Hereditary angioedema (HAE)

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Today's Topics

1. What is hereditary angioedema (HAE)?
2. HAE attacks (swelling or pain)
3. Reasons for delay in diagnosis / treatment
4. Global study results of Lanadelumab as prophylaxis treatment

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Mechanism of HAE Attacks

- Bradykinin has strong vascular hyperpermeability, and is an important mediator in causing edema in HAE[1].
- Bradykinin produced in excess by psychological and physical stress binds to the bradykinin B2 receptor, thereby increasing vascular permeability and causing edema.[2-5]

Normal

C1-INH deficiency or dysfunction in patients with HAE creates an environment conducive to overproduction of attack-inducing bradykinin

When receiving stimulus

Bradykinin, which is overproduced by stress and other stimuli, binds to the bradykinin B2 receptor, enlarging the gap between vascular endothelial cells and enhancing vascular permeability

During HAE attacks

When vascular permeability is increased, plasma components in the blood vessels leak from the intravascular space to the extravascular space, causing edema. Attacks usually last for 2 to 5 days

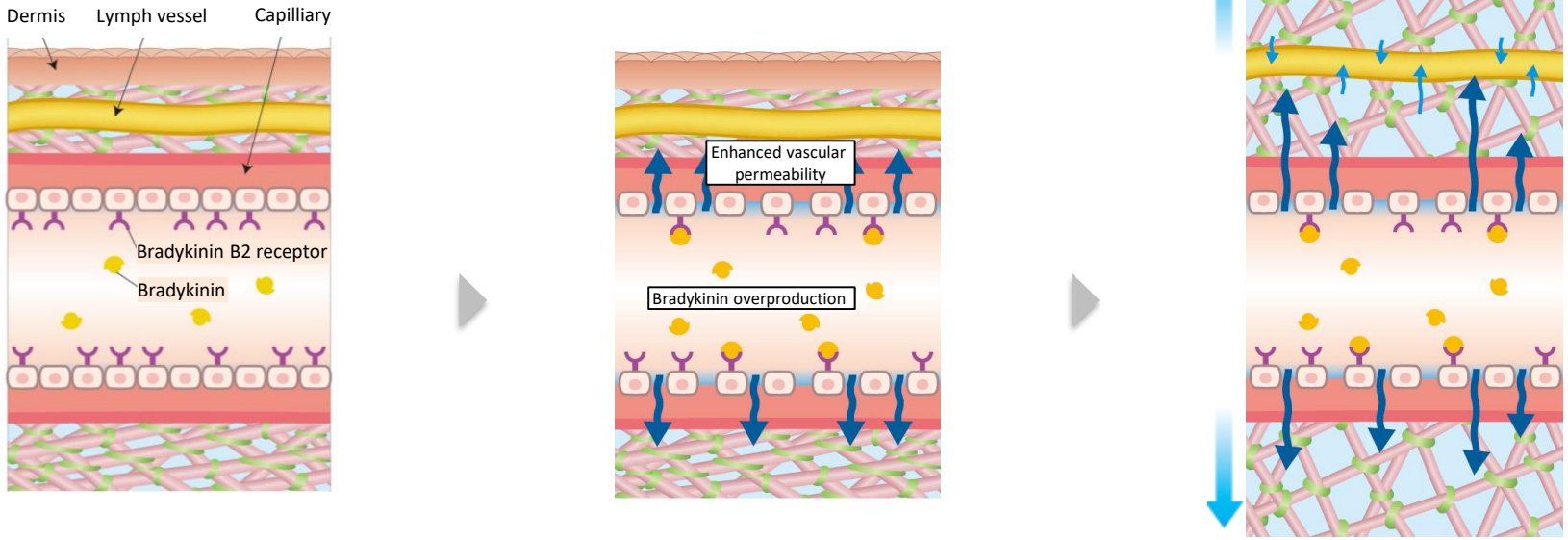
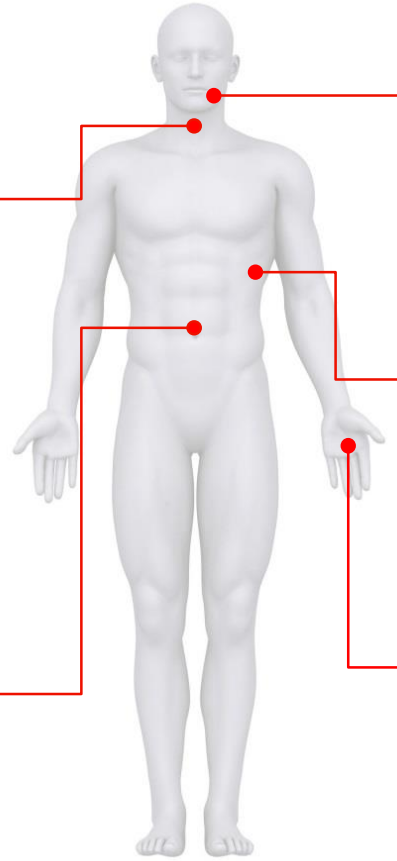


Illustration of Action Mechanisms:
Dr. Isao Osawa, the director of Saiyu Soka Hospital

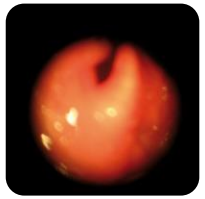
1. Zuraw BL. N Engl J Med. 2008; 359: 1027-36
2. Craig T, et al. World Allergy Organ J. 2012; 5: 182-99
3. Tse K, et al. Cleve Clin J Med. 2013; 80: 297-308
4. Shire. FIRAZYR (icatibant) Summary of Product Characteristics. June 2017
5. Han ED, et al. J Clin Invest. 2002; 109: 1057-63

Characteristics of HAE Attacks

HAE attacks may appear at multiple sites



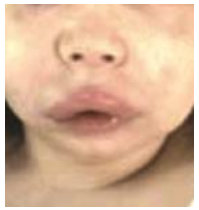
Laryngial edema [1,2]



- Dysphagia
- Hoarseness
- Voice change
- Shortness of breath
- Suffocation if severe

Photo: Bas, M., et al. 2006[3]

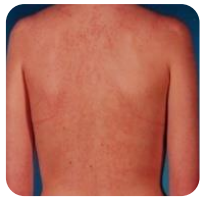
Facial edema [1]



- Facial and lip swelling
- Rarely with laryngeal edema

photo： 2016 haeimages.com

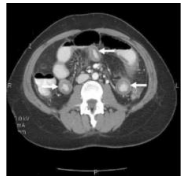
Rash [6, 7]



- Rare non-pruritus rash e.g. related erythema

photo： Bygum et al. 2009[7]

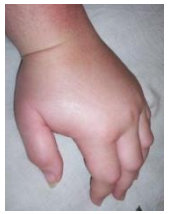
Gastrointestinal edema [1, 4]



- Nausea
- Vomiting
- Diarrhoea
- Colic-like pain

photo：LoCascio et al. 2010[5]

Skin edema of the extremities [1,8]

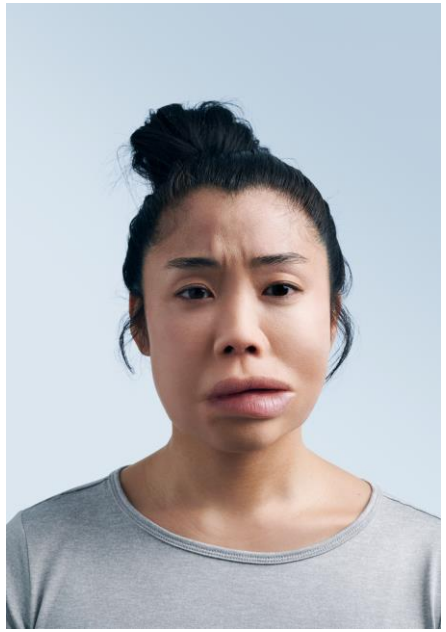


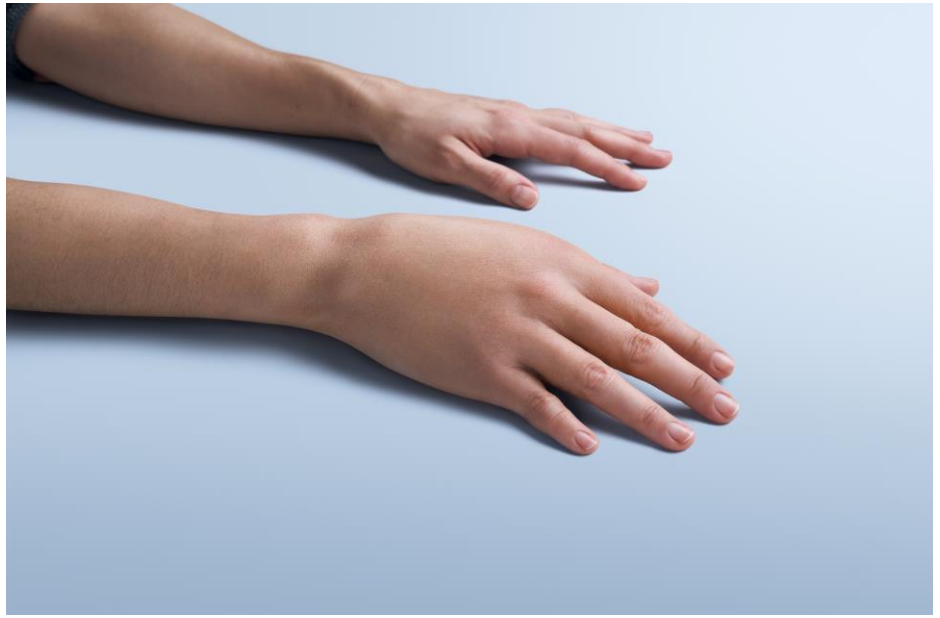
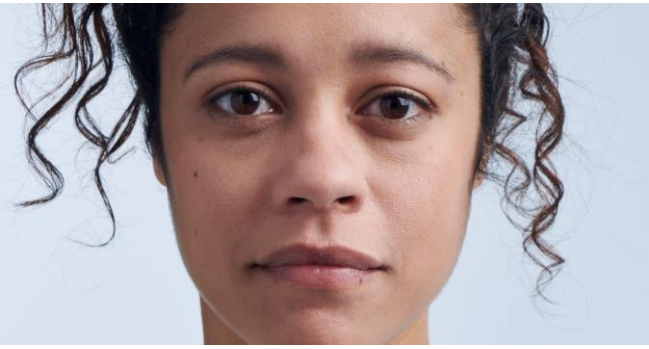
- Redundancy or blistering of the skin
- Swelling of the hands, arms, feet, lower limbs, and femoral region
- Limited range of motion

