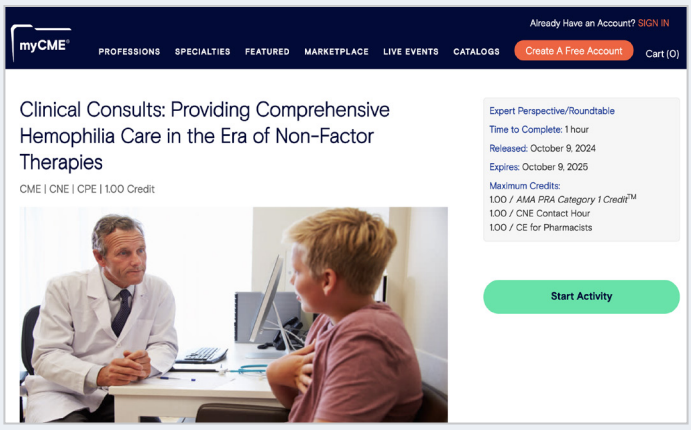
Hemophilia PERSPECTIVES™

October 2024

ECM™ collaborated with globally-recognized experts: Tammuella C. Singleton, MD, Meera Chitlur, MD, and Robert Sidonio, Jr, MD, MsC to provide their perspectives on new and emerging non-factor replacement hemophilia therapeutic strategies to achieve hemostatic balance and improved outcomes. This report highlights their respective presentations on the topic, which were presented in a web-based CME/CE-accredited virtual symposium currently available here.



Hemophilia: An Evolving Treatment Landscape

With new advances in the treatment and comprehensive care of people with hemophilia [PwH], individuals with the disorder can lead more normal lives, without necessarily feeling the full burden of chronic illness. In most developed countries, prophylaxis [PPX] is the accepted standard of care for patients with severe hemophilia A and B, respectively.

The latest guidelines recommend that all patients with severe hemorrhagic phenotypes should receive prophylactic treatment, defined as the regular administration of therapeutic products [either factor concentrates or non-factor replacement treatments], which aim to preserve hemostasis and prevent bleeding, especially into joints.

As these experts explored the changing hemophilia landscape, they have emphasized that prophylaxis is essential for preventing bleeds and debilitating arthropathy in patients with severe hemophilia; however, frequent infusions of replacement factor is associated with a high treatment burden.

Thus, clinicians treating PwH are challenged to keep abreast of new developments in their understanding of the pathophysiology of hemophilia, the role of thrombin generation in maintaining hemostasis, and the pharmacokinetic profiles of new and emerging agents with unconventional modes of action that may result in achieving normal hemostasis and improved outcomes in these patients.

ABOUT ECM™

Founded in 2003, Educational Concepts in Medicine, LLC [ECM™] develops educational programs on bleeding disorders such as hemophilia, as well as perioperative hemostasis, coagulation issues in trauma and ICU patients, and hematologic malignancies.

Our mission is to research practice gaps and the educational needs of healthcare professionals [HCPs], develop appropriate educational content, and implement accredited continuing education initiatives which provide HCPs with the information, expert opinion, and tools required for adopting practice-changing diagnostic and therapeutic strategies, which in turn, lead to improved patient-centered care and more positive patient-reported outcomes [PROs].

ECM™ educational concepts in medicine

Why Non-Factor Therapy?

Recent developments in non-factor replacement treatments and biotechnology have offered the hemophilia treatment community therapeutic alternatives for PwH, with or without inhibitors. These novel molecules that are subcutaneously [SQ]-delivered provide effective PPX by either substituting for the procoagulant function of clotting factors [e.g. emicizumab], or targeting the natural inhibitors of coagulation [i.e. antithrombin, tissue factor pathway inhibitor, or activated protein C]. These substitution and rebalancing therapies provide an opportunity for steady-state hemostatic control without exposure to immunogenic clotting factor proteins.

Tammuella C. Singleton, MD
Chief Science Officer
American Thrombosis and Hemostasis Network (ATHN)
Co-Director, Hemostasis and Thrombosis Program
Ochsner Clinic Foundation
New Orleans, LA

Dr. Singleton, who chaired the web-based virtual symposium, introduced the overall program and set the stage for the faculty's discussion of the current evidence and their opinions about more effective and longer-lasting non-factor treatment strategies; technological advances in treating people living with hemophilia; as well as the clinical and patient management challenges that can be associated with advancing the quality of comprehensive care.

