

# CASE CHALLENGES IN HEREDITARY ANGIOEDEMA:

*Innovative Therapeutic Strategies for a Normal Life*

Expert Panel Discussion Featuring a Patient





# An Overview of HAE: Diagnosis, Treatment, and Emerging Therapies

**William R. Lumry, MD**

*Clinical Professor, Internal Medicine*

University of Texas Southwestern Medical School

Dallas, TX



# Characteristics of Major Types of Angioedema



	<b>Mast-cell mediated or allergic</b>	<b>Bradykinin mediated or non-allergic</b>
<b>Onset</b>	Minutes to hours	Hours
<b>Urticaria</b>	+	-
<b>Pruritis</b>	+	-
<b>Pain/burning</b>	-	May be present
<b>Response to Epi or antihistamine</b>	+	-
<b>Response to steroids</b>	+	-

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# Pathophysiology and Epidemiology of HAE-C1INH



- **Cause** | Deficiency (Type 1) or dysfunction (Type 2) of C1 esterase inhibitor with dysregulation of contact/kinin pathway resulting in increased bradykinin production with localized vasodilation, vascular leak, and swelling
- **Estimated Prevalence** | Difficult to ascertain due to under recognition and under diagnosis
  - Autosomal dominant inheritance with near complete penetrance
  - Estimated - 1 in 30,000 to 1 in 80,000; 7,000 in the United States and 300,000 Worldwide
  - No known ethnic or gender differences
- **Average attack frequency** | One episode per 2-week period
- **Highly variable severity**
  - Between patients and within families (same mutation!)
  - No simple relationship between disease severity and C1 esterase inhibitor (C1-INH) level



# Erythema Marginatum

Photo courtesy of Lumry, ACAAI 2011

# Extremity Attacks



Affects 96% of patients



Functionally disabling

- Hands: Difficulty driving, typing, phone use
- Feet: Impedes walking, standing



Interferes with work and school



Rarely results in hospitalization



# Abdominal Attacks

- Occur in 93% of patients with HAE
- Mild-to-severe colicky pain
- Vomiting common; constipation/diarrhea may occur
- Functional intestinal obstruction
- Fluid loss may lead to hemoconcentration and hypovolemic shock
- Protuberant abdomen, tenderness, and rebound possible
- Symptoms mimic surgical emergencies, resulting in misdiagnosis and unnecessary surgery



Edematous  
Ileum



Normal  
Ileum

# Laryngeal Attacks

- Occur in ~50% of patients
- Require airway monitoring and management
- Survey of 58 patients with HAE
  - 40% incidence of asphyxiation in untreated laryngeal attacks



Photos courtesy of Lumry, ACAAI 2011

# Quality of Life and Disease Assessment Tools for Angioedema



## HAE-C1-INH

HAE Activity Score

HAE QoL

US HAEA-QoL

## Recurrent Angioedema

Angioedema Control  
Test

Angioedema QoL

Angioedema  
Activity Score

## General Health

SF-36

EuroQol  
5-Dimensions Survey

# Quality of Life Assessment Tools for HAE



## HAE Activity Score<sup>1</sup> Disease Severity/Control Snapshot

- Asks about: Number of attacks, emergency room visits, psychological/psychiatric treatment, absenteeism, general health, and impairment in everyday activities due to pain
- Primary Focus: Frequency and severity of attacks and their impact on daily activities

## HAE-QoL<sup>2</sup> Broad QoL Assessment

- Domains: Physical functioning, role functioning, bodily pain, general health, vitality, social functioning, emotional role, mental health, and health transition
- Focus: Comprehensive evaluation

## US HAEA QoL<sup>3</sup> US-Specific Tool

- Domains: Work, school, social, family, and physical activities, access to and burden of HAE treatment
- Focus: Tailored to the US patient population, addressing specific challenges, and treatment burdens faced by these patients

1. Forjaz MJ, et al. *J Investig Allergol Clin Immunol*. 2021;31(3):246-252; 2. Prior N, et al. *Health Qual Life Outcomes*. 2012;10:82;  
3. Castaldo AJ, et al. *Ann Allergy Asthma Immunol*. 2024;133(6):703-711.

# Domains and Items in the US HAEA QoL

## Access

- Having access to your HAE medications in case you need to treat an attack (carrying medication)
- Lack of access to medication during an attack (treatment)
- Being able to afford the cost of medication
- Healthcare payer denying you treatment
- That manufacturers will no longer make medications that you need

## Activities

- Your mental energy
- Your sleep
- Your physical energy
- Your ability to travel
- Your job, schoolwork, or other commitments
- Getting things done at home
- Doing activities for fun
- Enjoying life
- Exercise
- Being active

## Embarrassment

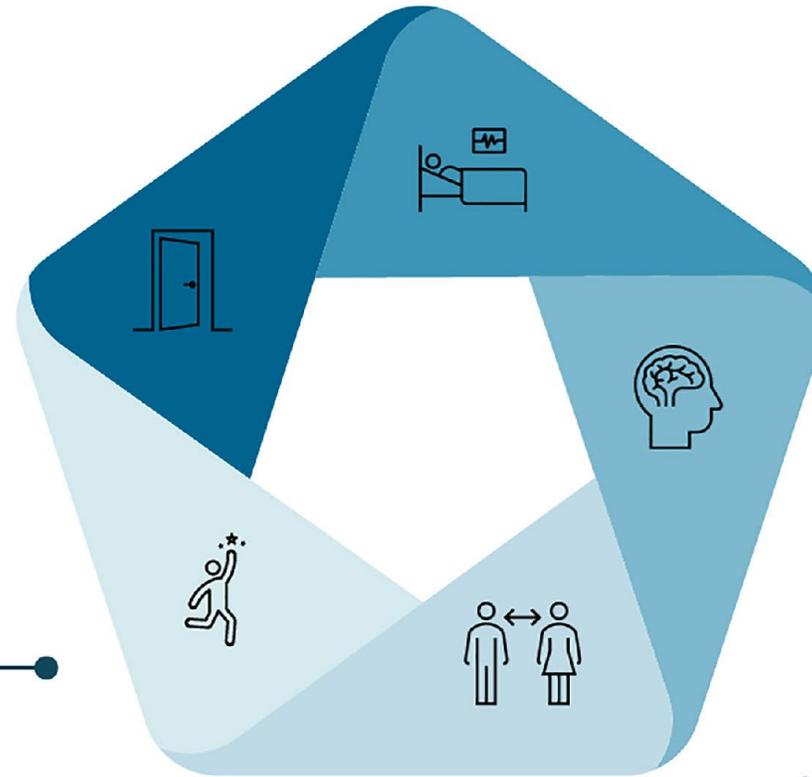
- That others will look at you when you are experiencing excessive swelling
- Willingness to go out in public

## Worries

- That doctors/nurses taking care of you do not understand HAE
- Lack of understanding of HAE from people around you
- Passing HAE onto your children
- Your actions or behavior triggering an attack
- That your HAE attacks will get worse in the future
- Suffering pain from HAE attacks
- Serious HAE attack where you would need to go to the emergency room
- Dying during an HAE attack
- HAE treatment will have side effects

## Feelings

- Your mood
- Feeling anxious or fearful
- Feeling depressed
- How you feel about yourself
- Feeling isolated or lonely



# Questions to Ask to Assess HAE Burden



Are there any **activities that you avoid** because of your HAE?

