotype), meaning that their medical history may be less well known to the HTC staff.

While certain features of the hemophilia navigator are designed to obtain a quick overview of patient data, one should not confound this with the aim to minimize the amount and length of patient contacts. Quite the opposite, we recommend that the hemophilia flowsheet should be completed collaboratively with the patient, which entails rotating the screen displaying the EHR in a way that allows the patient to view the flowsheet. During conventional digital note-taking, the screen may create a physical barrier that hinders communication with the patient who, additionally, is unable to see what the physician is documenting, as shown in Figure 1. When taking notes on paper, the patient is usually fully unaware of what is written during a consultation. By sharing a screen to complete the hemophilia flowsheet, the physician involves the patient in the documentation process. This certainly is

time-consuming, especially when the flowsheet is filled out for the first time, but with new, very effective therapies the hemophilia consultation will be less and less focused on assessing stigmas of joint bleeding, and the newly gained time can be used for holistic assessment of the patient's status. The systematic assessment of the patient's disease course together with the patient also allows the patient to gain awareness about his or her physical and mental health status and of the multiple implications the disease has on his or her daily life. This self-awareness works both ways: patients may, for example, become more aware of the positive impact of a new treatment or, conversely, be motivated to take action because the impact of the disease on their health and daily life is higher than expected. Patients may decide to switch to a new treatment or consider improving their adherence to bleeding prophylaxis or other prophylactic measures such as regular dental work-up.

Altogether, we see the disease-specific health record as an opportunity for patient-empowerment, complementing patient-centered digital health records, like the "MyChart" patient portal. Such patient portals allow patients to view parts of their medical record online, with potential additional functionalities depending on the institution they are used in.[22] They may be particularly beneficial when used for chronic diseases, such as hemophilia, which often require a high level of patient autonomy.[22] In fact, patient participation in outcome reporting and documentation has been recognized as one of the key elements of self-management in the latest World Federation of Hemophilia guidelines for hemophilia care.[23] Furthermore, the Epic EHR may be used to provide the patient with online educational material.[10]

The hemophilia navigator was designed as a tool to standardize hemophilia patient care inside our institution, but on a larger scale such hemophilia-specific EHRs could contribute to standardization of care on a national and even international level. Since we took into account the structure of hemophilia registries during the development phase, we anticipate that the navigator will streamline registry data collection in our institution. In fact, with the advent of new therapies and especially gene therapy, long-term collection of data on treatment safety and efficacy in international registries and safety surveillance databases such as the European Haemophilia Safety Surveillance system (EUHASS) is crucial.[24,25] Although web applications such as those of the EUHASS and the ATHNdataset exist for collecting

extensive health data of hemophilia patients[25,26], they are designed solely for data collection, unlike our hemophilia navigator which is designed for comprehensive clinical documentation.

The hemophilia navigator should also facilitate data collection for research and audit purposes, for example through the workbench report function provided in Epic which can be fed with flowsheet data. We are also optimistic that this approach could be useful for other HTCs as well. Given the high level of heterogeneity in EHR systems used in Belgium and the cost of switching to another system, it is advisable for other institutions to investigate the possibility of customizing their existing EHR systems. Furthermore, it is also worth noting that different HTCs may want to use different assessment tools and scoring systems. While the Epic navigator or similar navigators should contribute to the standardization of hemophilia care, they can still be customized to meet the unique needs and preferences of each center. In our hemophilia navigator we have incorporated the Haemophilia Joint Health Score (HJHS)[27] and Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)[28] for joint health assessment, but additional clinical scores such as the Haemophilia Activity List (HAL), Pediatric HAL (PedHAL), the Functional Independence Score in Haemophilia (FISH)[29] or the newly developed ACTIVLIM-Hemo[30] may be added to the navigator.

In addition, such navigators may be developed for other diseases. In our institution, we are presently creating similar navigators for von Willebrand disease and factor VII deficiency. Since it was the first time such a project was undertaken in our institution, it took 12 months from start to finish. We expect that the development of similar navigators for other diseases will be more fluent and less time-consuming. The navigator was first developed in French language, but we are working on a translation in English in order to make our developments available to a larger community.

