European Haemophilia Consortium (EHC)

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EHC Annual Conference 2023

Select Highlights

Zagreb, Croatia, 6-8 October 2023

AISBL European Haemophilia Consortium

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Introduction

The European Haemophilia Consortium (EHC) Annual Conference plays a pivotal role in advancing haemophilia and bleeding disorders across Europe.

Taking place in Zagreb, Croatia, the 2023 Conference brought together 400 attendees including patient advocates representing National Member Organisations (NMOs), healthcare professionals, and industry experts, to share the latest advancements in treatment, research findings, and best practices in patient care throughout Europe.

The conference serves as a platform for collaboration and knowledge exchange, fostering a multidisciplinary approach to the complex challenges associated with bleeding disorders. Through presentations and networking opportunities, participants gain valuable insights into emerging therapies, patient support programmes, and innovative strategies to improve the quality of life of individuals living with bleeding disorders.

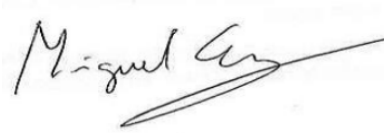
The EHC Annual Conference not only enhances the expertise of healthcare professionals but also empowers patients and advocates to actively contribute to shaping the future of bleeding disorders care in Europe. It plays a crucial role in promoting awareness and providing stimulating food for thought for our NMOs; inspiring, motivating, and energising them as they envision and organise their annual workplan to advocate for better care and outcomes in their countries.

The 2023 EHC Annual Conference was an entirely in-person meeting. Understanding that not all members were able to attend, we considered it paramount to share a written summary of essential messages and take aways from four sessions selected for their significant strategic importance in our community and the evolving bleeding disorders landscape.

The four sessions selected focused on Mental Health, Ageing, von Willebrand Disease, and Extremely Rare Bleeding Disorders (ERIN Programme). The below summary aims to provide our NMOs an important tool to disseminate key points about these important topics, in understandable language, to all their members and the entire community. It also offers useful information to assist NMOs as they organise and strategise their future plans. It is really for them, the NMOs and the patients they represent, that we created this summary.

The EHC extends its most sincere gratitude to all the speakers that collaborated in this important collective effort, through their work and conference presentations, and to Fiona Robinson, the medical writer who compiled, organised, and composed this comprehensive piece of knowledge advocacy.

Miguel Crato
EHC President



Abbreviations

AAV	Adeno-associated virus
ABR	Annualised bleeding rate
aPCC	Activated prothrombin complex concentrate
AT	Anti-thrombin
BPA	Bypassing agent
CCC	Comprehensive care centre
CGA	Comprehensive Geriatric Assessment
CVD	Cardiovascular disease
EHC	European Haemophilia Consortium
EIN	European Inhibitor Network
ERBD	Extremely rare bleeding disorder
ERIN	European Rare & Inhibitor Network
ERN	European Reference Network
EUHASS	European Haemophilia Safety Surveillance
FVIII	Factor VIII
FIX	Factor IX
FIXa	Activated factor IX
FX	Factor X
GI	Gastrointestinal
GP	General practitioner
HCP	Healthcare professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMB	Heavy menstrual bleeding
HTC	Haemophilia treatment centres
ICH	Intracranial haemorrhage
NFRT	Non-factor replacement therapies
NMO	National Member Organisation
PCI	Percutaneous coronary intervention
PWBD	Person/people with bleeding disorder(s)
PWERBD	Person/people with extremely rare bleeding disorder(s)
PWH	Person/people with haemophilia
PWH+I	Person/people with haemophilia and inhibitors
PWHA+I	Person/people with haemophilia A and inhibitors
PWHB+I	Person/people with haemophilia B and inhibitors
PWVWD	Person/people with von Willebrand disease
rFVIIa	Recombinant activated factor VII
siRNA	Small interfering ribonucleic acid
TFPI	Tissue factor pathway inhibitor
UK	United Kingdom
US	United States of America
VTE	Venous thromboembolism
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
WFH	World Federation of Hemophilia
WHO	World Health Organization

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Write up: Fiona Robinson, PhD (Consultant, Medical Writing and Editing)

Mental Health with a Chronic Condition – Focus on Coping Strategies

Speaker: Svetoslava Stoyanova, Associate Certified Coach (International Coaching Federation), Individual and Team Coach, Organisational and Well-Being Strategist, New Mindset Coaching and Training, Brussels, Belgium

Mental health is as important as physical health

The World Health Organization (WHO) defines good mental health as:

> "A state of mental well-being that enables people to cope with the stresses of life, realise their abilities, learn well and work well, and contribute to their community. It is an integral component of health and well-being that underpins our individual and collective abilities to make decisions, build relationships and shape the world we live in. Mental health is a basic human right. And it is crucial to personal, community and socio-economic development."

Improving and sustaining one's mental health is essential to one's own well-being and to one's ability to care for and contribute to the well-being of others.

Youth particularly at risk

Across Europe, the COVID-19 pandemic raised the profile of, and contributed to the worsening of, mental health problems, especially in young people. In 2020–2021 mental health problems doubled in young people (15–24 years old), according to the European Youth Forum. Nine million European adolescents (10–19 years old) experienced mental health problems, with suicide the second leading cause of death amongst European youth. Young people are particularly vulnerable; they are 30–80% more likely to report depression or anxiety than adults, but often only receive mental health support if they reach a state of crisis. The urgency of addressing this issue is reflected in the identification of mental health and well-being as one of the European Union's 2019–2027 Youth Goals. They emphasise inclusive, respectful, mental health provisions within all medical institutions and throughout society, prevention measures, and fighting stigma.

Chronic conditions further challenge mental health

People with chronic physical medical conditions face additional challenges to mental health and well-being, which may also negatively influence the chronic condition. Hospitalisation and reduced mobility or activity may lead to isolation. Excessive worry about the management or future progression of the condition can create a heavy mental burden. Long-term stress causes chemical and hormonal changes that activate inflammation which may, in turn, exacerbate some chronic physical conditions.

Five positive psychology strategies

Mental health and well-being can be improved and sustained through positive psychology, which focuses on appreciating positives rather than dwelling on challenges. Projecting hope rather than optimism, and intention rather than expectation, encourages a mindset focused on actively taking the first step toward improving one's situation rather than anticipating the entire climb one is facing. Five strategies rooted in positive psychology for actively improving or sustaining mental health and well-being are:

1. Move

Regular physical activity is associated with improved mood, reduced stress, and increased overall well-being. It can be a powerful tool for preventing mental health issues. Move as much as is comfortably possible, starting with something brief and simple that can be repeated daily.

2. Focus on strengths

Focusing on one's strengths and using them in daily life has been associated with increased life satisfaction and resilience. Start by identifying at least one core strength and share it with someone.

3. Make kindness routine

Performing acts of kindness for others has been shown to boost happiness and increase feelings of social connection. It can also reduce symptoms of depression and anxiety. Commit to something as small as smiling at someone everyday, and seek out further opportunities for acts of kindness.

4. Mindfulness meditation

Mindfulness meditation has been linked to reduced stress, improved emotional regulation, and enhanced overall mental health. Research indicates that it can be particularly beneficial for young people dealing with challenges, including a chronic condition. Deep breathing while observing, without judgement, how one's body feels or aspects of one's environment offers a brief meditation that can be practiced anywhere.

5. Gratitude

Practicing gratitude can improve overall well-being and reduce symptoms of depression and anxiety. Gratitude journaling, or writing down just one thing for which one is grateful every day, can have a positive impact in just a few days.

There are many ways to build on these five simple strategies to improve and sustain mental health and well-being. The EHC #ThisWay campaign exemplifies improving one's mental health by focusing on strengths rather than challenges, shifting perspective from that of someone who "suffers from disorder x" to someone who "lives with disorder x". There are three keys to individual well-being: the way we think, how we process emotion, and how we interact with others. We can actively and positively work on each of these, no matter what our situation, in order to improve and sustain our mental health and well-being. A number of online resources and apps have been developed that can help with this, but anyone experiencing anxiety or any other mental health concerns is highly recommended to consult a therapist or specialist. Professional therapy or specialised mental health guidance offer the optimal assistance, and we should not hesitate to consult these professionals and benefit from their expertise.

