Hereditary Angioedema Overview

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Learning Objectives

- Overview of Angioedema and specifically HAE
- Recognize challenges of treating HAE
- Integrate recent pediatric HAE study data
- Assess the impact of HAE
- Review treatment options for HAE patients

Differential Diagnosis

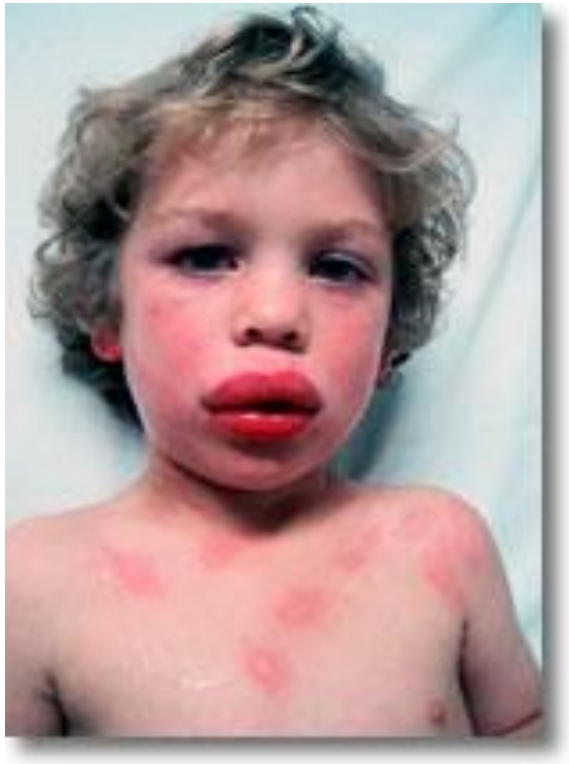
- Allergic or Pseudoallergic
- Idiopathic Angioedema
- Drug-induced angioedema
- Hereditary Angioedema
- Acquired Angioedema

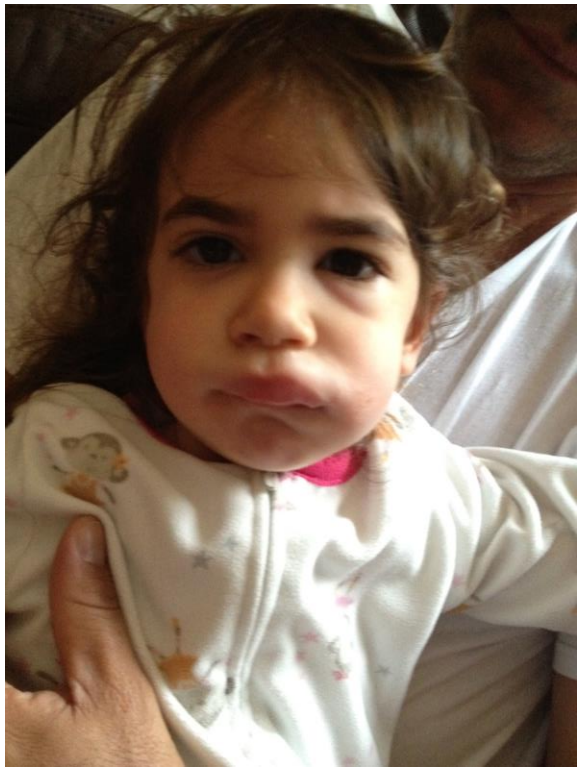
Sites of Angioedema

- 94% of patients get head and neck swelling
    - Complications include respiratory track involvement
- 82% of patients are managed medically
- 18% require intubation
- Edema can involve:
    - Head and Neck (incl. Tongue, Lips, Pharynx, Larynx)
    - Gastrointestinal Tract
    - Genitalia
    - Extremities

Megerian CA et al. Laryngoscope 1992;102(3)256-60

Allergic or Non-Allergic Angioedema?





With permission

History of HAE

YEAR	MILESTONE
1876	Disease first described[1]
1882	Name assigned to the disease[1,2]
1888	First complete clinical description[2]
1917	Mode of inheritance identified[2]
1963	Biochemical basis defined as insufficient activity of C1-INH[3]
1986	Defective gene identified and cloned[4,5]
2003	Bradykinin implicated as likely mediator of HAE attack symptoms[6]

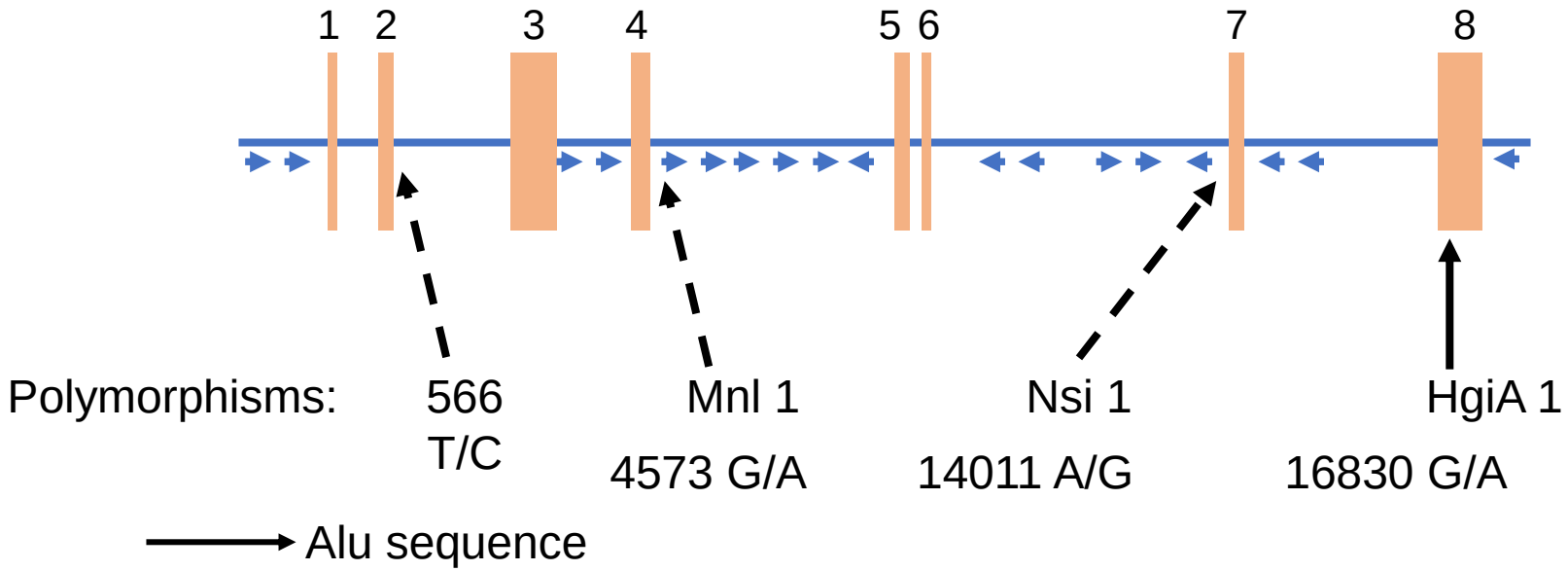
1. Nzeako UC, et al. *Arch Intern Med* 2001;161:2417-2429.
2. Agostoni A, Cicardi M. *Medicine* 1992;71:206-215.
3. Donaldson VH, Evans RR. *Am J Med* 1963;35:37-44.
4. Bock SC, et al. 1986 *Biochemistry* 1986;25:4292-4301.
5. Davis AE, et al. *Proc Natl Acad Sci* USA 1986;83:3161-3165.
6. Davis AE. *Clin Immunol* 2005;114:3-9.

Overview of HAE

- Rare, autosomal dominant disease[1,2]
- Caused by mutations in the gene for C1-esterase inhibitor (C1-INH)[2-4]
- Characterized by intermittent attacks of nonpitting, nonpruritic edema in the absence of urticaria[1,2]
- Prevalence estimated to be 1 in 10,000 to 1 in 50,000 persons[1,5,6]
- Not linked to race[7]
- Variable age of onset of symptoms[8]
- Women tend to be affected by a higher frequency and a greater severity of attacks than men[3]

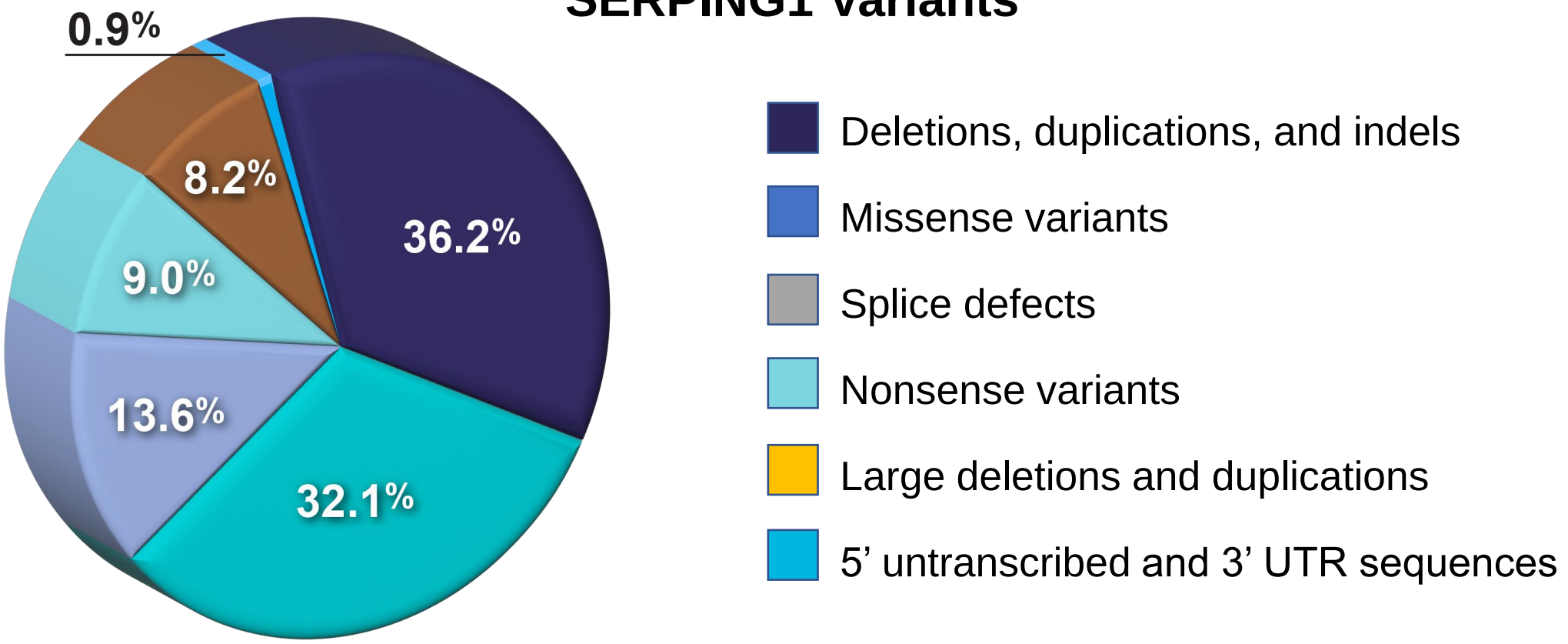
1. Gompels MM, et al. 2005.
2. Zuraw BL, 2008.
3. Bork K, et al. 2006.
4. Cugno M, et al. 2009.
5. Bowen T, et al. 2008.
6. Tosi M,1998.
7. Nzeako UC, et al. 2001.
8. Roche O, et al. 2005.