A limitation with this approach to development is the need for experienced clinicians who are able and willing to stretch their already busy schedules to work on such a project, as well as the need for IT specialists and/or specifically trained staff members. Even without being involved in software developments, staff members spend a considerable amount of time discovering Epic's features. From our and other health care providers' experience, Epic's user interface is non-intuitive to many clinicians at first[31] and learning how to perform basic tasks, all while managing numerous

incoming Epic notifications and alerts without losing focus, is time consuming. At the CUSL, almost 1000 educational videos had to be created for the initial training[5], after which clinicians still need to continuously adapt to software updates and new functions, demanding a certain flexibility and willingness to adapt.

Conclusion

Implementing a hemophilia-specific navigator in our hospital's EHR was feasible and was found to be an invaluable tool for ensuring a systematic and comprehensive assessment of each hemophilia patient, helping clinicians navigate the increasingly complex clinical management of hemophilia, marked by multiple therapeutic innovations and heterogenous patient populations. Moreover, such navigators provide an opportunity for patient empowerment through their active participation in outcome reporting and documentation. In the future, implementation of such hemophilia-specific navigators in EHRs should contribute to standardization of hemophilia care on an international level. Future studies should aim to compare clinical outcomes between HTCs using traditional paper records, standard EHRs and EHRs integrating a hemophilia-specific navigator.

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SECTION 5

General Discussion and Perspectives

General Discussion and Perspectives

Navigating the New Hemophilia Treatment Landscape

Effectively navigating the evolving treatment landscape for hemophilia is integral to modern hemophilia care and embracing a shared decision-making approach has been recognized as essential for reaching treatment decisions that are not only effective in managing and preventing bleeding, but also in promoting strong patient adherence.[1,2] The first section of this thesis focused on two significant advancements in treatment modalities, emicizumab and gene therapy, and their implementation in the clinical setting. When this thesis was commenced, emicizumab had been on the European market for almost 3 years for PWHAs with inhibitors and 2 years for PWHAs without inhibitors, while gene therapy was on the verge of commercialization.

Chapter 1, upon its publication in a peer-reviewed journal, marked the first reported evaluation of real-life eligibility of male PWHs for gene therapy within a single HTC, both within and outside a clinical trial environment. Our findings revealed that, after accounting for exclusion criteria of current gene therapy trials and psychosocial factors, only a relatively small number of PWHs were deemed eligible for participation in such trials. Notably, psychosocial factors such as conservatism, lack of motivation, geographic distance from the HTC, and language barriers, which were not typically considered in gene therapy trial protocols, significantly influenced patient eligibility. Half of the study cohort were deemed ineligible for gene therapy trial participation due to such psychosocial factors. We also noted an important number (60%) of AAV NAbs in PWHAs initially deemed eligible. Shortly after our findings were published, Fletcher et al. reported results of a qualitative study examining reasons why PWHs may not want to receive gene therapy.[3] Participants of this study cited reasons such as concerns about long-term safety and efficacy, treatment burden, loss of identity as an individual with hemophilia as well as concerns motivated by the previous HIV and HCV epidemic, for not wanting to undergo gene therapy.[3]

In future research, it will be interesting to determine if and how PWHs' attitudes toward gene therapy are going to change, considering that the first products are now commercially available, and that more and more long-term safety and efficacy data will be published.

In **Chapter 1**, alongside discussing the imperative for long-term safety and efficacy data on gene therapy, we underscored the unmet need for therapeutic decision-making tools supporting collaboration between PWHs and their healthcare providers. In 2021, Hermans et al. proposed an algorithm for shared treatment decisions in hemophilia care, integrating bleeding phenotype, joint status, adherence to treatment, venous access, and lifestyle.[1] Additionally, they suggested developing a patient-preference tool to complement this algorithm, providing a means to account for individual patient preferences alongside the objectively assessable criteria.[1] The WFH launched such a patient preference tool in 2023.[4] The WFH SDM tool comprises an online decision-making platform that encourages PWHs to contemplate their experiences living with hemophilia and articulate their personal treatment objectives, as well as online educational resources about currently available treatments.[5,6]

One aspect not currently covered by the tool and algorithm mentioned above is the transition between various emerging treatment options. This is largely due to the limited commercialization of these therapeutic agents thus far. For example, with many PWHs worldwide now utilizing emicizumab[7] and gene therapy for hemophilia beginning to extend beyond clinical trials, the issue of transitioning patients from emicizumab to gene therapy is now emerging.[8] According to Agarwal et al., based on a PK simulation study, PWHs on emicizumab may safely switch to gene therapy and various strategies may be adopted.[8]

