HAE: Diagnosing, Treating, and Managing the Patient With Hereditary Angioedema

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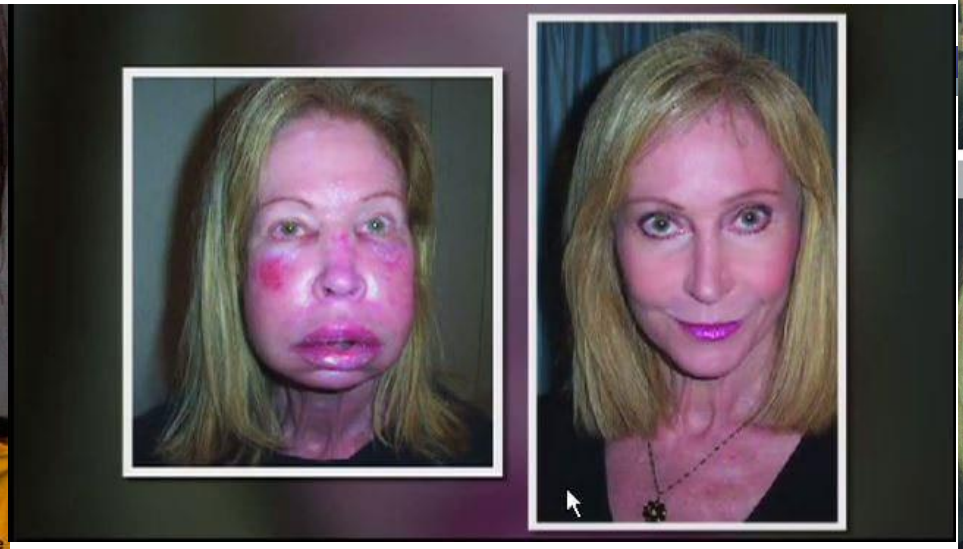
Honorary Board of Directors, Lam Dong Medical College

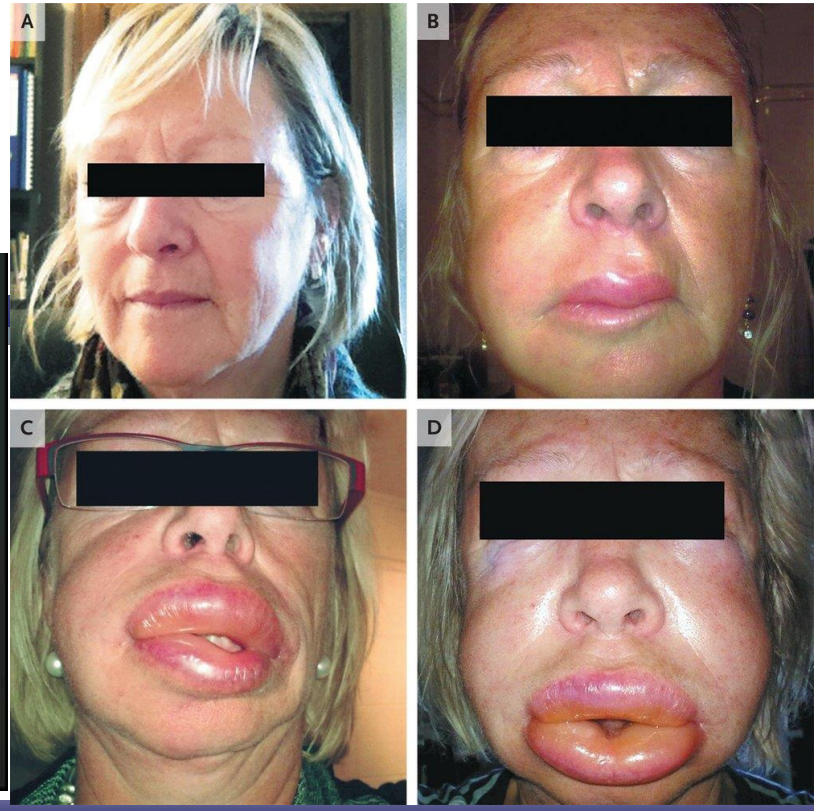
Conflicts Of Interest

Company	Research	Consultant	Speaker	Travel
CSL Behring	x	x	x	x
Ionis	x	x		
Takeda	x	x	x	x
Biocryst	x	x		x
BioMarin	x	x		
Kalvista	x	x	x	
Pharvaris	x	x		
Intellia	x	x		
Astria	x	x	x	

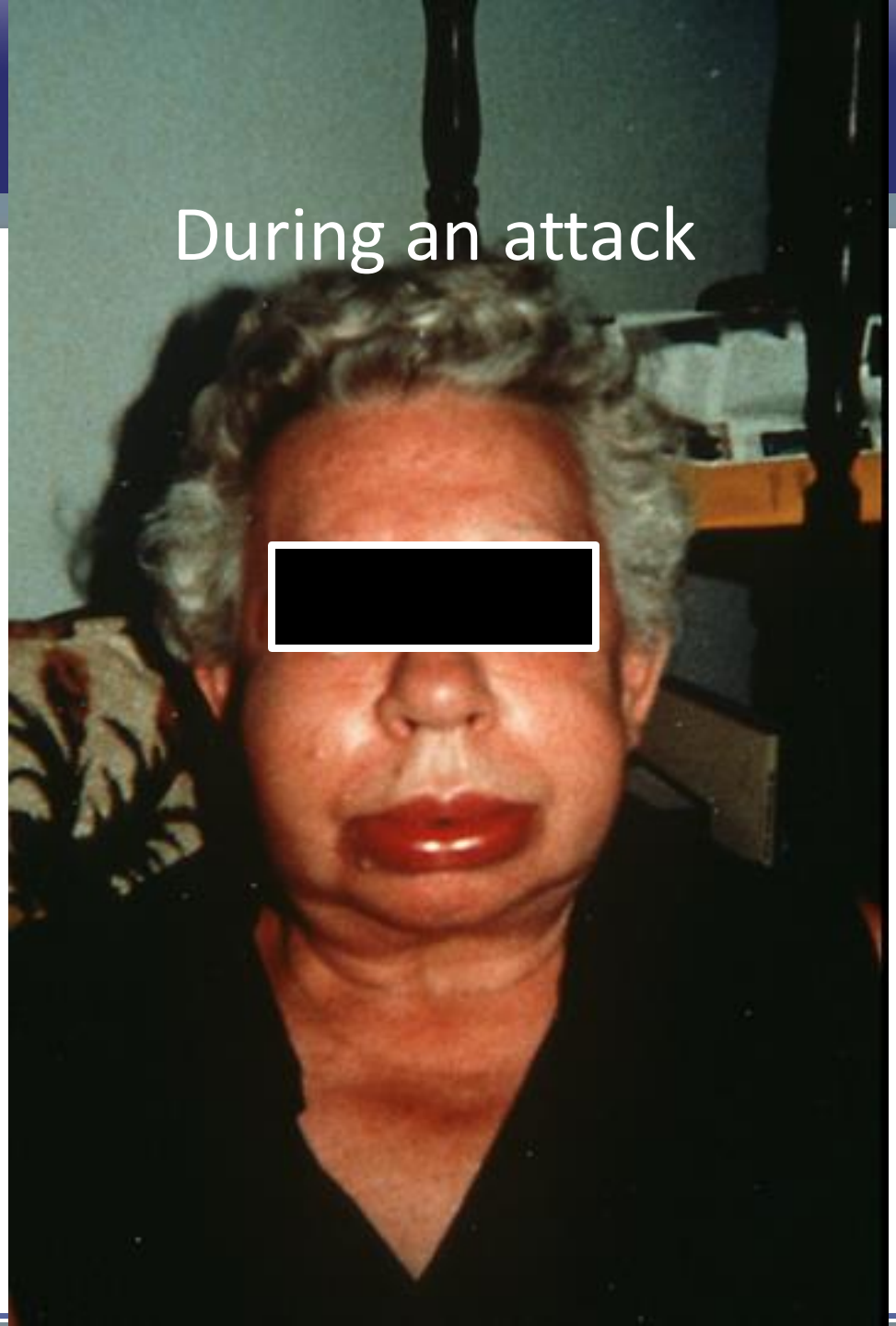
Objectives:

1. To improve your knowledge of the pathophysiology of Hereditary Angioedema (HAE)
2. To summarize the impact of HAE on those that have it
3. To compare the therapeutic options
4. To evaluate future therapies





During an attack



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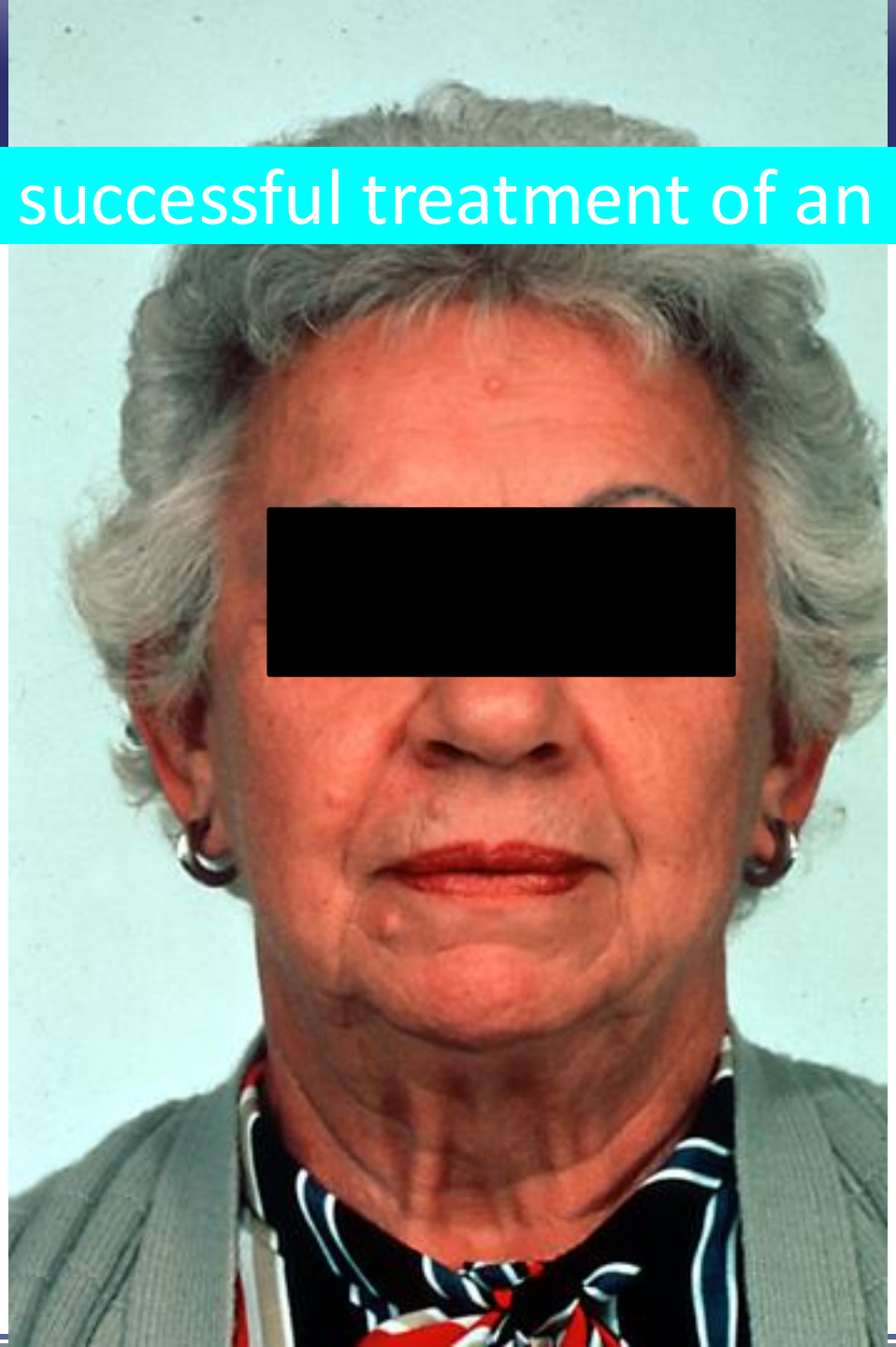
After successful treatment of an attack



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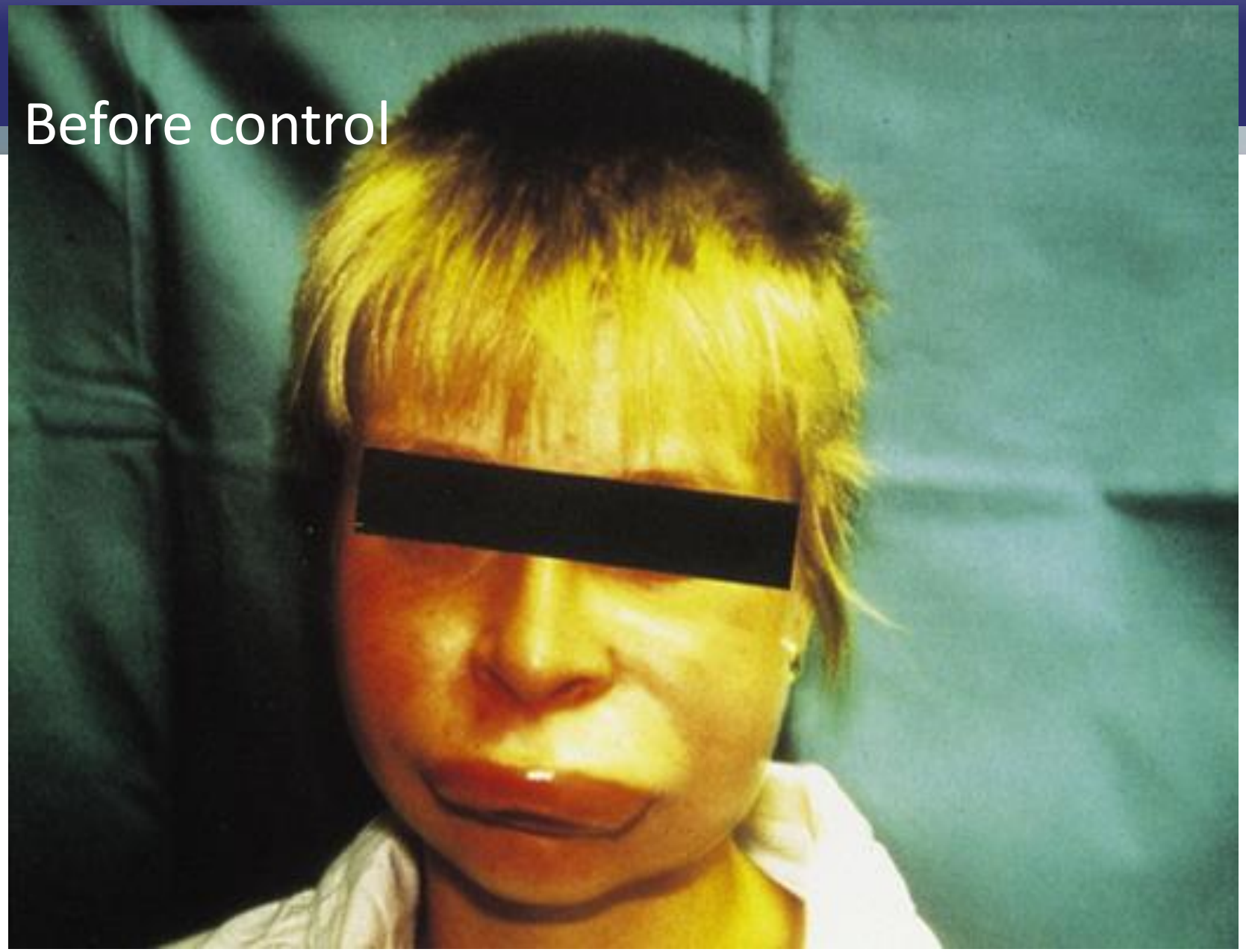
Before control



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After control

Tim Craig

Overview

- Disease state and diagnostic considerations in HAE
- Treatment of HAE
- New Therapies

Angioedema: Why Mechanisms Matter

- Angioedema
  - Global prevalence is 1% of population experience urticaria and/or angioedema
  - 25% will have urticaria and or angioedema during their lifetime
  - By far most are histamine induced
  - Mortality: 0.34 (95% CI 0.31-0.37) per million
  - Bradykinin-mediated angioedema results in a disproportionate number of deaths relative to other mechanisms
  - Effective treatment relies on identifying the underlying cause of angioedema
- Hereditary angioedema (bradykinin mediated)
  - Prevalence: ~1:50,000

Mast-Cell Mediated (most cases)

- IgE-dependent allergic reactions
- Direct mast cell release
- Changes in arachidonic acid metabolism within mast cells

Bradykinin Mediated

- ACE inhibitors
- **Hereditary C1-INH deficiency (HAE)**
- Acquired C1-INH deficiency
- Fibrinolytics

Unknown Mechanisms

- Idiopathic

C1-INH: C1-esterase inhibitor.