photo： 2016 haeimages.com

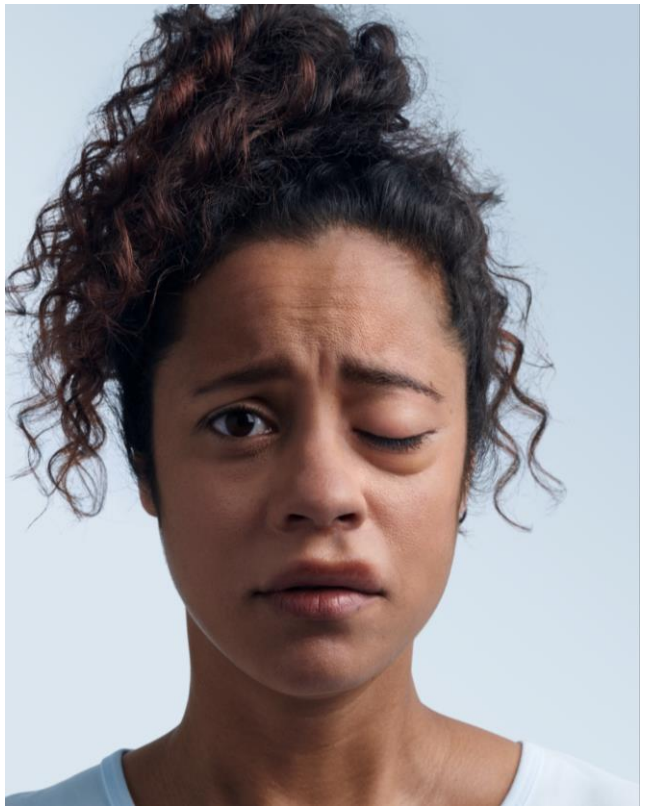
1. Bork, K., et al.：Am. J. Med., 2006, **119** (3), 267
2. Bork, K., et al.：J. Allergy. Clin. Immunol., 2012, **130** (3), 692
3. Bas, M., et al.：Allergy. 2006, **61** (12), 1490
4. Bork, K., et al.：Am. J. Gastroenterol., 2006, **101** (3), 619
5. LoCascio, E. J., et al.：West. J. Emerg. Med., 2010, **11** (4), 391
6. Magerl, M., et al.：Clin. Exp. Dermatol., 2014, **39** (3), 298
7. Bygum, A.：Br. J. Dermatol., 2009, **161** (5),1153
8. Craig, T., et al.：Ann. Allergy. Asthma. Immunol., 2009, **102** (5), 366

Symptom of HAE Attacks (1)



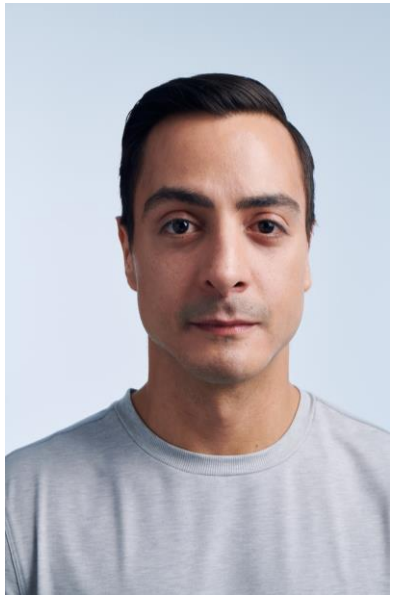



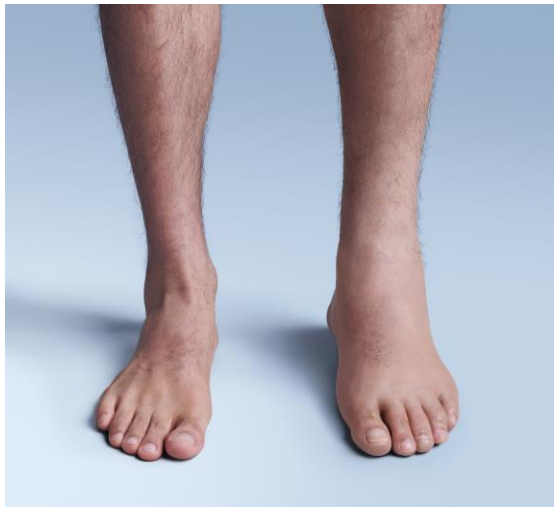


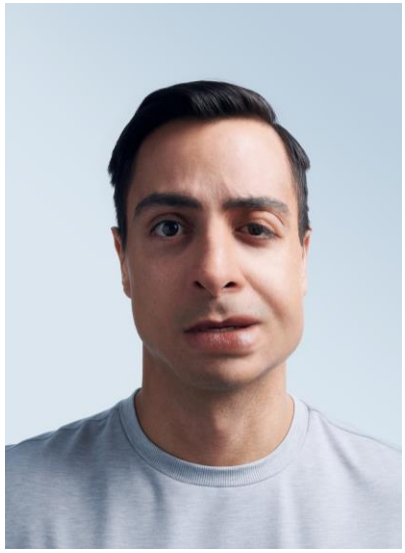


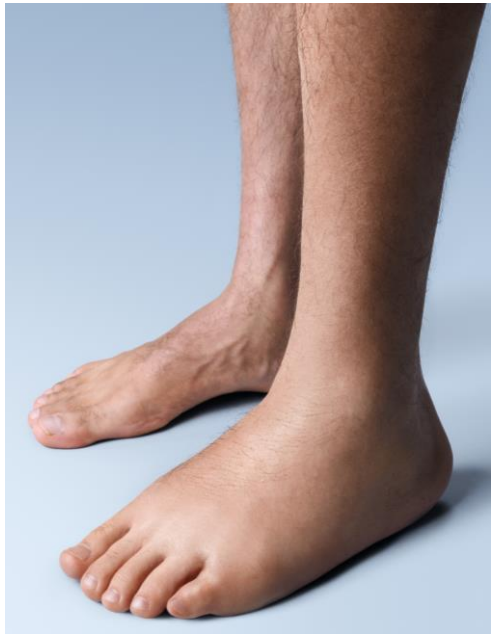
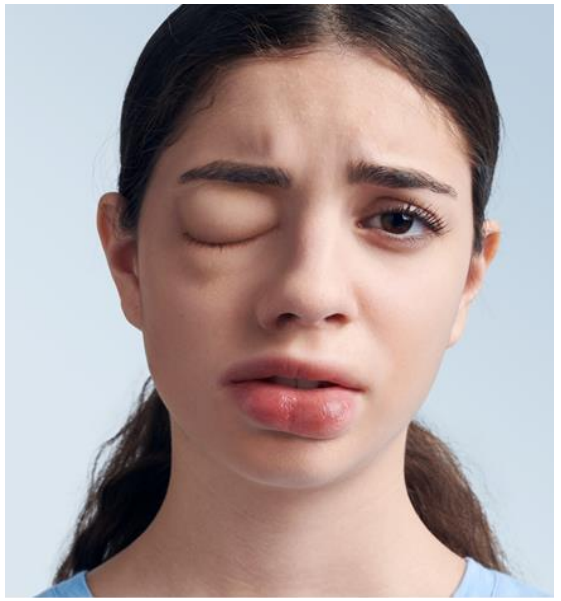
Not actual patients. Images showing HAE swelling for educational purpose

Symptom of HAE Attacks (2)





Not actual patients. Images showing HAE swelling for educational purpose

Epidemiology and Clinical Characteristics of HAE Patients

1. The incident rate is 1 out of 50,000 people, with an estimated 2,500 patients in Japan. The number of patients actually being treated is just over 400.
2. The average number of attacks is 17.9 per year, 55% of which are treated.
3. 27% of patients have more than 20 attacks per year.
4. Length of hospitalization is 9.9 days for each attack before diagnosis and 5.1 days after diagnosis.
5. 60% of patients have difficulty in their daily lives; in particular 29% have difficulty in attending school, 40% have difficulty traveling, and 41% have limits on their daily activities.