ECM: Dr. Singleton, you often refer to 'a balancing act' when discussing newer approaches to achieving hemostasis in patients with hemophilia. Can you elaborate on this topic?

In addition, Dr. Singleton discussed the issues and concerns about utilizing non-factor therapies [NFTs] to achieve hemostatic balance.

New and emerging NFTs include:

- Factor VIII mimetics [e.g., emicizumab]
- Antithrombin inhibitors [AT] [e.g., fitusiran]
- Tissue Pathway Inhibitors [TFPI] [e.g., concizumab, marstacimab]

Dr. Singleton: *"One of the things that I think is important to remember is that the patient is absolutely at the center of our treatment strategies, and it is no longer just about survival, or simply preventing bleeds, but decreasing an annualized bleed rate in terms of approaching zero bleeds." "Rebalancing therapies are based on the concept that the bleeding phenotype of PwH may be alleviated by altering the balance of hemostasis in favor of a more pro-coagulant state, with the end-game being thrombin generation."*

"With non-factor replacement therapies [NFTs], we have an opportunity to inhibit the anticoagulants, tipping the scale to procoagulants and encouraging thrombin formation, which is the goal of treatment, bypassing factor VIII or factor IX and sort of force-activating factor X."

KNOWLEDGE CHECK

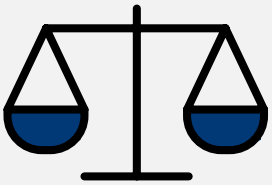
When considering the evolving treatment landscape for treating PwH, how confident are you about the pharmacology and pharmacokinetics underlying non-factor replacement therapies, which may improve hemostasis and ultimately, patient outcomes?

A. Extremely confident
B. Somewhat confident
C. Confident
D. Not too confident
E. Not confident at all

Treatment of hemophilia: A balancing act

Factor Replacement Therapy Restores the Balance

Standard half-life products
Extended half-life products
Bypass with APCC/FEIBA, rVIIa
Substituting FVIII



Anti-TFPI
Fitusiran
Concizumab
Marstacimab

Non-Factor Replacement Therapies In Development To Restore Balance

Gene therapy **Emicizumab**

FEIBA = activated prothrombin complex concentrate

TFPI = tissue factor pathway inhibitor

Why Non-Factor Therapy?

Meera Chitlur, MD
Professor of Pediatrics, Central Michigan University College of Medicine
Barnhart-Lusher Hemostasis Research Endowed Chair
Wayne State University,
Director, Hemostasis Treatment Center and Special Coagulation Laboratory, Children's Hospital of Michigan

Dr. Chitlur began her presentation by commenting that *"hemophilia has been very challenging over time with the spontaneous bleeding that can occur into the brain, joints, muscles, as well as bleeding related to trauma or surgery. So, the problem with managing hemophilia primarily has been the burden of therapy…the burden of having to have venous access and prophylaxis requiring multiple infusions over a week, makes it very challenging for our patients to care for themselves."*

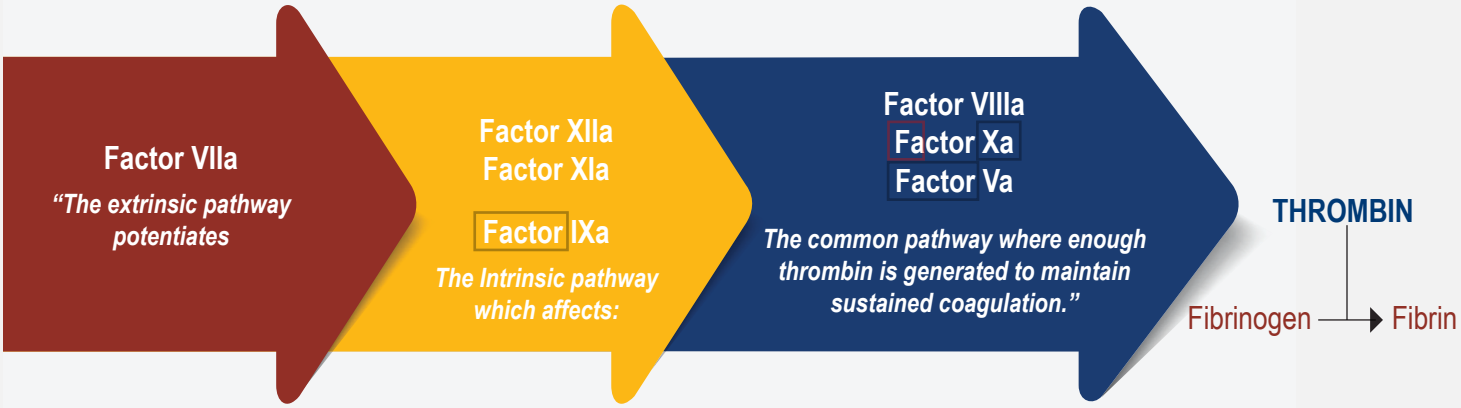
In her presentation: **Why Non-Factor Therapy?** Dr. Chitlur provided her perspective on the recent development of new non-factor replacement treatments [NFTs] that offer therapeutic alternatives for PwH, with or without inhibitors, providing an opportunity for steady-state hemostatic control without exposure to immunogenic clotting factor proteins. "So, when we are talking about the changing landscape of hemophilia, it is very important for providers, when we have all these choices, to pay close attention to how we determine what the best treatment for our patients is."