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.
Proper SP, et al. *Allergy Asthma Proc.* 2020;41(suppl 1):S3-S7.
Kim SJ, et al. *Ann Allergy Asthma Immunol.* 2014;113:630-634.
Crochet J, et al. *Clin Exp Allergy.* 2019;49:252-254.
Aygören-Pürsün E, et al. *Orphanet J Rare Dis.* 2018;13:73

Angioedema: Mast Cell-Mediated Versus Bradykinin-Mediated

	Mast Cell	Bradykinin
Reaction	May be allergic	Non-allergic
Mechanism	Related to mast-cell activation	Increase in vascular permeability
Symptoms	Skin and oropharyngeal symptoms predominant Most common on face (lips and periorbital area) Abdominal pain, GI symptoms uncommon Often associated with urticaria, erythema and/or pruritus	Swelling occurs in skin and mucous membranes Any skin surface Recurrent abdominal pain common 1-3% of attacks involve the upper airway Associated with erythema marginatum
Urticaria	Frequently, but not always	None
Duration	Rapid formation and resolution	Slow formation and persists days
Response to antihistamines, epi and corticosteroids	Sometimes	No
Mortality	Usually not life threatening unless in the setting of anaphylaxis	Upper airway swelling can cause asphyxiation Rapid, appropriate treatment is essential to reduce mortality

Maurer M, et al. *Clin Rev Allergy Immunol.* 2021;61:40-49.
Anderson J, et al. *Clin Transl Allergy.* 2022;12(1):e12092.
Azmy V, et al. *Allergy Asthma Proc.* 2020;41(suppl 1):S18-S21.
Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

Laboratory Diagnostic Tests of bradykinin induced disease

	HAE-I	HAE-2	Normal C1-INH	ACE-I angioedema	Acquired angioedema with low C1-inhibitor
Serum C4	Low	Low	Normal	Normal	low
C1-INH					
Protein Function	Low Low	Normal to elevated Low	Normal Normal	Normal Normal	Low Low C1q low in 75%
Genetic sequencing	Rarely needed	Rarely needed	Essential (many mutations not yet identified)	NA	May be needed in rare cases to rule out late onset HAE

Laboratory results must always be interpreted in conjunction with clinical history.
C1-INH: C1-esterase inhibitor; NGS: next generation sequencing.

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

Types of HAE

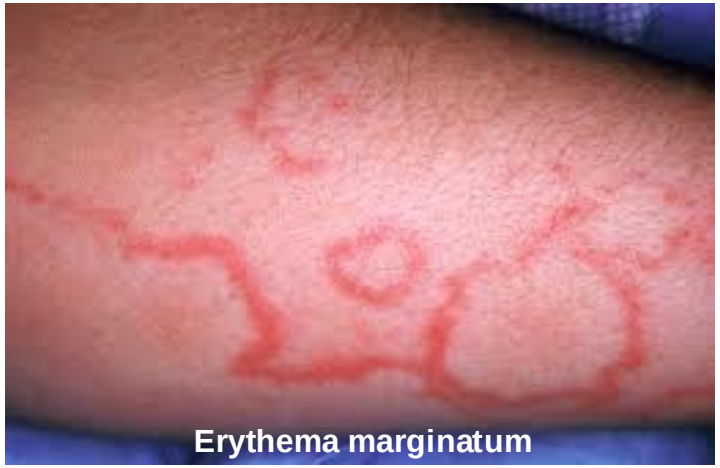
	HAE-I	HAE-2	Normal C1-INH
Genes affected	SERPING1	SERPING1	Coagulation factor XII (HAE-F12) Plasminogen (HAE-PLG) Angiopioetin-1 (HAE-ANGPT1) Kininogen-1 (HAE-KNG1) Myoferlin (HAE-MYO) Heparin (HAE-HS3ST6) Carboxypeptidase (HAE-CPN1) VEGF-R2 (HAE-DAB21P) Other unknown genes
Gene products affected and cause of angioedema	C1-INH	C1-INH	Coagulation factor XII- (bradykinin) Plasminogen- (bradykinin) Angiopioetin-1- (vascular leak or bradykinin?) Kininogen-1- (bradykinin) Myoferlin- (vascular leak or bradykinin?) Heparin- (bradykinin?) CPN1- carboxypeptidase N subunit 1 deficiency (bradykinin, anaphylatoxins?) urticaria & angioedema VEGFR2- (vascular leak or bradykinin?) urticaria & angioedema Other unknown gene products

SERPING1: serine esterase protease inhibitor G1; C1-INH: C1-esterase inhibitor; HS3ST6: heparin sulfate-glucosamine 3-sulfotransferase 6.

Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.
Denis V. JACI Global Sept 2024 PMID 39239323
D'Apolito M et al. JACI Sept2024 PMID 38823490

HAE type 1 and 2: Characterized by Recurrent, Localized, Often Painful Swelling

- Fluid extravasation in deep dermis, subcutaneous, or submucosal tissues
- Skin swelling (non-pitting, generally self-limited)
  - Any skin location, but most common: face, hands, feet, genital
  - Not accompanied by urticaria or pruritus
  - Prodromal symptoms in the majority, with erythema marginatum seen in ~30% of patients
- Submucosal tissue swelling
  - Upper respiratory tract: potentially life-threatening due to asphyxiation
  - GI tract: leads to severe abdominal pain, nausea, and vomiting



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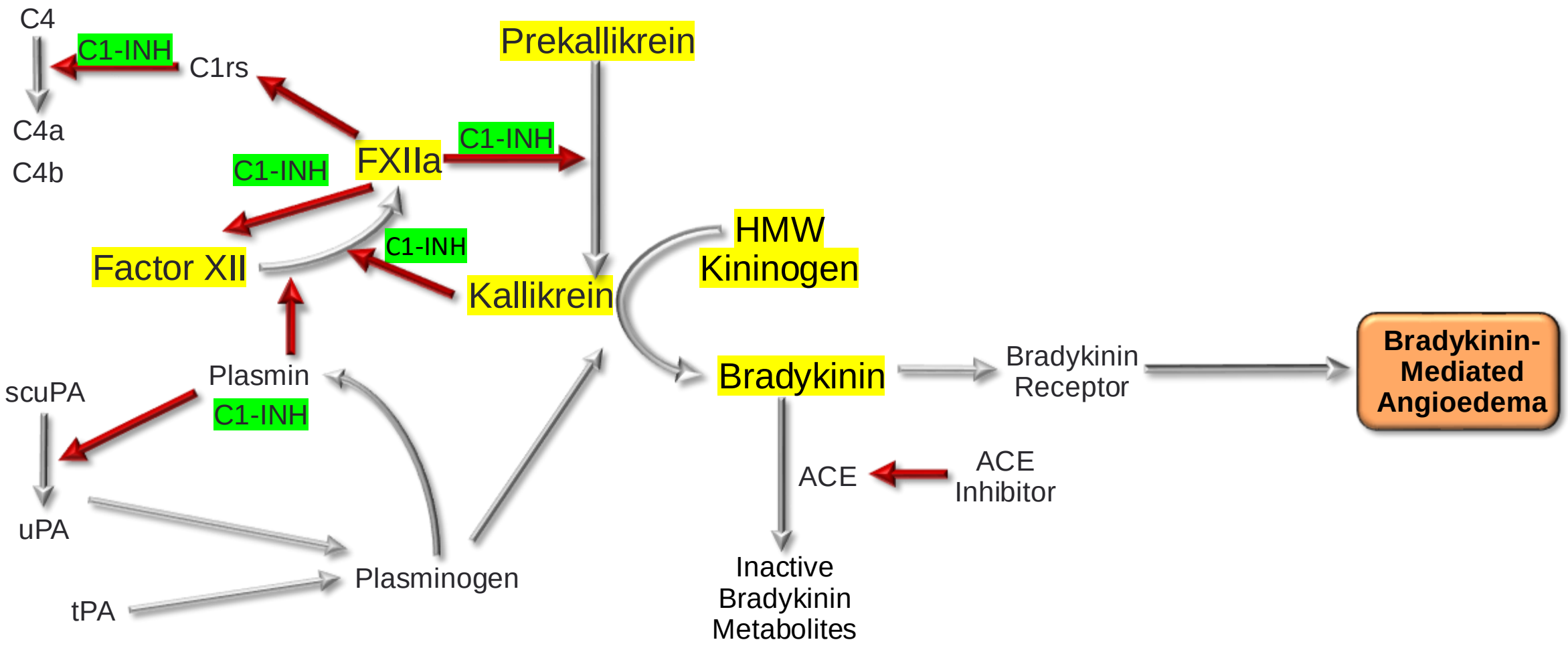
Busse PJ, et al. *N Engl J Med.* 2020;382:1136-1148.
Prematta M, Craig T. All Asthma Proceedings 2009 PMID 19843405

Mechanism of Angioedema for Type 1 and 2 HAE



C: complement; C1-INH: C1-esterase inhibitor; F12: coagulation factor XII; scuPA: single-chain urokinase plasminogen activator; uPA: urokinase-type plasminogen activator; tPA: tissue plasminogen activator; pd: plasma-derived; HMW: high-molecular-weight; ACE: angiotensin-converting enzyme.

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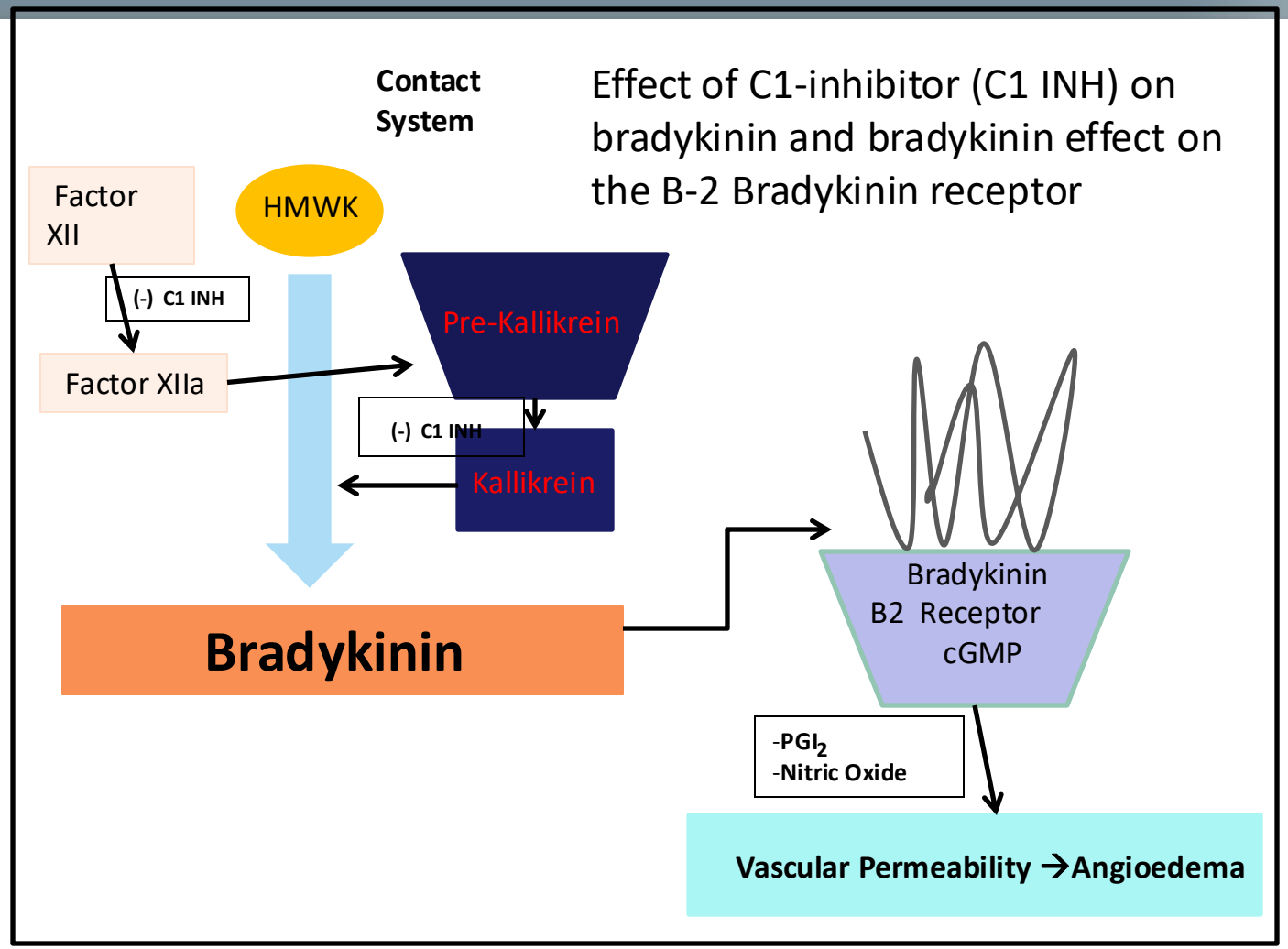
Pathophysiology of HAE



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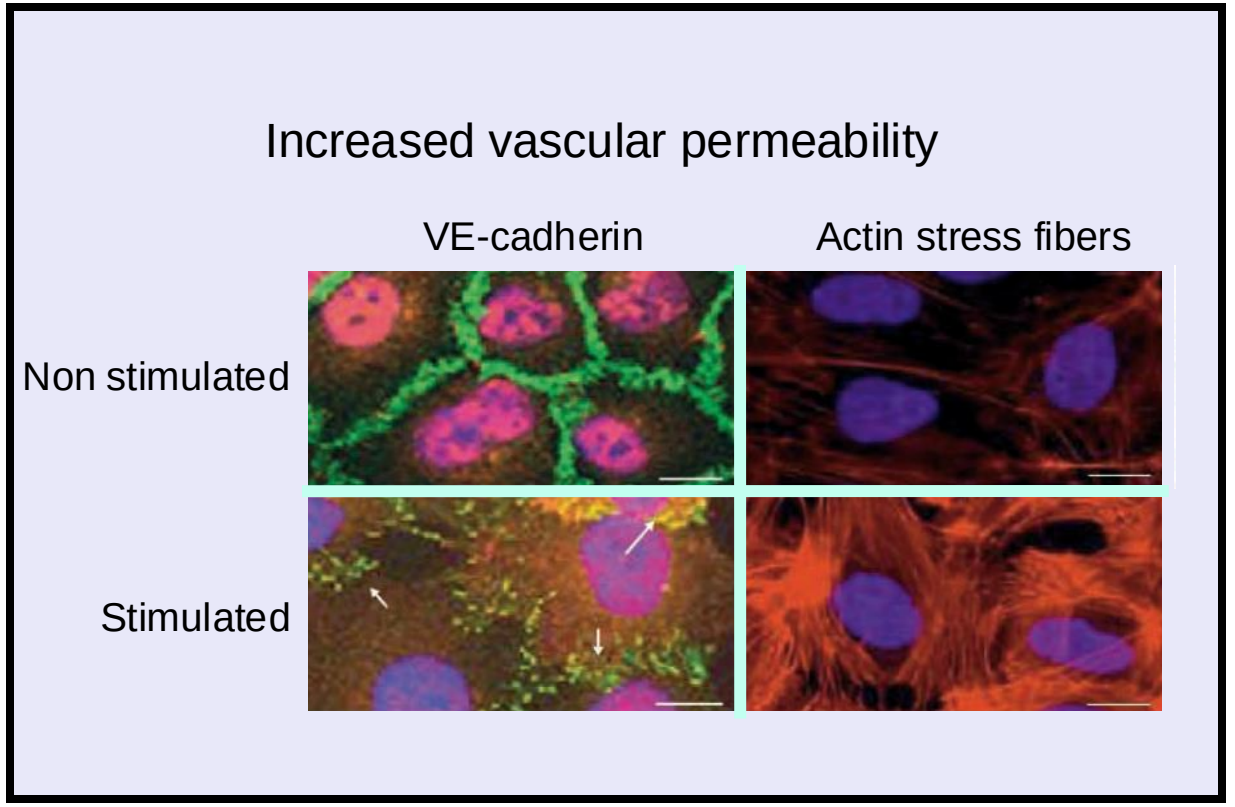
Pathophysiology of HAE

Bradykinin Effect on Endothelial Cells



From Tiruppathi C, et al. *Vascul Pharmacol*. 2003;39:173-185.

HAE:
Triggers and Patterns of Attacks

- Do most episodes have a known trigger?
- Episodes of HAE attacks
  - Frequency is highly variable
    - Occur from none to several times a week
    - Average from HAE-A is 20 per year, average from EU 16 per year
    - Many untreated patients have attacks every 1 to 2 weeks
    - Most untreated attacks last for 2 to 4 days
  - Swelling can occur in one or multiple parts of the body during an attack

Common Triggers of HAE Attacks

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Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
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HAE:
Triggers and Patterns of Attacks

- Many episodes do not have a known trigger
- Episodes of HAE attacks
  - Frequency is highly variable
    - Occur from none to several times a week
    - Average from HAE-A is 20 per year, average from EU 16 per year
    - Many untreated patients have attacks every 1 to 2 weeks
    - Most untreated attacks last for 2 to 4 days
  - Swelling can occur in one or multiple parts of the body during an attack

Common Triggers of HAE Attacks

- Emotional or physical stress
- Trauma
- Surgery
- Infections (colds, flu, etc)
- ACE inhibitors
- Estrogen

Azmy V, et al. *Allergy Asthma Proc.* 2020;41(suppl 1):S18-S21.
Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
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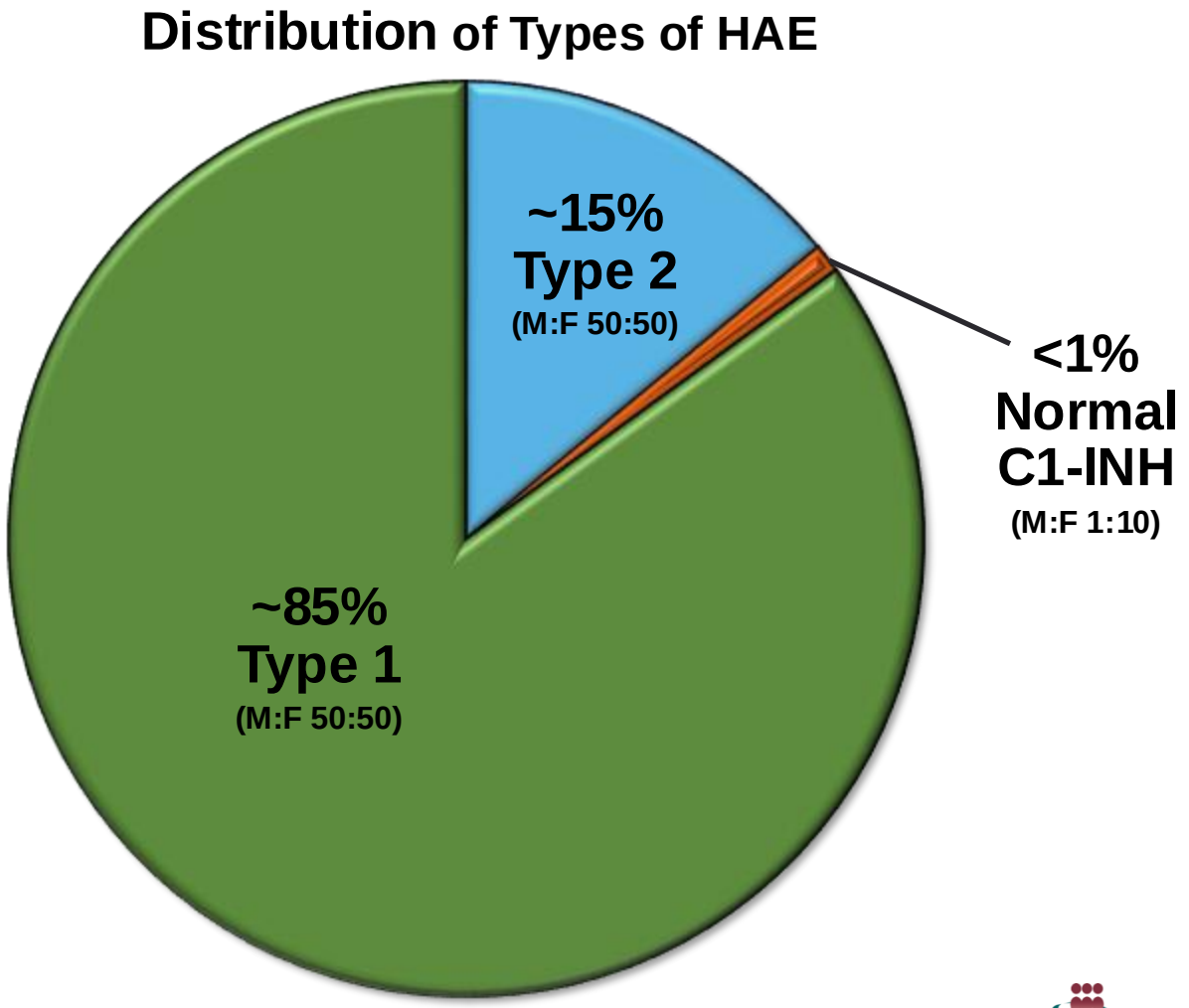
Onset of Symptoms

- Symptoms of HAE typically begin in childhood and worsen during puberty
- Family history of HAE (75% of cases)
  - Autosomal dominant inheritance pattern, variable penetrance
- Remaining 25% of cases have no family history of HAE
  - De novo mutations that subsequently follow autosomal dominant inheritance pattern



C1-INH: C1-esterase inhibitor.