Hereditary Angioedema (HAE) Guidelines Revised 2014 Version

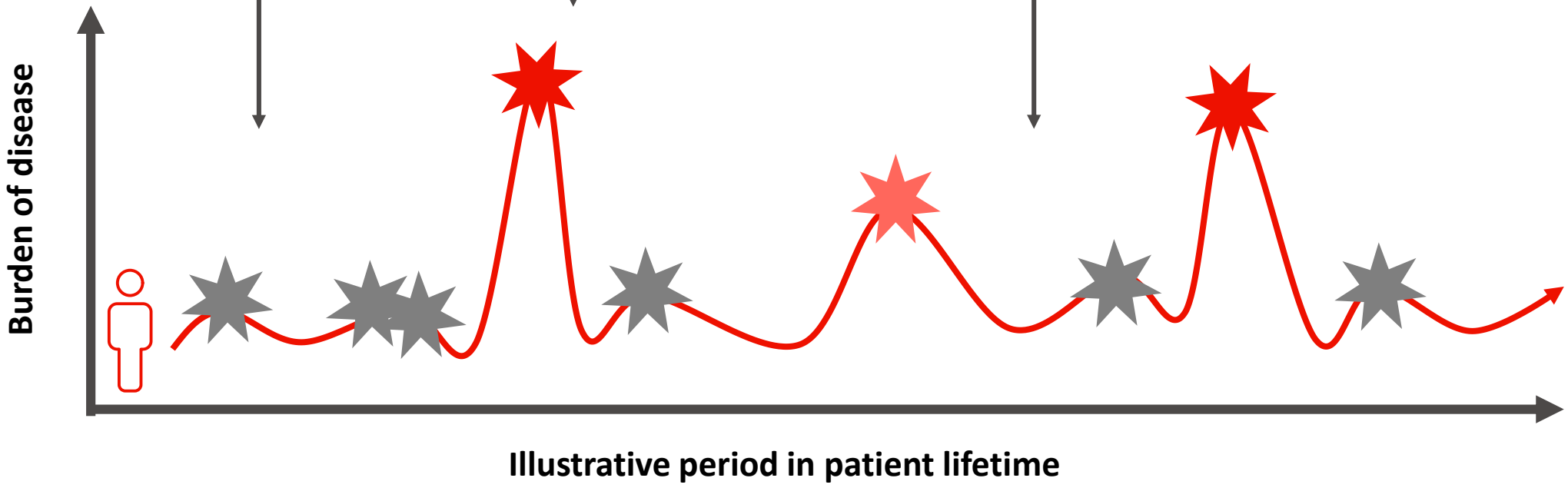
HAE disease activity and impact are variable over time, but all patients may experience severe, life-threatening attacks

Attack frequency and/or severity can be triggered by **procedures, minor illness, stressful life events, fatigue, hormonal factors, or unknown reasons.** Triggers tend to be identified during an attack[1,2]

Severe and life-threatening attacks may occur at any time, even after long periods of low disease activity. Symptoms include **pain, soreness and fatigue.** Attacks initiate an **acute treatment process**[1,2]

Between attacks, patients often experience **significant anxiety, fear and isolation** that affects their quality of life. Patients often **prepare for future attacks** which can facilitate **oppression, depression and low mood**[3,4]

Treatment aims to improve patients' **quality of life** to **achieve disease control**[5,6]



1. Busse PJ, Christiansen SC. Hereditary Angioedema. *N Engl J Med*. 2020;382(12):1136-1148. doi:10.1056/NEJMra1808012
2. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. *Br J Hosp Med (Lond)*. 2019;80(7):391-398.
3. Longhurst H, Bygum A. The Humanistic, Societal, and Pharmaco-economic Burden of Angioedema. *Clin Rev Allergy Immunol*. 2016;51(2):230-239.
4. Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of Illness in Hereditary Angioedema: A Conceptual Model. *Acta Derm Venereol*. 2015;95(6):706-710.
5. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575-1596.
6. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline [published correction appears in Allergy Asthma Clin Immunol. 2020 May 6;16:33]. Allergy Asthma Clin Immunol. 2019;15:72. Published 2019 Nov 25.

VIDEO

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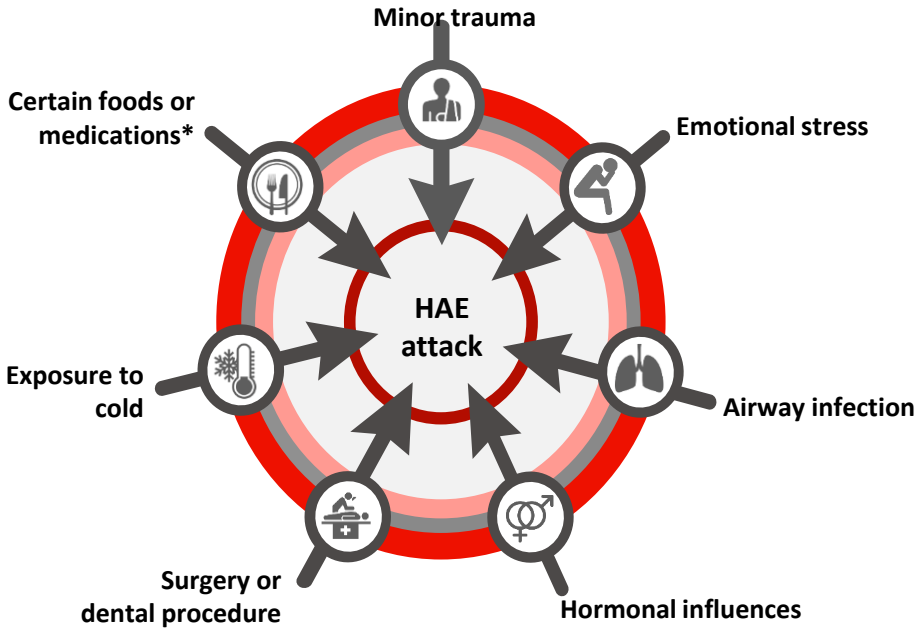
Triggers of HAE Attacks

Possible triggers for HAE attacks[1–4]



- Many attacks, particularly among children, occur **without a clear trigger**
- Common triggers include mechanical trauma, mental stress and airway infection
- Dental eruption is not a common trigger but can provoke an attack in some children
- Menstruation and ovulation are common triggers in adolescent girls
- The same trigger may not always provoke an attack

The trigger of an HAE attack is not always necessarily clear, and it is difficult to anticipate and take short-term measures to prevent an attack

*Medications include estrogen-containing oral contraceptives, hormone replacement therapies, ACE inhibitors.[1,2]

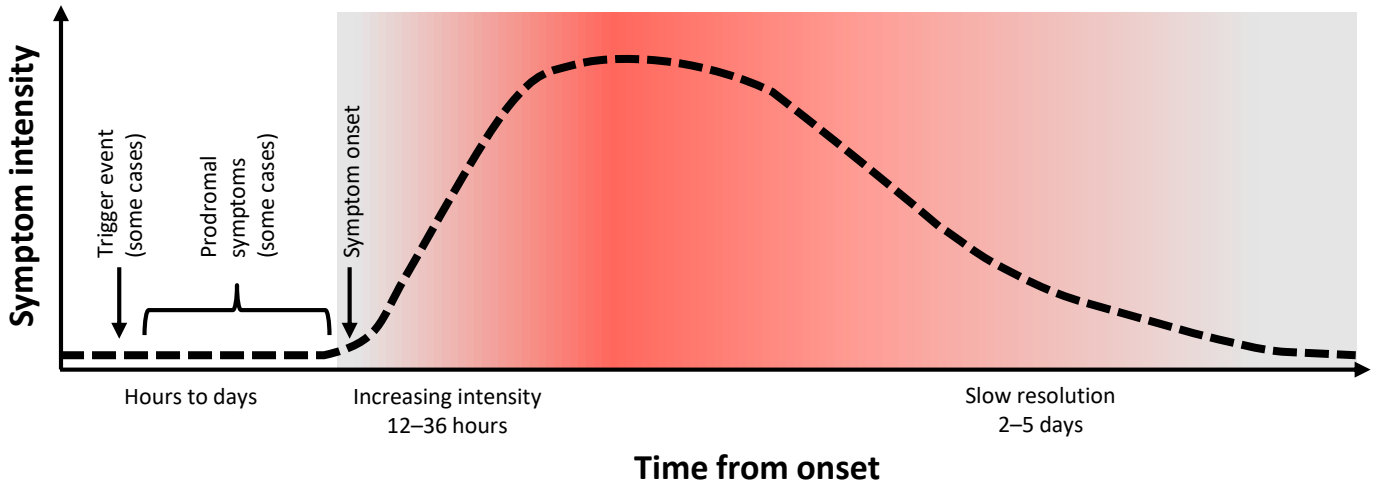
HAE, hereditary angioedema; US, United States

1. Lumry WR. *Am J Manag Care* 2013;19:S103–S110; 2. Farkas H, et al. *Allergy* 2017;72:300–13;
3. Steiner UC, et al. *Orphanet J Rare Dis*. 2018;13:90; 4. Caballero T, et al. *J Invest Allergol Clin Immunol*. 2016;26:383–86

Clinical Presentation and Course of HAE Attacks

- Symptoms typically worsen over the first 24 hours and subside over the next 48–72 hours
  - Attacks can last up to 5 days and may spread to another location before resolving

Course of a typical untreated HAE attack[1–3]



Once an attack begins, the symptoms rapidly increase in intensity, and then take time to fully disappear

HAE, hereditary angioedema

1. Zuraw BL. *N Engl J Med*. 2008;359:1027–36; 2. MacGinnitie AJ. *Pediatr Allergy Immunol*. 2014;25:420–7; 3. Banerji A, et al. *Ann Allergy Asthma Immunol*. 2013;111:329–36

The Voice of the Patient (U.S., 2018)

1. “[Among the various HAE attacks], laryngeal swelling has always been my and every HAE patient’s worst fear... This fear is something that we think about every day and often the last thing that we think about at night.” Patients speak of the trauma of emergency resuscitation.
2. “When my face swells up, it makes me look like a monster.” Children unable to go to school miss out on the experience of schoolwork, sports and holidays enjoyed by many ordinary, healthy students.
3. “I missed [almost] 70 days of school due to stomach pains.” Despite taking many different drugs, the pain was continuous.
4. “I had to quit my job because I could not hold anything. My hands would swell up too much.”
5. “Any time I had an attack, I would lose three to four days out of work… in and out of hospitals.”
   “[because of sudden attacks] you would feel that your colleagues could not depend on you.”
   “I have lost 14 jobs because of this disease.”
6. “I have no social life…” Anxiety and fatigue are always present, causing depression. “It [HAE] definitely affects all aspects of your life.”