References and resources

1. World Health Organization. Mental Health website: https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response
2. Moxon D, Bacalso C, and Șerban A. 2021. Beyond the pandemic: The impact of COVID-19 on young people in Europe. Brussels. European Youth Forum https://www.youthforum.org/files/European20Youth20Forum20Report20v1.2.pdf
3. European Youth Forum. Speak Up for Mental Health website: https://www.youthforum.org/news/speak-up-for-mental-health

4. European Union. European Youth Goals 2019-2027, #5 Mental Health & Wellbeing: https://youth-goals.eu/yg5
5. Renew Europe. Youth Mental Health website: https://www.reneweuropegroup.eu/campaigns/youth-mental-health
6. Balkan Barometer. Balkan Barometer 2023 Public Opinion website: https://www.rcc.int/balkanbarometer/results/2/public
7. Mental Health America. Reports and resources website: https://mhanational.org/get-information
8. Ackerman C. What Is Positive Psychology & Why Is It Important? https://positivepsychology.com/what-is-positive-psychology-definition/
9. European Haemophilia Consortium. 2021. #ThisWay Campaign: https://www.ehc.eu/join-the-ehc-for-thisway-campaign-in-2021/
10. Mayo Clinic. Mindfulness Exercises: https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/mindfulness-exercises/art-20046356
11. Plum Village. The Art of Mindful Living. https://plumvillage.org/mindfulness/mindfulness-practice

Ageing and Bleeding Disorders

Speakers:

- **Robert Klamroth**, MD, Haematologist, Haemophilia Treatment Centre Director, Department Head, Internal Medicine, Vascular Medicine and Coagulation Disorders, Vivantes-Klinikum im Friedrichshain, Berlin, Germany
- **Ana Boban**, MD, PhD, Haematologist, Head of Haemophilia Centre, University Hospital Centre Zagreb, Croatia
- **William McKeown**, MD, Royal College of Physicians (Edinburgh), Specialist Registrar in Care of the Elderly and Stroke Medicine, Royal Victoria Hospital in Belfast, Person with severe haemophilia A
- **Clive Smith**, LLB (Hons) & Barrister at Law, Chairman of The Board, The Haemophilia Society (UK), Person with severe haemophilia A

Introduction

Data from Europe and the United States (US) show that people with bleeding disorders (PWBD) are, in general, living longer and getting older (Figure 1).

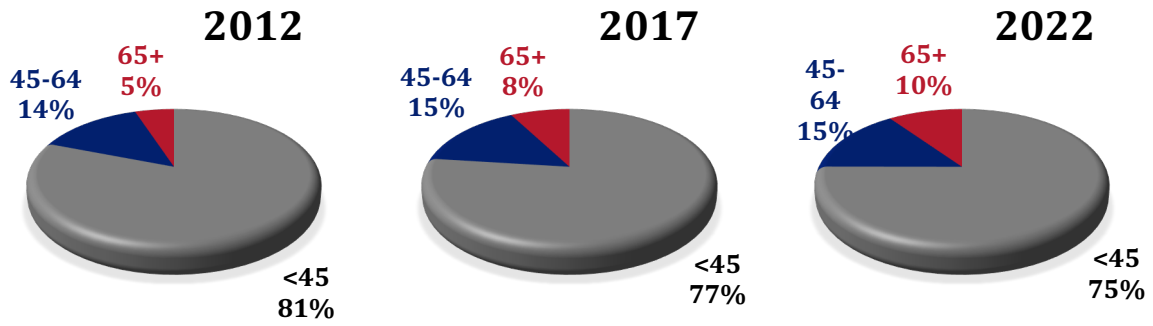


Figure 1. Proportion of people <45 years old, 45–64 years old, and 65 and older attending US Hemophilia Treatment Centers over two decades
Source: Centers for Disease Control and Prevention. Community Counts HTC Population Profile (September, 2023).
HTC: hemophilia treatment center, US: United States of America

This is thought to be primarily due to:

- Elimination of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) contamination from well-regulated plasma-derived replacement factor products
- Improvements in HIV treatments rendering infection chronically manageable rather than life-threatening
- Successful elimination of HCV from many people previously infected
- Relatively widespread availability of replacement factor products allowing prophylaxis of large proportions of populations, including adults
- Establishment and practice of multidisciplinary comprehensive care for PWBD in haemophilia treatment centres (HTCs) and comprehensive care centres (CCCs)

Just as for any other age group, the care and management of people ageing with bleeding disorders must be personalised.

Managing co-morbidities in ageing – A physician's perspective

As PWBD age, they encounter co-morbidities, or co-existing health conditions, related to their disorder as well as those faced by the general ageing population. Providing optimal care to people ageing with bleeding disorders requires knowledge and management of both. It is worth noting that little data has been collected specifically on women ageing with bleeding disorders, though women do tend to live longer than men.

Haemophilic arthropathy, permanent joint disease due to repeated bleeding into the joints, is the most common condition requiring surgery as people with haemophilia (PWH) age. Those with HIV and/or HCV may experience complications of these long-term infections. Persistent inhibitors, neutralising antibodies to replacement factor that do not resolve, constitute a challenge that must be carefully managed throughout the lives of those who develop them.

EUHASS (European Haemophilia Safety Surveillance) reported that in 2021 the top cause of death for PWBD was cancer. PWBD should be enrolled in cancer screening programmes associated with ageing (e.g., prostate, breast, uterine, and colon). It is also recommended to assess for signs and symptoms suggestive of cancer at each clinic visit:

- ☐ Breathing difficulties
- ☐ Haematospermia (blood in semen)
- ☐ Fever
- ☐ Smoking habit
- ☐ Haematuria (blood in urine)
- ☐ Bone pain
- ☐ Weight loss
- ☐ Constipation, nausea, vomiting, and rectal bleeding
- ☐ Enlarged lymph nodes
- ☐ Changes in urinary habit (urgency, frequency and nocturia)
- ☐ Erectile dysfunction

Further clinical examinations should be undertaken as required. Any invasive screening procedures must be carried out in close collaboration between cancer centres and HTCs, because they may cause bleeding.

PWBD who have been successfully treated to eliminate an HCV infection remain at an elevated risk for developing hepatocellular (liver) cancer and those with HIV are at a higher risk for lymphoma; their screening for these cancers should be regular and systematic. It does not appear that PWBD are at higher risk of developing other cancers.

Cardiovascular disease (CVD) is the other most common co-morbidity in the general ageing population. Increasing evidence suggests that PWH are at heightened risk of developing hypertension (high blood pressure) which is an important risk factor for CVD and for intracranial haemorrhage (ICH, also one of the most common causes of death for PWBD). Hypertension can easily be detected by incorporating regular blood pressure measurements into standard care, as recommended by the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia. The management of hypertension is well established and just the same for PWBD as for the general population. The bleeding disorder care team must ensure that an appropriate physician manages treatment, should it be required. This can be the individual's general practitioner (GP) or a specialist member of the bleeding disorders care team.

For a more detailed discussion of issues faced by ageing PWH and recommendations for their management, the reader is invited to consult Shapiro S and Makris M (2018) Haemophilia and Ageing.

Using anti-thrombotic medication in bleeding disorders

CVDs are the leading cause of death worldwide killing almost 18 million people in 2019; 85% of those deaths were from heart attack or stroke. PWBD, with their decreased ability to produce thrombin which is key for blood clot formation, are less likely to suffer from venous thromboembolism (VTE, a blood clot that blocks the flow of blood through the veins) and stroke. New therapies that "normalise" thrombin production capacity may, however, alter this context. The incidence of atrial fibrillation (a quivering or irregular heartbeat which can cause blood to pool in the heart where it may clot), ischaemic heart disease (chest pain or discomfort that occurs when the heart muscle does not receive enough blood due to narrowed arteries), and peripheral arterial disease (a circulatory problem causing reduced blood flow through the arteries) are all similar for PWBD to that of the general population, and increase with age.

Atherosclerosis (a hardening and narrowing of the arteries caused by cholesterol plaques lining the artery over time) is the first step in a number of CVDs. Risk factors for atherosclerosis are as high, or in some cases higher, in PWBD than in the general population (Table 1).