Kaplan ap, et al. *J Allergy Clin Immunol Pract.* 2020;8:892–900.
Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
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Program Overview

- Disease state and diagnostic considerations in HAE
- **Treatment of HAE**
- New Therapies

Treatment of HAE: Core Principles For All Patients With HAE

- Availability of Effective On-Demand Acute Therapy
- Early Treatment to Prevent Attack Progression
- Treatment of Attacks Irrespective of the Site of Swelling
- Incorporation of Short-Term Prophylaxis

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

FDA-Approved On-Demand Therapeutic Options

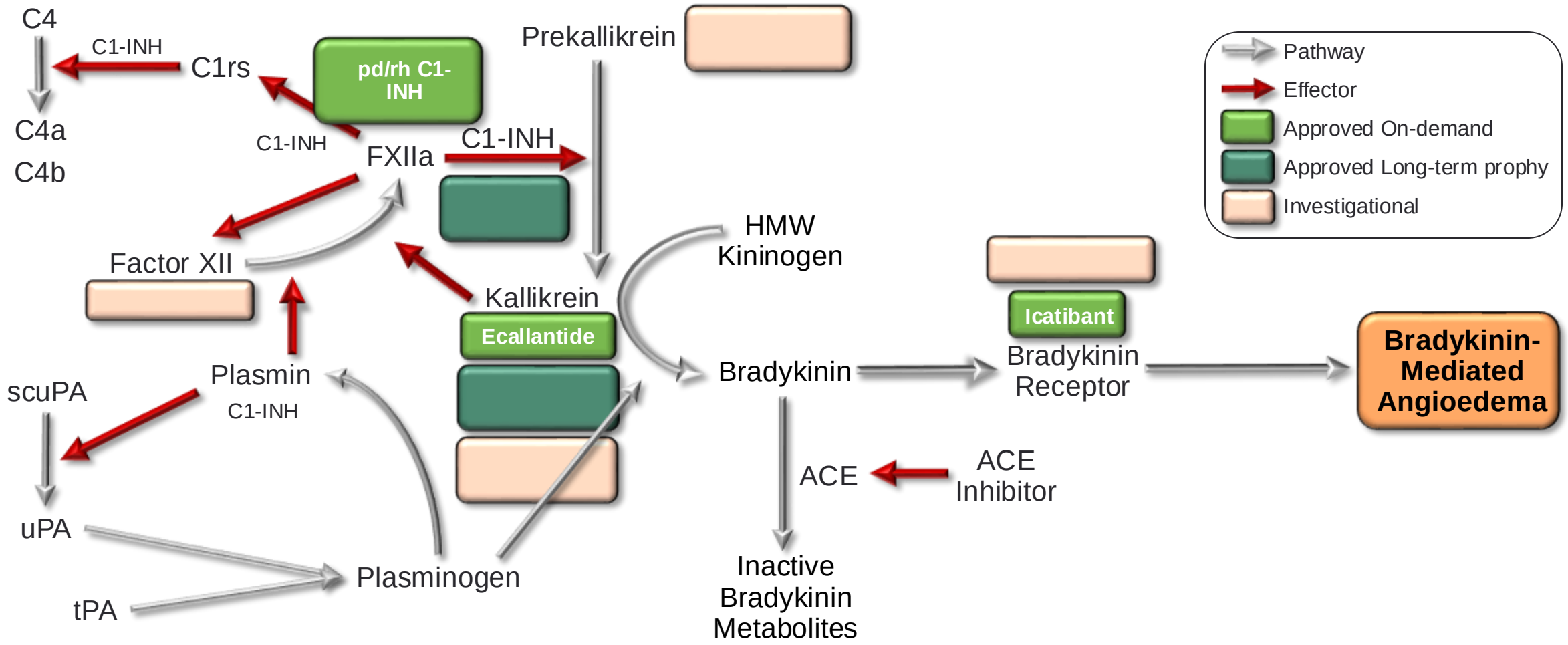
	Patients	Self Administered	Mechanism	Potential Adverse Events
Ecallantide	≥12 years of age	No (sc)	Inhibits plasma kallikrein	Uncommon Antidrug antibodies, risk of anaphylaxis
Icatibant	≥18 years of age* Down to 2 in EU	Yes (sc)	Bradykinin B2 receptor antagonist	Common Discomfort at injection site
C1-INH				
Plasma-derived	Children and adults†	Yes (iv)	Inhibits plasma kallikrein, coagulation factors Xlla, XIIf and Xla, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare Anaphylaxis
Recombinant	Adolescents and adults†	Yes (iv)	Inhibits plasma kallikrein, coagulation factors Xlla, XIIf and Xla, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon Risk of anaphylaxis in rabbit-sensitized persons

*In Europe, approved in ≥2 years of age.
†Also approved in Europe.

C1-INH: C1-esterase inhibitor.
MASP-1, -2, mannose-binding lectin-associated serine proteases 1, 2.

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

HAE Medications for On Demand Therapy



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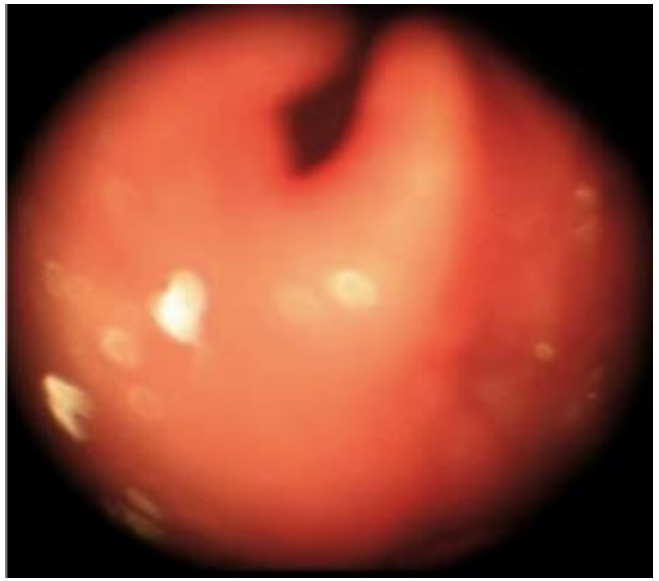
Pre-surgery case

*Mary has HAE with low C1-inhibitor (type 1)

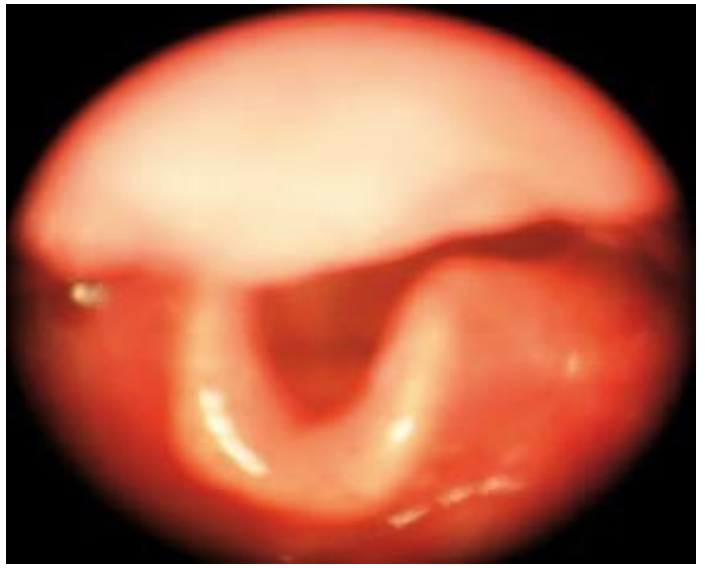
*She is scheduled for a “T and A” for sleep disordered breathing.

*Her medications are icatibant for rescue and lanadelumab for prophylaxis

?What would you want to do before surgery?



During an Attack



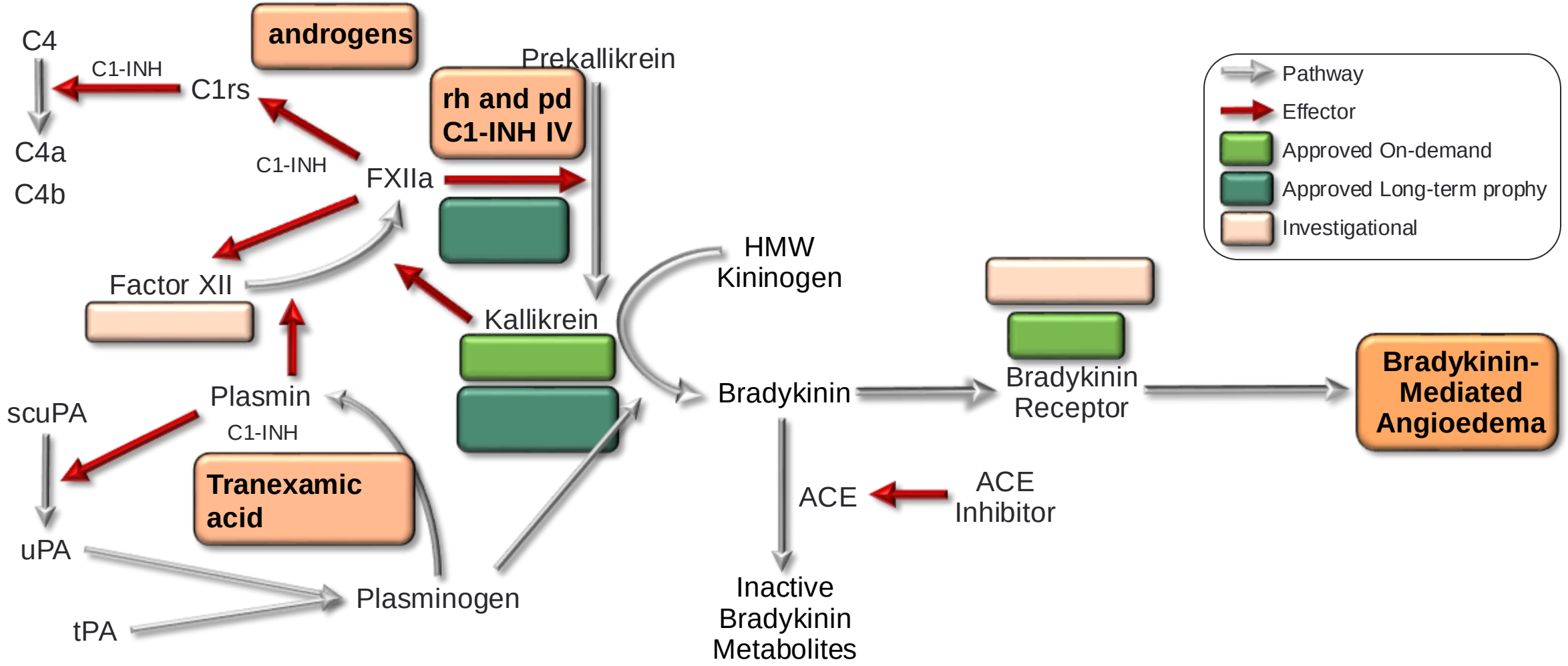
Normal

Thanks to M Riedl

Which treatment would you recommend before surgery?

- A. Pretreat with danazol 200 mg three times a day starting a day before surgery
- B. Just continue the lanadelumab
- C. Pretreat with icatibant
- D. Pretreat with C1-inhibitor SQ
- E. Pretreat with C1-inhibitor IV

HAE Therapies for short term prophylaxis



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RECOMMENDATION 10

We **recommend** considering short-term prophylaxis before medical, surgical or dental procedures as well as exposure to other angioedema attack-inducing events

94% agreement, evidence level C

RECOMMENDATION 11

We **recommend** the use of intravenous plasma-derived C1 inhibitor as first-line short-term prophylaxis

91% agreement, evidence level C

RECOMMENDATION 12

We suggest considering prophylaxis prior to exposure to patient-specific angioedema-inducing situations

90% agreement, evidence level D

Maurer M, Allergy. 2022 Jul;77(7):1961-1990

What dose of IV C1-inhibitor should you use for Pre-procedural prophylaxis?

Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study

Konrad Bork, MD,[a] Jochen Hardt, PhD,[b] Petra Staubach-Renz, MD,[a] and Guenther Witzke, PhD,[a] Mainz, Germany
JOHANNES GUTENBERG UNIVERSITY

Suggested 20 iu/kg of plasma derived C1-INH 1 hour before procedure. Alternative is rcC1-INH.

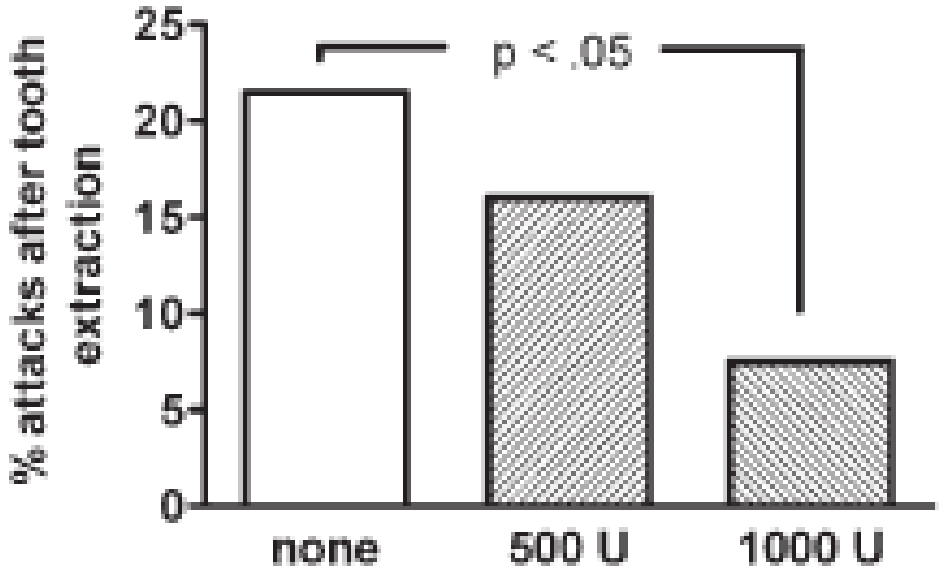


Fig. 2. Percentage of tooth extractions followed by attacks, without prophylaxis and with short-term prophylaxis with 500 U and 1,000 U C1 inhibitor concentrate.

How do we determine who needs long term prophylaxis?