How **often** do you **experience HAE attacks**?

How would you describe the **severity** of your HAE attacks?

How often does HAE cause you to **miss work**, school, or activities at home?

How often do you have to **use acute rescue medication** for each HAE attack and do you feel that you respond well?

What is the **average time from attack onset to treatment administration**?  
Time to initial symptom relief? Time to complete resolution of symptoms?

Have you had any **changes in life status** that may affect the activity of your HAE?

How often do you experience **fear/anxiety/depression** associated with your HAE?

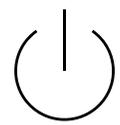
Have you had any **difficulties accessing or administering** your acute or prophylactic HAE **treatment**?

To what extent has HAE interfered with your **social life, family, relationships, or physical activities**?

How often have you had to visit the **hospital** for an HAE attack?

Have you made any **lifestyle modifications to avoid triggers**?

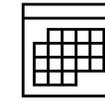
# Therapy for HAE



## On-Demand Treatment



## Short-Term Prophylaxis



## Long-term Prophylaxis

### Resolve

symptoms as quickly as possible during an attack

### Reduce

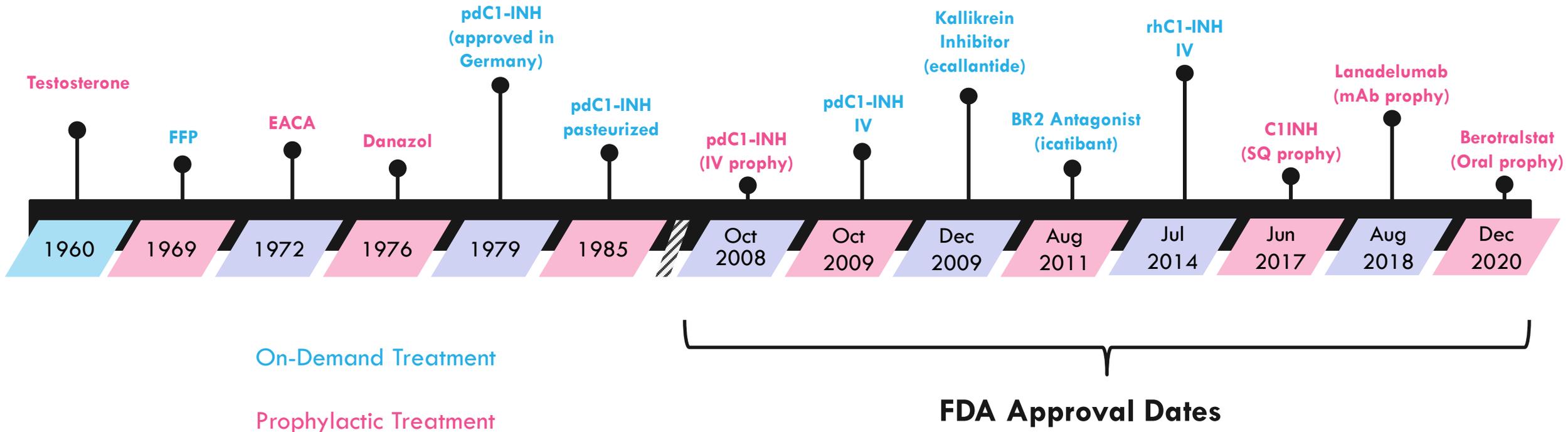
likelihood of swelling in response to **anticipated events** likely to precipitate attack (eg, medical/dental procedures)

### Decrease

overall number and severity of attacks

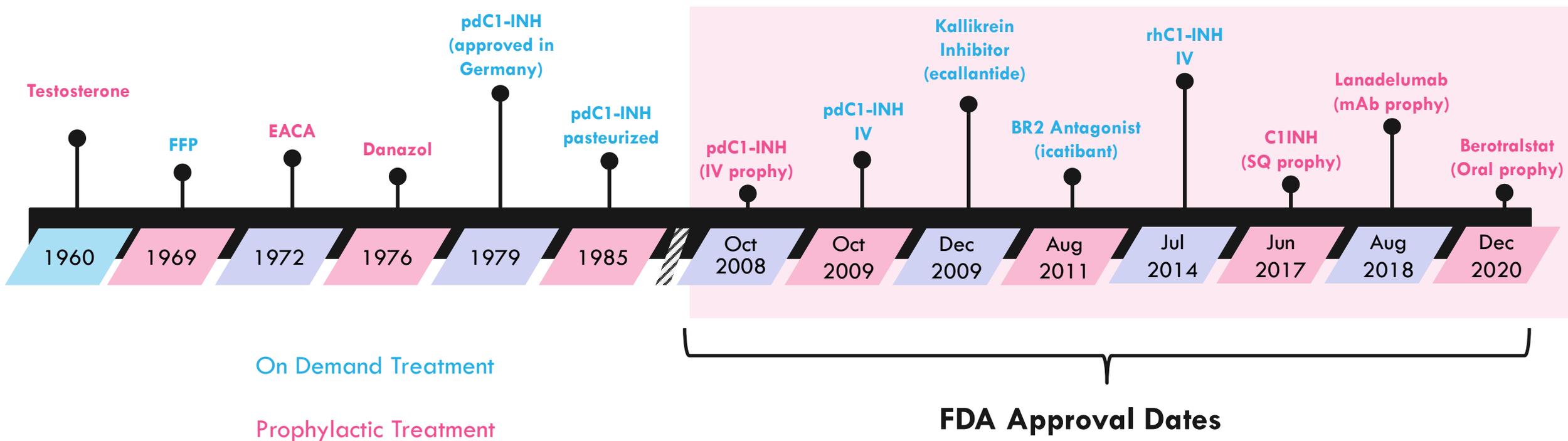
**Individualized Management Plan /  
Shared Decision Making**