In **Chapter 2** we reported data on real-world experiences with emicizumab, gathered through an online survey of 46 participating HTCs across Europe. Emicizumab was readily accessible, although certain countries were still in the process of ensuring availability for PWHs without inhibitors. Survey results indicated high overall satisfaction with the product for both PWHs with inhibitors and PWHs without inhibitors. However, a significant portion of respondents expressed concerns about potential misuse of the drug and the occurrence of thrombotic events. Thus far, these concerns, along with fears regarding the development of ADAs, have not been substantiated by subsequently published real-world evidence.[7] Most respondents identified laboratory assays in PWHs receiving emicizumab as a crucial unmet need. Additionally, they highlighted limited clinical experience, uncertainty about co-treatment modalities with FVIII or bypassing agents, and a lack of

guidelines as areas requiring attention. Since the publication of this chapter in a peer-review journal, some of these unmet needs have been further addressed by several authors, for example by reviewing real-world data on concomitant use of bypassing agents and by providing recommendations for the management of bleeding emergencies in PWHs on emicizumab.[9–11]

We concluded this chapter by suggesting that the uptake of emicizumab in Europe is likely to increase in the future. However, we also emphasized that several other promising treatment options are currently under development, underscoring once more the necessity for therapeutic decision-making tools. Moreover, it is important to acknowledge that widespread adoption of emicizumab could potentially lead to a stagnation in research participation among PWHs, as they may be less motivated to engage in clinical trials for other innovative treatments.[12]

A pertinent issue regarding newly commercialized products is their use in special patient populations, typically excluded from clinical trials, such as children, elderly individuals, or those with comorbidities. In **Chapter 3**, we described our experiences with the use of emicizumab in obese PWHs to enrich the very limited available data on the efficacy of emicizumab within this particular demographic. At the time of the analysis, none of the five described patients had experienced bleeding episodes since the start of emicizumab and treatment was overall well tolerated. Taking into account our experiences and data from the phase 1 emicizumab dose escalation study, where a relatively low dose of emicizumab effectively prevented bleeding[13], we suggested that an emicizumab dosing capped at 600 mg monthly could be envisaged in PWHs with a BMI above 30 kg/m^2.

An important limitation of the case series in **Chapter 3** is its limited sample size and lack of emicizumab PK data from the described individuals. We therefore hope that, in the future, further real-world evidence evaluating outcomes with emicizumab in PWHs with a high BMI, and in other special patient populations, will be published.

Achieving a Hemophilia-free Mind

In **Chapter 4**, we introduced the concept of a “hemophilia-free mind” as an aspirational goal that should guide both current and future therapeutic decision-making processes and comprehensive hemophilia care. Additionally, we advocated for a simple yet insightful clinical tool in order to measure the degree of liberation of the mind from hemophilia: asking patients about the number of "hemophilia-free days" they experience during a typical week. This approach offers a practical means to evaluate the mental impact of hemophilia and the extent to which it pervades the patient's mind.

To achieve a hemophilia-free mind, liberated from the constraints of hemophilia, it is imperative to go beyond merely selecting an efficacious prophylactic treatment. Achieving a hemophilia-free mind also involves getting a grasp of the patient’s overall psychological and social profile and to be alert regarding any repercussions hemophilia and its associated physical burden may have on the individual’s psychological wellbeing. A systematic review by Al-Huniti et al. revealed an alarming prevalence of anxiety, depression, and attention deficit hyperactivity disorder (ADHD) among PWHs[14] - conditions that cannot be remedied by solely asking PWHs about hemophilia-free days, but demand expert intervention and support.

While the importance of psychological well-being among PWHs has been acknowledged as essential in the latest WFH guidelines for the management of hemophilia[15], there remains a need for improving healthcare professionals' awareness of symptoms associated with anxiety or depression in PWHs, as highlighted by Ferri Grazzi et al.[16] Importantly, not only clinical psychologists are concerned, but all healthcare professionals that are part of the HTC, as not all HTCs can benefit from the presence of a psychologist.[17] Additionally, the need for mental health awareness in healthcare providers does not only apply to hemophilia care, but to other chronic diseases as well.[18] Furthermore, WGH, carriers and female caregivers of PWHs, and women with bleeding disorders in general, experience compromised mental health as well.[19-21] Therefore, our group has recently emphasized the importance of fostering a "hemophilia-free mind" among female members of the hemophilia community.[22] Consequently, individuals of all genders should be included in future quantitative and qualitative studies on mental health of people with bleeding disorders and gender-specific unmet needs be assessed.