Factors to Consider in Treatment Decision

- Overall burden of disease
- Angioedema attack frequency
- History of severe debilitating or life-threatening attacks
- Access to urgent care
- Anxiety about future attacks
- Ability to attend work or school
- Ability to plan future life events
- Ability to conduct activities of daily living
- Benefit-risk profile and treatment burden of available acute and prophylaxis therapies

Annals of Allergy Asthma and Immunology Craig et al 2018

RECOMMENDATION 13

We **recommend** that the goals of treatment are to achieve total control of the disease and to normalize patients' lives

100% agreement, evidence level D

RECOMMENDATION 14

We **recommend** that patients are evaluated for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration

96% agreement, evidence level D

RECOMMENDATION 19

We **suggest** all patients who are using long-term prophylaxis be routinely monitored for disease activity, impact, and control to inform optimization of treatment dosages and outcomes

98% agreement, evidence level A

Maurer M, Allergy. 2022 Jul;77(7):1961-1990

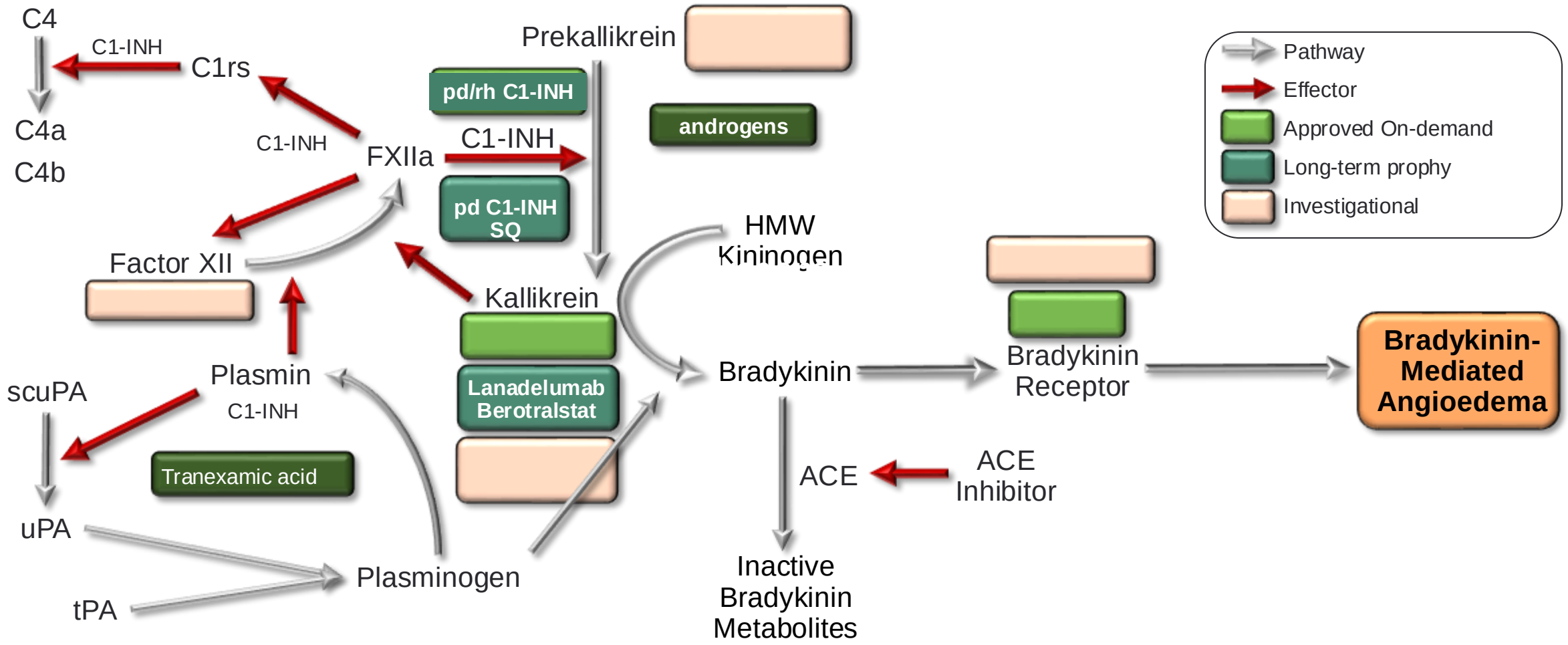
First-Line Long-Term Prophylactic Therapeutic Options

	Patients	Approved Initial Dose	Most Common Adverse Events
C1-INH			
Plasma-derived (iv)	≥6 years of age	Pediatric: 500 U every 3 to 4 days Adolescents/adults: 1000 U every 3 to 4 days (may increase to up to 2500 U)	Headache, nausea, rash, vomiting, and fever
Plasma-derived (sc)	≥6 years of age	60 IU/kg twice weekly	Injection site reactions, hypersensitivity, nasopharyngitis and dizziness
Lanadelumab (sc) (plasma kallikrein inhibitor monoclonal antibody)	≥2 years of age	300 mg every 2 weeks with adjustment for children	Injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea
Berotralstat (oral) (plasma kallikrein inhibitor)	≥12 years of age	150 mg qd taken with food	Abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease

C1-INH: C1-esterase inhibitor.

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

HAE Therapeutic Landscape for LTP



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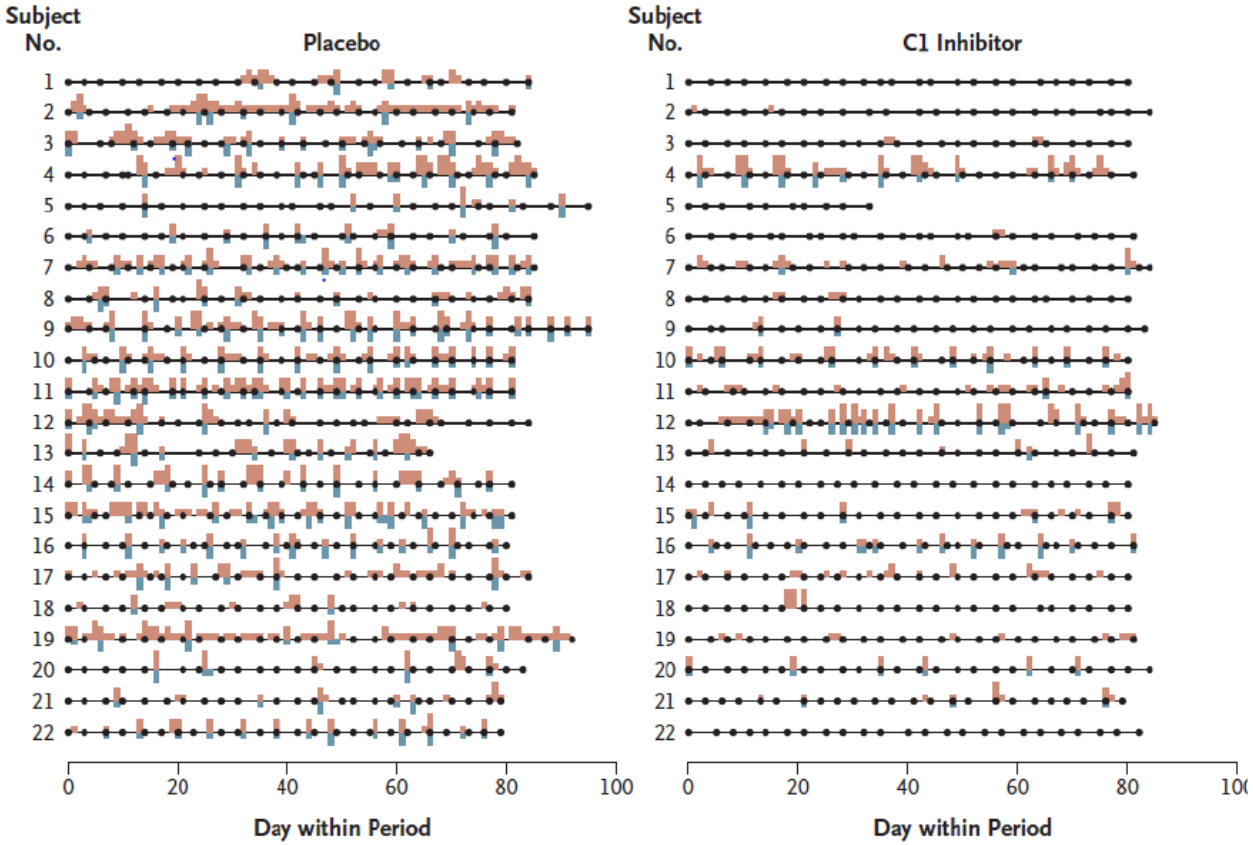
C1-INH IV 1000 mg every 3 to 4 days

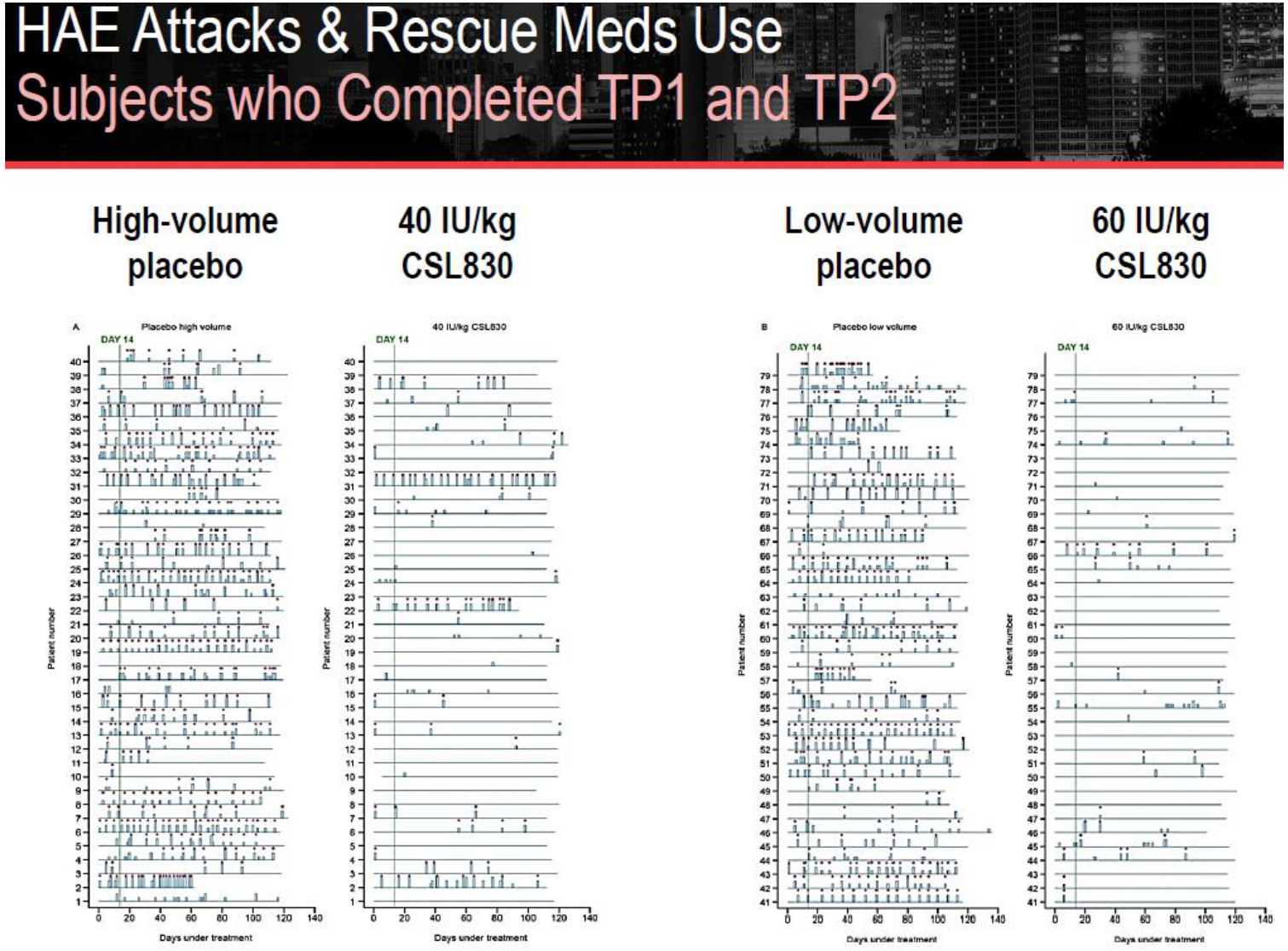
IV C1-INH Major Events During CHANGE Trial



Zuraw et al. *N Engl J Med*. 2010;363(6):513–22.

50% reduction of attacks

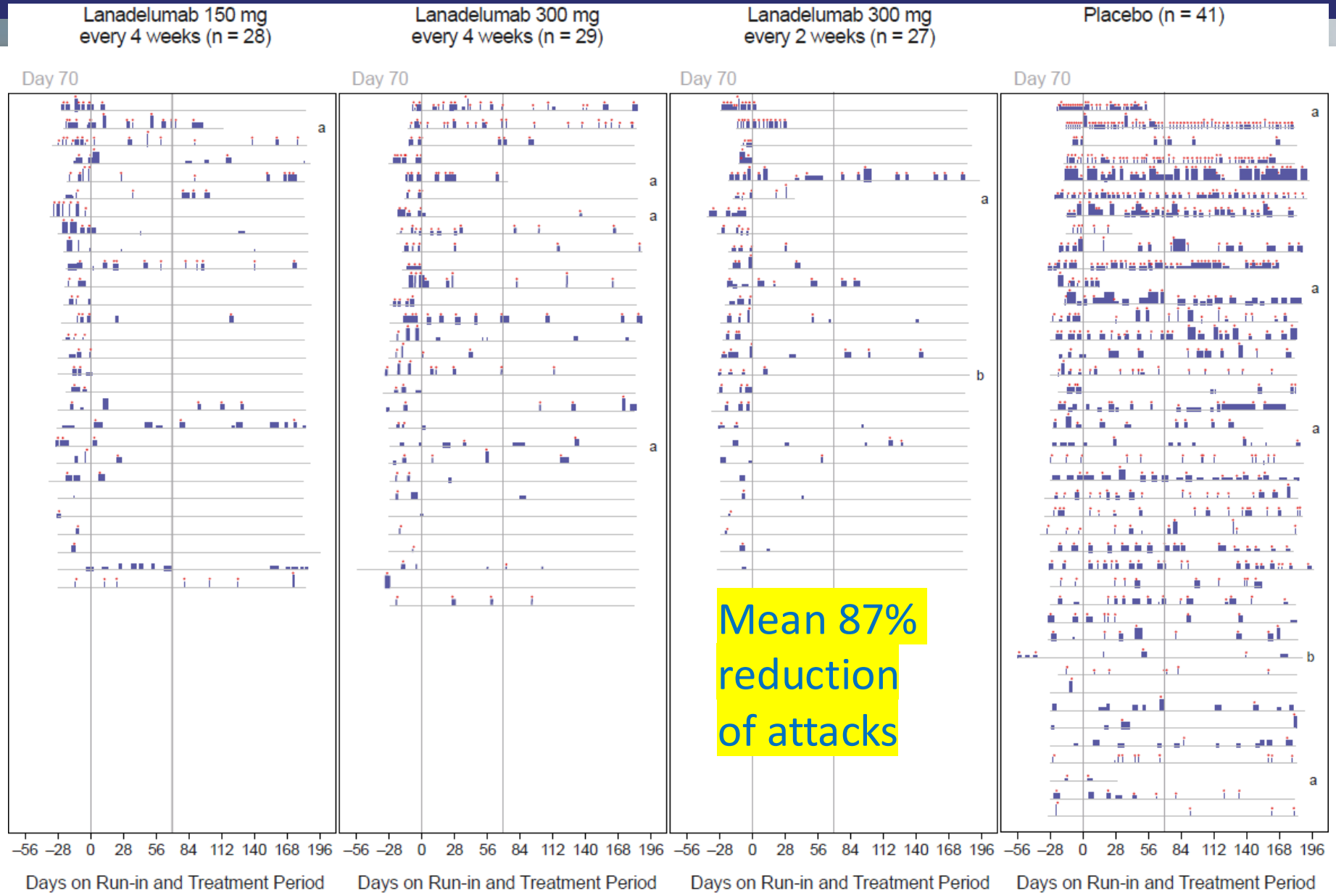
Reduction of attacks with SQ C1-inhibitor at 40 and 60 units per kg twice a week



Median 95% and mean 86% reduction of attacks

Longhurst, Cicard, Craig. NEJM 2017

Reduction of attacks with lanadelumab for prophylaxis

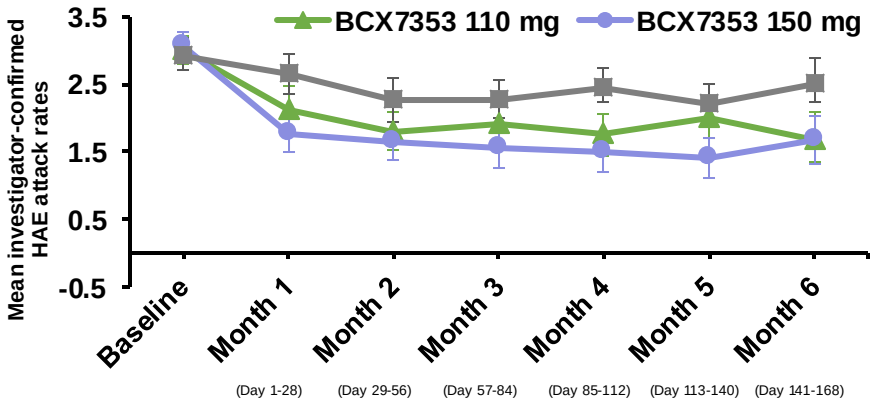


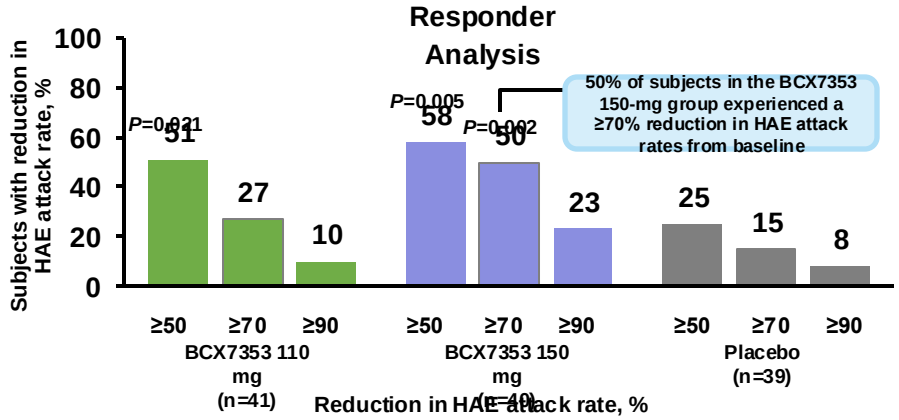
Banerji A. NEJM 2019 31012909

Reduction of attacks with berotralstat for LTP

Berotralstat

Once-daily, oral berotralstat for the prevention of HAE attacks; Approved for patients ≥12 years of age





Safety outcomes, n (%)	BCX7353 110 mg (n=41)	BCX7353 150 mg (n=40)	Placebo (n=39)
General abdominal pain	4 (9.8)	9 (22.5)	4 (10.3)
Vomiting	4 (9.8)	6 (15.0)	1 (2.6)
Diarrhea	4 (9.8)	6 (15.0)	0
Back pain	1 (2.4)	4 (10.0)	1 (2.6)

47% reduction of attacks

1. Aygören-Pürsün E, et al. *J Allergy Clin Immunol*. 2020 Feb;145(2):AB107.
2. Zuraw B, et al. *J Allergy Clin Immunol*. 2020 Oct 21;S0091-6749(20)31484-6.
3. Hwang JR, et al. *Immunotherapy*. 2019;11(17):1439-4.