Table 1. Risk factors for developing atherosclerosis and their likelihood in PWBD vs the general public

Risk factor for atherosclerosis	Likelihood in PWBD vs the general population
High cholesterol and triglyceride levels	No difference
High blood pressure	**Higher**
Smoking	No difference
Type 1 diabetes	No difference
Obesity	**Higher**
Physical inactivity	**Higher**

PWBD: people with bleeding disorders

CVDs are often treated with anti-thrombin (AT) therapies, which are medications that decrease the ability to form blood clots, either by interfering with the recruitment and activation of platelets or the formation of fibrin. A side effect of ATs in all people is increased bleeding, therefore avoiding their use by reducing risk factors (Table 1) and participating in prevention initiatives such as improving diet, ceasing smoking, increasing physical activity levels, and detecting and treating high blood pressure are particularly important for PWBD.

If a PWH has a condition that would, in a person without a bleeding disorder, require treatment with one or more AT therapies, deciding whether to commence AT therapy involves a detailed evaluation of their individual potential to bleed and to make thrombotic clots. The level of factor VIII (FVIII) or FIX produced by their bodies, whether they take emicizumab or factor replacement prophylaxis or on-demand factor, the precise condition driving the need for AT therapy, the specific AT therapy/ies indicated, and whether their replacement factor prophylaxis or on-demand regimen should be adjusted, must all be considered. Balancing the risks of thrombosis and bleeding in the same individual is very challenging; one guiding principle that has emerged is to use as little AT as possible for as short a time as possible. The reader is invited to consult the EHA-ISTH-EAHAD-ESO Clinical Practice Guidance, developed through an international collaboration of experts from the European Hematology Association, International Society on Thrombosis and Haemostasis, European Association for Haemophilia and Allied

Disorders, and European Stroke Organisation, for detailed discussions of the many different scenarios and the recommended approach to each.

Atrial fibrillation is a common CVD usually treated with AT therapies. The cardiologist must collaborate closely with the haematologist to evaluate and balance risks of bleeding and thrombosis in a PWBD and atrial fibrillation. Myocardial infarction (a heart attack) in a PWBD can be treated with the same percutaneous coronary intervention (PCI, a non-surgical procedure that uses a catheter to place a small stent to open up blood vessels in the heart) as in a person without a bleeding disorder, but their factor levels must be elevated prior to the intervention. PWBD can then receive AT for the following weeks, under close medical supervision to keep their factor level high enough. VTE is very rare in PWBD, but can be treated with specific AT therapies, always aiming for the shortest duration of treatment. The EHA-ISTH-EAHAD-ESO Clinical Practice Guidance provides detailed recommendations for the treatment of each of these CVDs in PWBD.

As PWBD age and increasingly face CVDs it is important to be well informed of the risk factors, prevention strategies, and treatment recommendations. More research is also required upon which to base treatment recommendations for this population.

Successful ageing in bleeding disorders – A geriatrician's perspective

Ageing successfully is defined by what is important to the people who are ageing. Research has shown that rather than living as long as possible, ageing people prioritise:

- Avoiding disease and disability
- Having high cognitive/mental/physical function
- Actively engaging in life
- Being psychologically well adapted in later life

A major challenge to ageing successfully is advancing frailty. Frailty is essentially physical resilience to stressor events, or how well you can continue to function at a high level and how quickly and completely you can return to your normal level of functioning, when something goes wrong. For example, a PWBD might have a bleed, they might have to take it easy and infuse a bit more factor for a few days, and then they might be back to their normal lives. Someone who is frail may experience a greater immediate loss of function, take longer to bounce back, and perhaps never get back to their previous level of functioning. Overall, frailty increases with age, but it is possible to age without becoming frail. The general population loses physical resilience as they age for a variety of reasons (e.g., decreasing cardiac or respiratory function); PWBD have the added challenges of hypertension, hepatitis, hemarthrosis and other co-morbidities that may complicate their multifactorial advancing frailty.

To partner with PWBD in ageing successfully, comprehensive care teams should routinely assess their frailty and develop a plan to address it, guided by the individual's priorities and goals. The Clinical Frailty Score (available from Dalhousie University, upon permission request) has been validated in people over the age of 65, a small but growing population for PWBD. It is a simple, easy to perform test which yields an individual frailty level score (Table 2). Men ageing with haemophilia have been demonstrated to have greater frailty than the general population, but no data are available for women or people with other bleeding disorders. These data must be collected and reported.

Table 2. Levels of frailty as measured by the Clinical Frailty Score

Level	Description	Level	Description	Level	Description
1	Very fit	4	Living with very mild frailty	7	Living with severe frailty
2	Fit	5	Living with mild frailty	8	Living with very severe frailty
3	Managing well	6	Living with moderate frailty	9	Terminally ill

A Comprehensive Geriatric Assessment (CGA) consists in carrying out a holistic, systematic, multidisciplinary assessment yielding an individualised list of problems, that are then mapped onto a list of corresponding solutions. Older people's health is complicated by multiple issues and resolving just one of them is not sufficient to truly improve their lives. Research in the general population shows that an older person admitted to hospital is more likely to be alive and in their own home six months later, if a CGA is conducted. For PWBD, the comprehensive multidisciplinary care team must expand to involve, or at least establish working relationships with, all of the specialties required to identify all of the individual's health problems and find solutions to each of them (Figure 2). For example, the single most important reversible risk factor for dementia, which could lead to the loss of the ability to self-infuse, is impaired hearing; working with an audiologist can be hugely impactful. Social isolation and mental health issues are drivers of, and may also result from, frailty. Involving mental health professionals and maintaining engagement with the local patient organisation can contribute important solutions.

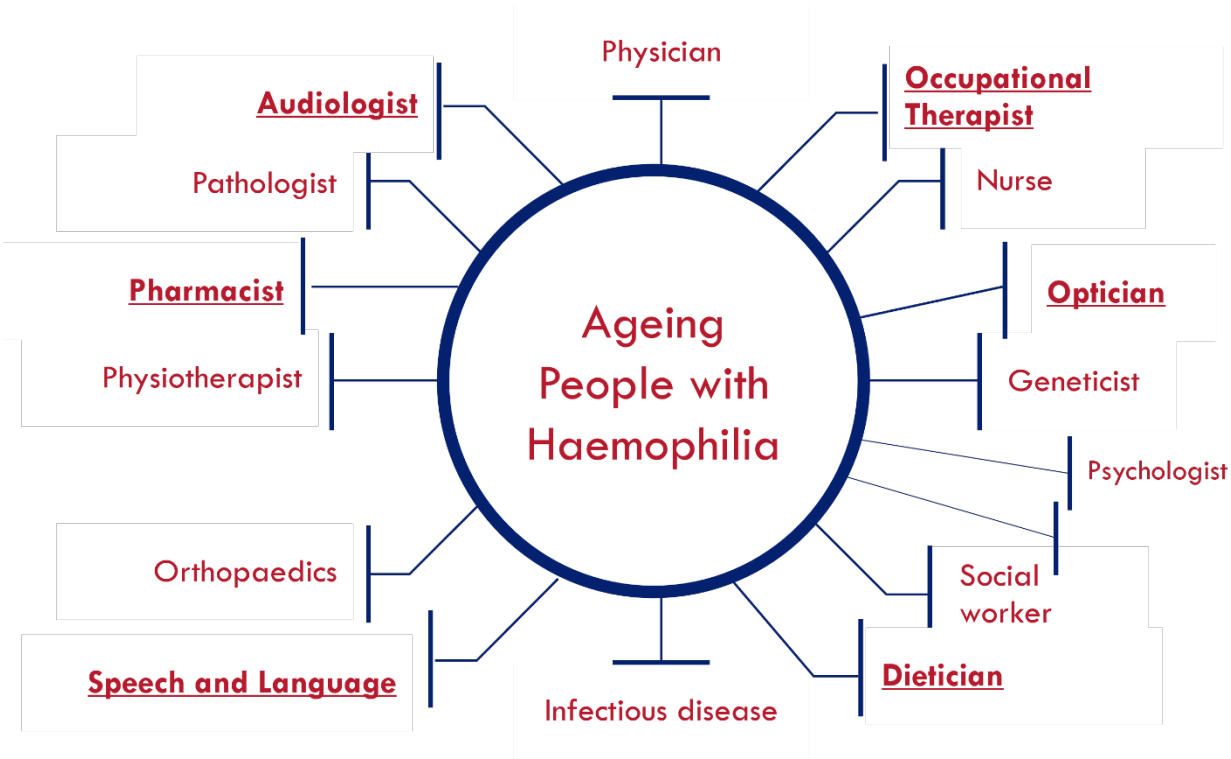


Figure 2. Partnering with PWBD to age successfully requires the multidisciplinary comprehensive care team to expand to include a wider variety of specialists.