The hemophilia-free mind concept has garnered significant interest within the hemophilia community, notably evidenced by its integration into the WFH SDM tool. The section “Reflect on your life with hemophilia”, where PWHs can rate several statements about their hemophilia, contains the statement “My hemophilia is always in the back of my mind” as well as graphics adapted with permission (see Appendix) from our article “Living with a « hemophilia-free mind” - The new ambition of hemophilia care?”, included in **Chapter 4** of this thesis.[5,23] At the Cliniques universitaires Saint-Luc (CUSL), we have incorporated “hemophilia-free days” as a variable in the hemophilia-specific Epic navigator described in **Chapter 6**.

Capturing all Carriers

Chapter 5 presented an initiative, thus far unprecedented, aimed at identifying the maximum number of hemophilia carriers within families of PWHs attending a single HTC, and comparing carriers of HA and HB. Our work underscores the critical importance of regularly updating family pedigrees of PWHs, a straightforward yet highly effective practice. This imperative extends beyond hemophilia to other X-linked recessive disorders, where carriers may be at risk of being overlooked. Furthermore, our findings highlight the challenges of proactively screening all female relatives of PWHs. Despite adopting a proactive approach, numerous obstacles impede this screening process. Thoroughly and consistently informing PWHs about the implications of hemophilia carriership emerges as a crucial step in overcoming some of these obstacles. Additionally, healthcare providers involved in the care of PWHs should be educated about these implications and equipped with the necessary resources to inform patients and families effectively and to conduct efficient carrier screening. Educational materials can be disseminated through various channels, including printed brochures, online platforms such as classical web pages and social media, as well as through webinars and video streaming services. Additionally, in-person meetings and medical congresses also present valuable opportunities for education.

We are optimistic that future international research endeavors will contribute to gathering more comprehensive data on hemophilia carriers, specifically regarding the prevalence of abnormal bleeding, coagulation factor levels, the effectiveness of different hemostatic treatments, and the above-mentioned

mental burden associated with being a carrier and/or affected by a bleeding disorder and caring for family members with hemophilia. National registries should include WGH to enhance and standardize data collection. In Belgium, the establishment of the Belgian Rare Bleeding Disorders Registry, which includes women and girls with bleeding disorders, is currently underway.

An invaluable resource for carrier screening and data collection is the EHR. At our center, the EHR's built-in pedigree function is utilized for establishing and updating pedigrees. Additionally, the hemophilia-specific navigator described in **Chapter 6** incentivizes clinicians to update pedigree data during review clinics and contains a section specifically designed for collecting clinical carrier data. This comprehensive EHR and hemophilia navigator are expected to facilitate systematic and standardized data collection on women with bleeding disorders and carriers. We anticipate that these advancements will pave the way for future studies, such as a hypothetical "PROCARRIERS2" study, that could build on the PROCARRIERS1 study described in this thesis and provide more longitudinal data.

Leveraging the EHR to the Benefit of People with Hemophilia

As previously outlined, the hemophilia navigator described in **Chapter 6** is currently in active use in routine clinical practice at the HTC of the CUSL. Real-life experience to date has demonstrated numerous benefits of this navigator, including standardized follow-up, integration of registry variables, alerts regarding active problems and the need for follow-up, and the opportunity to involve PWHs in the documentation process. However, we have also found that customizing Epic in general and initially importing baseline data into the hemophilia navigator are highly time-consuming tasks.

Consequently, we advocate for international collaboration among HTCs utilizing or transitioning to Epic or other customizable EHR systems. To this end, two meetings of Epic users have already been convened at the EAHAD 2024 and WFH 2024 congresses, aiming to share our experiences with interested users and collectively explore methods for sharing customized navigators or components thereof among HTCs. Given the time and resource-intensive nature of developing the hemophilia navigator and similar tools, it is wise to leverage and share existing progress, particularly in a landscape where the time and resources of HTCs are increasingly precious.

Conclusion and Perspectives for Future Research

The challenges in contemporary hemophilia care explored in this work are intricately linked, underscoring the complexity inherent in providing holistic hemophilia care. Modern, comprehensive hemophilia care embraces a multiprofessional and multidisciplinary approach, involving nursing professionals, physiotherapists, psychologists, social workers, pharmacists, and physicians from diverse specialties such as adult and pediatric hematology, orthopedic surgery, and obstetrics and gynecology.