# HAE Therapy Timeline



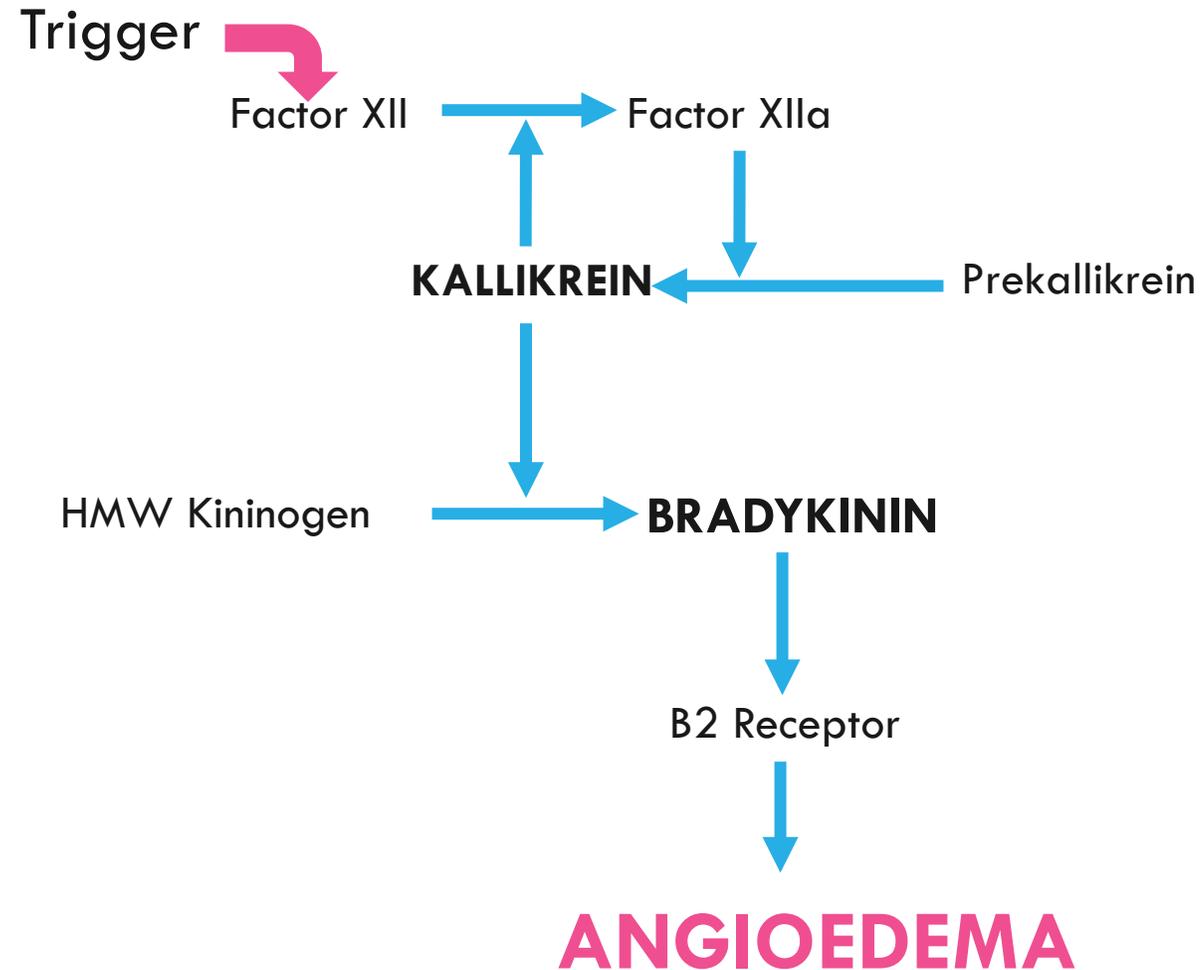
Cicardi M, et al. *J Allergy Clin Immunol*. 1997;99(2):194-196; Siles R. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/hereditary-angioedema/>. Published December 2017. Accessed June 2, 2020; Riedl M, et al. *The Lancet*. 2018;391(10128):1356; Gidaro A, et al. *J Allergy Clin Immunol*. 2017;139(2):AB237; Riedl, M. *Ann Allergy Asthma Immunol*. 2015;114(4):281-288; Lee, A. *Drugs*. 2021;81(3):405-409.

# HAE Therapy Timeline

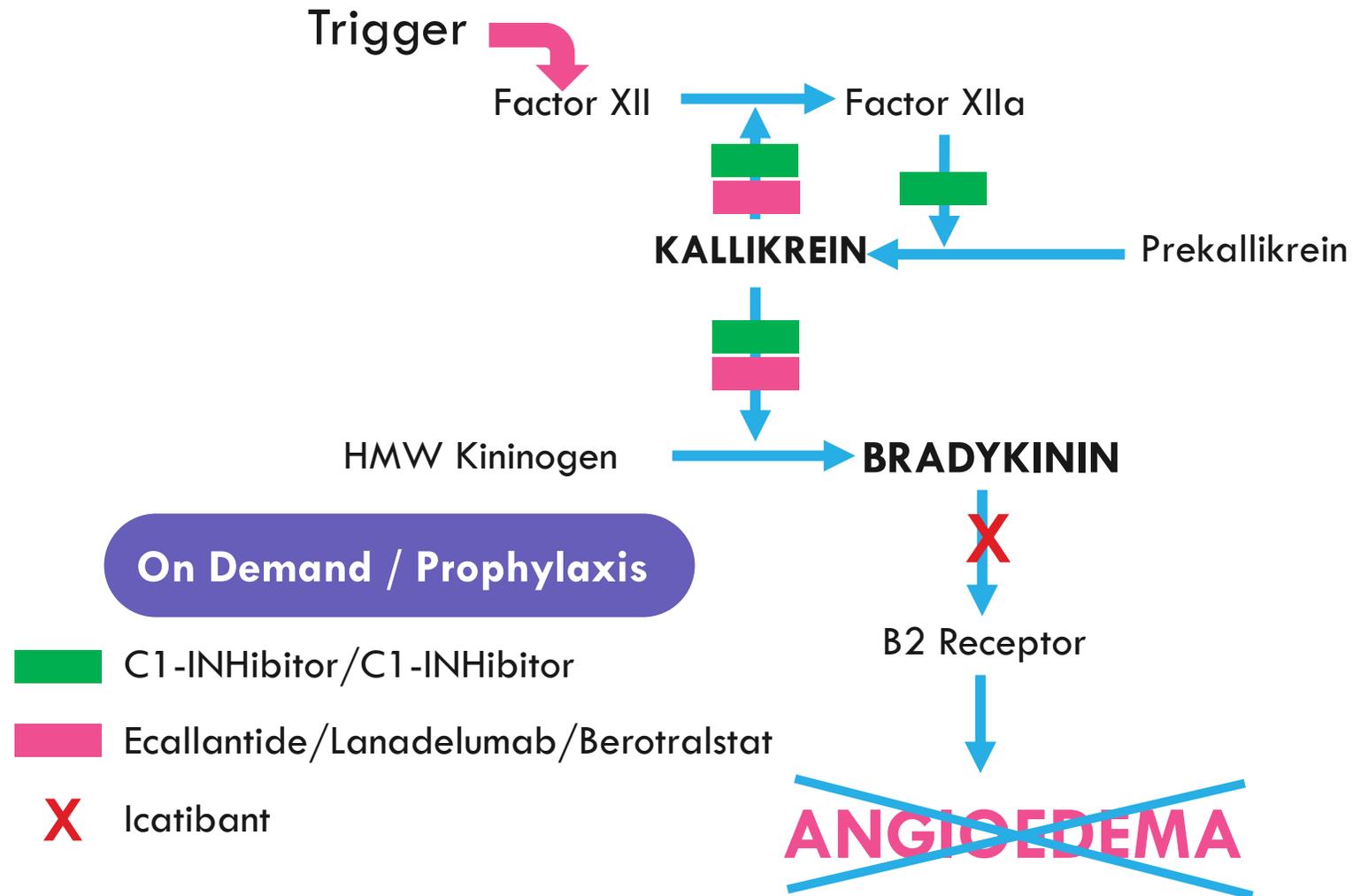


Cicardi M, et al. *J Allergy Clin Immunol*. 1997;99(2):194-6; Siles R. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/hereditary-angioedema/>. Published December 2017. Accessed June 2, 2020; Riedl M, et al. *The Lancet*. 2018;391(10128):1356; Gidaro A, et al. *J Allergy Clin Immunol*. 2017;139(2):AB237; Riedl, M. *Ann Allergy Asthma Immunol*. 2015;114(4):281-8; Lee, A. *Drugs*. 2021;81(3):405-409.