C1-INH Gene and Mutation Sites



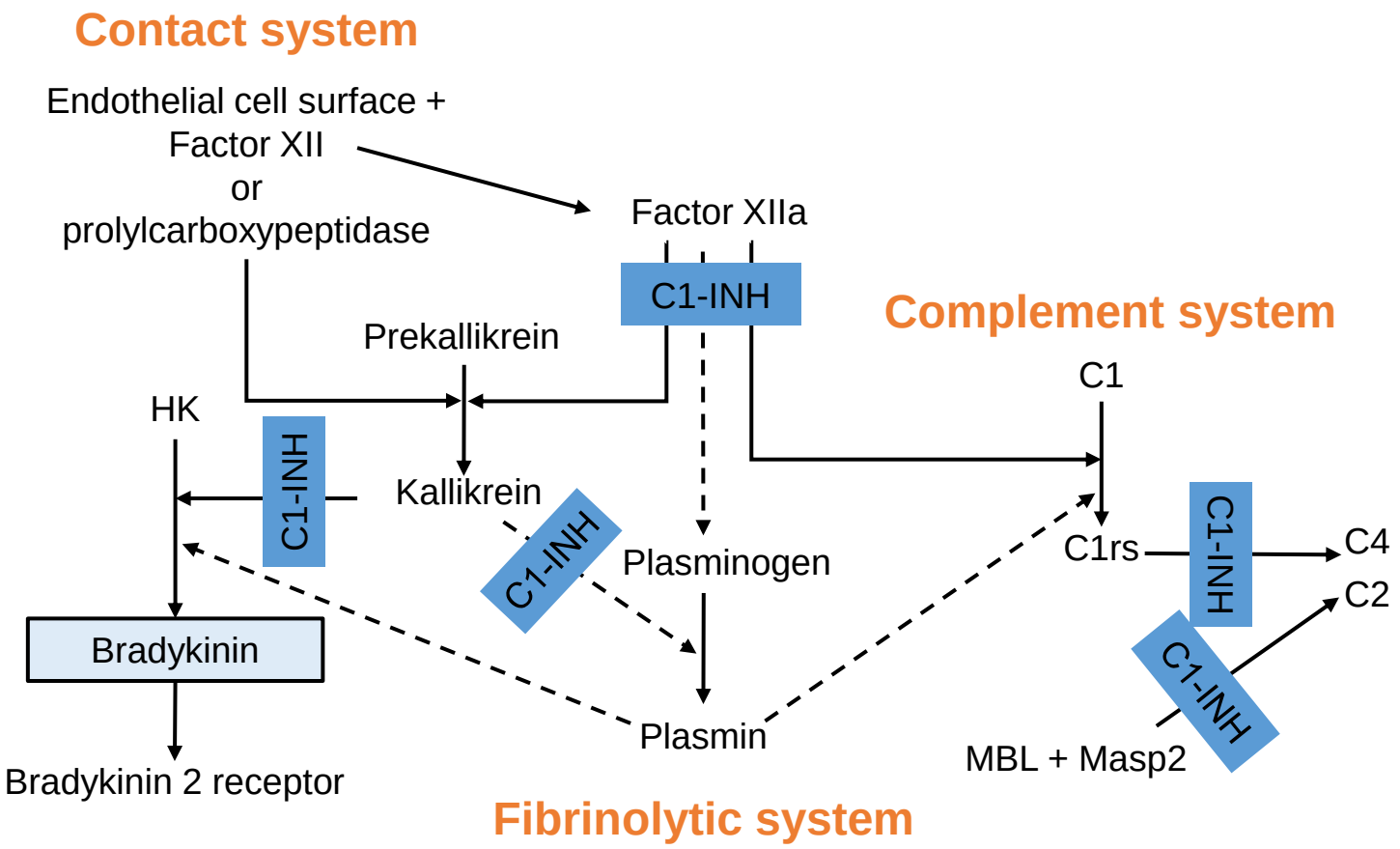
- Located on chromosome 11, consists of 8 exons and 7 introns, and is approximately 1.7 x 10^4 base pairs in length
- 25% of cases are spontaneous mutations without a family history

Gene Mutations



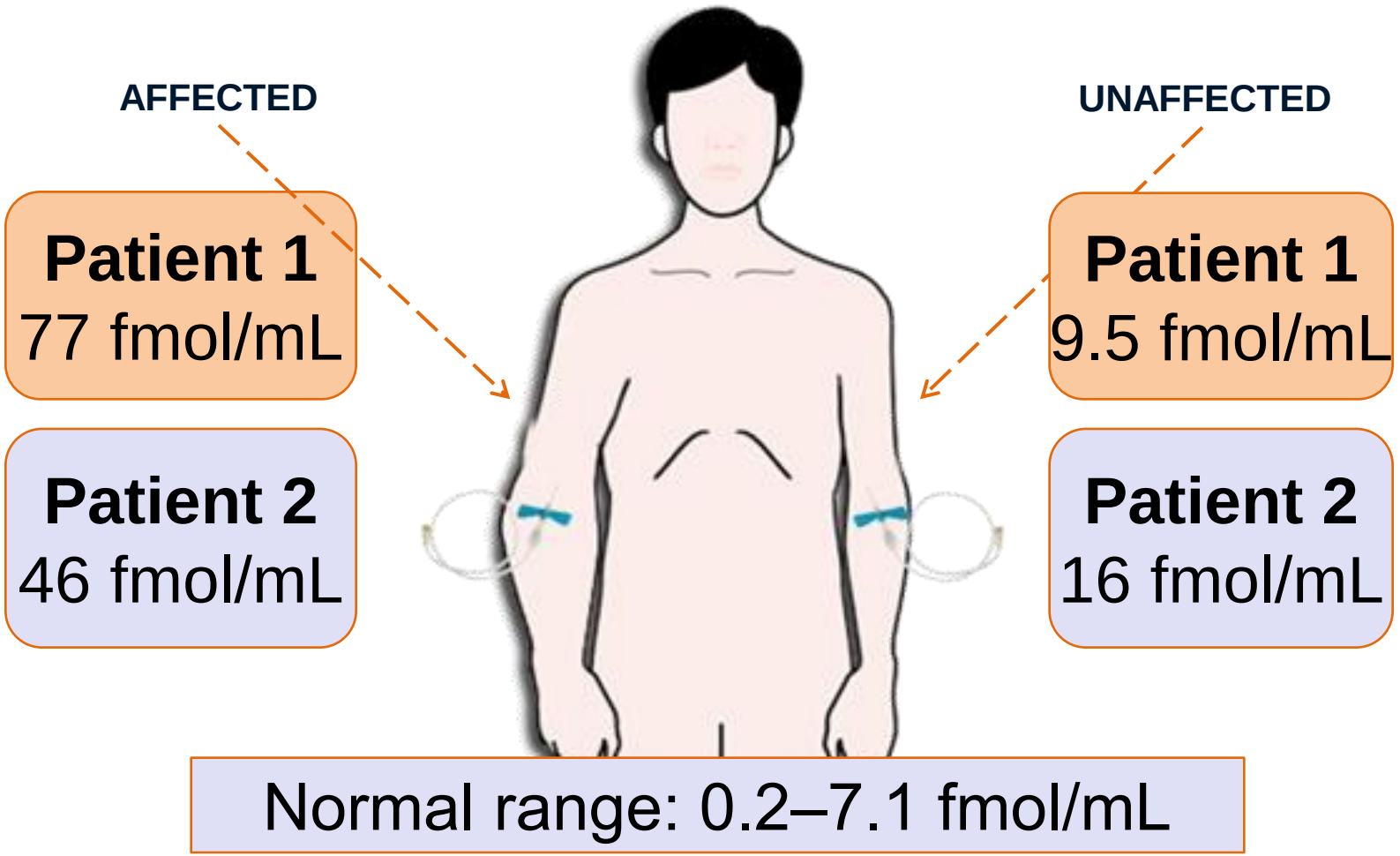
UTR: untranslated region.

Biologic Role of C1 Inhibitor



C1: complement component 1; C1rs: C1r and C1s complex; C2: complement component 2; C4: complement component 4; Factor XIIa: activated Factor XII; HK: high-molecular weight kininogen; Masp: MBL-associated serine proteases; MBL: mannose-binding lectin.

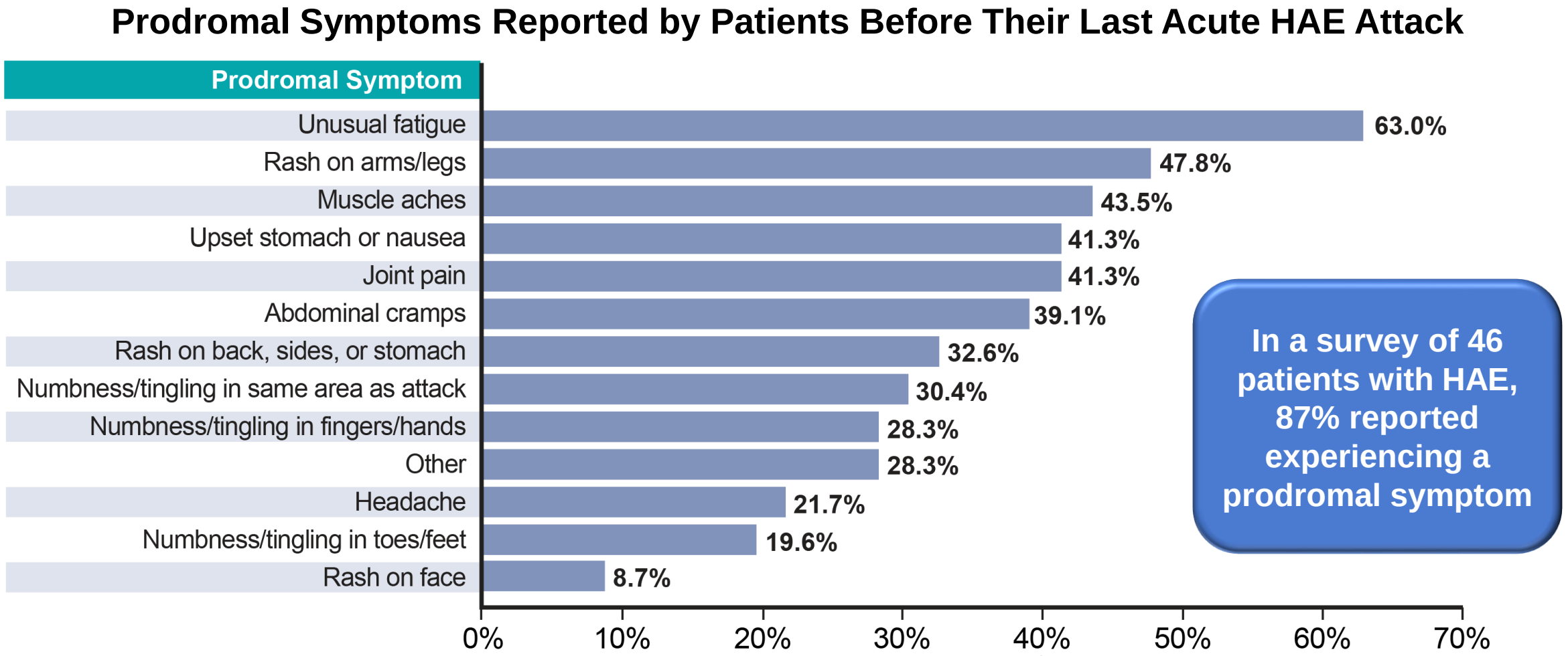
Elevation of Bradykinin During HAE Attacks



- During brachial attacks in 2 patients with HAE, bradykinin levels were 3- to 8-fold higher in blood drained from affected arm vs unaffected arm

Nussberger J, et al. *J Allergy Clin Immunol*. 1999;104(6):1321-1322.