Routinely, systematically, and holistically assessing people ageing with bleeding disorders allows the comprehensive care team to best partner with them in meeting their goals for successful ageing. It also provides the opportunity to conduct research and contribute much needed data upon which recommendations for the best care of this growing population can be developed.

Managing co-morbidities in ageing – A patient's perspective

Some PWBD embrace the outlook of a lifespan equal to that of a person without a bleeding disorder with a sense of gratitude and privilege, as the community has seen so many PWBD die far too young. It also comes, however, with some challenges as they must navigate an often disjointed healthcare system that is ill-prepared to meet their complex needs. It is imperative to evaluate what those needs will be and implement measures, now, that will facilitate successful ageing of all PWBD into the future.

PWBD partner with their comprehensive care team in the management of their disorder from an early age and they may expect those relationships to be adequate to see them through their old age. In fact, managing the co-morbidities of ageing, described above, requires specialised care beyond that usually available within the comprehensive care setting. Coordinating appointments at different locations, with healthcare professionals (HCP) who may have little knowledge of their bleeding disorder, poses many challenges to accessing optimal care, especially for people with reduced mobility or declining cognitive ability. If those hurdles prove too high, PWBD may resign themselves to missing appointments and simply not accessing the care they need. Men, in general, tend to hesitate to access care; in the face of significant obstacles they are even more likely to disengage.

The healthcare system must work around the ageing PWBD, rather than the other way around. Key to this is communication, coordination, and education. Patient organisations can accompany ageing PWBD, assist them in making, coordinating, and accessing multiple specialist appointments. They may also provide information on bleeding disorders for specialised HCPs. For example, the UK Haemophilia Society and World Federation of Hemophilia produce resources for dentists and other specialists (see References and resources section below). The members of the comprehensive care team have a responsibility to work closely with the ageing PWBD, their advocates, and specialist HCPs to provide the most cohesive or "joined up" care possible, offering solutions to all their health problems. As discussed above, this may require establishing new relationships with other departments and institutions, including social care provided in the home or an assisted living facility. PWBD must not be lost within this system or left to puzzle through it alone. Technology offers increasing opportunities to provide telemedicine and virtual care. While some older adults may require assistance with these modalities, younger PWBD are largely very comfortable with technology. Steps must be taken to capitalise on these opportunities now, for their future care.

PWBD have the same right to expect to enjoy their later years as everyone else. Anticipating their healthcare needs and proactively implementing solutions to anticipated challenges are essential to ensuring that the growing number of people ageing with bleeding disorders may do so successfully.

References and resources

1. Centers for Disease Control and Prevention. Community Counts HTC Population Profile (September, 2023): https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2023-9/index.html

2. Manco-Johnson MJ, Lundin B, Funk S, et al. 2017. Effect of Late Prophylaxis in Hemophilia on Joint Status: A Randomized Trial. Journal of Thrombosis and Haemostasis: https://www.jthjournal.org/article/S1538-7836(22)04386-0/fulltext
3. Srivastava A, Santagostino E, Dougall A, et al. 2020. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia Journal: https://onlinelibrary.wiley.com/doi/10.1111/hae.14046
4. Shapiro S and Makris M. 2018. Haemophilia and Ageing, British Journal of Haematology: https://onlinelibrary.wiley.com/doi/10.1111/bjh.15745
5. Badescu MC, Badulescu OV, Butnariu LI, et al. 2022. Cardiovascular Risk Factors in Patients with Congenital Hemophilia: A Focus on Hypertension. Diagnostics: https://doi.org/10.3390/diagnostics12122937
6. World Health Organization. Cardiovascular Diseases Fact Sheet: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
7. European Haemophilia Safety Surveillance (EUHASS) quarterly and annual reports of adverse events reported in people with bleeding disorders are distributed to participating centres and national patient organisations via EHC: https://web.euhass.org/info/results/
8. Schutgens REG, Jimenez-Yuste V, Escobar M, et al. 2023. Antithrombotic Treatment in Patients with Hemophilia: an EHA-ISTH-EAHAD-ESO Clinical Practice Guidance. HemaSphere: https://journals.lww.com/hemasphere/fulltext/2023/06000/antithrombotic_treatment_in_patients_with.18.aspx
9. British Geriatric Society. Website with many useful resources regarding frailty and ageing successfully: https://www.bgs.org.uk/
10. European Geriatric Medicine Society. Website with resources and news from national societies across Europe: https://www.eugms.org/home.html
11. Dalhousie University. Geriatric Medicine Research website with free access to (users must complete a Permission for Use Agreement) to, and information about, the Clinical Frailty Score: https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html
12. Ellis G, Gardner M, Tsiachristas A, et al. 2017. Comprehensive Geriatric Assessment for Older Adults Admitted to Hospital. Cochrane Database of Systematic Review: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006211.pub3/full
13. World Federation of Hemophilia eLearning Platform of resources for PWBD and healthcare professionals: https://elearning.wfh.org/
14. The Haemophilia Society (UK). 2017. The Dental Management of Adult Patients with Haemophilia and Other Congenital Bleeding Disorders (Dentist and patient versions available): https://haemophilia.org.uk/support/day-day-living/healthy-living/dental-care/

Von Willebrand Disease (VWD)

Speakers:

- **Fiona Brennan**, MSc, Patient Engagement Lead, formerly Von Willebrand staff liaison, EHC
- **Sunny Maini**, UK VWD Ambassador for The Haemophilia Society (UK), Person with Type 3 VWD, EHC VWD Committee Co-chair
- **Joanne Traunter**, Ed.D., Educator and Researcher, University of Hull, Person with Type 2 VWD, UK VWD Working Group, EHC VWD Committee Co-chair
- **Michelle Lavin**, MD, World Federation of Hemophilia VWD Committee Chair, Consultant Haematologist and Researcher, National Coagulation Centre, St James's Hospital and Irish Centre for Vascular Biology, Royal College of Surgeons of Ireland, Dublin, Ireland

Background

VWD is a bleeding disorder caused by dysfunction or deficiency in von Willebrand Factor (VWF). VWF is a protein with multiple roles in haemostasis including as a chaperone for FVIII, and in the adhesion and aggregation of platelets at the site of blood vessel injury. Individual VWF proteins group together into multimers, which is important for its function.

It is estimated that 1 in 1000 people have symptoms of VWD (much more common than haemophilia); VWD is inherited equally by men and women. There are three general types of VWD, based on the nature of the VWF deficiency or dysfunction, with Type 2 further subtyped by specific functional deficiency (Table 3).

Table 3. Type and subtype classification of VWD

VWD Type/subtype	Characteristic VWF deficiency or dysfunction
1	Partial quantitative deficiency
1C	Increased clearance resulting in partial quantitative deficiency
2	Qualitative abnormalities
2A	Reduced or absent high-molecular weight VWF multimers
2B	Increased affinity of high-molecular weight VWF multimers for platelets (gain of function)
2M	Reduced interactions with platelets or collagen
2N	Reduced binding to FVIII
3	Absence of VWF, with associated very low FVIII levels

FVIII: factor VIII, VWD: von Willebrand disease, VWF: von Willebrand factor

VWD patients' lived experience – Real-world evidence

In 2019–2020 the EHC conducted a survey of its members, through the NMOs, to better understand the lived experiences of people with VWD (PWVWD) and the burden of a VWD diagnosis. A detailed analysis of data from 220 adult PWVWD in 35 countries, primarily in Western Europe, has been submitted to the journal, *Haemophilia*. Upon publication it will be shared with EHC members. Several informative trends are summarised below. The majority (84%) of respondents were female, with good representation of Type 1 (38%), Type 2 (38%), and Type 3 (17%) VWD.

An important issue, widely experienced in the community and previously reported in the literature, highlighted by survey data is the time required for a PWVWD to receive an accurate diagnosis. The average time from initial test to accurate diagnosis ranged from 4.7 years for Type 3 VWD to 26.1 years for Type 1. Accurate diagnosis is essential to ensure adequate care and individual treatment thus preventing long-term bleeding complications and improving quality of life. An international collaboration recently developed detailed guidelines for the diagnosis and management of VWD, it is hoped that these will contribute to shortening long diagnostic delays.