# Contact/Kinin Cascade



# Contact/Kinin Cascade



# Recommendations for Treatment of Attacks



## On-Demand Therapy



Patients with HAE should have therapy available for treating an acute attack: **C1-INH inhibitor, Ecallantide, Icatibant**

## Carry 2 Doses



Patients should have 2 doses of on-demand therapy with them and be trained in self-administration

## Recognize and Treat



All attacks are eligible for treatment as soon as they are recognized

## Treat Early



Early treatment of attacks beneficial to reduce morbidity and complications

## Some Need 2 Drugs



Some patients use/require 2 on-demand medications with different MOA's

## Hospital Evaluation



Hospital evaluation is recommended for **laryngeal involvement** even after treatment

Cicardi M, et al. *Allergy*. 2012;67(2):147-157.

Craig T, et al. *World Allergy Organ J*. 2012;5(12):182-199.

Lang D, et al. *Ann Allergy Asthma Immunol*. 2012;109(6):395-402.

Betschel, et al. *Allergy Asthma Clin Immunol*. 2014;10:50.

Zuraw B, et al. *J Allergy Clin Immunol Pract*. 2013;1(5):458-467.

# Short-Term Prophylaxis of HAE



## Short-term Prophylaxis

Short-term prevention of an HAE attack (swelling)

## Triggers

- Oral/dental trauma
- Major surgical procedures (intubation)
- Other invasive surgical or medical procedures
  - Upper/lower endoscopy
  - Other procedures that traumatize tissue

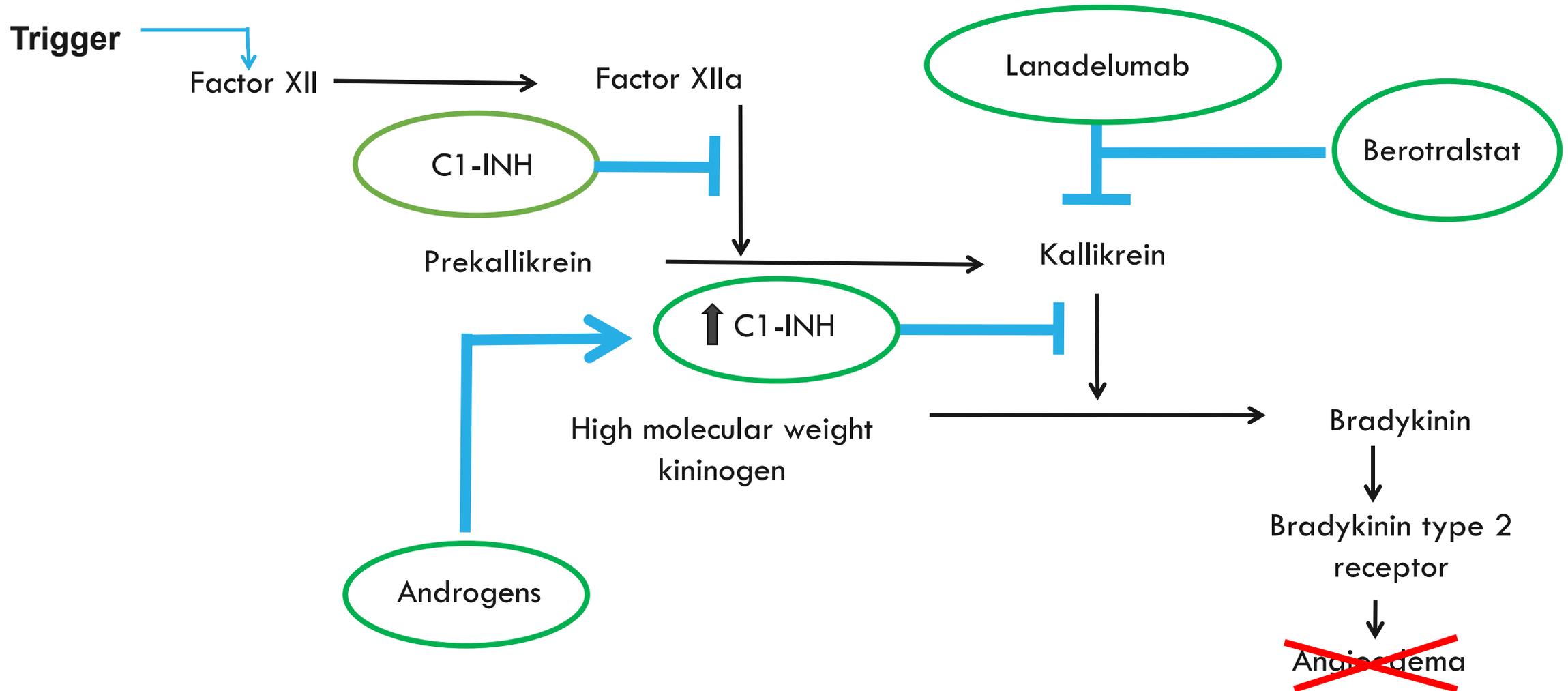
## Mechanism of Therapy

- Increase circulating C1 inhibitor
- C1 inhibitor concentrate
  - Attenuated androgen therapy
  - Fresh frozen plasma