The Voice of the Patient
A series of reports from the U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative "Hereditary Angioedema", May 2018
https://www.fda.gov/media/113509/download

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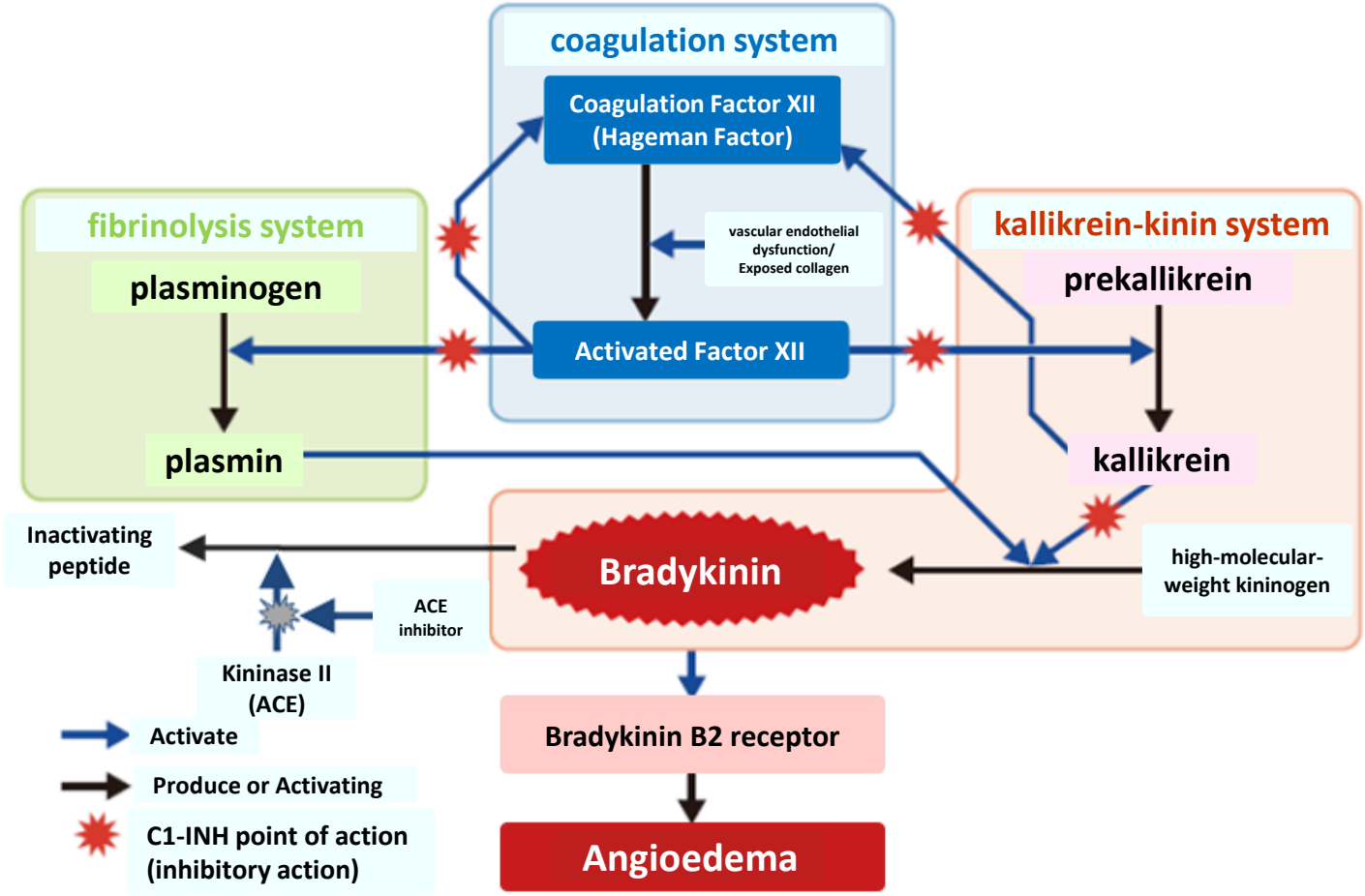
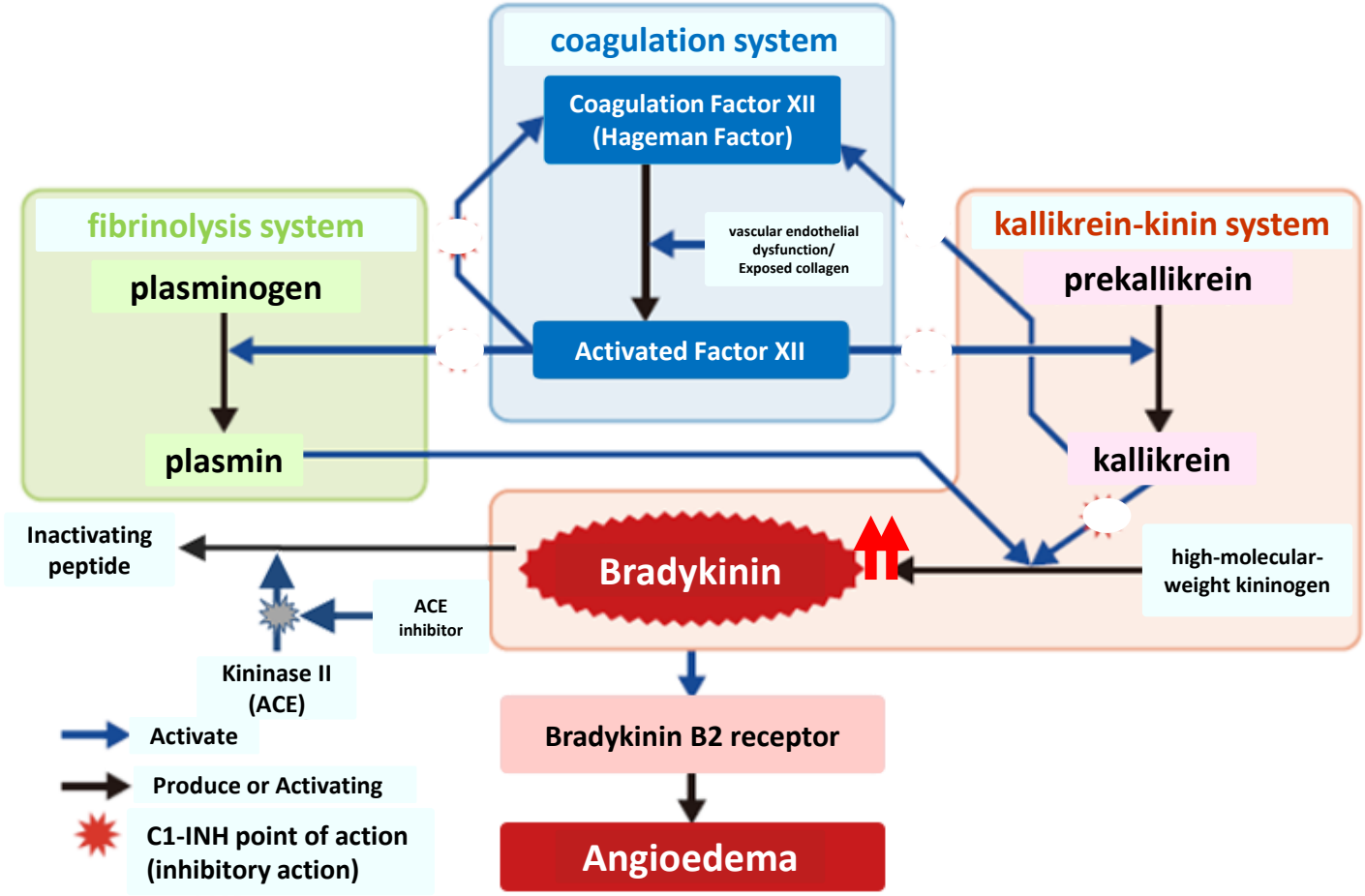
Involvement of C1-INH in Angioedema



- Bradykinin is produced by the decomposition of polymorphic kininogens after activation of factor XII (the contact system) and the activation of the kallikrein-kinin system. Plasmin also breaks down polymorphic kininogens and produces bradykinin.
- C1-INH suppresses bradykinin production in several steps in these pathways (✸ = C1-INH point of action).
- Deficiency/dysfunction of C1-INH and excessive function of factor XII all cause HAE by increasing blood levels of bradykinin.