Rationale for New HAE Therapies

- Improve treatment of HAE patients
  - Increased efficacy
  - Increased safety +/-
  - Reduction in treatment burden
  - Longer lasting prophylactic treatments
  - Oral medications
  - RNA interference therapies
  - Gene therapies
  - Hopefully, improved accessibility

Fijen LM, et al. *Clin Rev Allergy Immunol.* 2021;61:66-76.

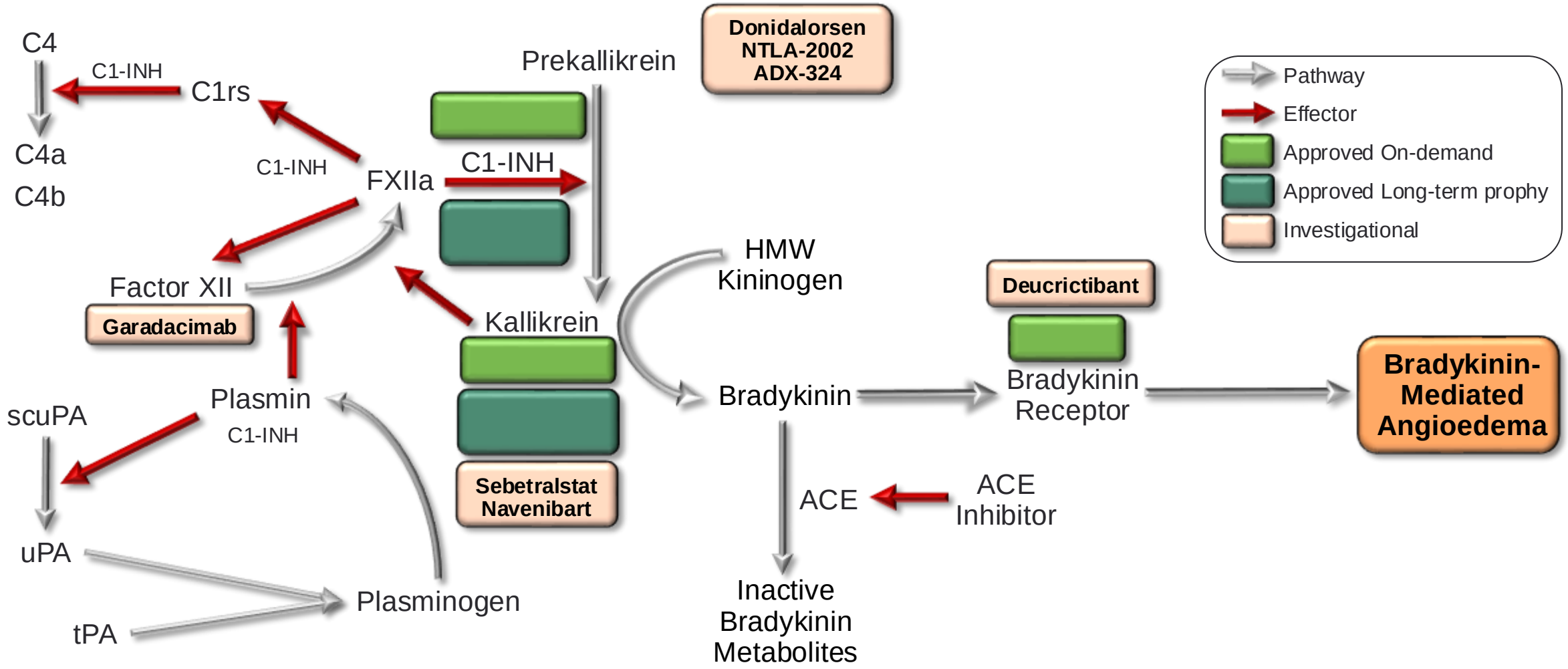
HAE:
Investigational Agents in Late-Stage Clinical Development

	Mechanism	Patients	Description
Sebetralstat (PO) Kalvista	Plasma kallikrein inhibitor	Adolescents/adults	KONFIDENT: on-demand therapy
Garadacimab (sc) CSL-B	Human anti-factor XIIa monoclonal antibody	≥12 years of age	Studies 3001 and 3002: long-term prophylaxis
Donidalorsen (sc) Ionis	Ligand-conjugated antisense oligonucleotide to reduce prekallikrein production	≥12 years of age	OASIS-HAE: long-term prophylaxis
ADX-324 ADARx	Short interfering RNA (siRNA) prevents pre-kallikrein production		
Navenibart (sc) Astria	IgG1 with modified FC and inhibits plasma kallikrein	> 18 fears of age	LTP with infrequent dosing
Deucrictibant (PO) Pharvaris	Selective B2-receptor antagonist	≥18 years of age ≥18 years of age	RAPIDe-1: dose-ranging for acute treatment HAE CHAPTER-1: dose-ranging for long-term prophylaxis
NTLA-2002 (iv) Intellia	CRISPR/Cas9 editing of KLKB1	≥18 years of age	Phase 1/2 dose-escalation study for long-term prophylaxis
BMN 331 (iv) BioMarin	AAV5-based, gene therapy	≥18 years of age	HAErmony-1 (phase 1/2): dose-escalation study for long-term prophylaxis

ClinicalTrials.gov.

CRISPR: clustered regularly interspaced short palindromic repeats.
Cas-9: CRISPR-associated protein 9.
KLKB1: kallikrein B1.
AAV: adeno-associated virus.

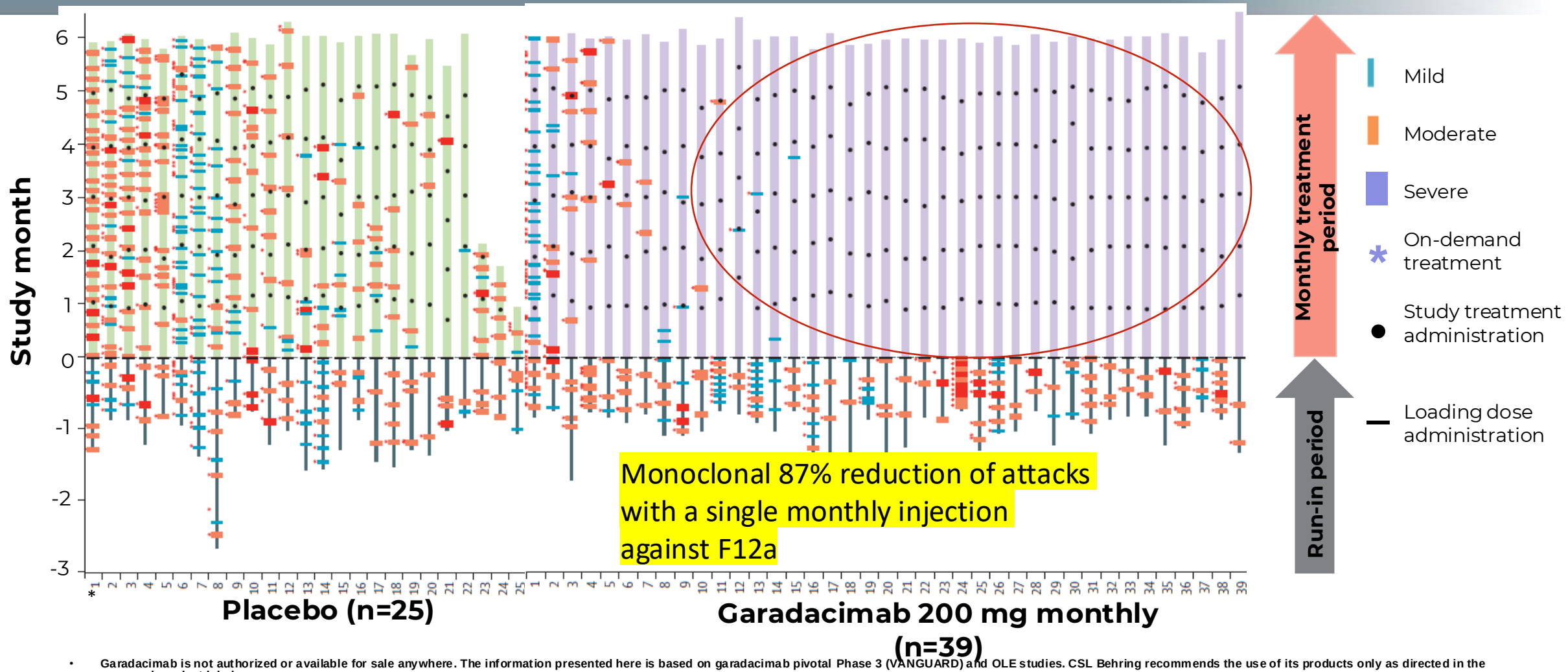
HAE Therapeutic Landscape: Current and Emerging Options



C: complement; C1-INH: C1-esterase inhibitor; F12: coagulation factor XII; scuPA: single-chain urokinase plasminogen activator; uPA: urokinase-type plasminogen activator; tPA: tissue plasminogen activator; pd: plasma-derived; HMW: high-molecular-weight; ACE: angiotensin-converting enzyme.

Busse PJ, et al. *N Engl J Med.* 2020;382:1136-1148; Riedl MA, et al. J Allergy Clin Immunol Pract. 2024;12:911-918; Smith TD, et al. Ann Allergy Asthma Immunol. 2024:S1081-S1206.

- HAE attack frequency and severity are significantly lower for garadacimab vs placebo in pivotal Phase 3 (VANGUARD) study

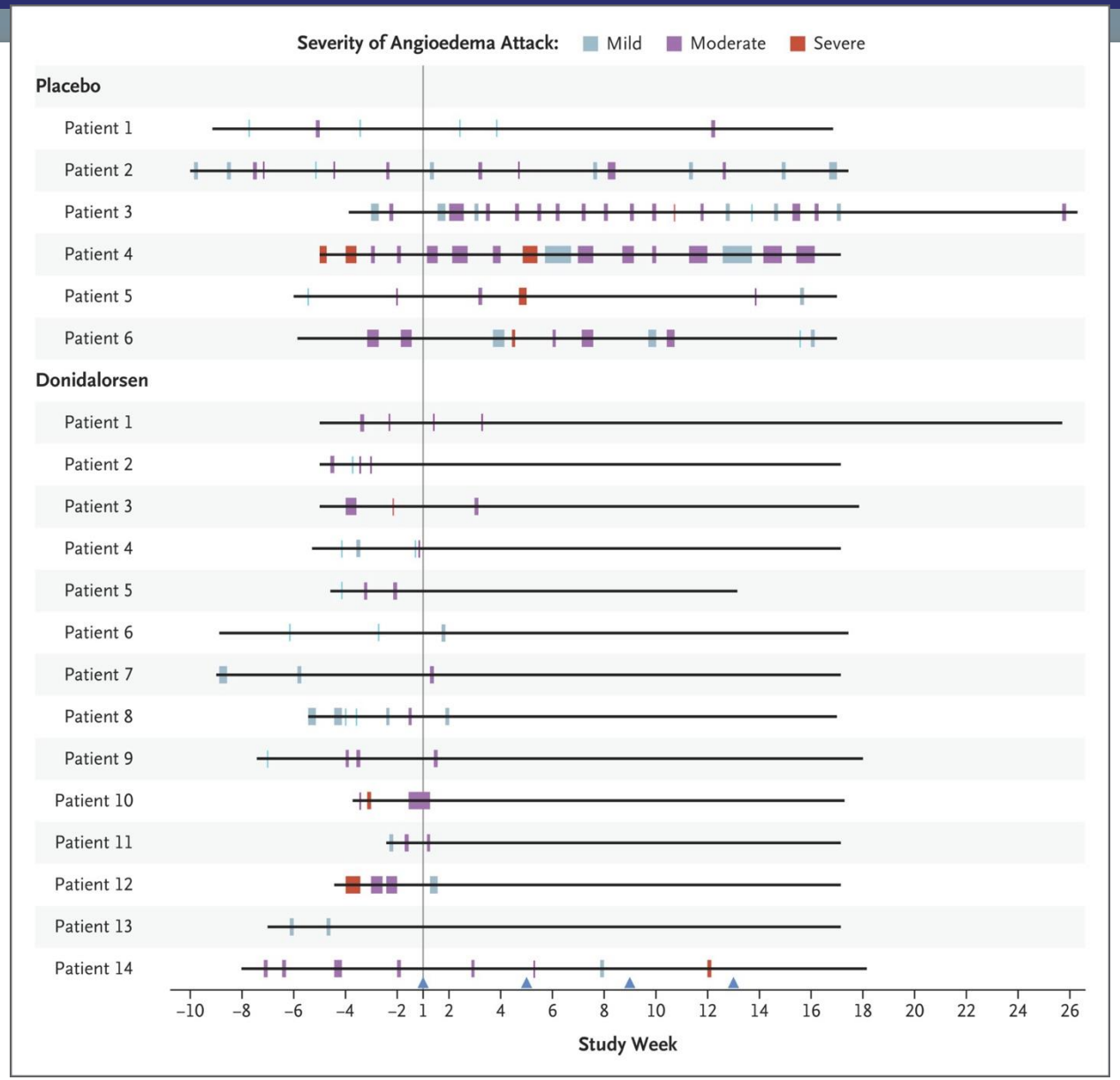


- **Garadacimab is not authorized or available for sale anywhere. The information presented here is based on garadacimab pivotal Phase 3 (VANGUARD) and OLE studies. CSL Behring recommends the use of its products only as directed in the approved product label.**

*The patient showing an atypical response to garadacimab has a complex medical history and ongoing medical conditions; these include musculoskeletal and connective tissue disorders (i.e., fibromyalgia and osteoporosis), vascular disorders (i.e. hypertension), respiratory disorders (i.e., allergic rhinitis), gastrointestinal disorders (i.e., gastric polyps, hiatus hernia), and neoplasms. HAE, hereditary angioedema; OLE, open-label extension; q1m, once monthly. 1. Craig TJ et al. *Lancet* 2023; 401:1079–1090 and supplementary appendix.

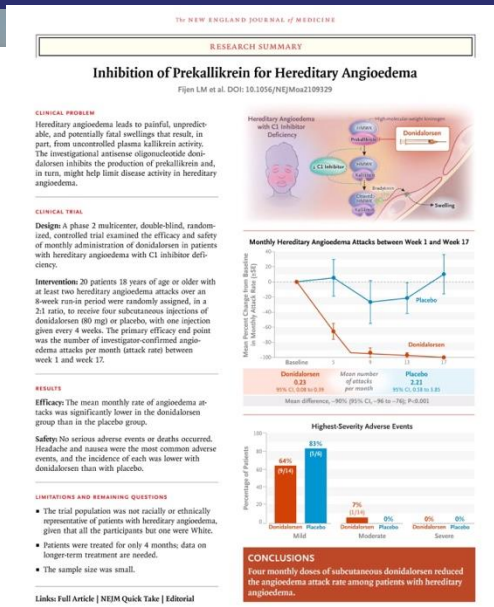
T Craig, Lancet 2022

Donidalorsen SQ injection every 4 to 8 weeks
mRNA inhibitor of prekallikrein



Placebo

Active therapy

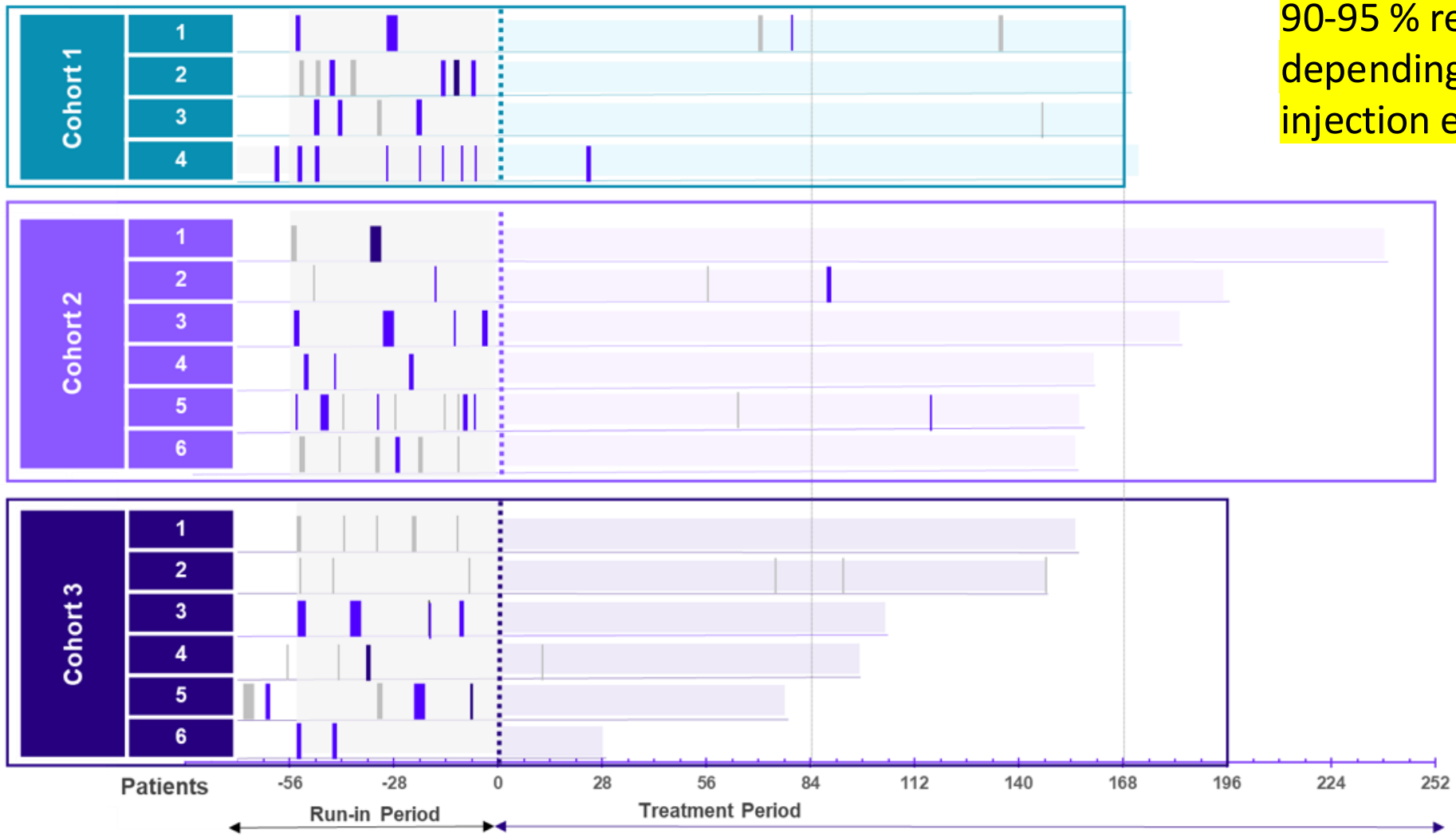


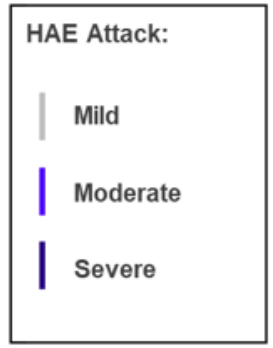
81% reduction of attacks at q 4 weeks
55% reduction of attacks at q 8 weeks