Most HAE Patients Report Prodromal Symptoms



In a survey of 46 patients with HAE, 87% reported experiencing a prodromal symptom

Prematta MJ, et al. *Allergy Asthma Proc*. 2009;30:506-511. Reproduced for educational purposes only.

Sample Case Presentation

- 8 year old Caucasian male presents to the ED with facial angioedema since waking up
- This is the 4th such episode in the past 3 months
- Symptoms resolve without any medication, but they may last 3 days
- He denies any associated urticaria
- He cannot recall any triggers
- PMH: allergic rhinitis, functional abdominal pain (IBS)
- Meds: None
- Doing well in 3rd grade. Older brother and sister, asymptomatic
- ROS unremarkable

HAE Acute Attack Symptoms

- Many patients experience one or more warning signs that an attack is coming, for example[1-3]:
  - Sudden mood changes, anxiety, or complete exhaustion
  - A tingling sensation in the soon-to-be-affected area
  - A painless, non-itchy rash, which may resolve in one location while developing in another location
- When an attack occurs, symptoms typically worsen for the first 24-36 hours, then slowly resolve during the next 36-48 hours[3]
- The frequency, severity, and location of HAE symptoms can vary widely, even in the same patient[2]

1. Zuraw BL, Christiansen SC. *Allergy Asthma Proc* 2009;30:487-492.
2. Bowen T, et al. Allergy Asthma Clin Immunol 2010;6:24.
3. Agostini A, et al. *J Allergy Clin Immunol* 2004;S51-S131

Triggers of HAE

- Any inflammation or stress including:
  - Infection
  - Trauma (incl dental work)
  - Barometric change
  - Pregnancy
  - Menstruation
  - Mental Stress
  - Drugs

Zuraw B. JACI 2012
Bork K Am J Med 2006

Prodromes of HAE

- Early signs of an attack include:
  - Nausea
  - Abdominal cramping
  - Rash (erythema marginatum)
  - Numbness/Tingling
  - Fatigue
  - Muscle Aches
  - Dysphonia

Craig T. World Allergy Org J 2012

Diagnosis of HAE

Features to prompt investigation for HAE[1]:

- Angioedema that is nonpruritic, nonurticarial, and unresponsive to antihistamine
- Serpiginous rash (erythema marginatum)
- Unexplained abdominal pain
- Family history of HAE

Gompels MM, et al. 2005.

Diagnosis of HAE

- Diagnosis of HAE requires laboratory testing[1]
  - Step 1: Measure C4 level
  - Step 2: Measure C1-INH function and C1-INH antigen level

	C4 Level	C1-INH Function	C1-INH Antigen Level	C1q
Type 1 HAE	Low	Low	Low	Normal
Type 2 HAE	Low	Low	Normal or high	Normal
HAE nC1inh	Normal	Normal	Normal	Normal
Acquired AE	Low	Low	Low	Low
ACE-i assoc'd	Normal	Normal	Normal	Normal

Zuraw BL, Christiansen SC, 2009.

Diagnosis of HAE

- Diagnosis of HAE [1]
  - For patients treated with androgens wait 3 weeks
  - For patients treated with C1-INH or FFP wait 1 week

  - Serum should not be left standing >4 hours

1. Wagenaar-Bos et al. 2008

Inaccurate Diagnosis of HAE

- HAE can be diagnosed with a blood test to measure C1-INH function, along with the patient's description of symptoms and family history[1,2]
- HAE is often undiagnosed or misdiagnosed [3]
- Reasons for non-diagnosis or misdiagnosis are that[3]:
  - HAE is rare
  - HAE symptoms may mimic symptoms of other conditions
  - As of 2005, the average time between onset of symptoms and diagnosis was 13.1 years[4]
  - Only 51-64% of physicians use C4 levels to aid in diagnosis[5]

1. Zuraw BL, Christiansen SC. *Allergy Asthma Proc* 2009;30:487-492.
2. Bowen T, et al. Allergy Asthma Clin Immunol 2010;6:24.
3. Agostini A, et al. *J Allergy Clin Immunol* 2004;S51-S131
4. Roche O, et al. *Ann Allergy Asthma Immunol.* 2005;94:498-503.
5. Riedl M et al. Ann Allergy Asthma Immunol 2011. 104(3);211-214

HAE with normal C1inh[1]

- Formerly known as Type III HAE
- First described in 2000
- Lack of clear diagnostic criteria
- Heterogeneity among affected patients
- Consensus criteria developed during 2009 symposium should help physicians better diagnose and treat these patients
- Subtypes expanding
- Treatment should not be used as a diagnostic aid

Zuraw et al Allergy Asthma Proc. 2012
Bork K Am J Med 2007
Duan QL JACI 2009

HAE with normal C1inh

- Compared to type 1 and type 2 HAE:
  - Present later in life (mean age 26.8 vs 11.7)
  - Have more prominent involvement of tongue, uvula and face 54% vs 12%
  - Less frequent abdominal attacks 50% vs 90%
  - Females affected more often and more severely
  - Less intense and more variable disease activity
  - Different cutaneous findings (less bruising and prodromes)
  - Low penetrance

Zuraw et al Allergy Asthma Proc. 2012
Bork K Am J Med 2007
Duan QL JACI 2009

Pathogenesis of normal C1inh HAE

- The mediator(s) responsible for swelling has not been definitively identified.
- Excess generation of bradykinin is major facilitator of angioedema in C1INH-HAE. Activation of the kinin system is also thought to be critical in HAE with normal C1INH, but this has not been conclusively demonstrated.
- Underlying molecular defect(s) for most patients with HAE with normal C1INH has not been determined, although pattern of affected family members in successive generations supports autosomal dominant mode of inheritance.

Kaplan SP JACI 2010

Normal C1inh HAE – Deeper Dive

- Hereditary angioedema (HAE) with normal C1-INH (HAEnCI) may be linked to specific mutations in the coagulation factor 12 (FXII) gene (HAE-FXII) or functional mutations in other genes that are still unknown.
- Mutation in plasminogen (PLG) gene c.9886A>G located in exon 9 leading to the missense mutation p.Lys330Glu (K330E) in the kringle 3 domain of the PLG protein in 4 of 7 families transmitted by AD trait.
- The PLG gene mutation was present in all studied symptomatic patients and also found in 9/38 index patients from 38 further families with HAEnCI. Most patients had swelling of face/lips/tongue (78.3%).
- 331/3795 tongue swellings (8.7%) were associated with dyspnea, voice changes, and imminent asphyxiation. Two women died by asphyxiation due to a tongue swelling.

Bork K et al. Allergy 2018 Feb;73(2):442-450. doi: 10.1111/all.13270. Epub 2017 Sep 7

Normal C1inh HAE – Deeper Dive

- Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema.

- Missense mutation (ANGPT1, c.807G>T, p.A119S) in a family with U-HAE, detected in all members of the index family with U-HAE but not in asymptomatic family members or an additional 20 patients with familial U-HAE, 22 patients with sporadic U-HAE, and 200 control subjects.

- Among 6 examined members of the other family, 3 suffer mainly tongue swellings and 2 healthy carriers detected. Last of the examined members of this family, despite not carrying the PLG K330E variant, was present with attacks of eyelid swelling and/or abdominal pain.

Bafunno V et al. JACI 2018 Mar;141(3):1009-1017.

Criteria for the Diagnosis of HAE-nl-C1INH (US HAEA Medical Advisory Board 2020 Guidelines for the Management of HAE)[1]

Required

- History of recurrent angioedema in the absence of concomitant urticaria
- No concomitant use of medication known to cause angioedema
- Documented normal or near normal C4, C1-INH antigen, and C1-INH function

Either (at least 1 required)

Demonstration of a genetic variant associated with the disease:

- *F12*
- *PLG*
- *MYOF*[2]
- Unknown genetic variant
- *ANGPT1*
- *KNG1*
- *HS3ST6*[2]

OR

A positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy* for ≥1 month or an interval expected to be associated with ≥3 attacks of angioedema, whichever is longer

Supportive

History of rapid and durable response to a bradykinin-targeted medication

AND

Predominant, documented visible angioedema; or in patients with predominant abdominal symptoms, evidence of bowel wall edema documented by CT or MRI

- *De novo* cases of HAE-nl-C1INH have been documented[3]
- The identified mutations account for a subset of HAE-nl-C1INH[1]
- Documented photos may be helpful for managed care approval

*ie, cetirizine at 40 mg/d or the equivalent.

ANGPT1=angiopoietin 1; CT=computed tomography; F12=coagulation factor XII; HAE-nl-C1INH=HAE with normal C1INH; HS3ST6=heparan sulfate-glucosamine 3-sulfotransferase 6; KNG1=kininogen 1; MRI=magnetic resonance imaging; MYOF=myoferlin; PLG=plasminogen; US HAEA=United States Hereditary Angioedema Association.

References: 1. Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150. **2.** Bork K, et al. *J Allergy Clin Immunol Pract.* 2021;148(4):1041-1048. **3.** Riedl MA. *J Allergy Clin Immunol Pract.* 2013;1(5):427-432.

HAE Normal Complement Mutations

Gene	*F12*	*PLG*	*ANGPT1*	*KNG1*	*MYOF*	*HS3ST6*
Mutation	T328K T328R c.971_1018 + 24del72 c.892_909dup	K330E	A119S A8V Q370H	M379K	R217S	T144S

F12: Factor XII; HS3ST6: heparin sulfate-glucosamine 3-O-sulfotransferase 6; KNG1: kininogen 1; MYOF: myoferlin; PLG: plasminogen.
Santacroce R, et al. *J Clin Med*. 2021;10:2023.

HAE Normal Complement Mutations

Hereditary angioedema with normal C1 Inhibitor associated with Carboxypeptidase N deficiency

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[*] Both authors share the senior authorship

Is the Diagnosis of HAE Elusive?