Specifically, this thesis provides new data on:

- The real-life eligibility of PWHs for gene therapy.
- Healthcare providers' experiences with emicizumab following its commercialization.
- The proportion of genetically tested female individuals within families of a single-center cohort of PWHs and practical aspects of carrier screening.
- Diagnostic circumstances, coagulation factor levels, bleeding symptoms, and hemostatic treatment requirements of HA and HB carriers.
- The development process and structure of a newly built hemophilia navigator within the Epic electronic health record system.

Moreover, this work advocates for setting ambitious goals, such as striving for a hemophilia-free mind, ensuring comprehensive care for ALL hemophilia carriers and WGH, and actively leveraging digital tools to improve hemophilia care. Overall, this thesis offers valuable contributions to the understanding and improvement of modern hemophilia care, shedding light on both the challenges and advancements in the field.

In light of the contemporary challenges in hemophilia care addressed in this thesis, there remains a necessity for further research in the field. Other HTCs should share their experiences regarding patient eligibility for gene therapy, providing data to better understand the patient profiles that would benefit most from this treatment. Furthermore, the role of gene therapy in LICs and LMICs will need to be established. Gene therapy holds the promise of curing PWHs, and consequently, to drastically reduce clotting factor consumption.

However, its high cost and the requirement for appropriate infrastructures for patient follow-up present significant challenges in countries with limited resources.

Emicizumab, approved in Europe for over 5 years, has become well established in our clinical practice. Further research is required to determine its efficacy, as well as that of bispecific monoclonal antibodies mimicking FVIIIa in general, in PWHs with a high BMI. And lastly, large-scale and systematic hemophilia carrier screening initiatives should be replicated by other centers, with results shared.

While this thesis explores significant challenges encountered by PWHs and their healthcare providers, it does not cover all issues in contemporary hemophilia care that require attention. One crucial issue not addressed in this thesis is the **accessibility of treatment, particularly in LICs**. While HICs have gained access to a wide array of innovative and efficacious hemophilia treatments, as mentioned earlier, a substantial number of PWHs in LICs remain undiagnosed and do not receive adequate treatment. It is estimated that about 75% of the global population of PWHs lack sufficient access to hemophilia therapy or have none at all.[24] The life expectancy disadvantage still observed in PWHs in HICs, is even greater in LICs and LMICs.[25] Humanitarian aid for PWHs is mainly provided through the WFH, through donations and an international twinning program.[26] One example of the latter is the twinning between Ivory Coast and the CUSL, which aimed to improve hemophilia care in Ivory Coast through non-substitutive strategies.[27]

As life expectancy of PWHs continues to rise, so does the number of elderly PWHs, making **comorbidities increasingly relevant in modern hemophilia care**. Some of these comorbidities are specific to individuals with bleeding disorders, such as hemophilic arthropathy, while others, like cardiovascular disease, also impact the general population.[28] On the other end of the age spectrum, the **successful transition from pediatric to adult hemophilia care is gaining attention**.[29]

Another aspect of modern hemophilia care is **ensuring patients receive regular follow-up**, particularly given the advent of newer, more efficacious treatments. The latter may inadvertently lead individuals with a severe bleeding phenotype and/or severe factor deficiency at baseline to believe they no longer require regular monitoring. Moreover, it is crucial not to

overlook those with mild hemophilia. Precautionary measures such as bleeding prophylaxis prior to surgical interventions, family testing, and screening for HCV in individuals born before 1990 remain pertinent for this demographic. The risk of undiagnosed or untreated HCV infection among individuals with mild hemophilia is a genuine concern, underscored by a brief report we published in 2021, demonstrating the potentially devastating consequences of such oversight.[30]