Rield M 2024

The NEW ENGLAND JOURNAL of MEDICINE

Navenibart SQ Monoclonal Expected to Sustain Exposure Above Target Threshold with Both Q3 and Q6 Month Dosing; against Kallikrein

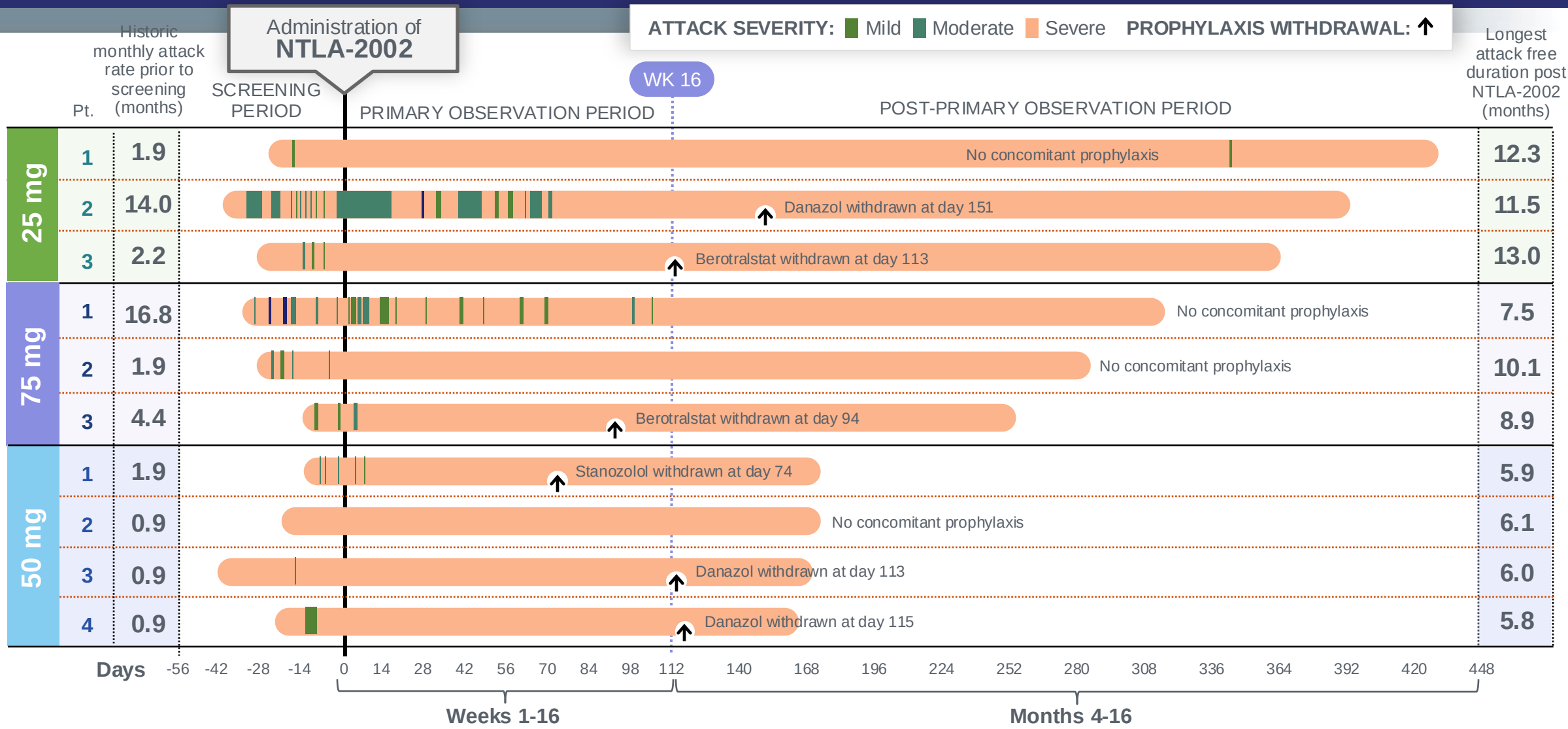




90-95 % reduction of attacks depending on the cohort with SC injection every 3 to 6 months

EADV Sept 25-28 2024
Netherlands

Durable HAE attack reductions observed in all patients after a single dose of NTLA-2002; Crispr removes prekallikrein

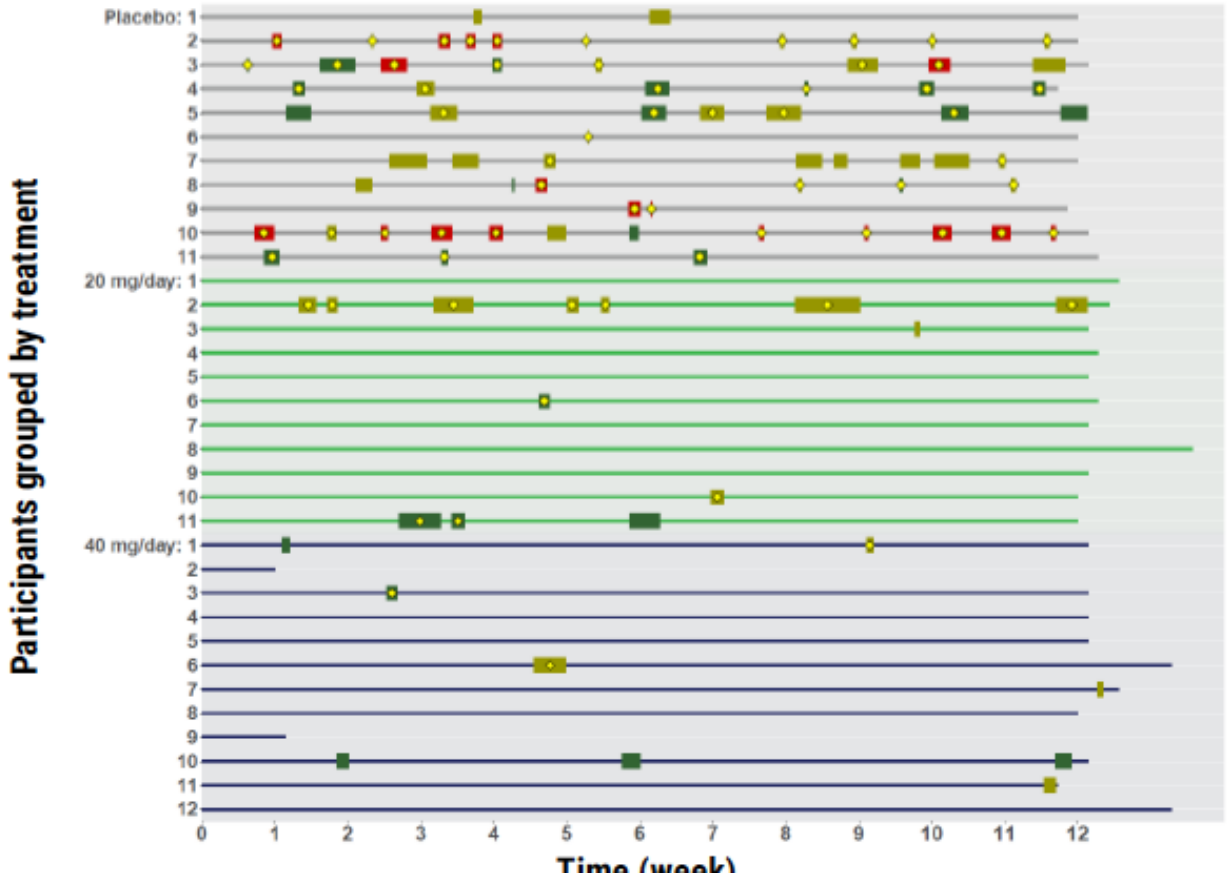


98% reduction of attacks

Abstract AAAAI 2024

Oral Deucrictibant for the Prevention of HAE Attacks; B2 bradykinin receptor antagonist

Significant attack reduction and no severe attacks with deucrictibant



Precent reduction of attacks
40 mg 85%
20 mg 79%
with once a day oral therapy

20 mg/day = deucrictibant immediate release (IR) capsules 10 mg twice daily.
40 mg/day = deucrictibant IR capsules 20 mg twice daily.

Riedl M, et al. *J Allergy Clin Immunol.* 2024;135. Abstract 031.

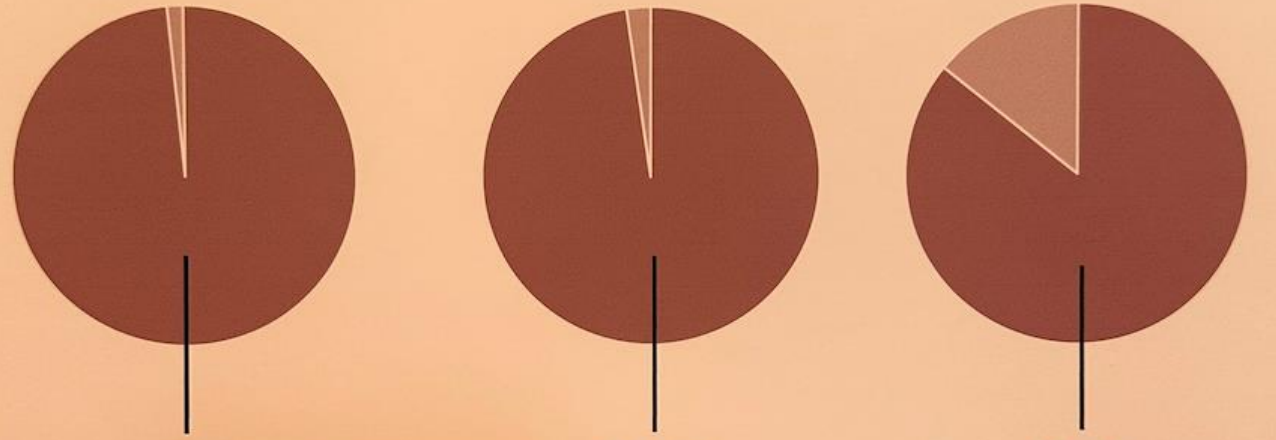
Oral Deucrictibant for Treatment of HAE Attacks; B2 bradykinin receptor antagonist

- Oral on demand therapy for attacks

Bradykinin Meetings, Berlin GR,
Sept 2024

- 85.8% (224/261) of attacks achieved complete attack resolution within 24 hours **(Figure 4)**. 90.2% (202/224) of attacks achieved this milestone with a single dose of deucrictibant IR capsule **(Figure 5)**.

Figure 4. Proportion of attacks achieving key efficacy endpoints



98.5%
(261/265) of attacks achieved onset of symptom relief using PGI-C by 12 hours

97.7%
(255/261[a]) of attacks achieved reduction in attack severity using PGI-S by 12 hours

85.8%
(224/261[a]) of attacks achieved complete attack resolution using PGI-S within 24 hours

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]261 attacks have non-missing pre-treatment PGI-S.

Oral Sebetralstat for Acute HAE Attacks; inhibits kallikrein

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

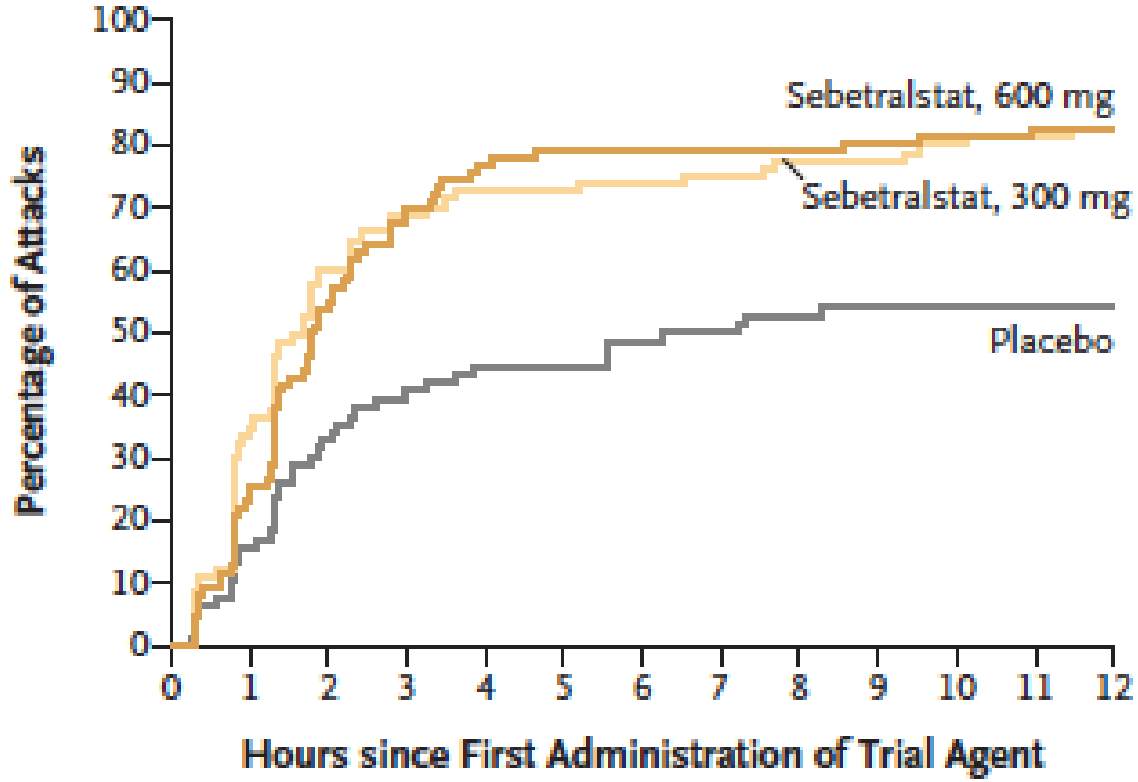
Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks

M.A. Riedl, H. Farkas, E. Aygören-Pürsün, F. Psarros, D.F. Soteres, M. Staevska, M. Cancian, D. Hagin, D. Honda, I. Melamed, S. Savic, M. Stobiecki, P.J. Busse, E. Dias de Castro, N. Agmon-Levin, R. Gower, A. Kessel, M. Kurowski, R. Lleonart, V. Grivcheva Panovska, H.J. Wedner, P.K. Audhya, J. Hao, M. Iverson, M.D. Smith, C.M. Yea, W.R. Lumry, A. Zanichelli, J.A. Bernstein, M. Maurer, and D.M. Cohn, for the KONFIDENT Investigators*

Oral on demand therapy for attacks

N Engl J Med 2024;391:32-43.