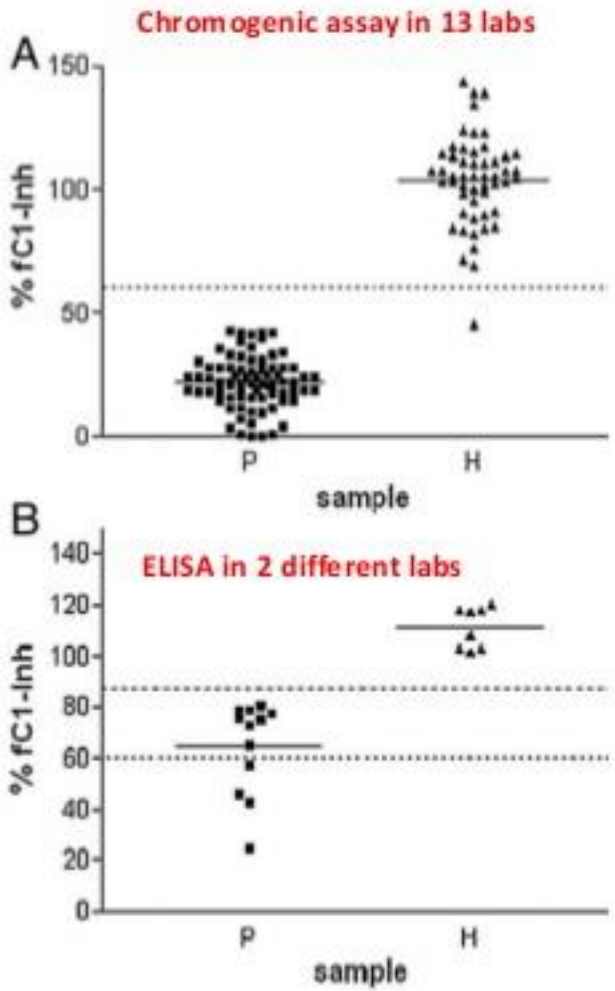
Not all assays are equal

- C1 inhibitor functional assay by ELISA
- ELISA assay detects the complexes formed between C1-INH and C1r or C1s following activation of C1
  - Traditional but low sensitivity
- Chromogenic C1 inhibitor functional assay
- Measures inhibition of C1s activity by plasma C1 inhibitor
  - PPV 98%; NPV 100%
  - limited availability
  - fC1inh stability plasma>serum; store at or below-20^{0}C

J Immunol Methods. 2008 Sep 30;338(1-2):14-20. doi: 10.1016/j.jim.2008.06.004. Epub 2008 Jul 23

Functional C1-Inhibitor diagnostics in hereditary angioedema: Assay evaluation and recommendations

Obj: evaluated performance of fC1- Inh assays in 15 different laboratories that are specialised in HAE diagnostics



- Chromogenic assay measures inhibition activity of target protease C1s by C1-Inh in the plasma sample to be tested
- ELISA assay detects complexes formed between C1Inh and C1r or C1s following activation of C1

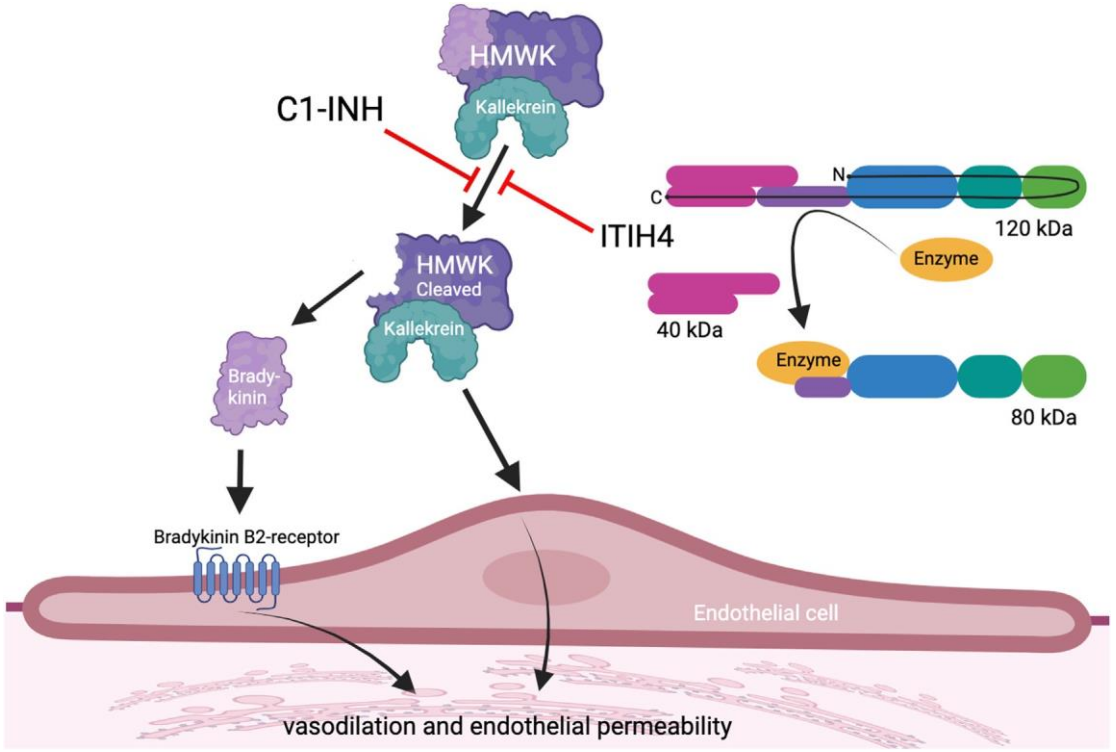
- Chromogenic assay:
  PPV 98 %
  NNV 100 %

- fC1-Inh is more stable in plasma than in serum and samples should be stored at or below –20 °C

Wagenaar-Bos I. et. al. Journal of Immunological Methods 2008;338:14–20

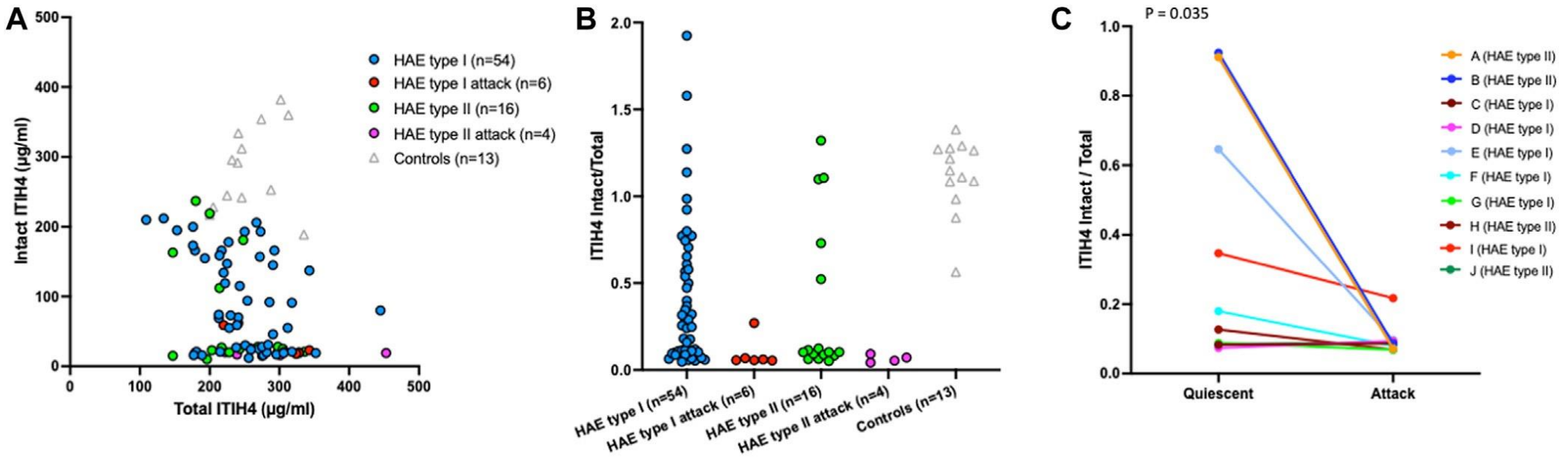
ITIH4 - inhibitor of cascades like KKS

- Cleaved by several human proteases; eg, plasma kallikrein
- Protease inhibitor
- Acts as bait that, on cleavage, forms noncovalent inhibitory complex with executing protease
- No impact of the freeze–thaw treatment as assay



Troldborg A et al. Inter-a-trypsin inhibitor heavy chain 4 (ITIH4) as a compensatory protease inhibitor in hereditary angioedema. J Allergy Clin Immunol 2024

ITIH4 - inhibitor of cascades like KKS



Troldborg A et al. Inter-a-trypsin inhibitor heavy chain 4 (ITIH4) as a compensatory protease inhibitor in hereditary angioedema. J Allergy Clin Immunol 2024

Diagnosis of HAE

- If labs are not helpful, consider other diagnoses in differential:
  - Autoimmune disorders
  - Thyroid disorders
  - Superior Vena Cava syndrome, tumors
  - Cheilitis granulomatosa (Miescher's cheilitis)
  - Melkersson-Rosenthal syndrome
  - Trichinosis
  - Hypereosinophilic Syndrome (incl. Gleich syndrome)
  - Urticarial Vasculitis

Levenson MJ et al. 1984
Weller PF Blood 1994
Jara LJ Curr Rheumatol Rep 2009

Confounding Medications

- ACE-I's
- Exogenous hormones (estrogens)
- NSAIDs and ASA
- Ca channel Blockers
    - Dihydropyridines (eg, amlodipine, nifedipine)
    - Nondihydropyridines (eg, diltiazem, verapamil)
- Herbal Tx: garlic, sanyak, and *Ecballium elaterium*
- sirolimus, everolimus, amiodarone, metoprolol, risperidone, paroxetine, and etanercept

Levenson MJ et al. 1984
Yusuf et al NEJM 2008
Abdi et al. Pharmacotherapy 2002
Southward Ann Pharmacol 2009
Micozzi MS Skinmed 2010
Kestler A NEJM 2003

Back to the Sample Case

- 8 year old Caucasian male with recurrent bouts of angioedema without urticaria or pruritus
- On further questioning, parents recall scrotal swelling in the 1st year of life.
- Has missed 5-10 days of school due to severe abdominal pain, diagnosed with Irritable Bowel Syndrome
- Labs show: C1inh level 4; C1inh function 22%, C4 level 3
- Parents concerned about the increased number of attacks and fear of laryngeal attacks as possibility. They would like prophylactic as well as on-demand medication.

Pediatric HAE Treatment Challenges

- Most attacks in children occur without obvious trigger
- Infections more common triggers of attacks in childhood
- Compulsory and recommended vaccinations for children are safe;
    - prevention of infections (eg, throat infections) may reduce attack frequency
- Triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) essential elements in this age group
- Restrictions of suspected triggers should be individualized and sensibly applied, along with use of prophylaxis where necessary
- Aim is to avoid any limitations in activities and lifestyle

- Management aim at all ages is to <u>normalize</u> the lives of HAE patients

Caballero T, Maurer M, Longhurst HJ, et al. J Investig Allergol Clin Immunol. 2016; 26(6): 383- 386.
Bouillet L, Longhurst H, Boccon-Gibod I, et al. Am J Obstet Gynecol. 2008; 199(5): 484. e481-484.
Saule C, Boccon-Gibod I, Fain O, et al. Benefits of progestin contraception in non-allergic angioedema. Clin Exp Allergy. 2013; 43(4): 475- 482.
Zotter Z, Csuka D, Szabo E, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. Orphanet J Rare Dis. 2014; 9: 44.
Farkas H, Martinez-Saguer I, Bork K, et al. Allergy. 2017; 72(2): 300- 313.