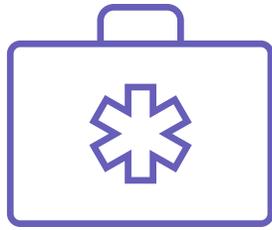
## Close Observation After Procedure

On-demand therapy on site

# Long-Term Prophylaxis of HAE | 2024



# New and Emerging Therapies for HAE



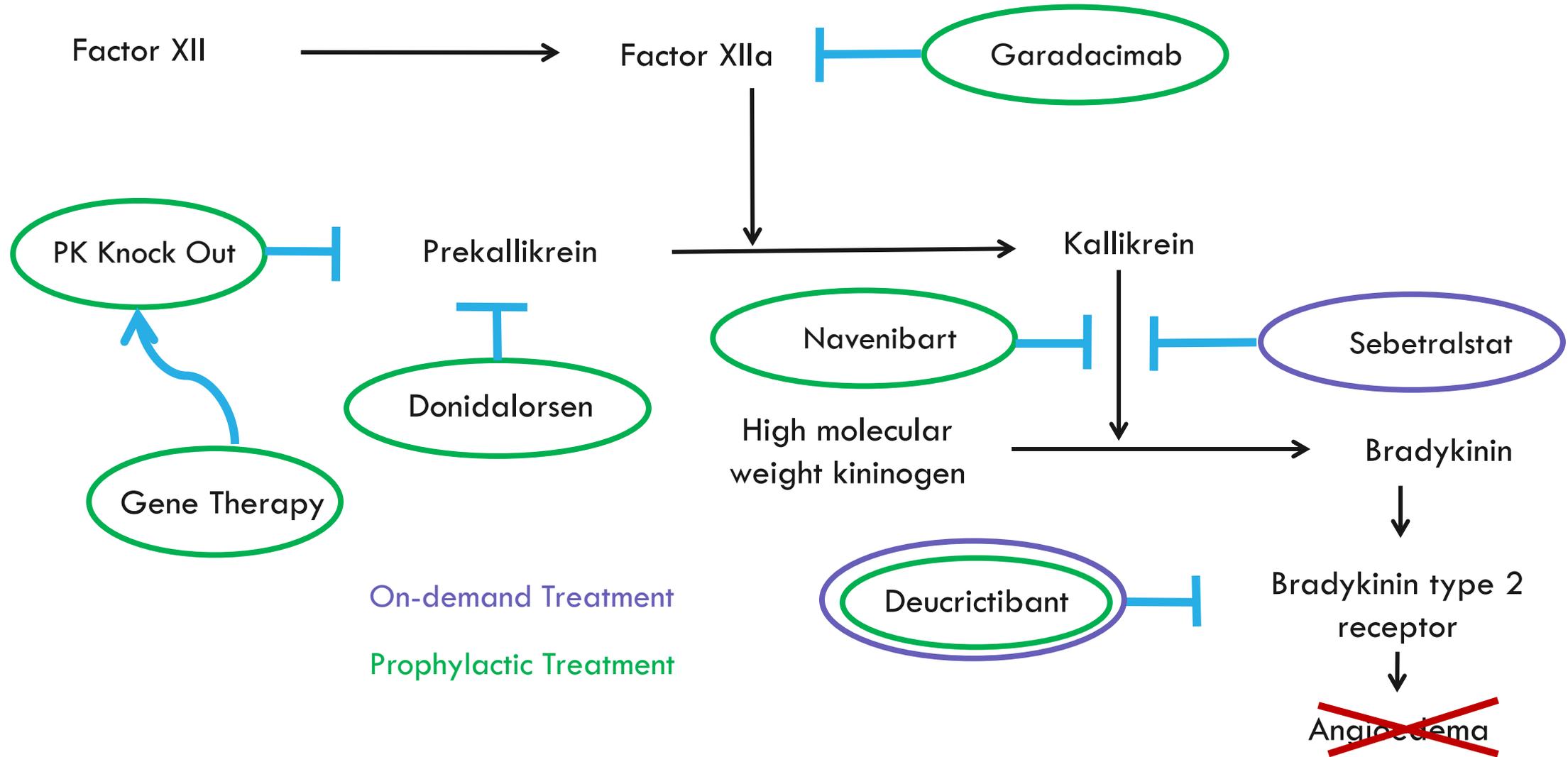
## Factors that will improve treatment

- Increased efficacy and safety
- Reduction in treatment burden
- Improved accessibility

## Innovations that may improve outcomes

- Targeted oral medications: On Demand and Prophylaxis
- Longer lasting prophylactic treatments
  - Modified Fc region longer lasting monoclonal antibodies
  - RNA interference therapies
- Gene therapy

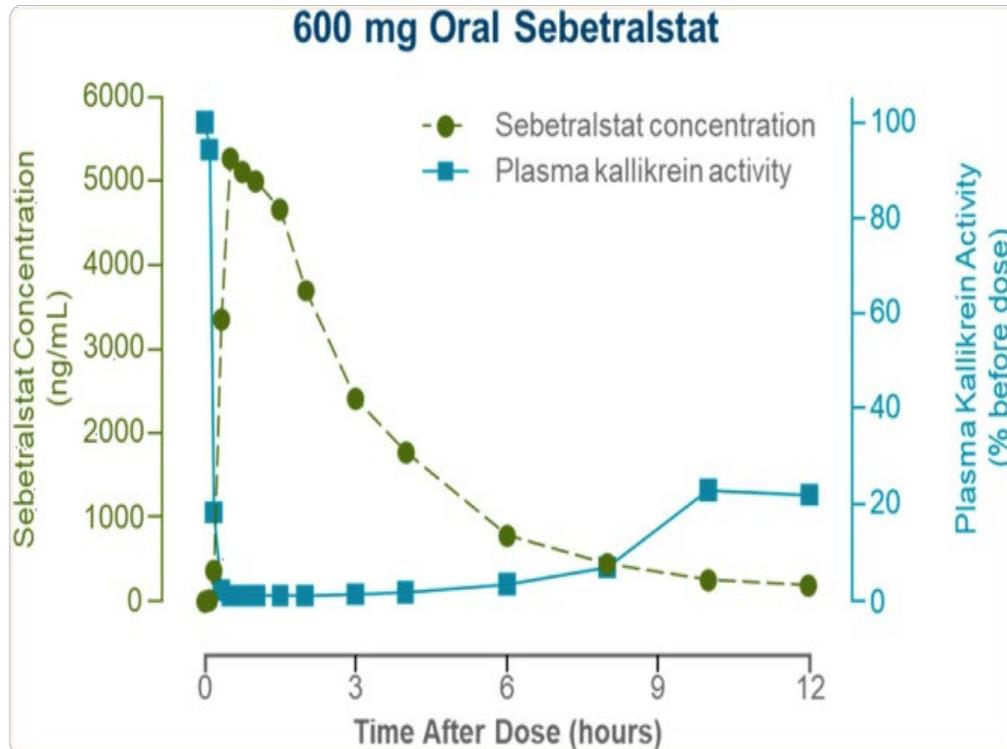
# HAE Therapy Pipeline | 2024



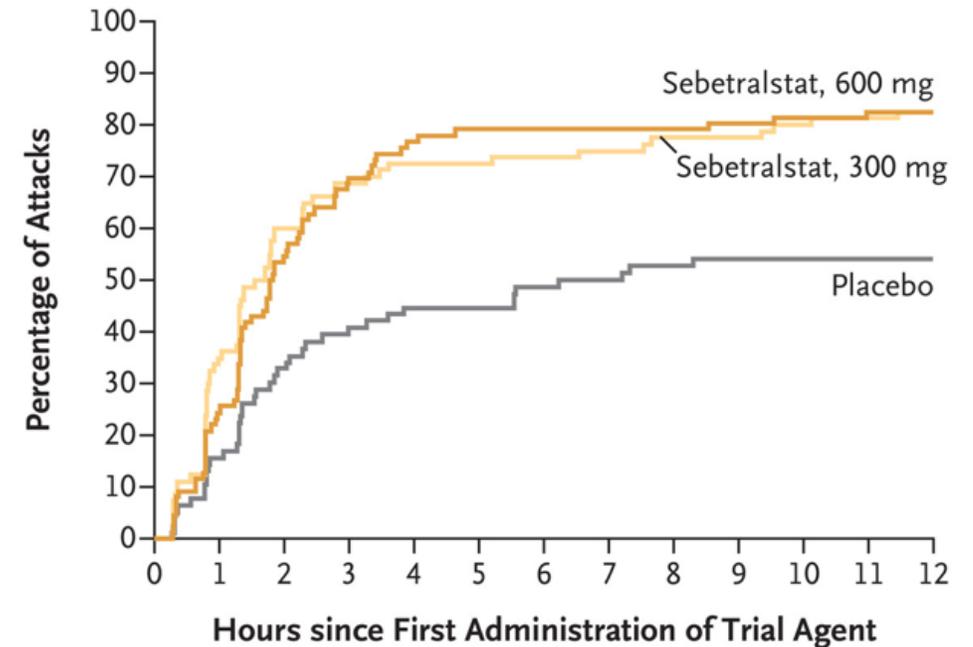
# On-Demand Therapy: Sebetralstat



Oral plasma kallikrein inhibitor | Rapidly absorbed | Quickly and significantly reduces attack symptoms