ECM: Dr. Chitlur, please comment on the coagulation process from your perspective on the changing hemophilia treatment landscape.

"The Coagulation 'process' is a circle."
– Meera Chitlur, MD

NFTs: Rebalancing Pro- and Anticoagulant Inhibitor Pathways to Sustain Coagulation

NFTs rebalance pro- and anticoagulant inhibitor pathways to generate enough thrombin to maintain coagulation.



Adapted from Zhao, Y et al. Pediatr Blood Cancer. 2021 May; 68(5): e28934

Dr. Chitlur: *"I essentially look at the coagulation process as a circle rather than a cascade. It starts with the extrinsic pathway, which then potentiates the intrinsic pathway, and you end up with enough thrombin generation to maintain coagulation. Having a good understanding of this is extremely important for us to then understand what we are trying to inhibit."*

"Rebalancing therapies restore the hemostatic capacity in the blood, mainly inhibiting different natural anticoagulant pathways, establishing the hemostatic balance even in the absence of FVIII or FIX and the presence of inhibitors."

Editor's note: The U.S. FDA approved marstacimab-hncq, a tissue factor pathway inhibitor, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A [congenital factor VIII deficiency without factor VIII [FVIII] inhibitors, or hemophilia B [congenital factor IX deficiency] without factor IX [FIX] inhibitors on October 11, 2024. Marstacimab-hncq is a new type of drug that, rather than replacing a clotting factor, works by reducing the amount, and therefore, the activity of, naturally occurring anticoagulation protein called tissue factor pathway inhibitor [TFPI]. This increases the amount of thrombin that is generated, and therefore reduces or prevents the frequency of bleeding episodes. This agent is the first and only anti-tissue factor pathway inhibitor [anti-TFPI] approved in the U.S. for the treatment of hemophilia and the first non-factor replacement agent approved in the U.S. to be administered subcutaneously via a pre-filled, auto-injector pen. [Source: US FDA News Release, October 11, 2024]

KNOWLEDGE CHECK

The development of these new therapeutic agents that act by enhancing coagulation and inhibiting anticoagulant pathways promises to improve the way hemophilia is treated. Which of the following clinical issues is most important to you?

A. Structuring prophylaxis regimens with non-factor agents

B. Transitioning patients from factor-replacement therapies to non-factor replacement therapies

C. Treating PwH with inhibitors with non-factor replacement therapies

D. Break-through bleeding with non-factor replacement therapies

E. Muscle bleeds while on non-factor replacement therapies

ECM interviewed Dr. Sidonio about the role of thrombin generation in the management of hemophilia.

Robert Sidonio, Jr, MD MsC
Associate Professor of Pediatrics
Hemophilia of Georgia Center for Bleeding and Clotting Disorders at Children's Healthcare of Atlanta, GA.

Dr. Sidonio: *"Thrombin plays an essential role in achieving and maintaining effective hemostasis and stable clot formation. A correlation has been found between the bleeding phenotype of PwH and the extent of thrombin generation [TG}, with individuals with increased TG being protected from bleeding and those with lower TG having increased bleeding tendency. The goal of all hemophilia therapies is to enhance TG with the aim of restoring effective hemostasis and preventing or controlling bleeding."*

In his presentation: "Practical Considerations and Challenges Associated with Emicizumab", Dr. Sidonio focuses on several issues that were recently discussed at the World Federation of Hemophilia meeting in which his publication about 'Unresolved Hemostasis Issues in Haemophilia" points out that the main goal of FVIII is to mediate thrombin generation at the site of the injury. "More recent data indicates that there is likely a role of FVIII that goes beyond just hemostasis, and that includes its role in bone mineral density, the formation of blood vessels, and immune function, specifically macrophages, some role in vascular function, and potentially a role in inflammation as it comes with diseases, and we know that there's wide-spread expression in multiple tissues."