1) Series from Swollen Abdomen Navi PRO https://www.harefukutsuu-hae.jp/

When C1-INH ceases to function…



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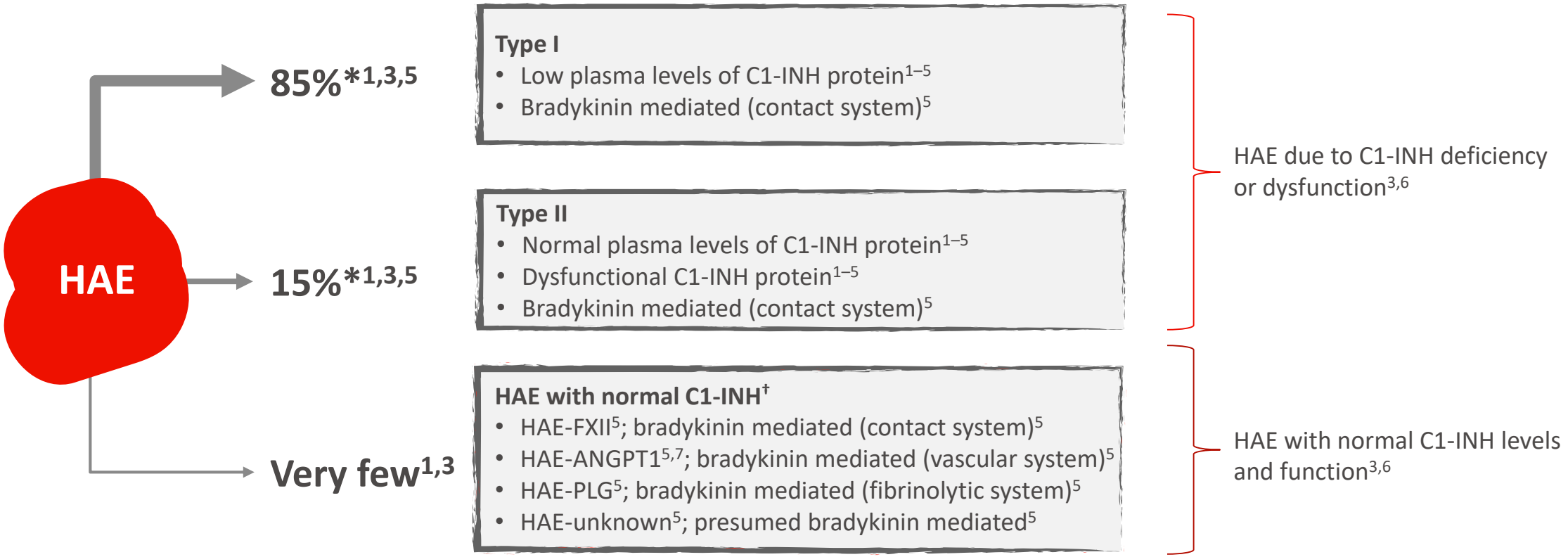
Classification of HAE disease type

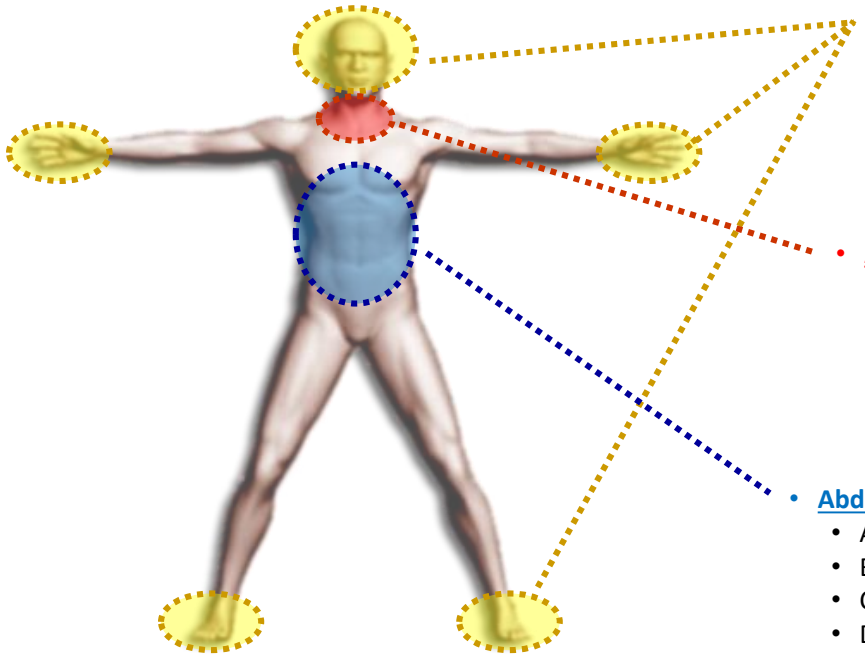
Several types of HAE have been identified:



*In Chinese patients, Type I and Type II HAE account for 98.7% and 1.3% of cases, respectively.[7] †Previously referred to as 'Type III'.[3,6]
C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; HAE-ANGPT1, HAE with an angiopoietin-1 gene mutation; HAE-FXII, HAE with a known Factor XII gene mutation; HAE-PLG, HAE with a mutation in the plasminogen gene.

1. Lumry WR. Am *J Manag Care* 2013;19:S103–S110; 2. Zuraw BL. *J Allergy Clin Immunol* 2018;14:884–845; 3. Zuraw BL. *N Engl J Med* 2008;359:1027–1036;
4. Cicardi M et al. *Allergy* 2014;69:602–616; 5. Longhurst HJ & Bork K. *Br J Hosp Med* 2019;80:391–398;
6. Bafunno V et al. *J Allergy Clin Immunol* 2018;141:1009–1017; 7. Zhi Y et al. *Eur J Dermatol* 2019;29:14–20.

Signs & symptoms of HAE are not specific and often lead to misdiagnoses



- **Cutaneous/mucosal swelling**
  - Allergy
  - Cutaneous disorders
  - Urticaria
  - Other forms of angioedema
- **Airway obstruction**
  - Allergy (incl. anaphylaxis)
  - Asthma
  - GERD
  - Infections of upper airways
  - Other forms of angioedema
- **Abdominal pain**
  - Appendicitis
  - Biliary disorders
  - Colitis
  - Diverticulitis
  - Endometriosis
  - Gastroenteritis
  - Irritable colon
  - Kidney problems
  - Pancreatitis
  - Peptic ulcer/GERD

In most of these conditions symptoms are often recurrent and combined

Diagnosis of HAE is not exclusive,
but should be considered as an option in differential diagnosis

Disorders are examples of diagnoses reported by HAE patients with other conditions misdiagnosed prior to HAE diagnosis or conditions to be considered for differential diagnosis of HAE.
Agostoni A et al. J Allergy Clin Immunol 2004; Bork K et al. Am J Med 2006; Farkas H. Allergy Asthma Clin Immunol 2010;
Papadopoulou-Alataki E. Curr Opin Allergy Clin Immunol 2010; Ali MA et al. Clin Exp Gastroenterol 2014; Zanichelli A et al. Ann Allergy Asthma Immunol 2016.

Importance of HAE Diagnosis for Reducing Mortality from Laryngeal Attacks*

29%

Mortality due to asphyxiation from laryngeal attacks in patients **undiagnosed** with HAE (n=63/214)

vs

3%

Mortality due to asphyxiation from laryngeal attacks in patients **diagnosed** with HAE (n=7/214)

- Lifespan of undiagnosed patients with HAE who die from laryngeal attacks is an average **31 years** shorter than undiagnosed patients who die from other causes

Diagnosis has significant impact on mortality rates

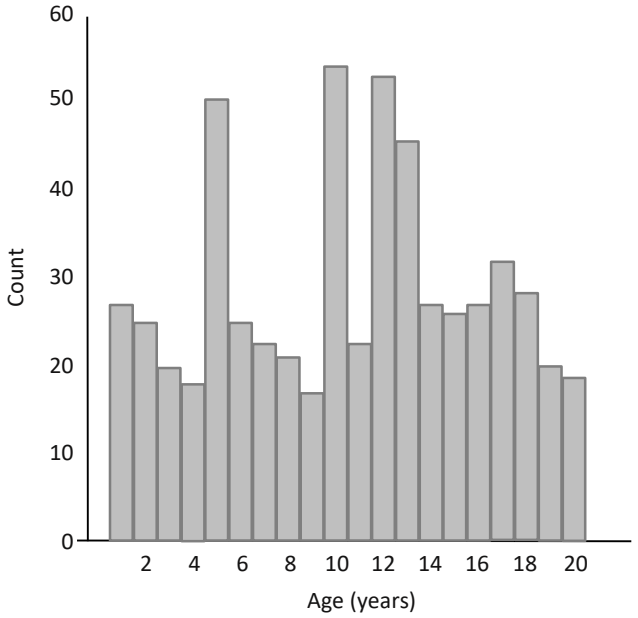
*Note: The information on this slide is from one study, which had a partly retrospective and partly prospective design and analyzed a total of 728 patients from 182 families with HAE-C1-INH. At the time of evaluation (October 2011), 214 patients had died.