## Time to Beginning of Symptom Relief



### No. of Attacks

Sebetralstat, 600 mg	93	65	39	26	20	18	18	18	18	17	16	15	15
Sebetralstat, 300 mg	87	52	32	25	22	22	21	20	18	18	16	15	14
Placebo	84	64	51	45	42	42	39	38	36	35	35	35	35

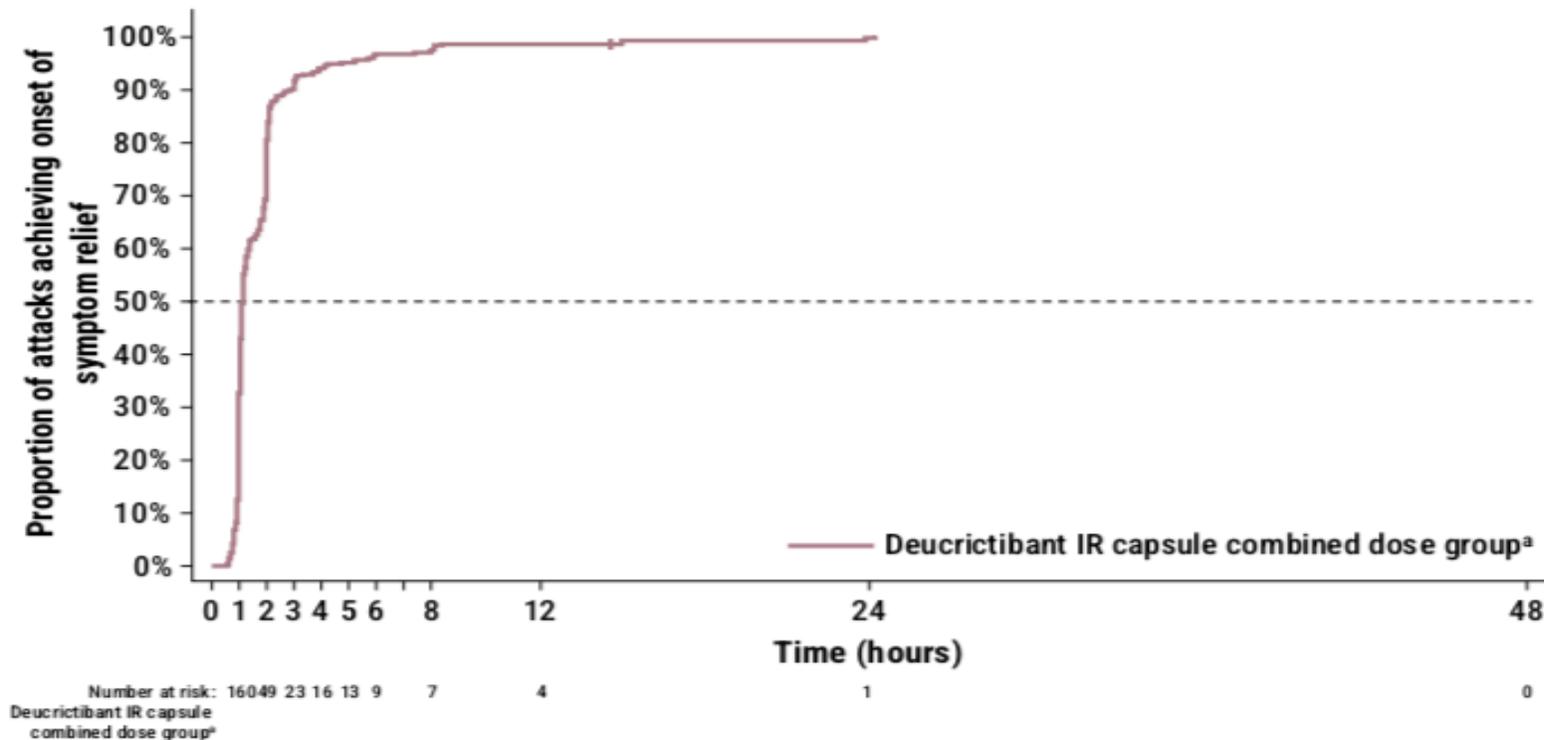
Davie RL, et al. *J Med Chem* 2022;65(20):13629-13644.  
 Aygören-Pürsün E, et al. *Lancet*. 2023;401(10375):458-469.  
 Riedl MA, et al. *N Engl J Med*. 2024;391(1):32-43.

# On-Demand Therapy: Deucricitibant



Oral bradykinin receptor antagonist | Rapidly absorbed | Quickly and significantly reduces attack symptoms

**Figure 3. Kaplan-Meier plot of time to onset of symptom relief**

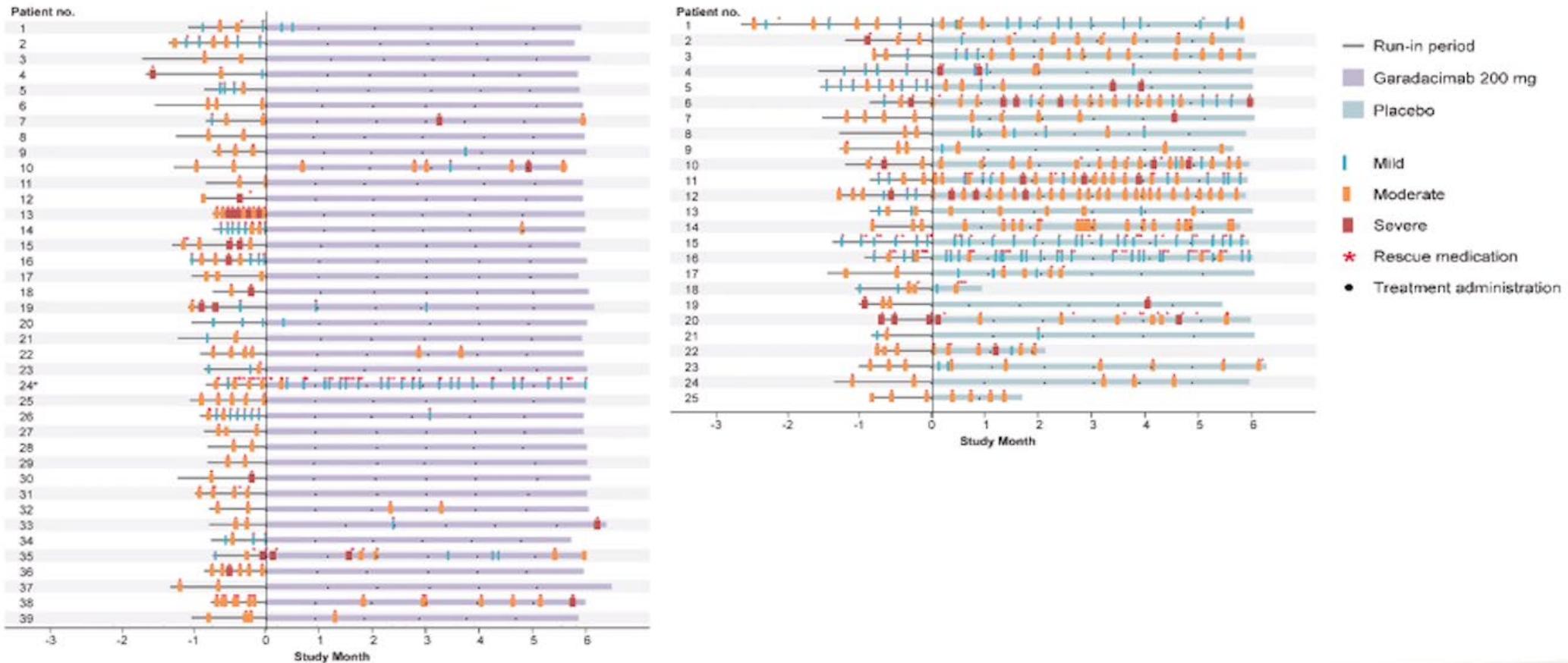


IR, immediate-release. <sup>a</sup>Includes 10 mg, 20 mg, and 30 mg dose groups.