The types of bleeds reported showed some very interesting trends. The most common bleeds (experienced by 82% of respondents) were nose, oral, and heavy menstrual bleeding (HMB). Almost 73% of female respondents reported HMB, with 50% of those with Type 1 and Type 2 VWD reporting a significant impact almost every single menstrual cycle. Gastrointestinal (GI) bleeds were reported most often by people with Type 2 VWD, and more so with increasing age. These bleeds are sometimes considered "minor", however EQ-5D (a well validated quality of life assessment tool) responses demonstrated their significant impact on the people experiencing them. Similarly, there have been suggestions that PWVWD do not bleed into their joints, despite studies reporting joint bleed rates as high as 50%. The survey results complement the latter, with one third of respondents reporting joint bleeds and chronic pain. As is well established in PWH, the pain and long-term damage of joint bleeds significantly decreased the quality of life of the PWVWD in the survey.

The VWD community has spoken for some time of "bleeding their way to treatment." Survey results appear consistent with this observation. Contrary to haemophilia, for which the standard of care is prophylaxis ideally initiated prior to any joint damage, to prevent bleeds and their sequelae, it seems PWVWD are often required to demonstrate repeated bleeds and their significant impacts, to access treatment. This increases their risk of long-term joint damage and chronic pain, with decreased quality of life also due to repeated GI, nose, oral and heavy menstrual bleeding.

The real-world experiences of PWVWD documented by the survey prompt a call for several important changes:

- Recognition that the impact of "minor" bleeds such as HMB, and GI, nose, and oral bleeds on PWVWD is far from minor
- Recognition that joint bleeds and chronic pain are very real aspects of VWD
- Improved clinical understanding of the different types of VWD and their manifestations
- A shift from treating bleeds to preventing bleeds in managing VWD
- Education of PWVWD and all of the HCPs they may encounter on the above four points

While many diagnostic and treatment services are in place in HTCs, advocacy and education for both PWVWD and HCPs is essential. This will facilitate improvements in comprehensive care services, access to appropriate treatment and ultimately improve outcomes for PWVWD across Europe.

Redefining needs for the VWD community

VWD is complex, individual symptoms and experiences vary greatly between and within the different types. Defining policies and practices to meet the needs of the entire VWD community is also, therefore, complex. The EHC VWD Committee seeks to understand the needs of the community and to identify and develop initiatives and resources to meet those needs. Many discussions since its creation (first as an EHC Working Group in 2020) highlighted several recurring themes:

- Having a lifetime of symptoms dismissed remains a relatively common, alienating, and sometimes devastating experience
- PWVWD often suffer significant psychosocial burden from not having a diagnosis, being misdiagnosed, and waiting a long time to be accurately diagnosed
- Many HCPs, PWVWD, and the general public lack adequate knowledge of the symptoms and management of VWD
- PWVWD struggle to receive appropriate treatment for their symptoms and, therefore, suffer undue negative impacts on their daily lives and long-term health
- Experiences with the healthcare system risk leaving PWVWD feeling isolated, anxious, and uncertain about their future health

In addition to the immediate and long-term physiological consequences of abnormal bleeding, many PWVWD must also contend with negative impacts of undiagnosed and sub-optimally managed bleeding including financial sequelae with loss of time from work and school, psychosocial and mental health sequelae of uncertainty, limitations on normal physical and social activities, and in some cases not being believed or taken seriously by HCPs. Frequent visible bruising, for example, can present a substantial burden on the quality of daily life and social interactions.

A number of EHC VWD Committee initiatives seek to begin to address these issues, including:

- Public awareness raising campaigns such as the "How Did That Happen" exhibition and tattoo campaign, marking the first VWD Awareness Day on February 1, 2023
- An NMO handbook (under development) to guide the establishment of VWD strategy, education, and advocacy by every EHC NMO
- Co-creation of an education programme in partnership with European Reference Network (ERN) EuroBloodNet: a series of webinars co-presented by PWVWD and clinicians
- The survey of real-world experiences of PWVWD summarised above, to be published in a peer-reviewed journal
- Building the #VWDunited community to embrace all PWVWD in Europe

Throughout the conference, participants were asked (through an automated response tool): "What do you consider to be the challenges in meeting the needs of the VWD community?" An informal analysis of the 56 responses echoed many of the themes identified above (Figure 3): the struggle to obtain a diagnosis, lack of recognition, lack of treatment options, the need for education and awareness raising, and the importance of community.

Figure 3. Word cloud analysis (top 50 words) of the 56 free text Mentimeter responses received during the EHC 2023 Conference to the question: "What do you consider to be the challenges in meeting the needs of the VWD community?"
EHC: European Haemophilia Consortium, VWD: von Willebrand disease

The EHC VWD Committee is committed to continually cultivating active listening and learning from the community to orient ongoing and future initiatives. Anyone wishing to join the #VWDunited community, provide input, or simply connect is invited to email vwd@ehc.eu.

Potential future therapies for people with VWD

Establishing a culture of prophylaxis

Improving the future treatment of PWVWD starts with a progression in the way currently available therapies are used. Replacement factor prophylaxis to prevent bleeds, ideally started before bleeds cause any real damage and continued long-term, is the standard in haemophilia care. In a big step forward, international VWD management guidelines very recently (2021) first suggested (not recommended, due to a lack of available evidence) long-term prophylaxis for PWVWD with a history of severe and frequent bleeds. This means, precisely as PWVWD assert above, that they must bleed their way to prophylaxis. Recombinant and plasma-derived VWF concentrates are now available, yet clinical studies generating data to inform strong guideline recommendations remain few. A cultural shift from one of bleed expectation to bleed prevention through prophylaxis, and the research data to support it, are required.

In addition to a strong culture of prophylaxis, haemophilia benefits from considerable investment in the development of novel therapies. None of these novel haemophilia therapies have been approved for the treatment of VWD. Progress in discovering new treatment options for VWD is very slow, increased investment and urgency is needed to accelerate confirmation of the promising results demonstrated so far in a few small studies.

Antibodies

Emicizumab (Hemlibra®) is a bispecific antibody that carries out the function of FVIII (bringing FIXa and FX together early in the coagulation cascade) improving the ability of PWH A to form blood clots. Lab experiments with blood from PWVWD, and in mice who have VWD, suggest that emicizumab might also improve blood clotting in certain types of VWD (e.g., 1 and 3) but not others (e.g., 2A). A few publications report successful bleed prevention in PWVWD with emicizumab – most of these very few individuals had Type 3 VWD with inhibitors to replacement VWF therapy, leaving them with very few treatment options. A clinical trial is currently underway (US) to study the use of emicizumab in a specific subset of PWVWD.

The normal function of protein S is to prevent too much blood clotting. VGA039 is an antibody that binds to protein S, inhibiting this anti-coagulation activity, which might be helpful in rebalancing haemostasis in someone with a clotting deficiency. Laboratory studies with blood from PWVWD suggested that it might increase the ability to make thrombin, a key step in blood clotting. A first study of this in humans is expected to start soon.

Modified recombinant FVIII

Efanesoctocog alfa (ALTUVIIIO) is a recombinant FVIII protein with several additions: an Fc moiety, a fragment of the VWF protein that covers up the part of FVIII that normally binds to VWF, and a custom designed XTEN series of amino acids (the building blocks of proteins). The result is a FVIII with a very long half-life that PWH only need to infuse once a week. People with certain types of VWD (such as 2N and some Type 3) have very low levels of FVIII and experience FVIII-related bleeding; this product might be expected to improve their ability to form blood clots. A small clinical trial (just six PWVWD) examining this concluded in 2022, data have not yet been published.

Small molecules

BT200 (rondoraptivon pegol) is a small molecule that binds to a part of the VWF protein (the A1 domain) involved in its clearance from the body. Occupying this site is proposed to slow down VWF clearance, and since VWF binds to FVIII, levels of both should go up. A first study in humans supported this, and in a small trial (five people with Type 2B VWD) BT200 appeared to cause increases in FVIII, VWF, and platelet levels, encouraging researchers to continue studying it. Another approach is to use a nanobody (an artificial, very small antibody) to attach VWF to albumin, a protein that naturally has a very long half-life. Early experiments in animals suggest that this may increase the half-life of the VWF.