HAE, hereditary angioedema; HAE-C1-INH, hereditary angioedema due to C1 inhibitor deficiency

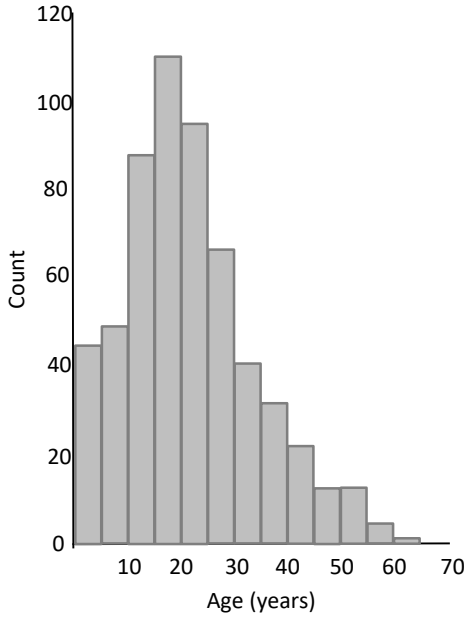
Bork K, *et al. J Allergy Clin Immunol*. 2012;130:692–7

Diagnosis of Hereditary Angioedema is often delayed

Age at onset of first swelling
(mean = 11 years)



Age at diagnosis
(mean = 19 years)



Median delay in diagnosis = 8 years (range 0-55)

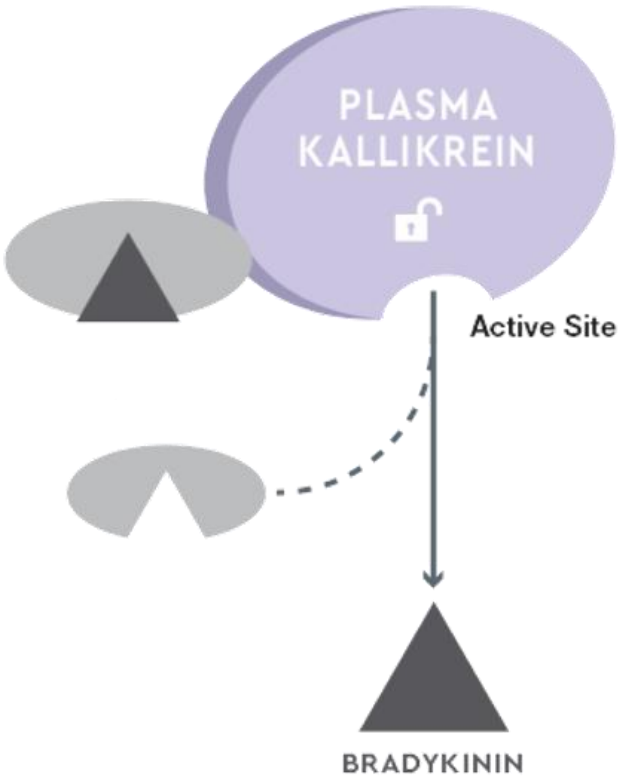
HAE, hereditary angioedema.
Retrospective study in 581 US patients with HAE. Christiansen SC et al. Clin Pediatr 2016.

Today's Topics

1. What is hereditary angioedema (HAE)?
2. HAE attacks (swelling or pain)
3. Reasons for delay in diagnosis / treatment
4. **Global study results of Lanadelumab as prophylaxis treatment**

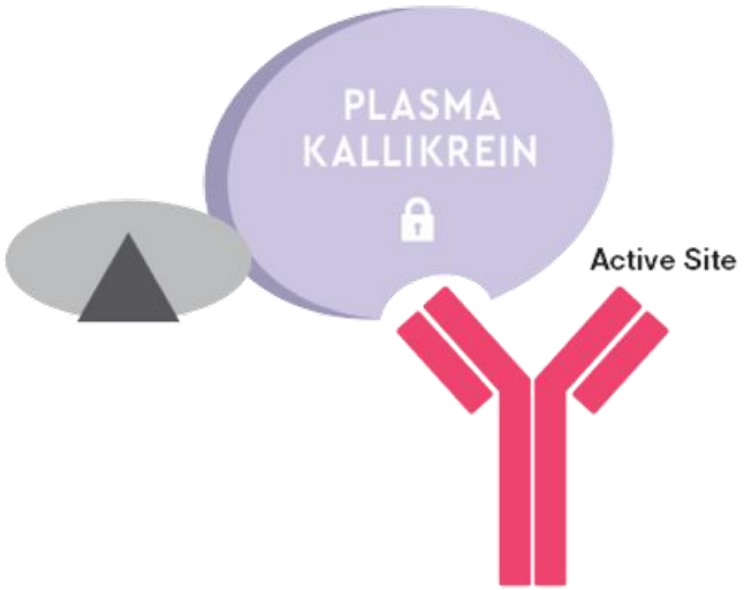
Mechanism of Action of Lanadelumab

MECHANISM OF DISEASE



Uncontrolled plasma kallikrein activity leads to excessive bradykinin production and, ultimately, HAE attacks

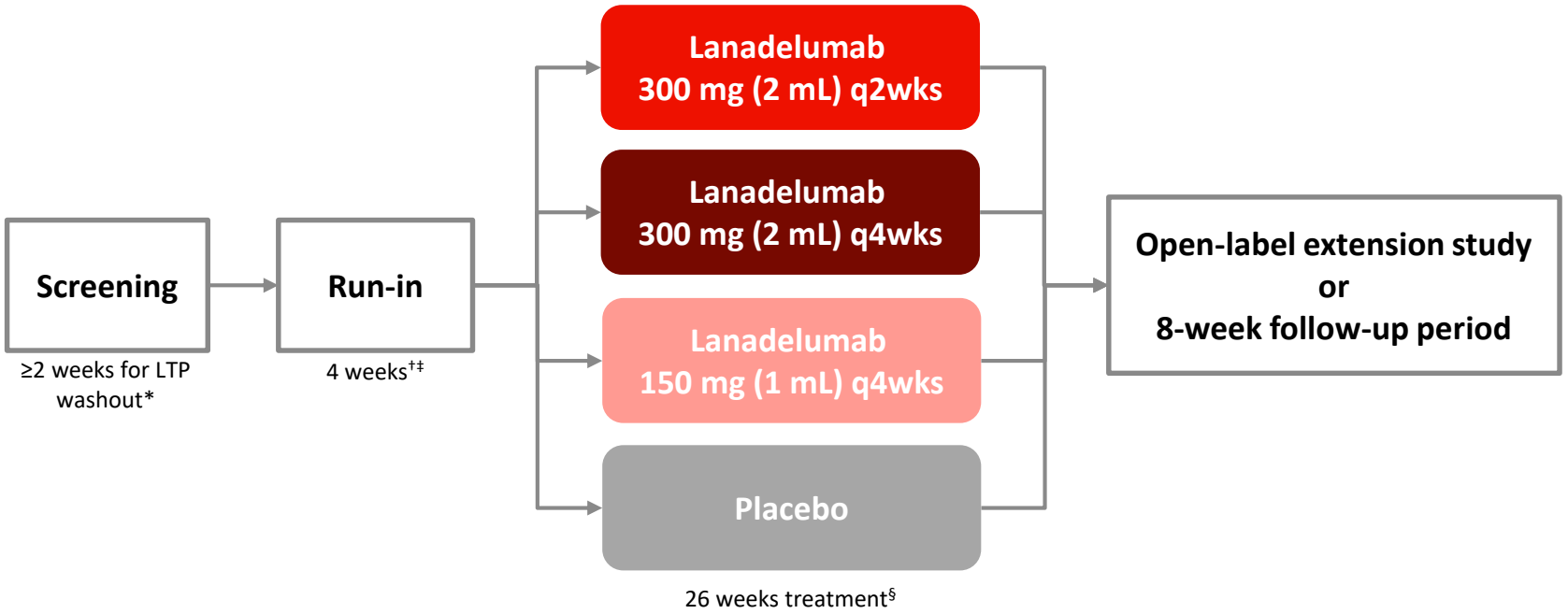
MECHANISM OF ACTION



Direct inhibition of active plasma kallikrein limits bradykinin production

The HELP Study: A Randomized, Double-blind, Placebo-controlled, Parallel-arm, Multicenter Phase 3 Study[1–5]

Objective: Investigate the efficacy and safety of lanadelumab for long-term prophylaxis (LTP) against HAE attacks in patients with HAE with C1-INH deficiency (C1-INH-HAE)