# Prophylactic Therapy: Garadacimab

Factor XIIa antagonist monoclonal antibody | Lowers HAE attack frequency and severity

VANGUARD Phase 3 Study: Onset of HAE attacks, severity, and treatment with rescue medication during run-in and treatment period

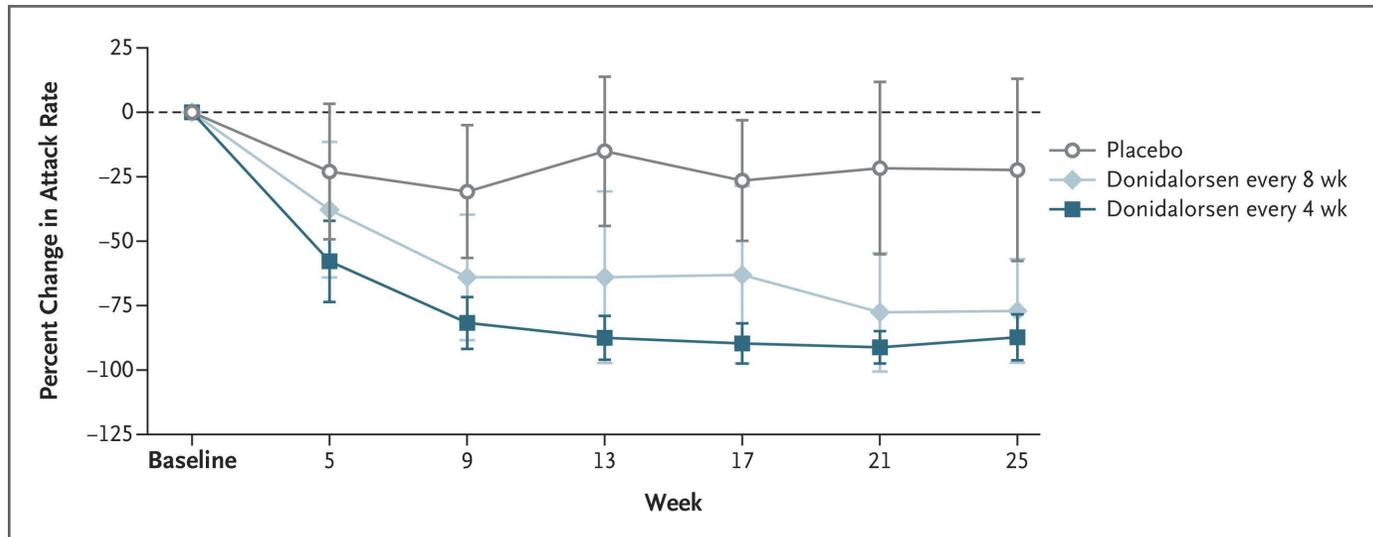


# Prophylactic Therapy: Donidalorsen

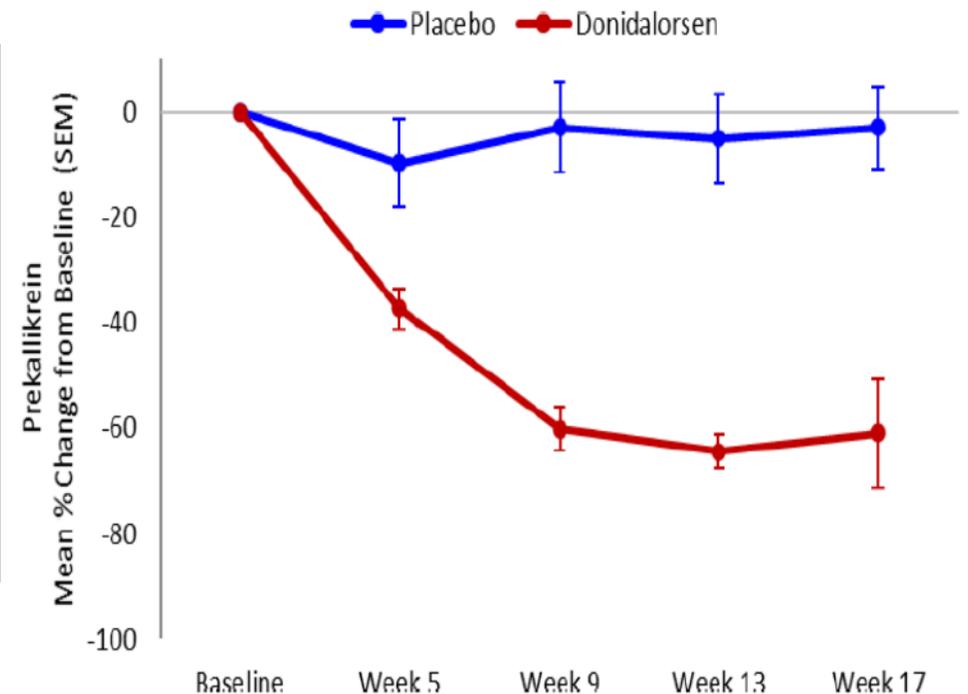


mRNA anti-sense oligonucleotide | Lowers prekallikrein production | Lowers HAE attack frequency and severity

### Change in HAE Attacks<sup>1</sup>



### Plasma Prekallikrein Levels<sup>2</sup>



1. Riedl MA, et al. *N Engl J Med.* 2024;391(1):21-31.  
2. Fijen LM, et al. *N Engl J Med.* 2022;17;386(11):1026-1033.

# Gene Therapy: NTLA-2002 CRISPER Cas9



Targets KLKB1 Gene Decreasing Plasma PreKallikrein Production | Decreases HAE Attack Frequency

## Eight of 11 Patients Were Completely Attack Free Following a Single 50 mg Dose



# Practical Takeaways



- HAE guidelines emphasize early diagnosis, an individualized treatment plan, prompt treatment of attacks, on-demand and prophylactic medications, and patient quality of life
- Most HAE specific treatments reduce bradykinin production or block the BK2 receptor that reduces vasodilation, vascular leak, and swelling
- Availability of oral on-demand and less frequent prophylactic treatments will lower burden of treatment

# Panel Discussion



# Lisa

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- Family history
- Diagnosis
- Life before treatment
- Life after treatment
- Challenges with treatment
- Pregnancy and children