Impact of HAE on the Pediatric Patient

- Most studies and approved therapies were initiated in adult HAE patients
- Only recently have studies extended to the pediatric population
- Also just recently was the expansion in age indication of therapies down to the younger pediatric population of HAE

- This age category remains an area of unmet need
- Many pediatricians will continue following patients until their 20’s
- More studies for novel therapies are in the pipeline

Tools to Help Better Understand Patient Needs

AECT[1,2]

- Based on patient-reported outcomes
- Validated objective tool
- Quick and easy
- Can be done in the clinic

Shared decision-making tool – US HAEA[3]

- Patient can complete ahead of visit
- Questions based on what is most important to patients (job, travel, and medication side effects)
- Makes visits more efficient

1. Weller K, et al. J Allergy Clin Immunol Pract. 2020;8:2050-2057; 2. Weller K, et al. Allergy. 2020;75:1165-1177; 3. US HAEA. Accessed August 1, 2024. https://haea.sdm.health/

Four-Week AECT

1. In the last 4 weeks, how often have you had angioedema?

O very often (0 points)	O often (1 point)	O sometimes (2 points)	O seldom (3 points)	O not at all (4 points)

2. In the last 4 weeks, how much has your quality of life been affected by angioedema?

O very much (0 points)	O much (1 point)	O somewhat (2 points)	O a little (3 points)	O not at all (4 points)

3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?

O very much (0 points)	O much (1 point)	O somewhat (2 points)	O a little (3 points)	O not at all (4 points)

4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?

O not at all (0 points)	O a little (1 point)	O somewhat (2 points)	O well (3 points)	O very well (4 points)

- Weller K, et al. J Allergy Clin Immunol Pract. 2020;8:2050-2057.

Current Treatment Options

Acute therapy

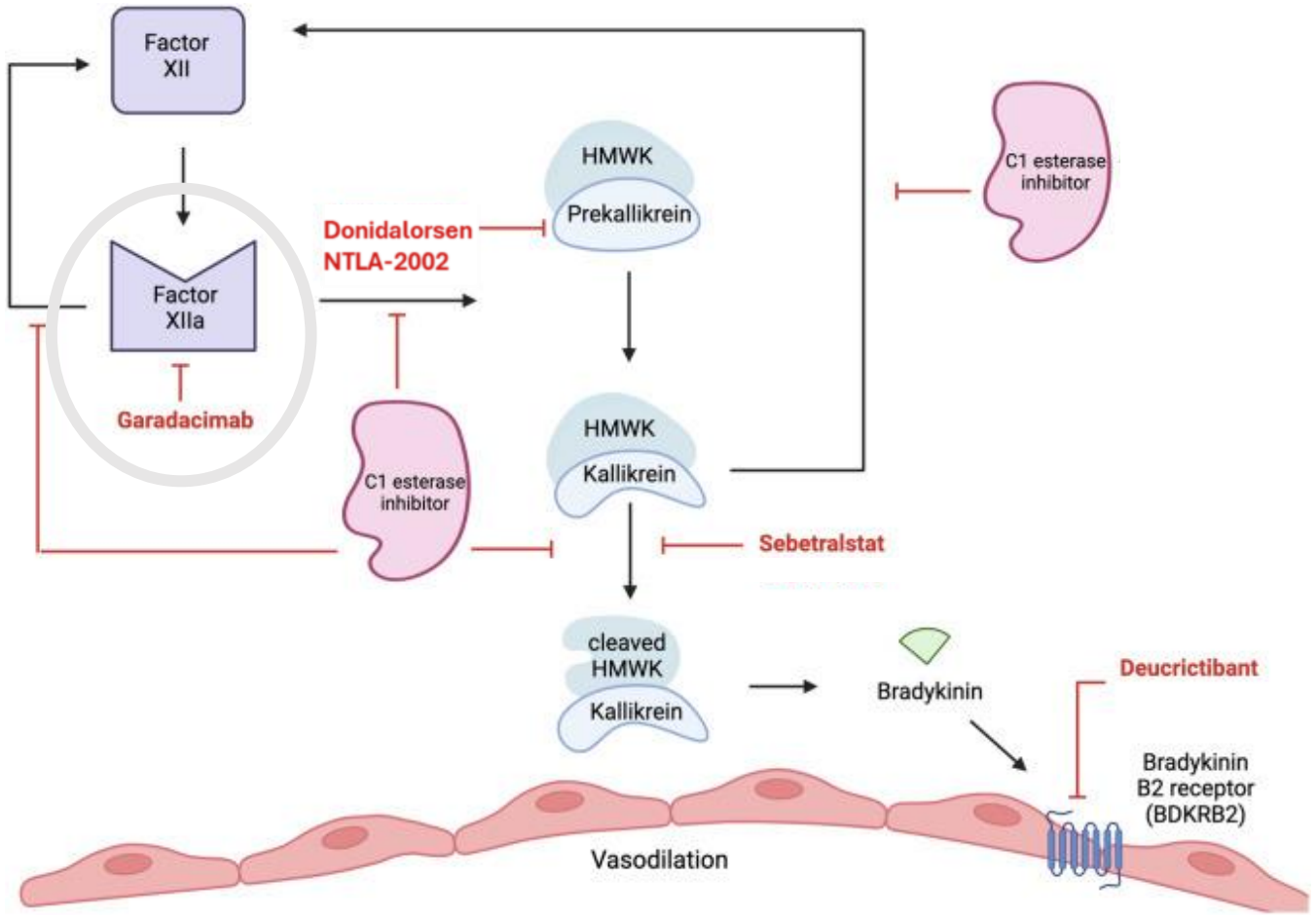
Product	Indication
IV C1 esterase inhibitor (plasma-derived)[1]	Indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients
Ecallantide[2]	Indicated for treatment of acute attacks of hereditary angiodema in patients 12 years of age and older
Icatibant injection[3]	Indicated for treatment of acute attacks of (HAE) in adults 18 years of age and older
IV C1 esterase inhibitor (recombinant)[4]	Indicated for treatment of acute attacks of HAE in adult and adolescent patients

Prophylactic therapy

Product	Indication
Berotralstat[5]	Indicated for the prevention of attacks in patients 12 years or older with hereditary angiodema (HAE)
IV C1 esterase inhibitor [plasma-derived][6]	Indicated for routine prophylaxis against angiodema attacks in patients 6 years or older with Hereditary Angiodema (HAE)
SC C1 esterase inhibitor [plasma-derived] [7]	Indicated for routine prophylaxis against angiodema attacks in patients 6 years and older with Hereditary Angiodema (HAE)
Lanadelumab (Monoclonal Anti-plasma Kallikrein)[8]	Indicated for routine prophylaxis against angiodema attacks in patients 2 years and older with Hereditary Angiodema (HAE)

1. http://cslbehring.vo.llnwd.net/o33/u/central/PI/US/Berinert/EN/Berinert-Prescribing-Information.pdf .
2. KALBITOR® (ecallantide) Full Prescribing Information. Dyax Corp., Cambridge, Massachusetts, December 2009
3. Firazyr® (icatibant injection) Full Prescribing Information, Shire Orphan Therapies, Inc., August , 2011.
4. Ruconest® (Ruconest) Full Prescribing Information. Pharming Corp., Leiden, Netherlands, July 2014.
5. https://orladeyohcp.com/#
6. http://pi.shirecontent.com/PI/PDFs/Cinryze_USA_ENG.pdf
7. https://labeling.cslbehring.com/PI/US/HAEGARDA/EN/HAEGARDA-Prescribing-Information.pdf
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761090s010lbl.pdf

Garadacimab, a Monoclonal Antibody Targeting Factor XIIa



- HMWK, high-molecular-weight kininogen; MOA, mechanism of action.
- Smith TD, et al. Ann Allergy Asthma Immunol. 2024;133:380-390.

Garadacimab, a Factor XIIa Inhibitor for HAE Attack Prevention

VANGUARD: phase 3, randomized, and placebo-controlled trial

Garadacimab 200 mg SC once monthly [first dose is loading dose (400 mg)]
Number of participants = 39

Placebo
Number of participants = 25

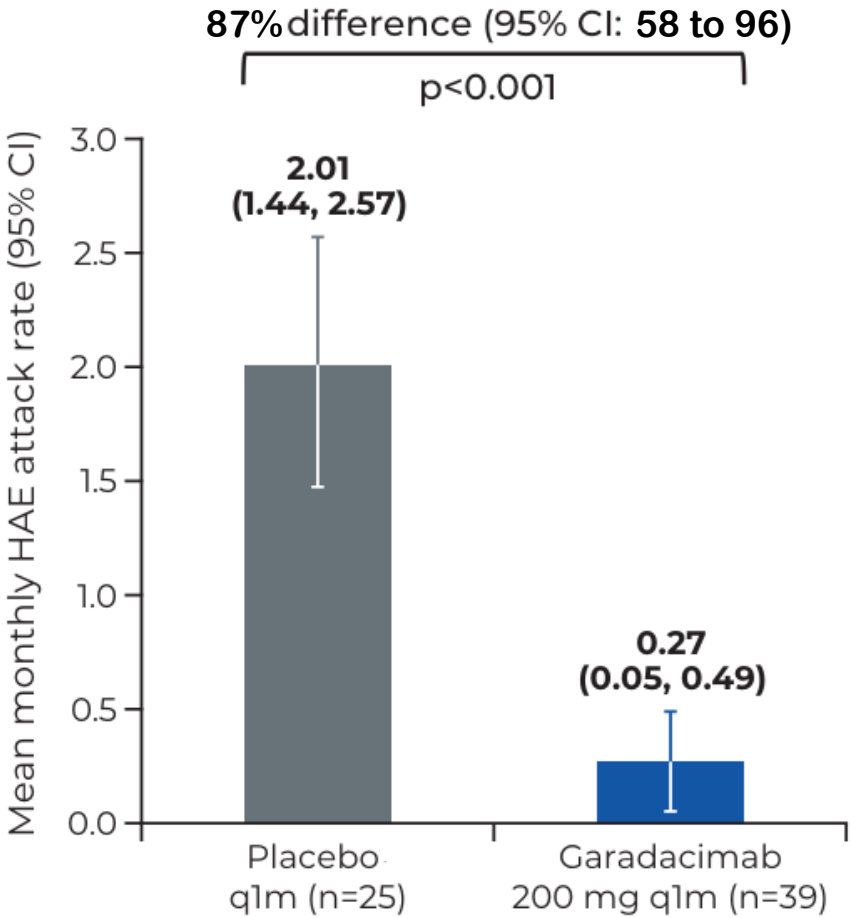
Eligibility criteria:
- HAE type I/II diagnosis
- Age ≥ 12 years
- ≥ 3 attacks during the 3 months before screening

- Craig TJ, et al. Lancet. 2023;401:1079-1090.

Garadacimab
Findings From VANGUARD

- Efficacy
- Over 6 months, garadacimab significantly lowered the number of attacks compared with placebo
- Safety
- Most common TEAEs: upper respiratory tract infections, nasopharyngitis, headaches
- Factor XIIa inhibition was **not** associated with an increased risk of bleeding or thromboembolic events

- **HAE Attack Rate Per Month (Primary Endpoint) and Difference vs Placebo**



- Craig TJ, et al. Lancet. 2023;401:1079-1090.