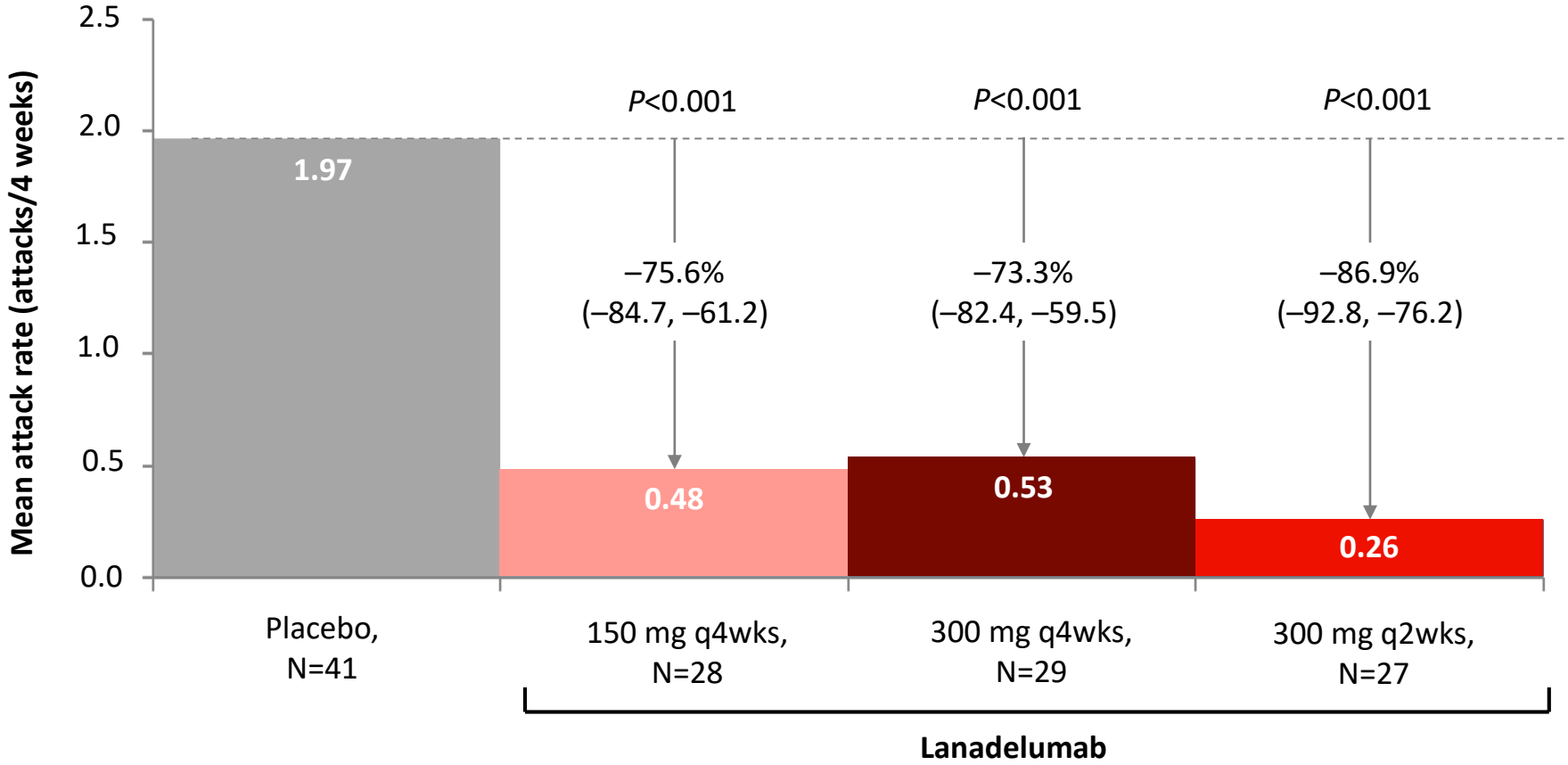


*LTP washout only for patients ≥18 years of age; †Run-in period could be shortened if patient experienced ≥3 attacks before completion of 4 weeks, and period could be extended to 8 weeks if patient did not experience any attacks during 4 weeks; ‡To assess the efficacy and safety of lanadelumab by baseline attack frequency relative to placebo, randomization was stratified by baseline attack rate (1 to <2, 2 to <3, or ≥3 attacks/month [defined as a 4-week period or 28 days])[3]; §Treatments administered as 2 separate 1 mL injections in the upper arm every 2 weeks to maintain the blind.

C1-INH = C1 esterase inhibitor; C1-INH-HAE = HAE with C1-INH deficiency; HELP = Hereditary angioEdema Long-term Prophylaxis; LTP = long-term prophylaxis; q2wks = every 2 weeks; q4wks = every 4 weeks

1. Clinicaltrials.gov [NCT02586805]. Accessed April 2018; 2. Banerji A, *et al.* Presented at the American College of Allergy, Asthma and Immunology (ACAAI) 74th Annual Scientific Meeting, October 26–30, 2017, Boston, MA; 3. Riedl MA, *et al.* Presented at the 2018 American Academy of Allergy, Asthma and Immunology (AAAAI)/World Allergy Organization (WAO) Joint Congress, March 2–5, 2018, Orlando, FL; Poster #151; 4. Johnston DT, *et al*. Presented at the American College of Allergy, Asthma and Immunology (ACAAI) Annual Scientific Meeting, November 15–19, 2018, Seattle, WA; Poster P166; 5. Zuraw BL, *et al*. Presented at the American College of Allergy, Asthma and Immunology (ACAAI) Annual Scientific Meeting, November 15–19, 2018, Seattle, WA; Poster P170

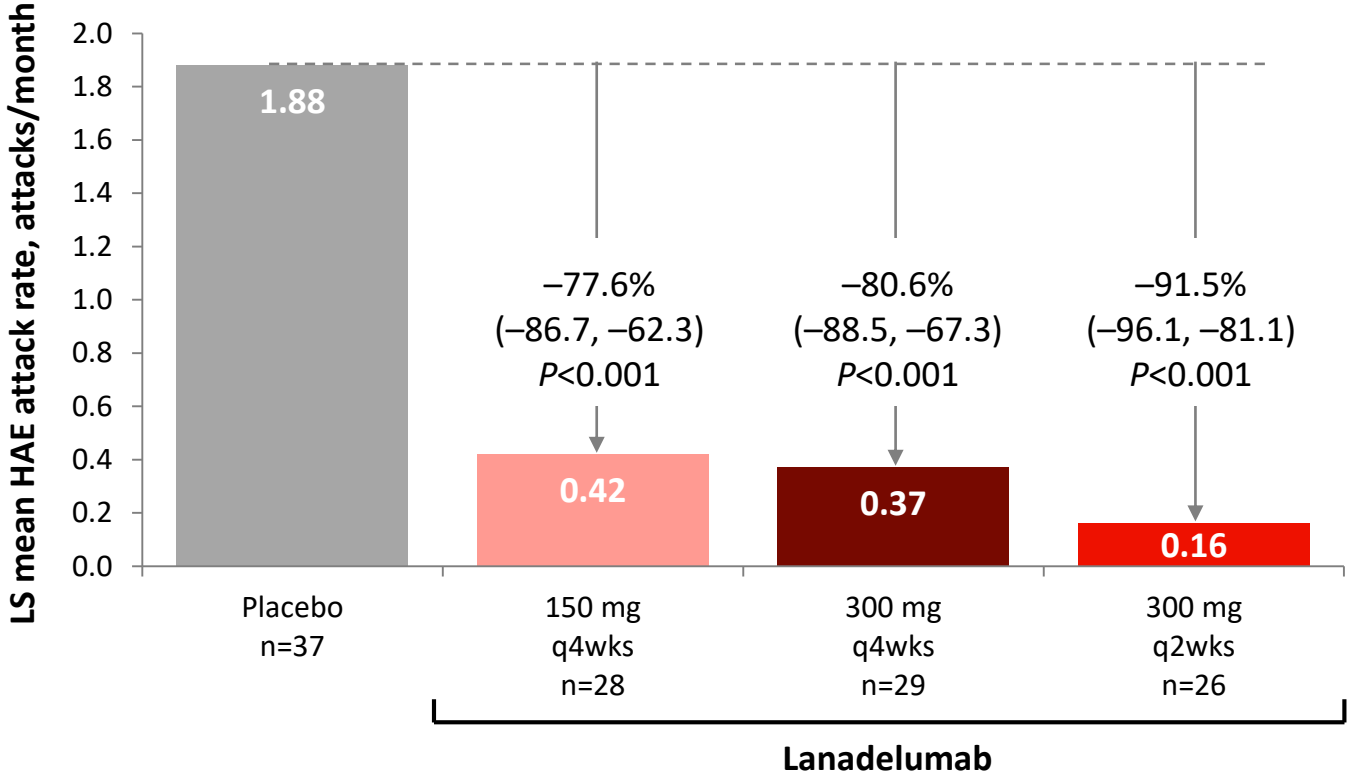
Primary Endpoint: Lanadelumab Significantly Reduced Mean Attack Rates



Attack rates are presented as /4 weeks (95% CI). Results are from a Poisson regression model; treatment group and normalized baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period wa san offset variable. Adjusted P-values are shown.
q4wks = every 4 weeks; q2wks = every 2 weeks
Banerji A, *et al.* Presented at the American College of Allergy, Asthma and Immunology Annual 74th Annual Scientific Meeting, October 26–30, 2017, Boston, MA

At Steady State (Days 70–182), Lanadelumab Significantly Reduced Mean Attack Rates[1,2]

Exploratory Endpoint*



At steady state (Days 70–182), LS mean monthly HAE attack rate was significantly reduced in all lanadelumab treatment arms vs the placebo arm

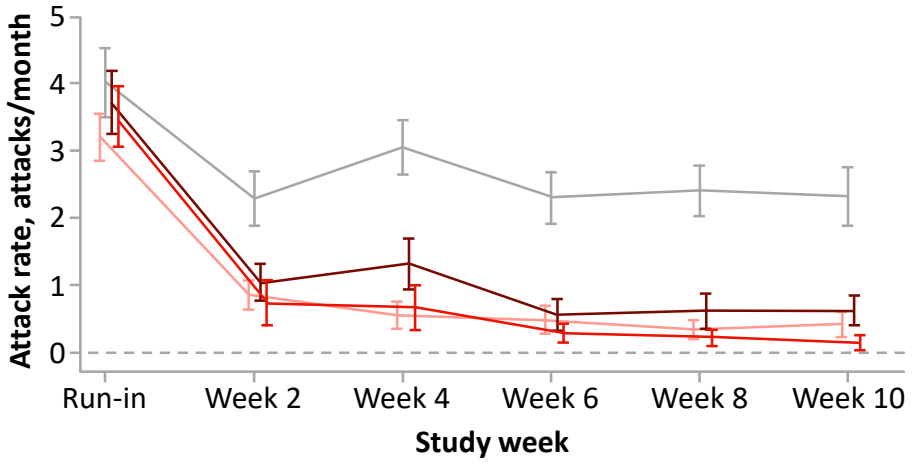
Attack rates are presented as attacks/4 weeks and are adjusted for baseline attack severity. Results are from a Poisson regression model.
Percentages are reduction in attack rate vs placebo (CI). P-values are not adjusted for multiplicity; **post hoc* sensitivity analysis.
HAE = hereditary angioedema; LS = least squares; CI = confidence interval; q2wks = every 2 weeks; q4wks = every 4 weeks