Gene therapy

Current gene therapy for haemophilia A and B, uses adeno-associated virus (AAV) vectors to deliver a copy of the *F8* or *F9* gene, respectively, to liver cells to produce functional FVIII or FIX. Gene therapy for VWD, unfortunately, appears to be more complex than this simple gene addition. The *VWF* gene is too big to be delivered by an AAV vector, and the VWF protein is normally made by epithelial cells lining blood vessels, not in the liver. Individual VWF proteins group together into multimers, so even if a *VWF* gene could be delivered to an epithelial cell, and "good" VWF protein produced there, if that new protein multimerised with the problematic VWF already in the body, it might not do much good. CRISPR-Cas9 is a genetic technology that allows a very precise part of a gene to be targeted, removed, and replaced with a custom (repaired) sequence. Research attempting to use this technique to correct Type 3 VWD has started in dogs, but a lot more work is required to determine if it really can be done in humans. It is important to note that this technique would have to be tailored to each individual genetic

mutation, which would be very expensive and technically demanding. Not all VWD, especially Type 1, is caused by a single mutation in the *VWF* gene.

Conclusion

Advocacy, grounded in data documenting the lived experiences of PWVWD and driven by their compelling stories, must establish a culture of prophylaxis in the management of VWD, and motivate further studies of promising potential novel therapies.

References and resources

1. James PD, Connell NT, Ameer B, et al. 2021. ASH ISTH NHF WFH Guidelines on the Diagnosis of von Willebrand Disease. Blood Advances: https://ashpublications.org/bloodadvances/article/5/1/280/474888/ASH-ISTH-NHF-WFH-2021-guidelines-on-the-diagnosis
2. Connell NT, Flood VH, Brignardello-Petersen R, et al. 2021. ASH ISTH NHF WFH Guidelines on the Diagnosis of von Willebrand Disease. Blood Advances: https://ashpublications.org/bloodadvances/article/5/1/301/474884/ASH-ISTH-NHF-WFH-2021-guidelines-on-the-management
3. World Federation of Hemophilia. ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD Supporting Materials: https://elearning.wfh.org/resource/ash-isth-nhf-wfh-guidelines-on-the-diagnosis-and-management-of-vwd/
4. World Federation of Hemophilia. Von Willebrand Disease eLearning Centre: https://elearning.wfh.org/elearning-centres/von-willebrand-disease/#resources
5. European Haemophilia Consortium. Resources for People with von Willebrand Disease: https://www.ehc.eu/resources-for-people-with-von-willebrand-disease/
6. European Haemophilia Consortium. European von Willebrand Platform: https://www.ehc.eu/european-von-willebrand-platform/
7. Lillicrap D, James P. 2009. Von Willebrand Disease : An Introduction for the Primary Care Physician. Treatment of Hemophilia (WFH): https://www1.wfh.org/publication/files/pdf-1204.pdf
8. Stufano F, Baronciani L, Peyvandi F. 2017. Diagnosis of von Willebrand Disease: Phenotypic Characterization. Treatment of Hemophilia (WFH): https://elearning.wfh.org/resource/diagnosis-von-willebrand-disease-phenotypic-characterization/
9. Baronciani L, Goodeve A, Peyvandi F. 2017.Molecular Diagnosis of von Willebrand Disease. Treatment of Hemophilia (WFH): https://elearning.wfh.org/resource/molecular-diagnosis-von-willebrand-disease/
10. Peyvandi F. 2018. Diagnosis and Management of Patients with von Willebrand's Disease in Italy: an Expert Meeting Report. Blood Transfusion: https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC6034766&blobtype=pdf
11. Abshire TC, Federici AB, Alvarez MT, et al. 2013. Prophylaxis in Severe Forms of von Willebrand's Disease: Results from the von Willebrand Disease Prophylaxis Network (VWD PN). Haemophilia: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2012.02916.x
12. van Galen KPM, de Kleijn P, Foppen W, et al. 2017. Long-term Impact of Joint Bleeds in von Willebrand Disease: A Nested Case-control Study. Haematologica: https://haematologica.org/article/view/8183

13. Sidonio RF Jr, Bryant PC, Di Paola J, et al. 2023. Building the Foundation for a Community-generated National Research Blueprint for Inherited Bleeding Disorders: Research Priorities for Mucocutaneous Bleeding Disorders. Expert Review of Hematology: https://www.tandfonline.com/doi/full/10.1080/17474086.2023.2171983
14. European Reference Networks (ERN) | EuroBloodNet von Willebrand Disease (VWD) website of resources, events and reference centres and experts: https://eurobloodnet.eu/disease-groups/20/von-willebrand-disease
15. Srivastava A, Santagostino E, Dougall A, et al. 2020. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia: https://onlinelibrary.wiley.com/doi/10.1111/hae.14046
16. Ay C, Pabinger I, Kovacevic KD, et al. 2022. The VWF Binding Aptamer Rondoraptivon Pegol Increases Platelet Counts and VWF/FVIII in Type 2B Von Willebrand Disease. Blood Advances: https://ashpublications.org/bloodadvances/article/6/18/5467/485752/The-VWF-binding-aptamer-rondoraptivon-pegol
17. Leong L, Byun T, Kim B, et al. 2022. Pre-Clinical Characterization of VGA039, an Anti-Protein S Monoclonal Antibody Being Developed as a Universal Hemostatic Agent for Various Bleeding Disorders. Blood: https://ashpublications.org/blood/article/140/Supplement%201/1666/489008/Pre-Clinical-Characterization-of-VGA039-an-Anti

European Rare & Inhibitor Network (ERIN)

Speakers:

- **Víctor Jiménez-Yuste**, MD, Haematologist, Member of the Executive Committee of the Spanish Society of Haematology and Haemotherapy, Professor of Medicine and Head of Haematology Department, University of Madrid, Servicio de Hematología, Hospital Universitario La Paz, Madrid, Spain
- **Miguel Crato**, EHC President, ERIN Working Group Member, European Association for Haemophilia and Allied Disorders Gene Therapy and Centre Certification Committees Member, Lisbon, Portugal
- **Marc Dooms**, Pharm D, Vice Chair of the International Rare Diseases Research Consortium, Senior Pharmacist, University Hospitals Leuven, Leuven, Belgium

Current and future needs of people with haemophilia and inhibitors

People with haemophilia and inhibitors (PWH+I) have greater morbidity (specific negative health outcomes associated with a condition) and mortality (death from the condition), and a lower quality of life than PWH without inhibitors. PWH+I face all the same challenges as PWH, but because their body produces antibodies that make replacement factor ineffective (inhibitors), until very recently they have had few options to manage these challenges. Many PWH+I have access to bypassing agents (BPAs) including activated recombinant factor VII (rFVIIa) or activated prothrombin complex concentrates (aPCCs), which contain a mix of clotting factors such as II, VII, IX, X and their activated forms. These can be used on-demand to treat bleeds or as adaptable or routine prophylaxis, which can lower the annualised bleeding rate (ABR) of PWH+I by 45–72%. It is rare, however, to achieve an ABR of zero (complete prevention of spontaneous bleeds).

The development of novel non-factor replacement therapies (NFRTs) offers exciting new possibilities for PWH+I. Emicizumab (Hemlibra®), a bispecific antibody that carries out the function of FVIII (bringing FIXa and FX together early in the clotting cascade), has been approved by European regulators for routine prophylaxis in PWH A and FVIII inhibitors (PWHA+I), as well as some PWHA without inhibitors. Concizumab is an antibody that binds to tissue factor pathway inhibitor (TFPI) and decreases its anti-clotting activity in PWHA and B, with and without inhibitors. Fitusiran is a small interfering ribonucleic acid (siRNA) that targets anti-thrombin (AT) and limits its ability to break down thrombin (key to blood clotting) in PWHA and B, with and without inhibitors. While neither of these two latter have been approved by European regulators, some PWHA+I and PWHB+I have accessed them through clinical trials, with encouraging results.