# Case Studies in HAE: Overcoming Challenges and Improving Quality of Life

**Marc A. Riedl, MD, MS**

*Professor, Medicine*

*HAE Community Endowed Chair*

*Clinical Director, US HAEA Angioedema Center*

*Clinical Service Chief and Training Program Director*

*Division of Rheumatology, Allergy & Immunology*

*University of California, San Diego*

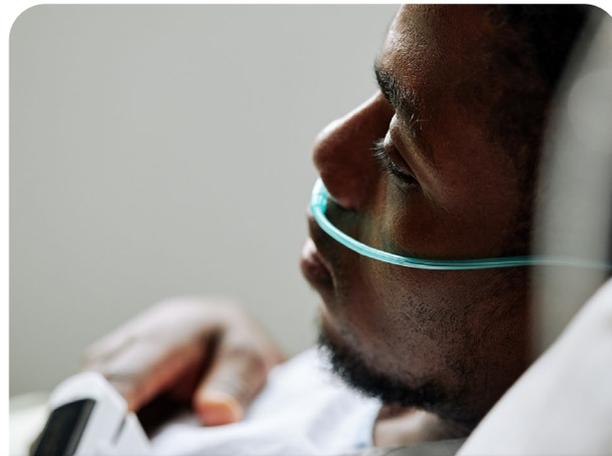
*San Diego, CA*



# Cases



Sarah



David



Maria



# Sarah's Frequent Attacks



Sarah



32-year-old woman  
with HAE

Experiences frequent  
abdominal attacks

Despite prophylactic  
therapy, she still suffers  
from unpredictable  
attacks every few  
weeks

Finds it difficult to  
adhere to medication  
due to side effects

Attacks disrupt her  
work and social life

Struggles with the fear  
of attacks and the  
uncertainty they bring,  
leading to significant  
anxiety and stress



Sarah



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Thoughts on Sarah's Case?

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Managing side effects

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Improving adherence

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Using QoL assessment tools in practice

# Lisa

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**Describe how HAE affected your life and mental health before you started treatment.**

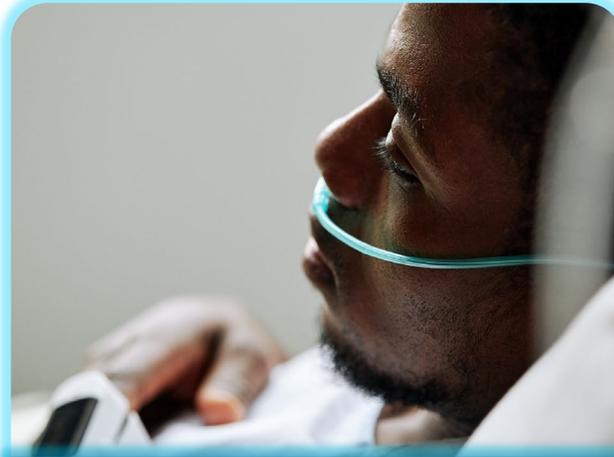
**Are providers doing enough to help address these challenges?**



# Cases



Sarah



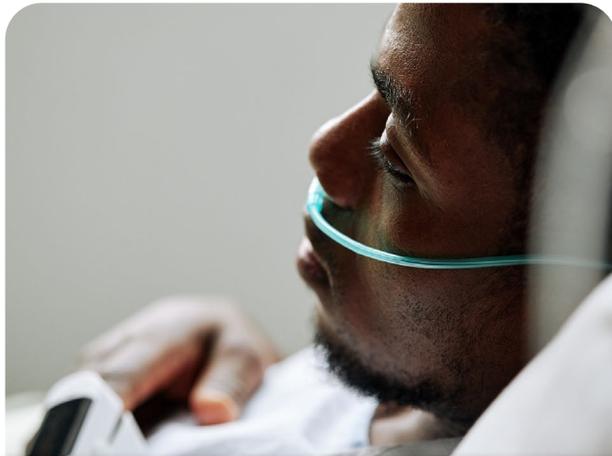
David



Maria



# David's Emergency Room Visits



David



25-year-old man with HAE

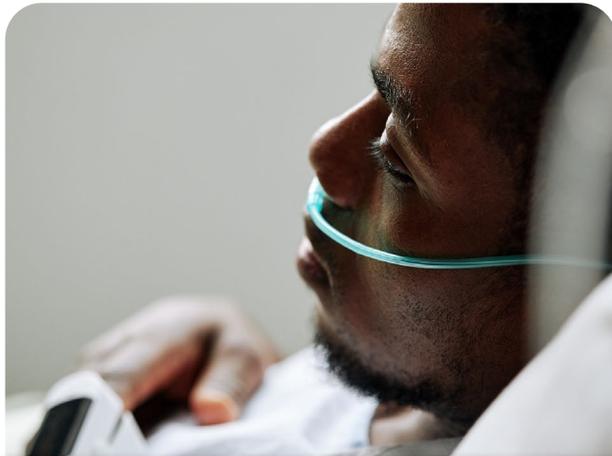
Often ends up in the emergency room due to laryngeal attacks

Despite carrying on-demand medication, he delays treatment, hoping the symptoms will resolve

Delay worsens symptoms and leads to emergency room visits

Finds it challenging to recognize severity of his attacks and administer appropriate treatment promptly

Faces difficulties accessing specialized care during emergencies, leading to prolonged hospital stays and increased costs



David



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Thoughts on David's Case?

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Patient Education: Recognizing attack severity

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Patient Education: When to administer on-demand medication

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Accessing specialized care during emergencies

Lisa

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**Describe how you recognize when it is time to use on-demand medication.**

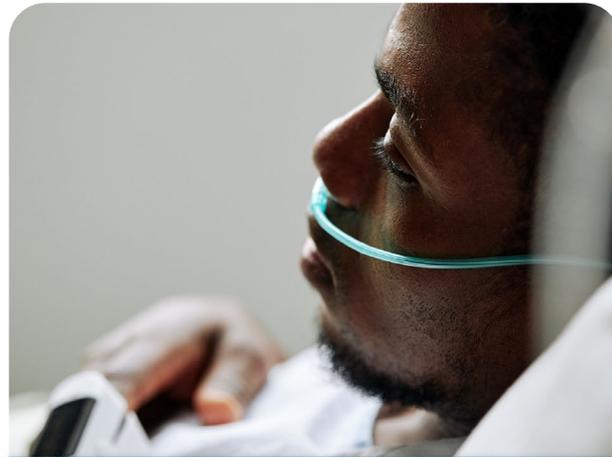
**What can providers do better to educate patients on this important matter?**



# Cases



Sarah



David



Maria



# Maria's Treatment Accessibility



Maria



40-year-old woman with HAE

Lives in a rural area with limited access to specialized healthcare

Struggles to find a local provider knowledgeable about HAE. Needs to travel for medical consultations and treatments

Challenges and delays with insurance coverage has led to inconsistent, unreliable medication access

Her frequent treatment gaps have led to increased severity and frequency of attacks

Feels isolated and unsupported in managing her condition due to lack of local resources and financial constraints



Maria



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Thoughts on Maria's Case?

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Strategies to address the lack of specialized services in rural areas

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Overcoming lack of coverage and treatment gaps

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Addressing isolation and lack of support for remote patients