Garadacimab: Open Label Extension Study

VANGUARD: Phase 3 Study

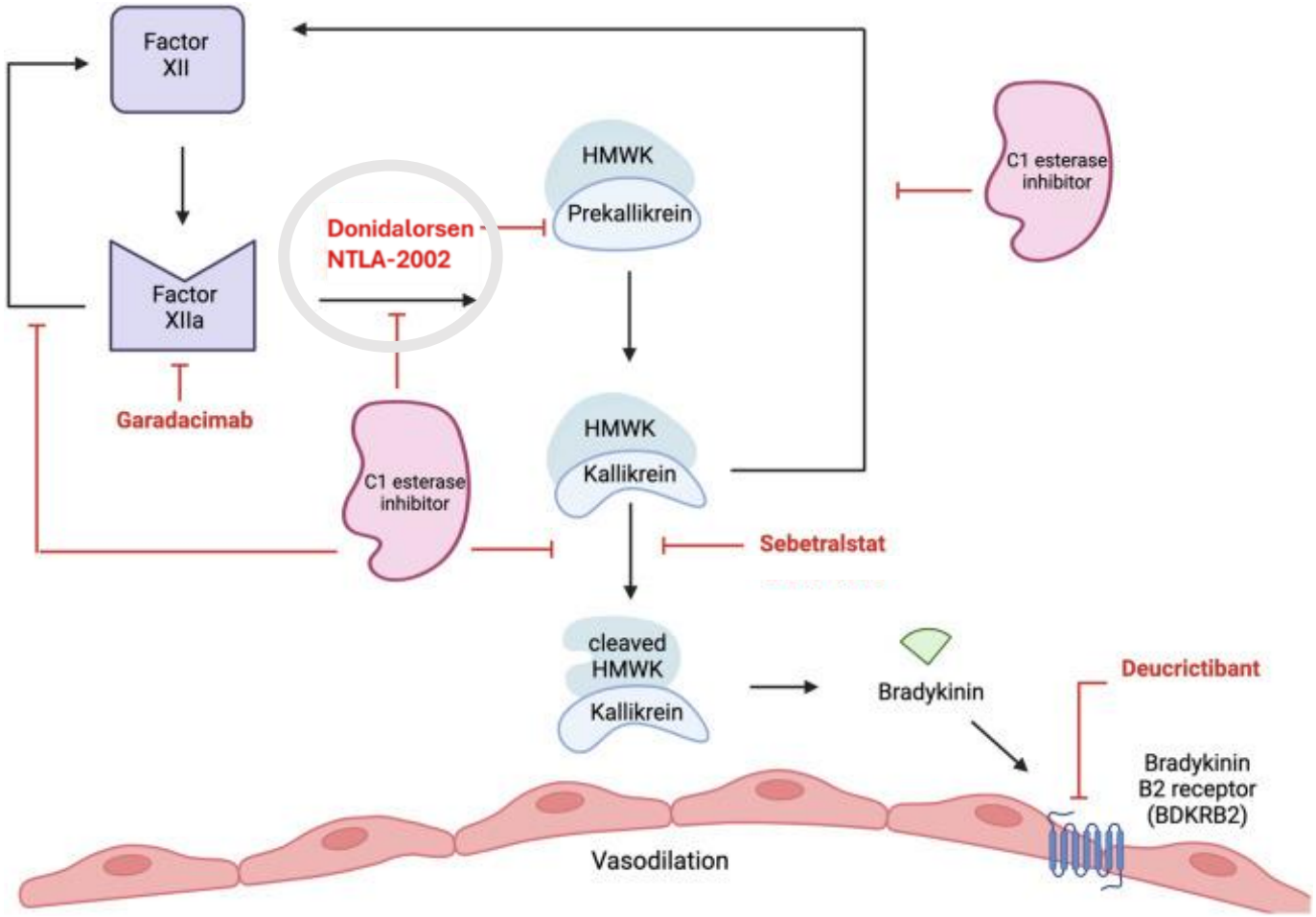
- Patients received garadacimab 200 mg SC, once monthly for ≥ 12 months (loading dose 400 mg SC)
- Primary endpoint: treatment-emergent adverse events

Findings

- A 95% reduction in mean HAE attack rate
- 60% of patients were attack free
- Favorable long-term safety profile: most TEAEs mild or moderate

- TEAE, treatment-emergent adverse event.
- Reshef A, et al; VANGUARD Study Group. Allergy. 2024. doi: 10.1111/all.16351[Epub ahead of print].

Donidalorsen, an Oligonucleotide That Degrades Prekallikrein Messenger RNA in Hepatocytes



- Smith TD, et al. Ann Allergy Asthma Immunol. 2024;133:380-390.

Donidalorsen, an Antisense Oligonucleotide to Reduce Prekallikrein Expression

- OASIS-HAE: phase 3, double-blind, and randomized trial

Donidalorsen 80 mg SC every 4 weeks
Number of participants = 45

Donidalorsen 80 mg SC every 8 weeks
Number of participants = 23

Placebo every 4 or 8 weeks
Number of participants = 22

Eligibility criteria:

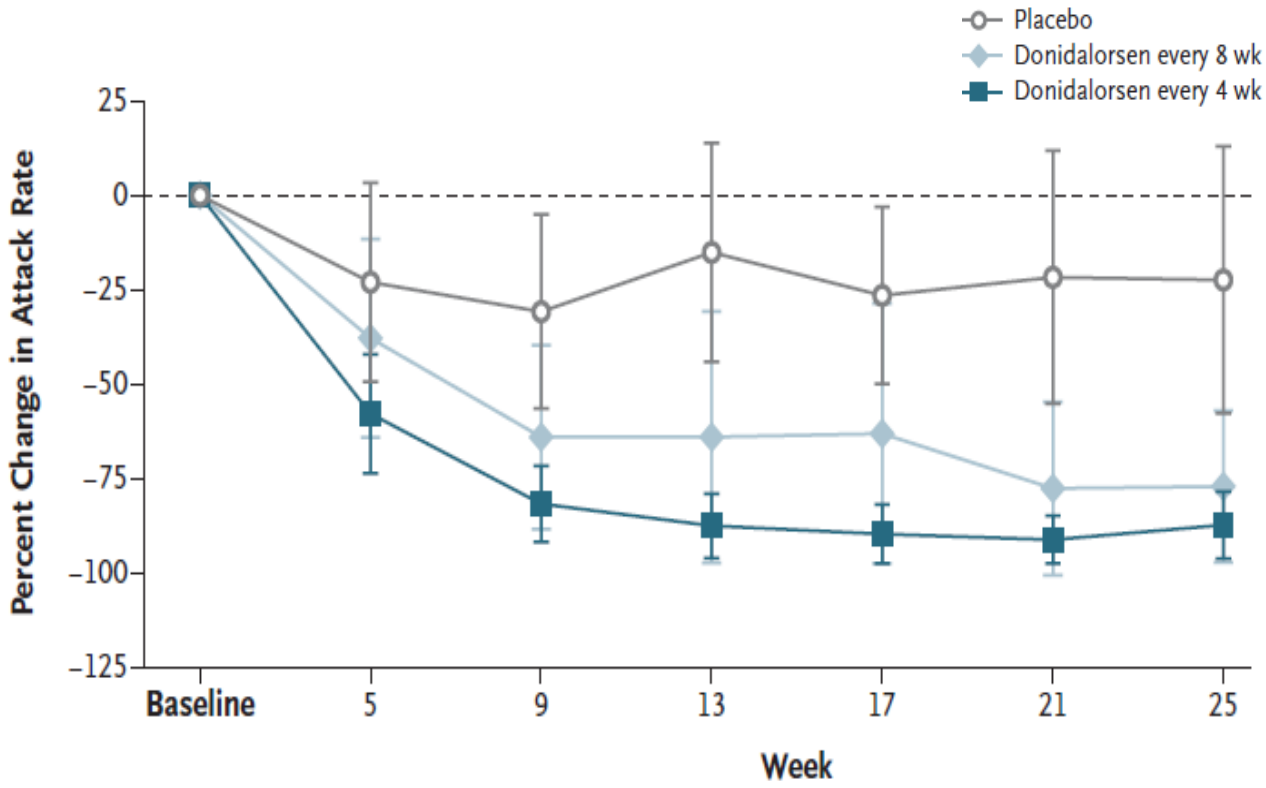
- HAE type I/II diagnosis
- Aged ≥ 12 years
- Patients must have had ≥ 2 HAE attacks during the run-in period

- Riedl MA, et al; OASIS-HAE Team. N Engl J Med. 2024;391:21-31.

Donidalorsen
Findings From OASIS-HAE

- Efficacy
- Donidalorsen (every 4 or 8 weeks) significantly reduced the mean attack rate during week 1 to 25
  - 81% lower in the 4-week group vs placebo
  - 55% lower in the 8-week group vs placebo
- Safety
- Most common AEs: erythema at the injection site, headache, nasopharyngitis

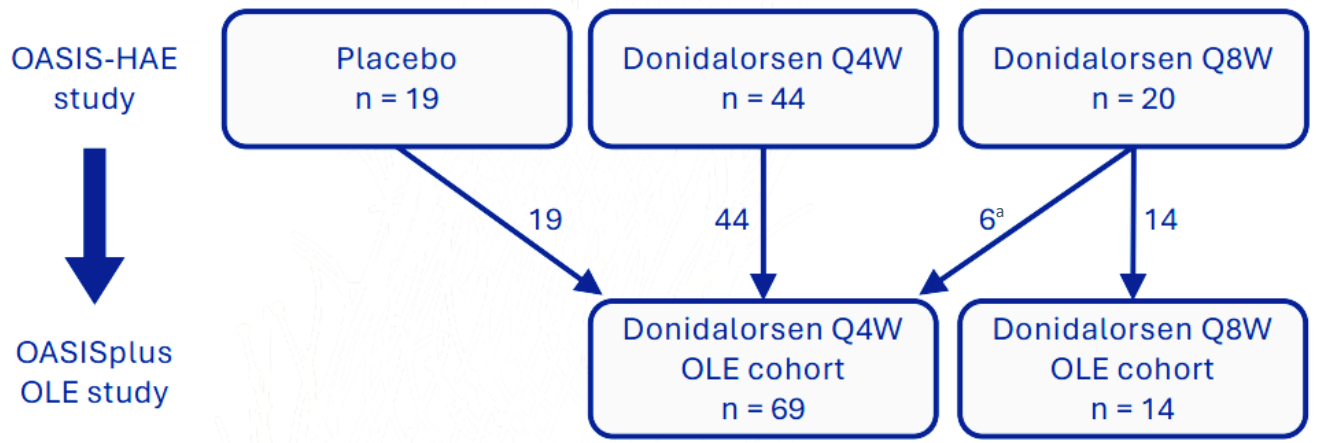
- **Change in Attack Rate**



- Riedl MA, et al; OASIS-HAE Team. N Engl J Med. 2024;391:21-31.