In clinical trials, prophylaxis of PWHA+I with emicizumab, and of PWHA+I or PWHB+I with concizumab or fitusiran, resulted in ≥85% decrease in ABR compared to on-demand BPAs, and an ABR of zero for 60–70% of participants. These novel products are, however, not without complications. The clinical trials for each encountered thrombotic events (when a blood clot, or a piece of a blood clot that comes loose, blocks a blood vessel and causes a negative outcome) which caused serious concern. Strategies have been developed to minimise the risk of these thrombotic events. In the case of emicizumab, they occurred in PWHA+I also taking aPCCs, therefore this combination is to be avoided. For concizumab and fitusiran, expert consideration of the individual's thrombotic risk factors and the amount (dose) of NFRTs used is important in avoiding thrombotic events. These products are not the same as

replacement factor: taking more to treat a suspected bleed is ineffective and can even be dangerous, and the potential for thrombotic events requires expert management of their use.

PWH+I experience more joint pain, reduced mobility, and more arthropathy than PWH. More data are needed to fully understand the impact of NFRTs on joint health in PWH+I, but in trials with emicizumab 95% of target joints appeared to be resolved (they had no more spontaneous bleeds). Orthopaedic surgery in PWH+I is particularly complex as the effectiveness of BPAs in establishing enough clotting for safe surgery is hard to predict. A number of successful major and minor surgeries on PWHA+I in the emicizumab clinical trials suggest a safe approach combining rFVIIa and emicizumab, though clear protocols still need to be established. Data is not yet available on the use of other NFRTs in surgery on PWH+I.

With improved prophylaxis, and increasing access to surgeries, PWH+I are expected to live longer and their quality of life to improve. Participants in the clinical trials for emicizumab, concizumab and fitusiran reported increases in their quality of life. As they live longer, PWH+I will encounter the same co-morbidities of ageing as PWH, and the potential for thrombotic complications of NFRTs (especially with concizumab and fitusiran) must be considered in their management (please see Ageing section above).

These new products are expensive, but so are BPAs, and a cost-benefit analysis suggests it may be more efficient to treat PWHA+I and PWHB+I with the novel products. Access to NFRTs, and BPAs, will be a critical issue in many countries, and must be addressed with appropriate advocacy to ensure the future well-being of all PWH+I.

European Rare and Inhibitor Network (ERIN)

In 2015 EHC launched a programme to identify and address the needs of PWH+I, recognising that there are often too few such individuals in each country or NMO to effectively organise and do this work. In 2021 the EHC Inhibitor Working Group concluded that they had successfully met their initial objectives for PWHA+I, though PWHB+I remain underserved due to the lack of good prophylaxis options. They sought to capitalise upon their learnings and strengths to identify and address the needs of an even less well represented group: people with extremely rare bleeding disorders (PWERBD). Thus the European Inhibitor Network (EIN) became the European Rare and Inhibitor Network (ERIN).

ERIN recruited committee members to lead this work: PWERBD, their family members and caregivers, medical professionals, and EHC staff and Steering Committee members (Table 4). The Committee continues to seek contact with more EHC members, to expand their perspectives and understanding of the wide range of extremely rare bleeding disorders (ERBD) (Table 5).

Table 4. ERIN Committee members

Member	Expertise
Amy Owen-Wyard	UK NMO
Christina Burgess	Psychosocial expert, UK
Dominik Cepic	Croatian NMO
Ildiko Kaslik	Hungarian NMO
Maja Søndergaard Knudsen	Danish NMO
Dr Maria-Elisa Mancuso	Haematologist, Italy
Jim O'Leary	Adviser to the Committee, Irish NMO
Nathan O'Hagan Doyle	Irish NMO

Miguel Crato	EHC Steering Committee
Evelyn Grimberg	EHC Steering Committee
Kristine Jansone	EHC Staff

EHC: European Haemophilia Consortium, NMO: national member organisation, UK: United Kingdom

Table 5. Extremely rare bleeding disorders ERIN seeks to represent

Haemophilia B with inhibitors	Glanzman Thrombasthenia
Haemophilia A with inhibitors	Bernard Soulier Syndrome
Factor II deficiency	Factor V deficiency
Factor VII deficiency	Factor X deficiency
Factor XI deficiency	Afibrinogenemia
Dysfibrinogenemia	Hypofibrinogenemia

ERIN: European Rare and Inhibitors Network

PWERBD are few and far between, distributed across the vast geography of Europe, often without contact with EHC NMOs or other PWERBDs. The ERIN Committee is working to reach out to them, connect them to one another and to EHC NMOs, learn from them, and work with them to advocate for their needs. A needs assessment survey circulated through EHC NMOs (closed Jan 1, results to be reported in 2024) will provide a foundation of data upon which to define needs and design initiatives and programmes.

In addition to data collection and needs assessment, ERIN is working in two key areas:

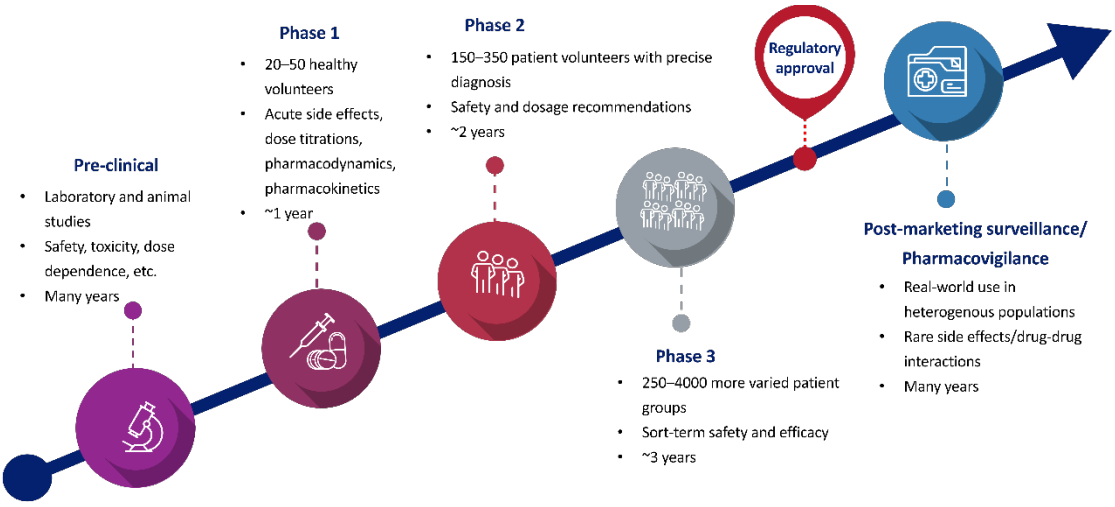
- Education and awareness raising
  - PWERBD – need more information about their disorders and management options, to know that they are not alone, and connection to peers with whom they can share, and work together to advance their common concerns.
  - Clinicians and HTCs – must be aware of and able to recognise ERBDs, learn how best to diagnose and manage them, and include PWERBDs in research.
  - NMOs – have an important role to play in seeking out PWERBD, welcoming them into the community, and initiating or adapting programmes to meet their needs and advocacy goals. The ERIN Committee will work closely with NMOs to facilitate this important expansion.
- Advocacy
  - For research into ERBD, including inclusion of PWERBD in clinical trials
  - For proper diagnosis, treatment, and care of PWERBD
  - For the development of principles of care for PWERBD, as have been developed for women and girls with bleeding disorders.

In December 2022 the ERIN Committee brought PWERBD and PWH+I together, for the first time, for education and advocacy. While the number of PWERBD attending was low, the group were highly motivated and expressed their collective passion in a signed manifesto outlining the challenges they face and issuing an urgent call for them to be addressed at national and European levels.

ERIN will hold a second summit in 2024, to advance their collaborative work and further plans and initiatives to achieve a world where PWERBD live normal and fulfilled lives with excellent treatment and support in all countries.

Basket trials – Shared etiologies in bleeding disorders

The development of medicines to treat disorders has, for many years, followed a linear pathway that progresses from pre-clinical assessment, through Phase 1 and Phase 2, to Phase 3 clinical trials to generate the data submitted to regulators for its approval (Figure 4). The process takes many years and must start with a huge number of promising candidate products or compounds tested in pre-clinical trials. At each phase, many candidates are dropped as they prove unsafe, ineffective, or otherwise inappropriate. Very few actually make it to the final phase of being submitted to regulators, the process must be extremely rigorous to ensure that only truly safe and effective products are approved for use in humans. It takes many years, many promising candidates, and a lot of resources (financial, human, and infrastructure) to achieve one indication (approved use for a specific medical condition or purpose) for one product. For rare and extremely rare disorders these challenges are particularly onerous, few companies or institutions are prepared or able to make the huge investment required to develop a therapeutic that may only be used by a very small number of people.