ECM: Dr. Sidonio, you have shown that there are functions of FVIII beyond its established role as a coenzyme to FIXa to expedite thrombin generation. As hemophilia treatment shifts to non-factor replacement alternatives, will clinicians consider these extra-hemostatic roles when deciding on therapies for their patients?

Dr. Sidonio: *"Yeah, I think that right now, the benefits of non-factor therapies outweighed some of these theoretical concerns about the extra-hemostatic roles of FVIII and then, more recently, as you start to see more extended or ultra long FVIII products, it really has been shifted. And, really the consideration has mostly been about convenience."*

Another issue discussed by Dr. Sidonio is the dramatic increase in the number of muscle bleeding events in hemophilia A patients on emicizumab. Dr. Sidonio raises several hypotheses as to why increased muscle bleeds are observed in these patients.

"Is it possible that there's poor adherence to emicizumab? Certainly, we have patients who have skipped more doses than we would have expected.

Untreated bleeds in individuals treated with standard prophylaxis in the noninterventional study (NIS) followed by emicizumab in HAVEN 1-3

Untreated Bleeds (%)		
	Cohort C: Adults/adolescents without FVIII inhibition	
Prophylaxis	**FVIII (n = 48)**	**Emicizumab (N= 48)**
Total No. of Bleeds	74	150
Location		
Joint, n (%)b	45 (60.8)	21 (14.0)
Knee	12 (26.7)	5 (23.8)
Elbow	9 (20.0)	1 (4.8)
Ankle	13 (28.9)	13 (61.9)
Other	11(24.4)	2(9.5)
Muscle, n (%)b	16.(21.6)	74 (49.3)

Adapted from Callaghan et al. RPTH. 2022; 6:e12782

It's possible this has altered the way the bleeding event happens. And, so they're not recognizing the bleeding event as they would have on FVIII. But one of the other theories we are exploring is this idea of reducing thrombin generation at sites of injury."

Dr. Sidonio elaborated on biomolecular studies in murine models created to explain blood clots at **the site of muscle injury**: Indirectly, this work explained how Factor VIII plays more of a role in coagulation at the site of muscle injury than previously understood. He explains that myosin released during injury enhances prothrombinase activity on the surface of the injury, thereby initiating **enhanced** thrombin generation at the site of muscle injury. As Dr. Sidonio elucidates "If you don't have Factor VIII there, you may be missing out on this extra location of improved hemostasis." Also, myosin may provide a surface for vWF binding, facilitating FVIII delivery to the injury site. In this way, myosin, vWF, and Factor VIII are intertwined in stimulating coagulation at the site where the muscle is injured. Thus, thrombin generation is **augmented by the presence of Factor VIII** in the patients' system.

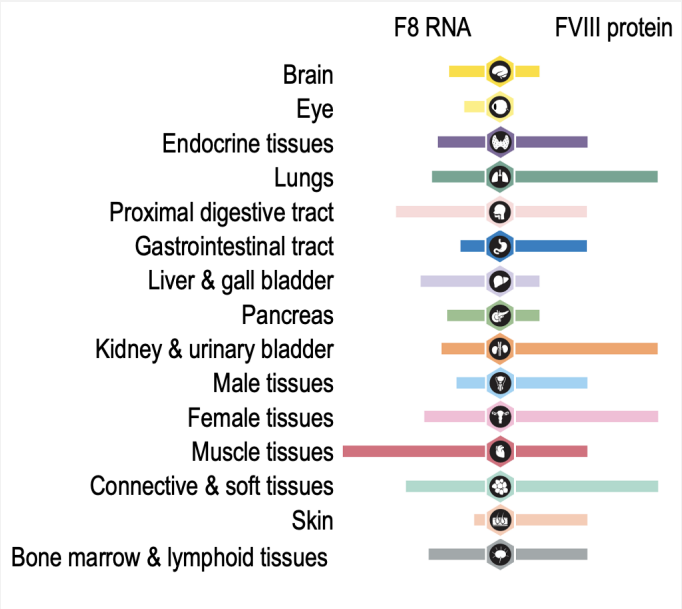
Dr. Sidonio added that skeletal muscle myosin [SkM] may play a key role in muscle bleeds. *"Myosin may indirectly accelerate thrombin generation by providing a surface for vWF binding."*

Reductively then, when patients are not routinely being infused with Factor VIII for their prophylactic therapy for Hemophilia A - and are receiving emicizumab - they have lost this 'back-up system' of coagulation to compensate for muscle injury. This may be an additional explanation as to why experienced hemophilia clinicians are observing increased muscle bleeds in patients treated with emicizumab.