Donidalorsen
OASISplus Open-Label Extension Study

- Patients previously on placebo or donidalorsen in the phase 3 OASIS-HAE study received 80 mg donidalorsen per their original dosing schedule (Q4W or Q8W) or Q4W if not attack-free for ≥ 8 weeks
- Primary endpoint: incidence and severity of TEAEs



- AECT, angioedema control test; OLE, open-label extension; q4w, 4 times a week, q8w, 8 times a week.
- a. Patients not attack free for ≥ 8 weeks
- Tachdjian R, et al. EAACI Congress 2024. Presentation

Findings From OASISplus OLE Study

Primary endpoint: incidence and severity of TEAEs

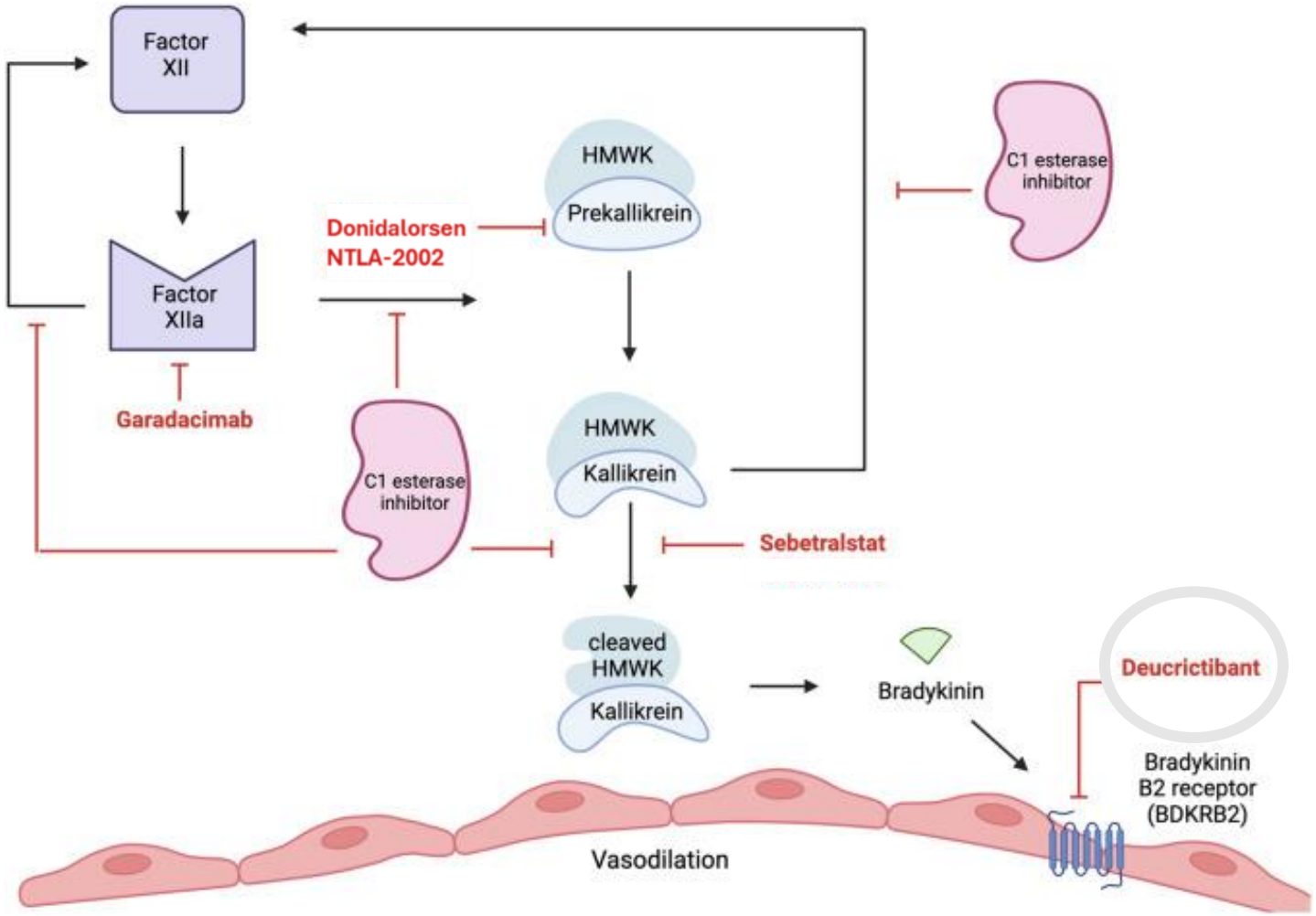
- No discontinuations due to TEAEs
- No serious TEAEs related to study drug
- Most TEAEs were mild or moderate in severity
- Most common TEAEs: influenza, nasopharyngitis, URTI, back pain, headache

Other endpoints

- Reduction of monthly HAE attack rate was similar between Q4W (93%) and Q8W (92%) dosing
- Quality of life and disease control
  - Patients reported a ≥ 24-point improvement in mean AE-QOL scores
  - > 90% of patients reported well-controlled disease

- AE, adverse event; URTI, upper respiratory tract infection.
- Tachdjian R, et al. EAACI Congress 2024. Presentation

Deucrictibant, a B2 Receptor Antagonist



- Smith TD, et al. Ann Allergy Asthma Immunol. 2024;133:380-390.

Deucrictibant Extended Release, an Oral Bradykinin B2-Receptor Antagonist

- CHAPTER-1: phase 2 study

Deucrictibant 20 mg/day
Number of participants = 11

Deucrictibant 40 mg/day
Number of participants = 12

Placebo every 4 or 8 weeks
Number of participants = 11

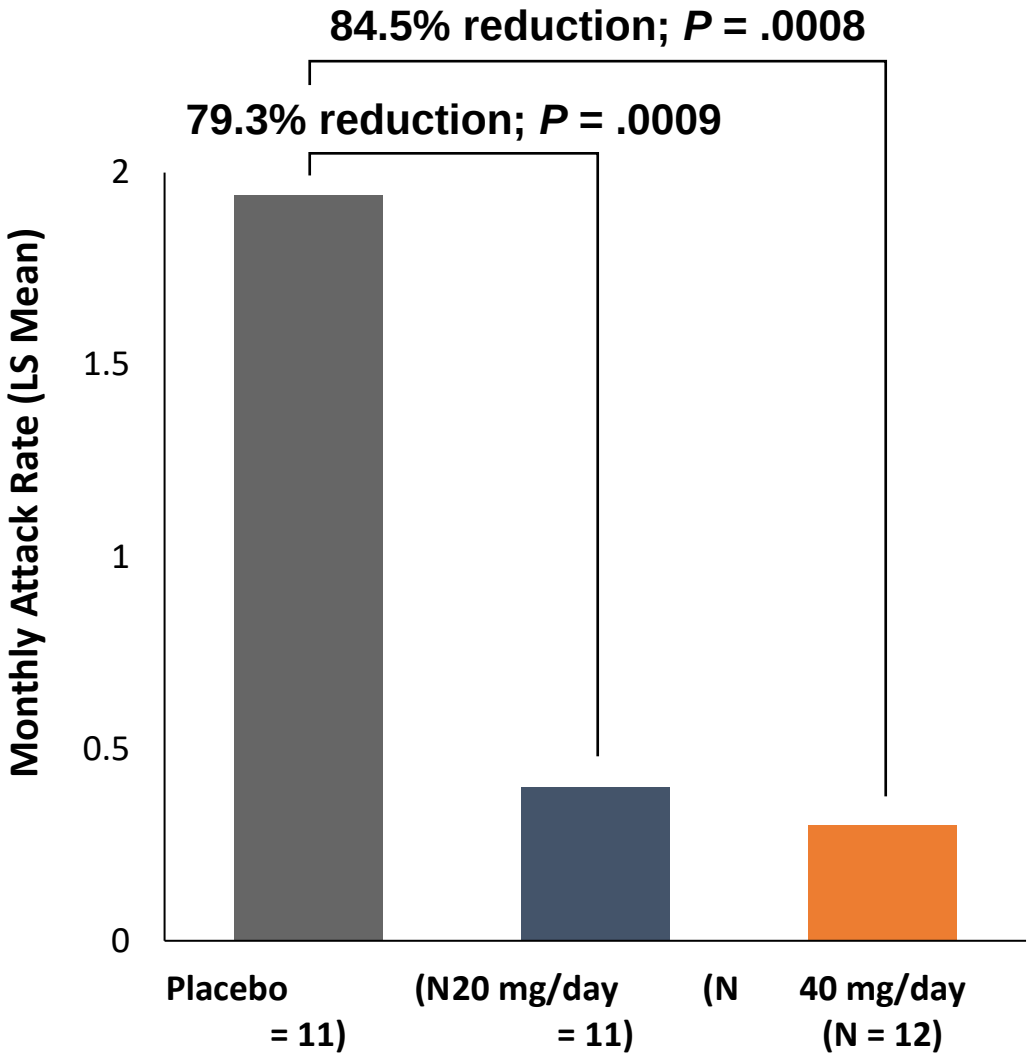
Eligibility criteria:

- HAE type I/II diagnosis
- Age ≥ 18 years and ≤ 75 years
- Experienced ≥ 3 attacks in last 3 consecutive mo prior to screening or ≥ 2 attacks during screening

- Aygoren-Pursun E, et al. EAACI Congress 2024. Presentation ; Riedl M, et al. J Allergy Clin Immunol. 2024;153: Abstract 031.

Deucrictibant: Findings From CHAPTER-1

- Efficacy
- Significant reductions in the mean monthly attack rate with deucrictibant
- Deucrictibant 40 mg reduced the occurrence of attacks treated with on-demand medication (92.6%)
- Safety
- TEAEs were mild in severity: nausea, dizziness, headache, and increased GGT



- GGT, gamma-glutamyl transferase.