Phase success rate	**30.4%**	**19.4%**	**8.6%**	**1.9%**	**1.2%**
% Calculated to achieve one approval	**3%**	**5%**	**12%**	**54%**	**83%**

Figure 4. Conventional route for the development of therapeutics, progressing individually through the various phases of clinical trials.

Basket trials are a variation on this approach which may offer considerable savings of time and resources. They take the same approach of screening candidate products through the series of trial phases, but for a whole basket of potential indications, not just one. Disorders that are caused by the same kind of genetic mutation, but in different genes, might be screened together. Or those caused by different mutations in the same gene. Or those that involve different genes in the same pathway. Basket trials in cancer research have resulted in single products being approved for eight or even more indications. The efficiencies, compared to going through the whole process in Figure 4 eight or more times, are impressive. To date, bleeding disorders clinical trials do not appear to have attempted to

basket more than haemophilia A and B together; one might imagine looking at different types of VWD together, or deficiencies in any of the clotting factors in the coagulation cascade, for example.

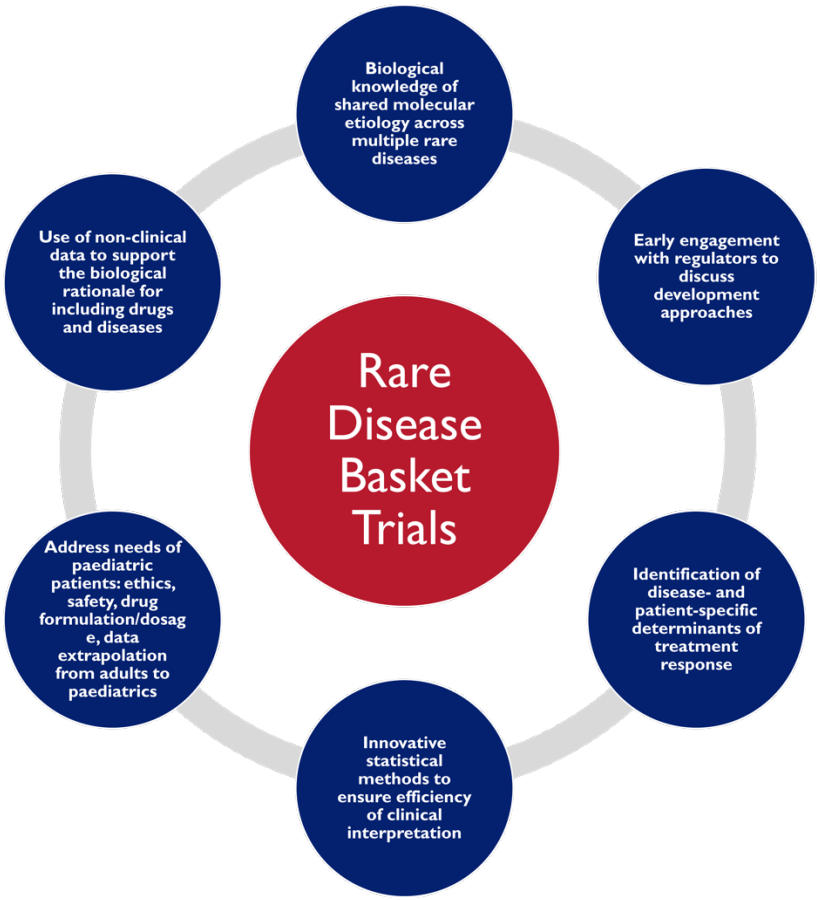


Figure 5. Key considerations in the application of basket trials to rare diseases, such as extremely rare bleeding disorders.

Successfully conducting basket trials in rare diseases requires careful consideration of a number of points (Figure 5) including a sound understanding of the molecular etiology (mechanisms) of the disorders being studied, and close communication with regulators. Regulators take a standard approach to reviewing data that fits the conventional approach to developing therapeutics (Figure 4). Basket trials require distinct statistical methods and approaches – these must be discussed and cleared with regulators before starting the trial, to ensure the process yields the information that regulators require in a format they can analyse. It is important to ensure that regulators understand and approve the entire approach being taken. The efficiencies offered by basket trials, and the similar etiologies of multiple ERBDs, suggest that they might be a winning combination in the effort to develop therapeutics for people who currently have few treatment options.

References and resources

1. European Haemophilia Consortium. Resources for People with Inhibitors: https://www.ehc.eu/resources-for-people-with-inhibitors/

2. European Haemophilia Consortium. Resources for People with Rare Bleeding Disorders: https://www.ehc.eu/resources-for-people-with-rare-bleeding-disorders/
3. European Haemophilia Consortium. Extremely Rare Bleeding Disorders: https://www.ehc.eu/bleeding-disorders/rare-bleeding-disorders/
4. World Federation of Hemophilia. Rare Clotting Factor Deficiencies eLearning Centre: https://elearning.wfh.org/elearning-centres/rare-clotting-factor-deficiencies/
5. World Federation of Hemophilia. Inherited Platelet Disorders eLearning Centre: https://elearning.wfh.org/elearning-centres/inherited-platelet-disorders/
6. Rare Bleeding Disorders Network. Pro-RBDD collaboration network website: http://eu.rbdd.org/index.php?option=com_content&view=article&id=30&Itemid=101
7. Orphanet. Portal for Rare Diseases and Orphan Drugs: https://www.orpha.net/consor/cgi-bin/index.php
8. Nugent D, Acharya S, Baumann KJ, et al. 2023. Building the Foundation for a Community-generated National Research Blueprint for Inherited Bleeding Disorders: Research Priorities for Ultra-rare Inherited Bleeding Disorders. Expert Review of Hematology: https://www.tandfonline.com/doi/full/10.1080/17474086.2023.2175661
9. Scalone L, Mantovani LG, Mannucci PM, et al. 2006. Quality of Life is Associated to the Orthopaedic Status in Haemophilic Patients with Inhibitors. Haemophilia: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2006.01204.x
10. Callaghan M, Negrier C, Paz-Priel I, et al. 2021. Long-Term Outcomes with Emicizumab Prophylaxisfor Hemophilia A with or without FVIII Inhibitors from the HAVEN 1-4 Studies. Blood: https://ashpublications.org/blood/article/137/16/2231/474603/Long-term-outcomes-with-emicizumab-prophylaxis-for
11. Kruse-Jarres R, Peyvandi F, Oldenburg J, et al. 2022. Surgical Outcomes in People with Hemophilia A Taking Emicizumab Prophylaxis: Experience from the HAVEN 1-4 Studies. Blood Advances: https://ashpublications.org/bloodadvances/article/6/24/6140/486138/Surgical-outcomes-in-people-with-hemophilia-A
12. Mahlangu JN. 2021. Progress in the Development of Anti-tissue Factor Pathway Inhibitors for Haemophilia Management. Frontiers in Medicine (Lausanne): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8131856/
13. Peyvandi F, Kavakli K, El-Beshlawy A, et al. 2022. Management of Haemophilia A with Inhibitors: A Regional Cross-talk. Haemophilia: https://onlinelibrary.wiley.com/doi/10.1111/hae.14638
14. Swan D, Mahlangu J, Thachil J. 2022. Non-factor Therapies for Bleeding Disorders: A Primer for the General Haematologist. eJHaem: https://onlinelibrary.wiley.com/doi/10.1002/jha2.442
15. Jiménez-Yuste V, Rodríguez-Merchán EC, Matsushita T, et al. 2021. Concomitant Use of Bypassing Agents with Emicizumab for People with Haemophilia A and Inhibitors Undergoing Surgery. Haemophilia: https://onlinelibrary.wiley.com/doi/10.1111/hae.14322
16. Zanello G, Garrido-Estepa M, Crespo A, et al. 2023. Targeting Shared Molecular Etiologies to Accelerate Drug Development for Rare Diseases. EMBO Molecular Medicine: https://www.embopress.org/doi/full/10.15252/emmm.202217159