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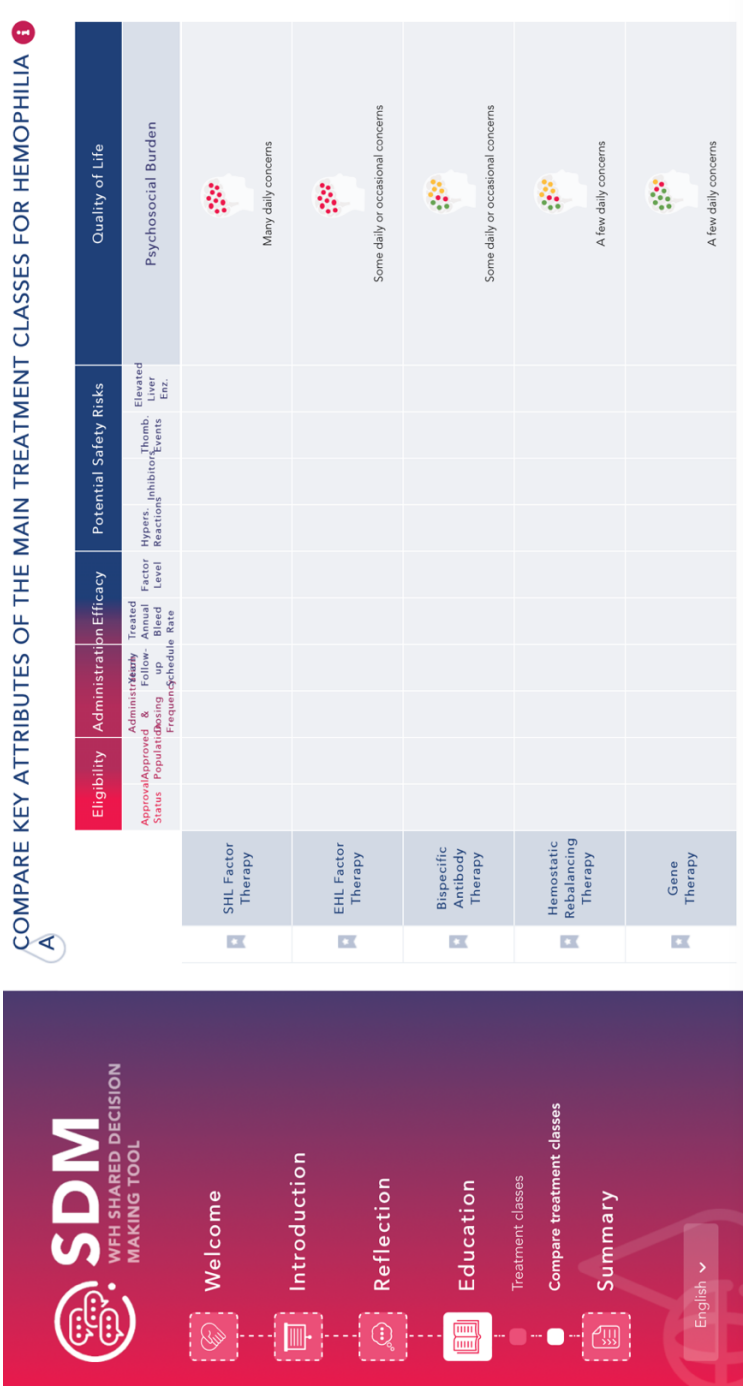
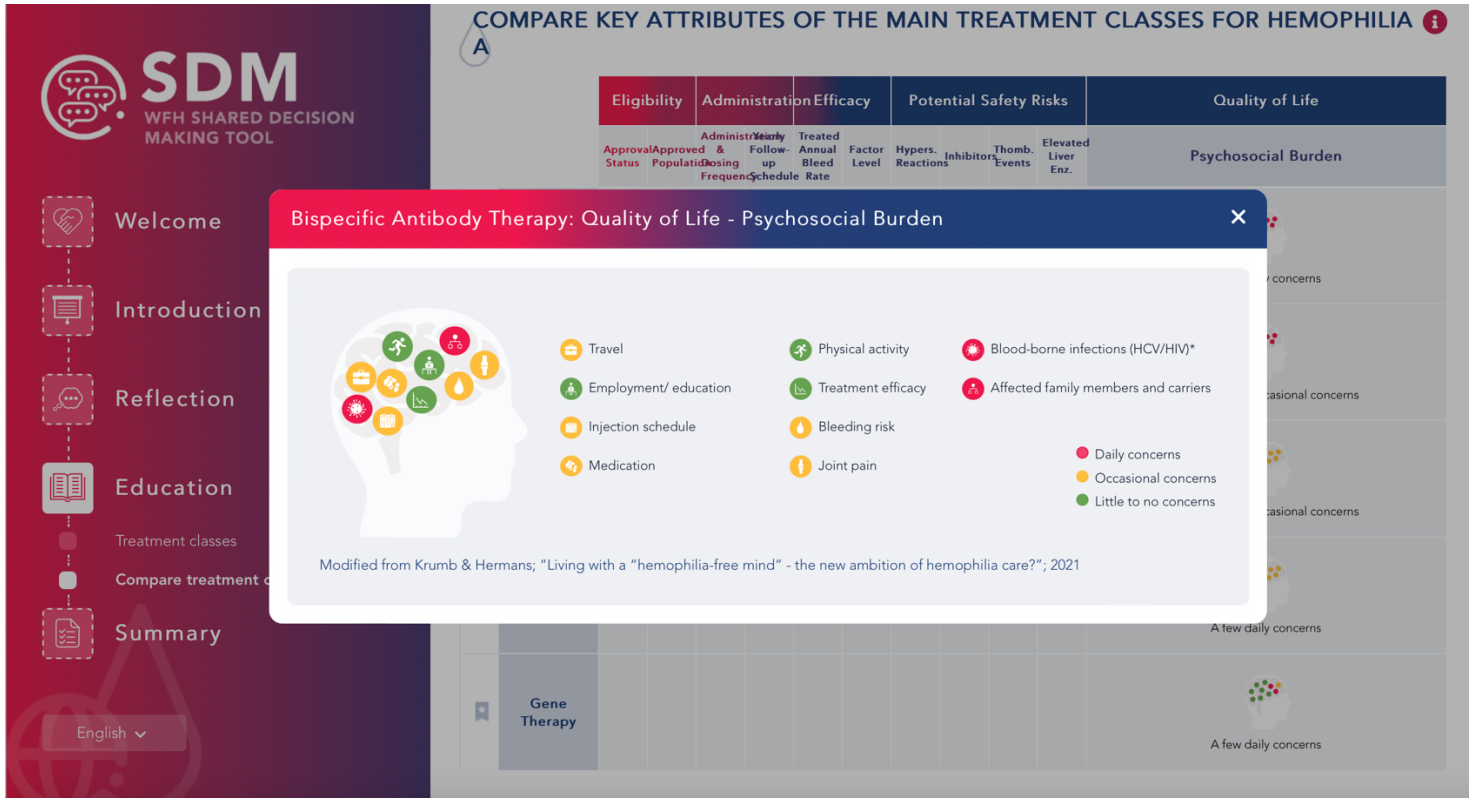
Index of Figures