A 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

Oral Sebetralstat for Acute HAE Attacks; inhibits kallikrein

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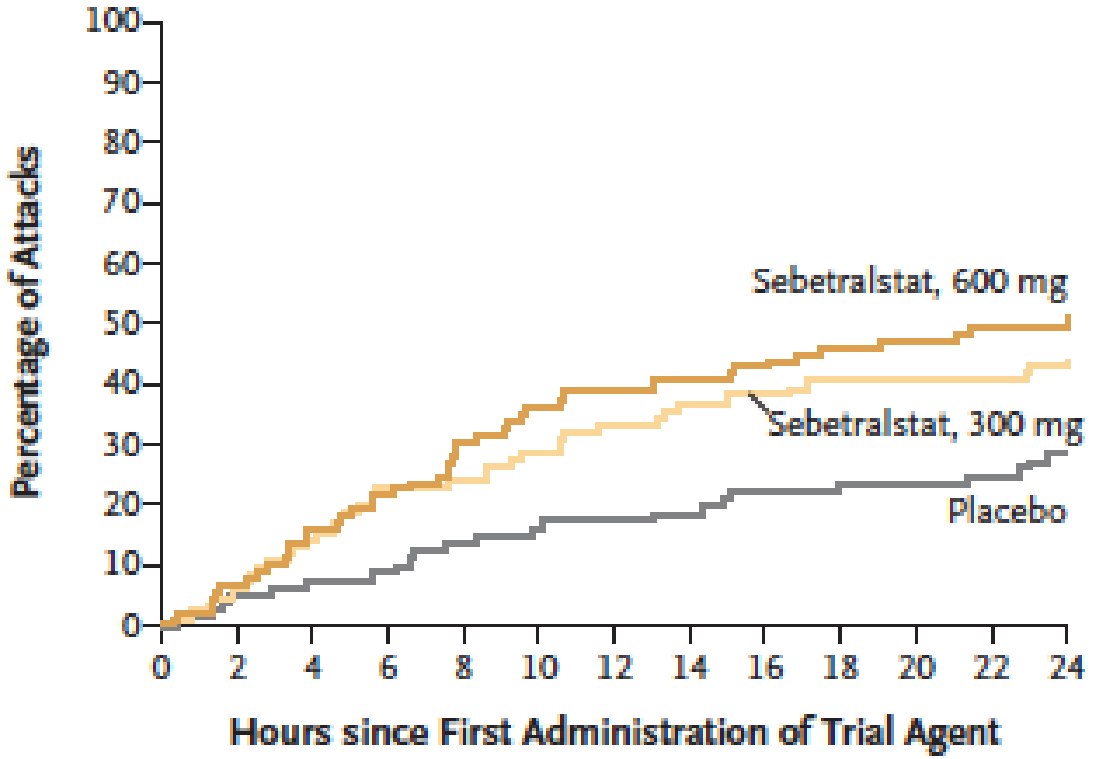
N Engl J Med 2024;391:32-43.

C Complete Resolution of the Attack



No. of Attacks													
Sebetralstat, 600 mg	93	83	75	70	62	57	54	53	51	48	47	45	45
Sebetralstat, 300 mg	87	79	72	65	64	60	56	53	52	50	50	50	48
Placebo	84	77	75	74	70	68	67	66	63	62	62	61	58

- MS is a 41 yo female
- Abd symptoms of pain started 2011
- Facial swelling started in 2012
- She failed fexofenadine 180 bid
- Genetic testing for F12 gain of function and biochemical test for HAE were normal
- 2012-17 swelling ceased but returned 2017 with tongue swelling and generalized body swelling
- Since antihistamines did not work in
- 2017 an allergist administered IV p-C1-INH which helped and was diagnosed as having HAE type 3
- FH Dad was adopted
- SC C1-INH, berotralstat, lanadelumab failed to be beneficial
- She now administers r-C-1-INH twice a day 4200 units , takes berotralstat 150 daily, and uses IV C-1-INH 1500 iu almost daily for rescue through a port.
- She has had DVTs times 2 including 1 arm DVT, and has 4 different ports, 1 port infection
- Depression
- Intubated twice despite therapy
- Additional dose of rc-C1-INH or p-C1-INh resolves her swelling in minutes almost immediate.
- EpiPen helps symptoms if all else fails
- She is free of symptoms only 5 days a month
- She was seen in a HAE referral center and told she has HAE with normal C1-INH from a yet undetected gene defect

Types of HAE

	HAE-I	HAE-2	Normal C1-INH
Genes affected	SERPING1	SERPING1	Coagulation factor XII (HAE-F12) Plasminogen (HAE-PLG) Angiopioetin-1 (HAE-ANGPT1) Kininogen-1 (HAE-KNG1) Myoferlin (HAE-MYO) Heparin (HAE-HS3ST6) Carboxypeptidase (HAE-CPN1) VEGF-R2 (HAE-DAB2P) Other unknown genes
Gene products affected and cause of angioedema	C1-INH	C1-INH	Coagulation factor XII- (bradykinin) Plasminogen- (bradykinin) Angiopioetin-1- (vascular leak vs bradykinin?) Kininogen-1- (bradykinin) Myoferlin- (vascular leak vs bradykinin?) Heparin- (bradykinin?) CPN1- carboxypeptidase N subunit 1 deficiency (bradykinin, anaphylatoxins?) urticaria & angioedema VEGFR2- (vascular leak?) urticaria & angioedema Other unknown gene products

SERPING1: serine esterase protease inhibitor G1; C1-INH: C1-esterase inhibitor; HS3ST6: heparin sulfate-glucosamine 3-sulfotransferase 6.

Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.
Denis V. JACI Global Sept 2024 PMID 39239323
D'Apolito M et al. JACI Sept2024 PMID 38823490

Special Article

US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema

Paula J. Busse, MD[a,*], Sandra C. Christiansen, MD[b,*], Marc A. Riedl, MD, MS[b,*], Aleena Banerji, MD[c], Jonathan A. Bernstein, MD[d], Anthony J. Castaldo, MPA[e], Timothy Craig, DO[f], Mark Davis-Lorton, MD[g], Michael M. Frank, MD[h], H. Henry Li, MD, PhD[i], William R. Lumry, MD[j], and Bruce L. Zuraw, MD[b,k,*] *New York and Mineola, NY; La Jolla and San Diego, Calif; Boston, Mass; Cincinnati, Ohio; Fairfax City, Va; Hershey, Pa; Durham, NC; Chevy Chase, Md; and Dallas, Tex*

HAE-nl-C1INH	
Required	A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
Required	Documented normal or near normal C4, C1-INH antigen, and C1-INH function
Either (at least 1 required)	(1) Demonstration of a mutation associated with the disease; OR (2) A positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (ie, cetirizine at 40 mg/d or the equivalent) for at least 1 mo or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer
Supportive	(1) A history of rapid and durable response to a bradykinin-targeted medication; AND (2) Predominant documented visible angioedema; or in patients with predominant abdominal symptoms, evidence of bowel wall edema documented by CT or MRI

Received: 16 September 2021 | Revised: 22 November 2021 | Accepted: 8 December 2021
DOI: 10.1111/all.15214

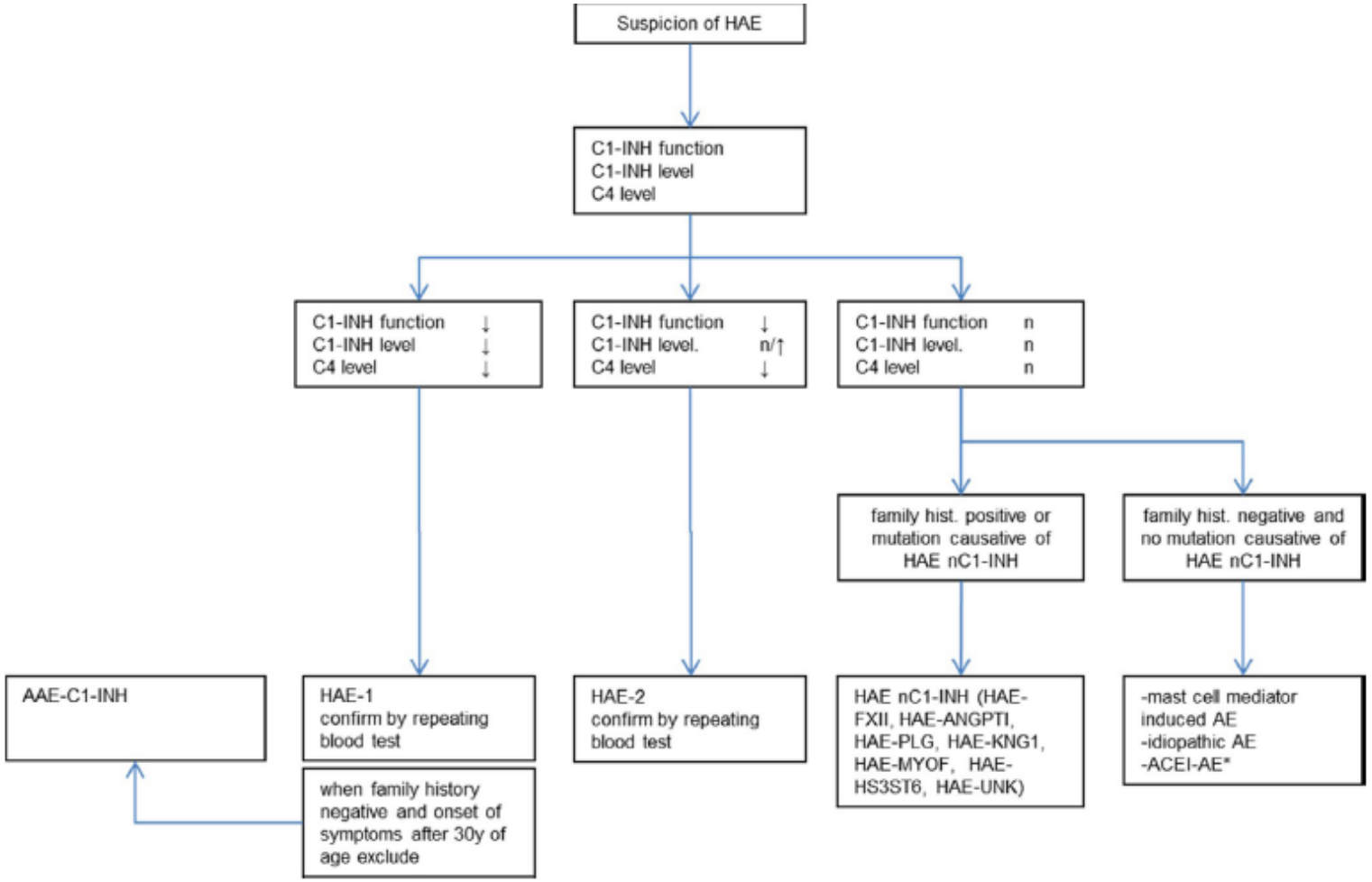
POSITION PAPER

Allergy EAACI WILEY

The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update

RECOMMENDATION 3

We recommend that patients who are suspected to have HAE and have normal C1-INH levels and function are assessed for known mutations underlying HAE-nC1-INH



HAE nC1-INH diagnosis:

*Genetic testing

If negative

*Family history

*Fail antihistamines

*Possibly omalizumab, epi, corticosteroid, cyclosporin

Original Article

Hereditary Angioedema With Normal C1 Inhibitor: US Survey of Prevalence and Provider Practice Patterns

Marc A. Riedl, MD, MS[a], Mark Danese, MHS, PhD[b], Sherry Danese, MBA[b], Julie Ulloa[b], Andreas Maetzel, MD, MSc, PhD[c], and Paul K. Audhya, MD, MBA[d] *San Diego and Agoura Hills, Calif; Cambridge, Mass; and Toronto, Ontario, Canada*

How does this study impact current management guidelines? This study describes diagnostic and management strategies of physicians caring for HAE-nl-C1INH patients, providing real-world data for comparison with current guideline recommendations. Results may be helpful for future clinical studies in this population.

Response to medication was commonly used to inform diagnosis (antihistamine response or nonresponse used by 73% of physician respondents, corticosteroids by 57%, or HAE-specific medications by 74%), and Factor XII genetic testing was used by 43%.

TABLE I. Demographic and practice characteristics of physicians and survey respondents

Characteristic	Physicians, n (%) (n = 81)
Specialty	
Allergy and/or immunology	81 (100)
Years in practice	
Mean (SD)	15.9 (8.5)
Median	14.0
Practice setting, %	
Solo private practice	20
Private group practice	51
Community hospital	—
Academic medical center	28
Government-affiliated practice (including veterans hospitals)	—
Prescription volume*	
Low prescribers (2-21 hereditary angioedema–related prescriptions/y)	51 (63)
High prescribers (32-314 hereditary angioedema–related prescriptions/y)	30 (37)

*Results are based on aggregate data.

Original Article

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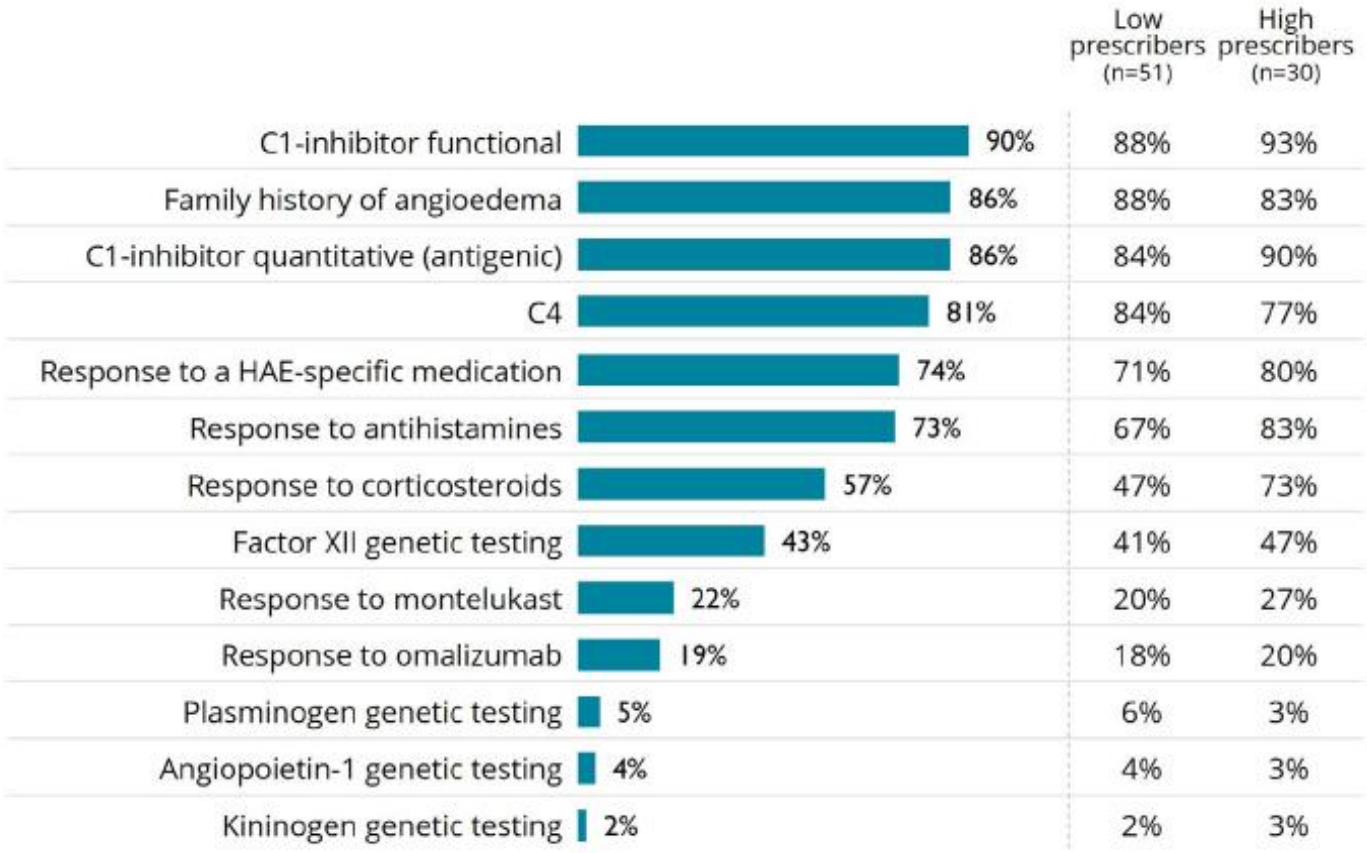
From this survey they estimated between 1230-1332 patients in the USA with HAEnC1



What dose of antihistamines?

Minimal use of omalizumab!

What dose of omalizumab?

Why so little genetic testing?

FIGURE 2. Physician reported assessments used to inform diagnosis of hereditary angioedema (HAE) with normal C1-INH levels, overall and by physician prescription volume (n = 81).

Original Article

Hereditary Angioedema With Normal C1 Inhibitor: US Survey of Prevalence and Provider Practice Patterns

Marc A. Riedl, MD, MS[a], Mark Danese, MHS, PhD[b], Sherry Danese, MBA[b], Julie Ulloa[b], Andreas Maetzel, MD, MSc, PhD[c], and Paul K. Audhya, MD, MBA[d] *San Diego and Agoura Hills, Calif; Cambridge, Mass; and Toronto, Ontario, Canada*

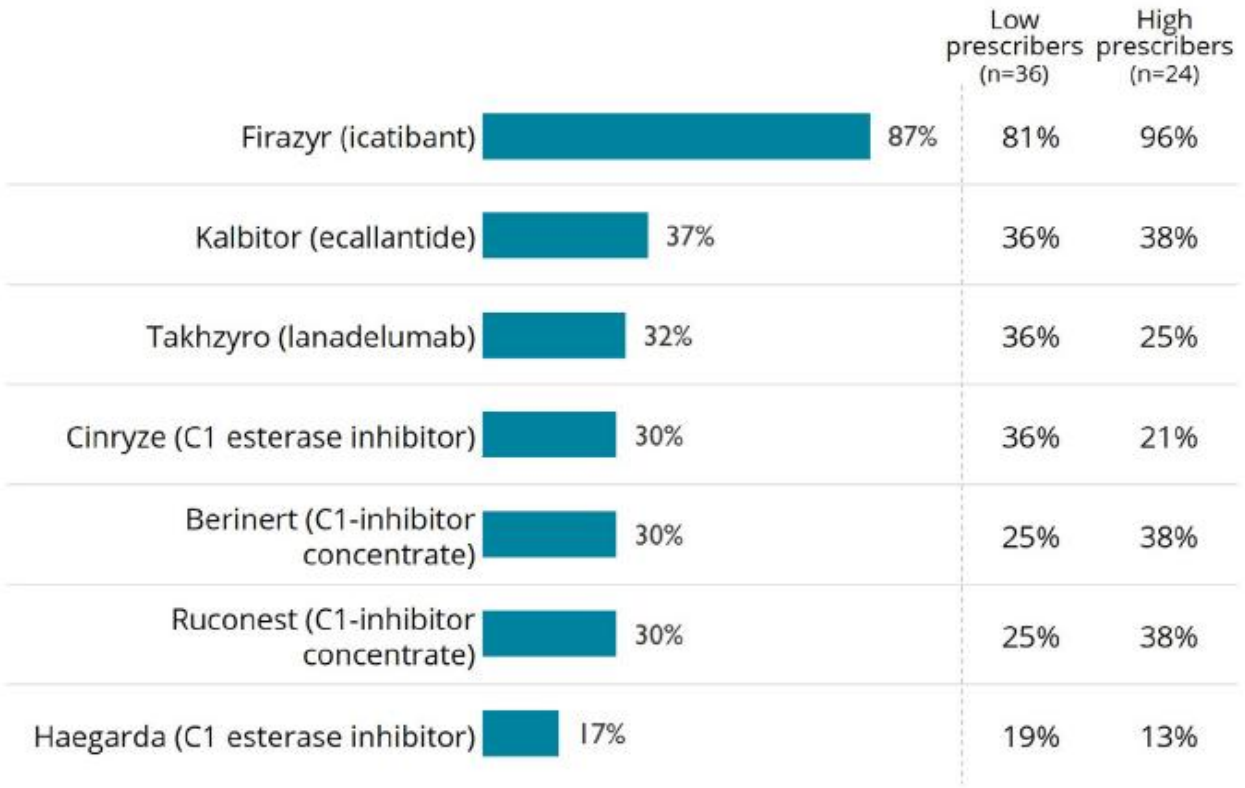


FIGURE 3. Physician-reported hereditary angioedema (HAE)-specific medications used to inform diagnosis of HAE with normal C1-INH levels (n = 60).