Aygoren-Pursun E, et al. EAACI Congress 2024; Presentation

Long-Term Safety and Efficacy of Deucrictibant

CHAPTER-1 OLE Study

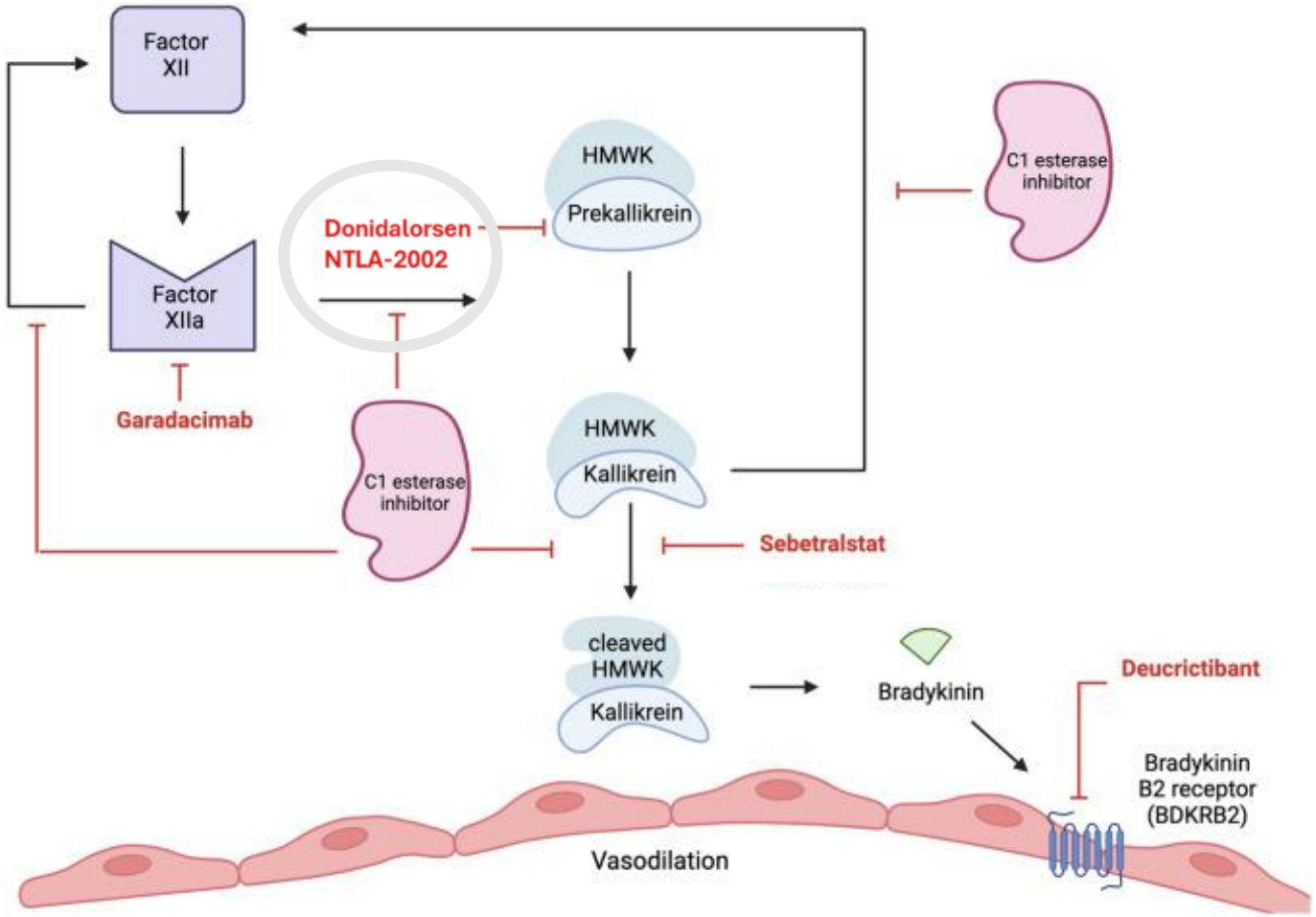
- Participants received open-label treatment with deucrictibant 40 mg/day

Conclusions

- Deucrictibant 40mg/day treatment resulted in early-onset reduction in attack rate, which remained low through 1.5 years of treatment
- The rates of “moderate and severe” attacks and attacks treated with on-demand medication remained low
- Continued to be well-tolerated, with no safety signals observed

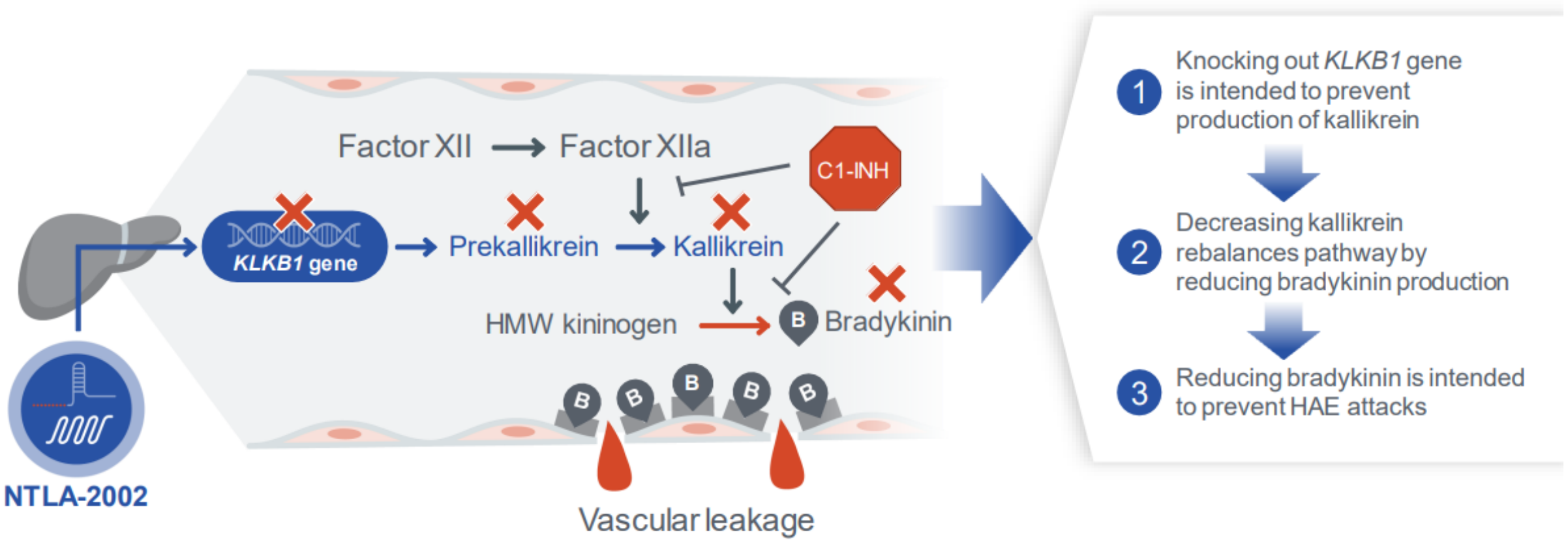
- Anderson J, et al. Ann Allergy Asthma Immunol. 2024;133(suppl):S35.

NTLA-2002, Plasma Kallikrein Protein Reduction



- Smith TD, et al. Ann Allergy Asthma Immunol. 2024;133:380-390.

NTLA-2002
CRISPR-Based LTP for HAE



- Longhurst, et al. EAACI Congress 2024. Presentation

NTLA-2002
Phase 2 Efficacy and Safety

Phase 2 Study

- Adults randomized 2:2:1 to receive NTLA-2002 in a single dose of 25 mg or 50 mg or placebo
- Primary end point: monthly attack rate from week 1 to 16

Results

- Estimated mean monthly attack rate
  - 25 mg group: 0.70
  - 50 mg group: 0.65
  - Placebo: 2.82
- Most common adverse events: headache, fatigue, and nasopharyngitis

- Cohn DM, et al. N Engl J Med. 2024. doi: 10.1056/NEJMoa2405734[Epub ahead of print].

Acute Treatment Options in Children

- Pediatric HAE patients need treatment action plan with 2 doses of on-demand therapy available all times
- pdC1-INH IV is the only approved on-demand treatments in pediatric HAE
- rC1-INH IV and ecallantide are approved for on demand HAE attacks in age 12 and older
- ecallantide must be administered by a HCP due to risk of anaphylaxis
- Icatibant is approved for on-demand treatments in HAE patients 18 and over
- These are effective, well tolerated and show a good safety profile
- Abdominal attacks: consider parenteral fluids as children are more susceptible to hypovolemia and dehydration, with substantial extravasation into peritoneal cavity and intestinal lumen

Reshef A, Grivcheva-Panovska V, Kessel A, et al. Pediatr Allergy Immunol. 2019; 30(5): 562- 568.
Lumry W, Manning ME, Hurewitz DS, et al. J Pediatr. 2013; 162(5): 1017– 1022. e1011-1012.
Farkas H, Reshef A, Aberer W, et al. J Allergy Clin Immunol Pract. 2017; 5(6): 1671- 1678. e1672.
Lumry W, Soteres D, Gower R, et al. Pediatr Allergy Immunol. 2015; 26(7): 674- 680.
Farkas H, Csuka D, Zotter Z, et al. J Allergy Clin Immunol. 2013; 131(3): 909- 911.
https://www.fda.gov/media/77803/download https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125277s081lbl.pdf https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022150s000lbl.pdf

Prophylactic Treatment Options in Children

- Lanadelumab approved in children ≥2 years of age for long-term prophylaxis
- IV and SC pdC1-INH are approved in children ≥6 years of age for long-term prophylaxis
- When C1-INH concentrate not available, antifibrinolytics (ie, tranexamic acid) are preferred to androgens because of their better safety profile
  - Not FDA approved for HAE
- Androgens not recommended for long-term prophylaxis in children and adolescents prior to Tanner Stage V
  - Androgens require careful safety monitoring.
  - Masculinization and hypogonadism in boys; menstruation irregularities in girls
  - Unfavorable effects on behavior possible
  - Reduction in ultimate body height from premature closure of epiphyseal growth plates

Farkas H, Martinez-Saguer I, Bork K, et al. Allergy. 2017; 72(2): 300- 313.
Frank MM, Zuraw B, Banerji A, et al. Management of children with hereditary angioedema due to C1 inhibitor deficiency. Pediatrics. 2016; 138(5):e20160575.
Wahn V, Aberer W, Aygoren-Pursun E, et al. Hereditary angioedema in children and adolescents. Pediatr Allergy Immunol. 2020; 31(8): 974- 989.
Farkas H, Csuka D, Zotter Z, Varga L, Fust G. Prophylactic therapy in children with hereditary angioedema. J Allergy Clin Immunol. 2013; 131(2): 579- 582. e571-572.
Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents-a consensus on therapeutic strategies. Eur J Pediatr. 2012; 171: 1339- 1348.
Cinryze (C1 esterase inhibitor [human]). PI. https://www.fda.gov/media/75907/download. HAEGARDA® (C1 esterase inhibitor subcutaneous [human]) PI. https://www.fda.gov/media/105611/download
Takhzyro (lanadelumab-flyo) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761090s000lbl.pdf Zuraw B, et al. *J Allergy Clin Immunol*. 2021;148:164-172.e9.
Danazol (danocrine) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017557s033s039s040s041s042lbl.pdf. Lysteda (tranexamic acid) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022430s009lbl.pdf.

Sample Case – Follow Up

- Parents are very pleased with the control of swelling attacks.
- They have screened their 2 other children and were negative
- The patient reports that he no longer gets stomach aches every month like before
- They still carry 2 doses of on demand therapy

Patient Support

- Providing pediatric patients and family with appropriate information
  - Helps adopt suitable lifestyle and avoid complications
- Educators, teachers, and HCP responsible for child at day care or school should receive education on the disease:
  - advice on the management of HAE attacks
  - urgency of treatment for airway attacks
  - Ensure 2 doses for emergency use available at hospital, home, school, and travel
- HAE patients have a potential for receiving human blood products
  - Vaccinations for hepatitis A and B are recommended by many experts
- All patients should be considered to receive influenza vaccine and other routine vaccinations
- Identify patients early – test family members of index case
  - Early diagnosis helps with an earlier action plan

Farkas H, Martinez-Saguer I, Bork K, et al. Allergy. 2017; 72(2): 300- 313.

Other Patient Support

HAEA.org

Get Educated

Find an HAE Expert

School Packet

School Nurse Letter

504 Plan

Pam King Scholarship

Family counseling

Educate the Community

Self-administration?

HAE Advocate

Test Early

Conclusions

- Diagnosing and Treating HAE continues to evolve and guidelines should provide us with optimal parameters
- Age-specific indications are available and should be discussed with the HAE specialist
- Approved treatments for acute attacks and prophylactic management of HAE continue to expand
- Updated guidelines, new treatments, and comprehensive care should help reduce the morbidity and mortality associated with HAE

Busse PJ et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema J Allergy Clin Immunol Pract. 2021 Jan;9(1):132-150.
Maurer M et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy 2022 Jul;77(7):1961-1990.