Appendix

WFH Shared Decision-Making Tool




SDM
WFH SHARED DECISION MAKING TOOL
Welcome
Introduction
Reflection
Education
Treatment classes
Compare treatment c
Summary
English
COMPARE KEY ATTRIBUTES OF THE MAIN TREATMENT CLASSES FOR HEMOPHILIA A
Eligibility
Administration
Efficacy
Potential Safety Risks
Quality of Life
Approval Status
Approved Population
Administration & Dosing Frequency
Yearly Follow-up Schedule
Treated Annual Bleed Rate
Factor Level
Hypers. Reactions
Inhibitors
Thromb. Events
Elevated Liver Enz.
Psychosocial Burden
Gene Therapy
A few daily concerns
A few daily concerns
Bispecific Antibody Therapy: Quality of Life - Psychosocial Burden
Travel
Employment/ education
Injection schedule
Medication
Physical activity
Treatment efficacy
Bleeding risk
Joint pain
Blood-borne infections (HCV/HIV)*
Affected family members and carriers
Daily concerns
Occasional concerns
Little to no concerns
Modified from Krumb & Hermans; "Living with a "hemophilia-free mind" - the new ambition of hemophilia care?"; 2021

List of all Hemophilia-related Publications (Co-)Authored by Evelien Krumb

- Krumb E, Lambert C, Van Damme A, Hermans C. **Proactive Systematic Hemophilia Carrier Screening: A Step Toward Gender Equity in Hemophilia Care**. Blood Adv. Published online August 21, 2024. doi:10.1182/bloodadvances.2024013866

- Hermans C, Krumb E, Rotellini D, Pierce GF. **The underevaluated impacts of the therapeutic revolution of hemophilia on women and girls**. J Thromb Haemost. 2024;22(4):915-918. doi:10.1016/j.jtha.2023.12.027

- Krumb E, Vanlangendonck N, Lambert C, Lobet S, Van Damme A, Hermans C. **Building a haemophilia-specific navigator in Epic® Electronic Health Records: Single-centre preliminary experience**. Haemophilia. 2023;29(5):1219-1225. doi:10.1111/hae.14846

- Hermans C, Gruel Y, Frenzel L, Krumb E. **How to translate and implement the current science of gene therapy into haemophilia care?**. Ther Adv Hematol. 2023;14:20406207221145627. Published 2023 Jan 12. doi:10.1177/20406207221145627