What is a response to HAE specific drugs?

How long does it take on-demand therapy to work?

How do you assess response to LTP?

Takeda did a study on these patients with lanadelumab and the result was no difference on placebo or lanadelumab

43 of 120 patients did not respond to antihistamines

LETTER TO THE EDITOR Open Access

High occurrence of antihistamine resistance in patients with recurrent idiopathic angioedema

Zonne L. M. Hofman[1,2], Nikki van West[3], C. Erik Hack[2], André C. Knulst[2,3], Coen Maas[1] and Heike Röckmann[3*]

Abstract

Antihistamines are the most prescribed therapy in recurrent idiopathic angioedema, yet little is known about their efficacy. Herein, we report on clinical improvement with antihistamine therapy in 120 patients evaluating angioedema attack frequency. A high incidence (36%) of antihistamine refractory cases was observed. Forty percent of patients on antihistamine prophylaxis suffered from 1 or more angioedema attacks per month. Our findings stress the need for additional treatment options for recurrent idiopathic angioedema.

Keywords: Angioedema, Idiopathic angioedema, Antihistamines, Omalizumab

Hofman et al. Clin Transl Allergy (2019) 9:35
https://doi.org/10.1186/s13601-019-0274-7

Omalizumab for treatment of idiopathic angioedema

Vinay P. Goswamy, MD*; Kristine E. Lee, MS†; Elizabeth M. McKernan, BS*;
Paul S. Fichtinger, BS*; Sameer K. Mathur, MD, PhD*; Ravi K. Viswanathan, MD*

* Division of Allergy, Pulmonary and Critical Care, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
† Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Prerandomization treatment regimens included H_1 with or without H_2 antagonist therapy, with H_1-antagonist dosing ranging from as needed to 4 times approved dosing. We excluded those patients with a diagnosis of chronic urticaria with or without AE, hereditary or acquired AE (confirmed by evaluation of complement profile), ACE-I–associated AE, a recent history of life-threatening AE, a history

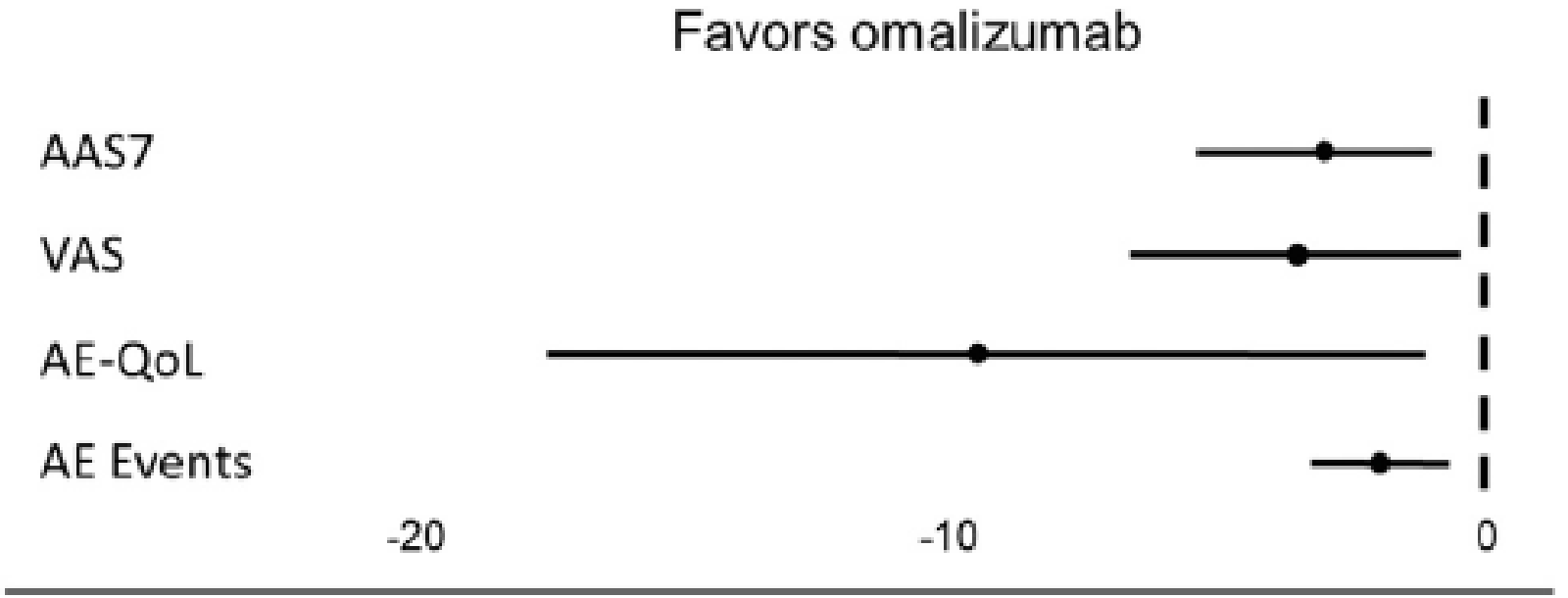


Figure 5. Generalized linear regression results for omalizumab compared with placebo for AAS7 (binary: difference in ln(odds)), VAS (binary: difference in ln(odds)), AE-QoL (continuous: difference in score), and AE events (count: difference in ln(count)). AAS7, Angioedema Activity Score for 7 days; AE, angioedema; AE-QoL, Angioedema Quality of Life Questionnaire; VAS, Visual Analogue Scale.

In histamine non-responders chronic spontaneous angioedema omalizumab is effective when compared to placebo

High-dose omalizumab use in patients with chronic spontaneous urticaria

Mehran Alizadeh Aghdam, MD, Fenne van den Broek, MD, Feiko Rijken, MD, PhD, Andre Cornelis Knulst, MD, PhD, and Heike Röckmann, MD, PhD

Clinical Implications

- Updosing omalizumab shows a clinical benefit in 61% of the patients with insufficient response to the standard dose of omalizumab.

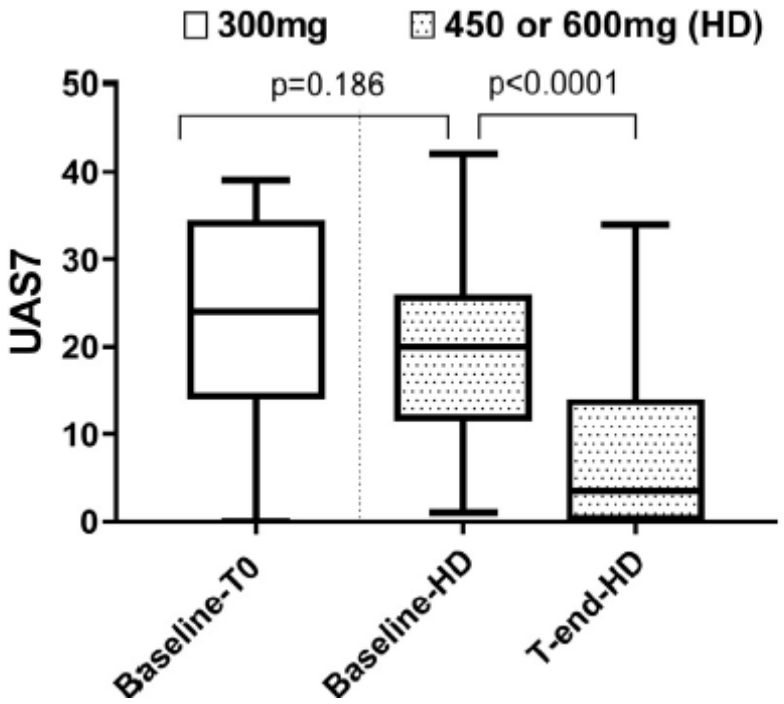


TABLE I. Treatment response to standard-dose and HD treatment

Treatment response based on UAS7 and UCT score*	Standard dose	HD
Complete responders	0 (0)	14 (32)
Partial responders	13 (30)	13 (30)
Nonresponders	23 (52)	14 (32)
Missings	8† (18)	3‡ (7)

61% of patients that did not respond to 300 every month responded to up-dosing of omalizumab

J ALLERGY CLIN IMMUNOL PRACT
VOLUME 8, NUMBER 4

Oral Sebetralstat for Acute HAE Attacks; inhibits kallikrein

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ORIGINAL ARTICLE

Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks

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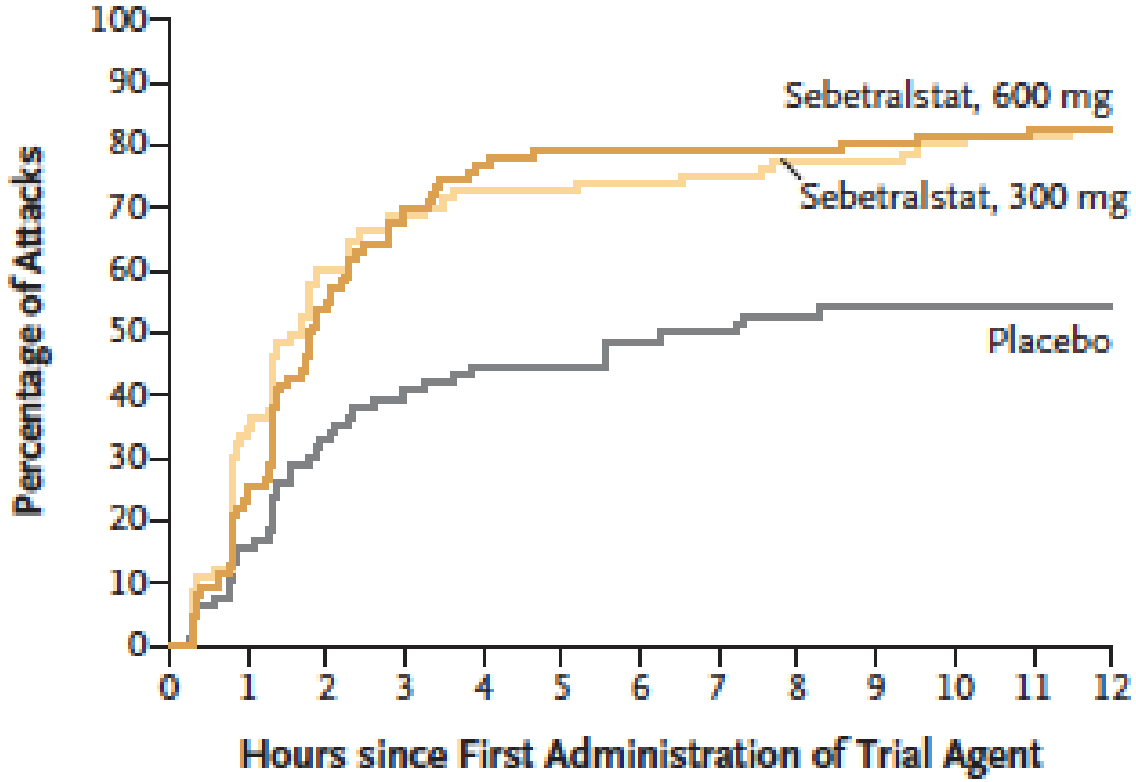
Can you predict response to HAE medications with one dose?

N Engl J Med 2024;391:32-43.

A 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

Takeda study in HAE-n-C1INH

Expanded Access for the Prevention of Acute Attacks of 1) Hereditary Angioedema (HAE) in Children and 2) Non-histaminergic Angioedema With Normal C1-Inhibitor (C1-INH) in Teenagers and Adults

No difference in response between those on lanadelumab and placebo

Results were never published

ClinicalTrials.gov

Grand Rounds Review

Angioedema With Normal Complement Studies: What Do We Know?

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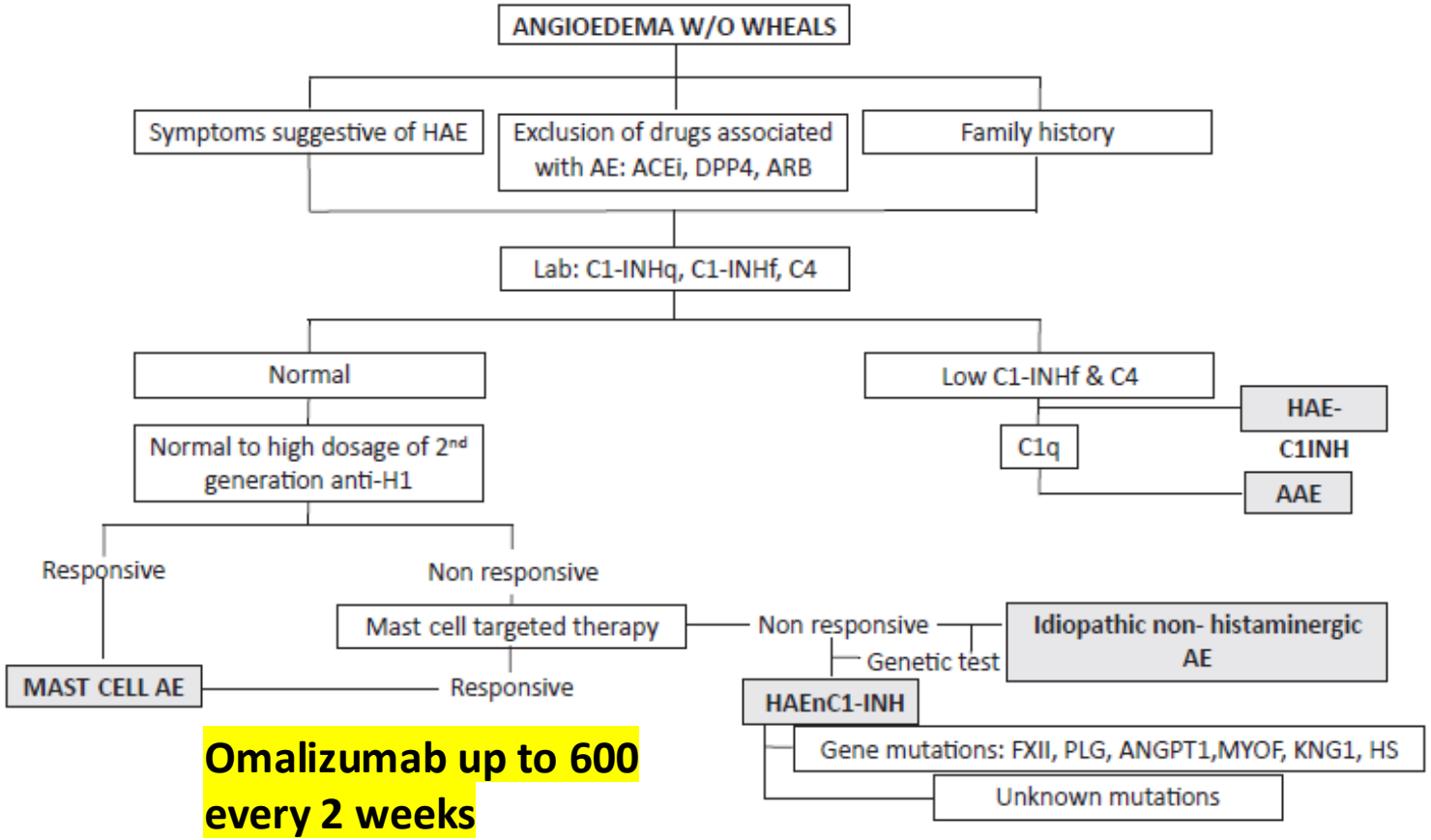
Max dose of antihistamines



Genetic testing

Omalizumab up to 600 every 2 weeks

FIGURE 1. Proposed algorithm for diagnosis of angioedema without (W/O) wheals. *ACEi*, angiotensin converting enzyme inhibitor; *AE*, angioedema; *ANGPT1*, HAE-angiopoietin-1; *ARB*, angiotensin receptor blocker; *C1-INH*, inhibitor of C1 esterase; *DPP4*, dipeptidyl peptidase-4; *FXII*, Factor XII; *HAE*, hereditary angioedema; HAEnC1-INH, HAE with normal C1-INH; *HS*, heparan sufate with *HS3ST6, HAE-HS3ST6*; *KNG1*, HAE-KNG1; MYOF, myoferlin gene; *PLG*, plasminogen.

- In the past we focused on treating attacks.
- Now we focus on preventing attacks.
- Newer medications in development seem to have increase efficacy and less burden
- My suspicion is that we are approaching a “relative cure” for HAE and we need better guidelines that focus on who should be on prophylaxis, and which agent is most appropriate for specific populations.
- For HAE-nl-C1INH, if genetic negative, patients should fail max dose of antihistamines and max dose of omalizumab
- Most importantly, we need to increase access for patients in low and middle-income countries to these therapies

Thank you from Allergy, Asthma and Immunology Penn State University, Hershey, PA, USA

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