Additionally, Dr. Sidonio analyzed the fact that **untreated muscle bleeds were in much higher percentages** than untreated *joint bleeds* in a retrospective analysis of the HAVEN 1-3 trials. In analyzing this data, Dr. Sidonio observes that in HAVEN 1-3, clinician-researchers had a high threshold for treatment intervention in muscle bleeds – but he reminds us; "…muscle bleeds can contribute to long-term disability in hemophilia patients." Taking all these factors into consideration, in this clinical setting, Dr. Sidonio recommended vigilance for muscle bleeds and subtle long-term soft-tissue joint events in patients receiving non-factor prophylactic therapy. He suggests ongoing observation of these potential complications can foster dialogue and consensus from hemophilia-treatment communities. And he notes, for certain subsets of patients,

Potential roles of FVIII beyond hemostasis

F8 mRNA and FVIII protein show widespread expression in multiple tissues*



Hemophilia patients show disruptions in:

Bone metabolism – Lower bone mineral density (BMD)

Angiogenesis – Abnormal vascular remodeling in damaged joints not seen in other joint conditions

Macrophage function – Disrupted macrophage differentiation and debris clearance

Vascular function – Dysfunctional endothelial activity and higher prevalence of hypertension

Inflammation – Changes in both acute and chronic inflammation serum markers

*Adapted from the Human Protein Atlas.1

1. Human Protein Atlas https://www.proteinatlas.org/ENSG00000185010-F8/tissue, accessed 22.11.2022; 2. Hua B et al. Haemophilia 2017; 23: e294-300; 3. Holstein K et al. Ann Hematol 2020; 99:1531-42; 4. Bhat V et al. Am J Hematol 2015; 90:1027-35; 5. Knowles LM et al. Thromb Haemost 2019; 119:234-45; 6. Sartori MT et al. Haemophilia 2008; 14:1055-62; 7. Böhmert S et al. Hämostaseologie 2019; 39:195-202; 8. Barnes RFW et al. Int J Hypertension 2016; 2016:2014201; 9. Samuelson Bannow B et al. Blood Rev 2019; 35:43-50.

consideration for concomitant, ongoing Factor VIII therapy is warranted.

In the final chapter of this presentation, Dr. Singleton summarized the proceedings of this virtual symposium on providing comprehensive hemophilia care in the era of non-factor therapies:

- We have explored the evolving hemophilia treatment landscape as well as the clinical rationale for utilizing non-factor therapeutic options
- Additionally, we discussed the clinical and patient management challenges associated with the development of these newer options based on our perspectives on rebalancing the coagulation cascade
- And, we have reviewed the issues of both patient and caregiver disease burden as well as concepts for improved HRQoL and outcomes

To access the above free, accredited virtual symposium, please click here.

KNOWLEDGE CHECK

When employing non-factor therapies [NFTs] for PwH, clinicians can:

A. Monitor patients by measuring aPTT levels weekly

B. Attain steady-state factor VIII levels

C. Achieve significantly lower annualized bleeding rates [ABRs], compared with standard of care

D. Use any current and emerging NFTs in both hemophilia A and B

E. None of the above

See correct answer below.

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About BloodMedEd.com

BloodMedEd.com is a dedicated website focused on sharing information and creating awareness about bleeding disorders, hematologic malignancies, and other related diseases treated by hematology/ oncology practitioners.

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When employing non-factor therapies [NFTs] for PwH, clinicians should: choose answer C.

Explanation: In a pooled analysis of long-term results from Haven 1-4 Phase 3 studies of emicizumab prophylaxis [PPX] in PwHA, patients receiving emicizumab demonstrated significantly reduced ABRs, with large percentages of participants [70.8-82.4%] demonstrating zero treated bleeds. After week 24, at least 97% of participants demonstrated less than or equal to 3 bleeds.

For more on this subject, go to our web-based CME/CE-accredited virtual symposium currently available at https://www.mycme.com/courses/hemophilia-care-in-the-era-of-non-factor-therapies-9739