- Krumb E, Lambert C, Hermans C. **Emicizumab dose capping in obese patients with Haemophilia A: Early outcomes at a single centre**. Haemophilia. 2022;28(6):e245-e247. doi:10.1111/hae.14644

- Krumb E, Hermans C. **Living with a "hemophilia-free mind" –The new ambition of hemophilia care?** Res Pract Thromb Haemost. 2021;00:e12567. https://doi.org/10.1002/rth2.12567

- Krumb E, Fijnvandraat K, Makris M, et al. **Adoption of emicizumab (Hemlibra®) for hemophilia A in Europe: Data from the 2020 European Association for Haemophilia and Allied Disorders survey**. Haemophilia. 2021;27(5):736-743. doi:10.1111/hae.14372

- Krumb E, Lambert C, Horsmans Y, Hermans C**. Diagnosis of hepatitis C-related liver disease in patients with mild hemophilia**. Eur J Intern Med. 2021;91:102-103. doi:10.1016/j.ejim.2021.05.033

- Krumb E, Lambert C, Hermans C. **Patient selection for hemophilia gene therapy: Real-life data from a single center**. Res Pract Thromb Haemost. 2021. doi:10.1002/rth2.12494

List of all Hemophilia-related Abstracts (Co-)Authored by Evelien Krumb

- **Poster, European Association for Haemophilia and Allied Disorders (EAHAD) 2024 Congress:** Hermans C, Krumb E, Van Dievoet M-A, Lambert C. **Cardiovascular safety and brain protective effect of emicizumab in patients with haemophila older than 40**. 17th Annual Congress of European Association for Haemophilia and Allied Disorders 2024, 6-9 February 2024, Frankfurt. *Haemophilia*, 30: 34-188. https://doi.org/10.1111/hae.14919

- **Poster, European Association for Haemophilia and Allied Disorders (EAHAD) 2024 Congress:** Krumb E, Lambert C, Van Damme A, Hermans C. **Promoting gender equity in haemophilia care through proactive and systematic screening of haemophilia carriers: Results of the PROCARRIERS1 study**. 17th Annual Congress of European Association for Haemophilia and Allied Disorders 2024, 6-9 February 2024, Frankfurt. *Haemophilia*, 30: 34-188. https://doi.org/10.1111/hae.14919
    - ❖ **Top scoring abstract**

- **Oral, American Society of Hematology (ASH) 2023 Annual Meeting:** Krumb E, Lambert C, Van Damme A, Hermans C. **Proactive Systematic Hemophilia Carrier Screening: A Step Towards Gender Equity in Hemophilia Care**. Blood 2023; 142 (Supplement 1): 288. doi: https://doi.org/10.1182/blood-2023-185067
    - ❖ **Abstract achievement award**

- **Poster, European Association for Haemophilia and Allied Disorders (EAHAD) 2023 Congress:** Krumb E, Lambert C, Van Damme A, Hermans C. **Barriers to haemophilia carriers' identification, screening and counselling – an interim analysis of the PROCARRIERS1 study**. 16th Annual Congress of European Association for Haemophilia and Allied Disorders 2023, 7-10 February 2023, Manchester. *Haemophilia*. 2023;29 Suppl 1:5-207. doi:10.1111/hae.14713
    - ❖ **Top scoring abstract**

- **Poster, European Association for Haemophilia and Allied Disorders (EAHAD) 2022 Congress:** Hermans C, Krumb E, Lobet S, Lambert C. **Prophylaxis and Zero Bleeds for all Adult Patients with Severe Hemophilia: An achievable Ambition with New Treatment Options**. 15th Annual Congress of European Association for Haemophilia and Allied Disorders 2022, 2-4 February 2022, Virtual Meeting. Haemophilia. 2022;28 Suppl 1:6-126. doi:10.1111/hae.14477

- **Poster, International Society on Thrombosis and Hemostasis (ISTH) 2021 Congress:** Krumb E, Fijnvandraat K, Makris M, Peyvandi F, Ryan A, Athanasopoulos A, Hermans C. **Adoption of Emicizumab for Hemophilia A in Europe: Data from the 2020 European Association for Haemophilia and Allied Disorders Survey**. *Res Pract Thromb Haemost*. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/adoption-of-emicizumab-for-hemophilia-a-in-europe-data-from-the-2020-european-association-for-haemophilia-and-allied-disorders-survey/.

Cover Illustration:

Oskar Schlemmer
Bauhaus Stairway, 1931 - 1932
Städel Museum Collection, Frankfurt am Main, Germany