1. Maurer M, *et al.* Presented at the 2018 European Academy of Allergy and Clinical Immunology (EAACI) Congress, 26–30 May 2018, Munich, Germany; Poster #0525;
2. Shire Data on File: SHP643-002

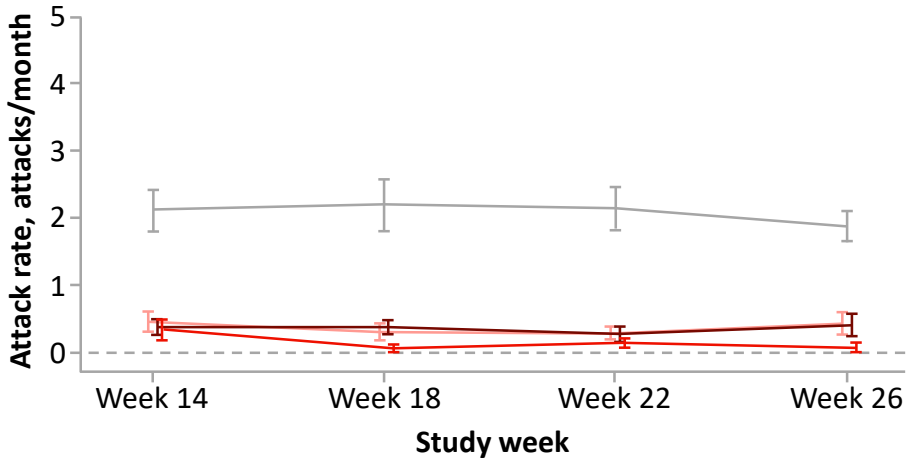
HAE Attack Rate During Days 0–69 of Treatment and During Steady State

Ad hoc analysis

HAE attack rate during days 0–69 of treatment*



HAE attack rate during the steady state period†



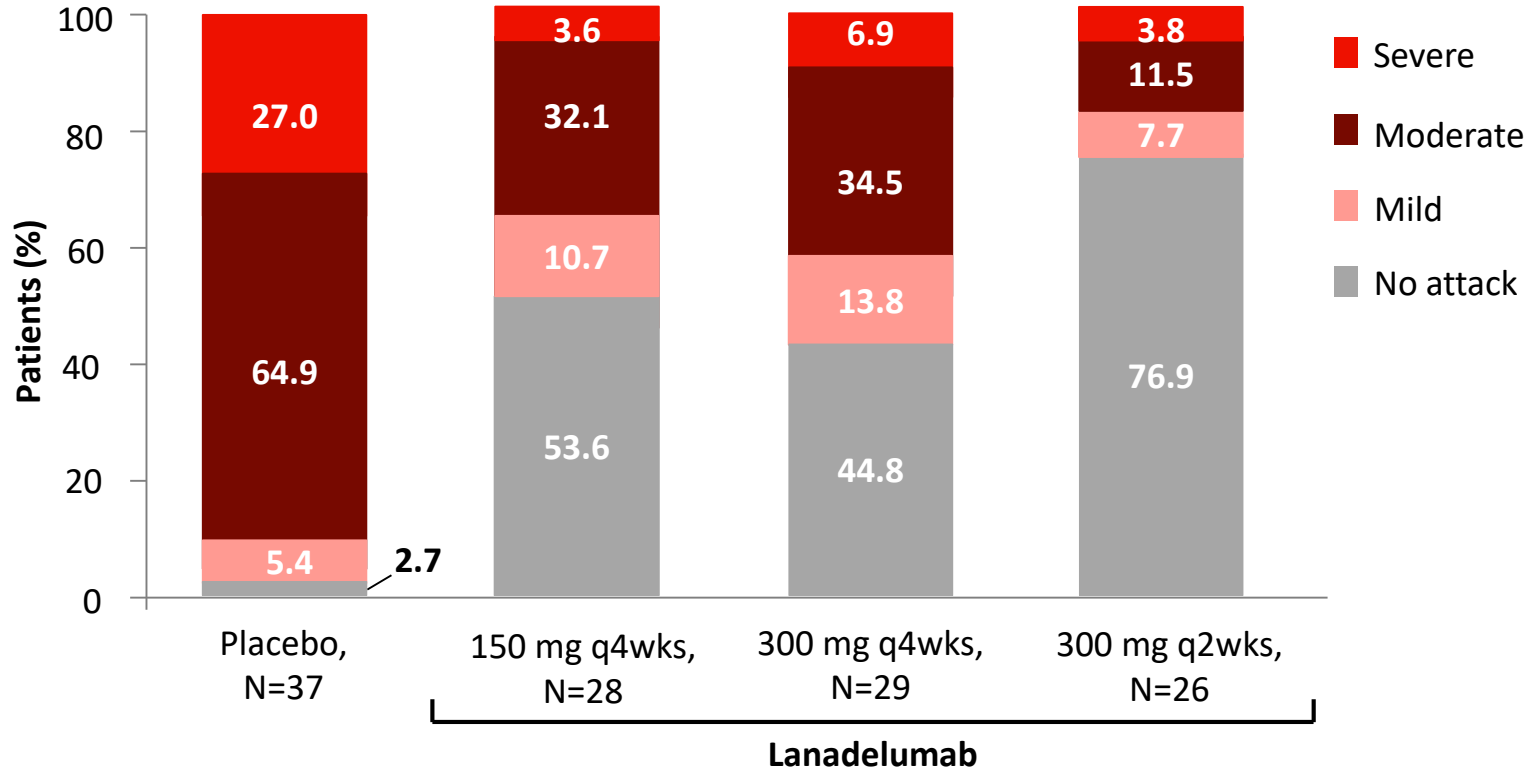
Placebo | Lanadelumab 150 mg q4wks | Lanadelumab 300 mg q4wks | Lanadelumab 300 mg q2wks

Efficacy with lanadelumab was observed within the first 2 weeks of treatment and was maintained over time

*Attack rates were based on attacks occurring within 2 weeks before each time point. A month was defined as 28 days. Error bars indicate the standard error of the mean.
†Attack rates were based on attacks occurring within 4 weeks before each time point. A month was defined as 28 days. Error bars indicate the standard error of the mean.
HAE = hereditary angioedema; q2wks = every 2 weeks; q4wks = every 4 weeks
Maurer M, *et al.* Presented at the European Academy of Allergy and Clinical Immunology (EAACI) Congress, June 1–5, 2019, Lisbon, Portugal; Poster PD0369

At Steady State (Days 70–182), Even More Lanadelumab-treated Patients were Attack-free and Fewer Experienced a Moderate or Severe Attack[1,2]

Exploratory Endpoint*



At steady state 76.9% of patients receiving lanadelumab 300 mg q2wks were attack-free compared with 2.7% of placebo-recipients

Analysis of maximum attack severity; **post hoc* sensitivity analysis.
q4wks = every 4 weeks; q2wks = every 2 weeks

1. Maurer M, *et al.* Presented at the 2018 European Academy of Allergy and Clinical Immunology (EAACI) Congress, 26–30 May 2018, Munich, Germany; Poster #0525;
2. Shire Data on File: SHP643-002

Safety: Overview of Adverse Events

	Placebo, N=41 n (%)	Lanadelumab			
		150 mg q4wks, N=28 n (%)	300 mg q4wks, N=29 n (%)	300 mg q2wks, N=27 n (%)	Total, N=84 n (%)
Any AE	31 (75.6)	25 (89.3)	25 (86.2)	26 (96.3)	76 (90.5)
Any treatment-related AE*	14 (34.1)	17 (60.7)	14 (48.3)	19 (70.4)	50 (59.5)
Any serious AE	0 (0.0)	0 (0.0)	3 (10.3)	1 (3.7)	4 (4.8)
Any related serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths due to AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to AE	1 (2.4)†	0 (0.0)	1 (3.4)	0 (0.0)	1 (1.2)

There were no deaths or treatment-related serious AEs

*Adverse events that were judged by the investigator to be related to the use of the investigational product.
†One patient withdrew due to a HAE attack and is not included.
AEs were collected over the entire treatment period and were assigned to the treatment group, irrespective of type of injection (i.e., placebo or active drug in the 150 mg q4wks and 300 mg q4wks groups).
AE = adverse event; HAE = hereditary angioedema; q2wks = every 2 weeks; q4wks = every 4 weeks
Banerji A, et al. JAMA 2018;320:2108–21

Safety: Adverse Events Reported in ≥5% of Lanadelumab-treated Patients

	Placebo, N=41 n (%)	Lanadelumab			
		150 mg q4wks, N=28 n (%)	300 mg q4wks, N=29 n (%)	300 mg q2wks, N=27 n (%)	Total, N=84 n (%)
Any AE	31 (75.6)	25 (89.3)	25 (86.2)	26 (96.3)	76 (90.5)
Injection site pain	12 (29.3)	13 (46.4)	9 (31.0)	14 (51.9)	36 (42.9)
Viral upper respiratory tract infection	11 (26.8)	3 (10.7)	7 (24.1)	10 (37.0)	20 (23.8)
Headache	8 (19.5)	3 (10.7)	5 (17.2)	9 (33.3)	17 (20.2)
Injection site erythema	1 (2.4)	4 (14.3)	2 (6.9)	2 (7.4)	8 (9.5)
Injection site bruising	0 (0.0)	3 (10.7)	2 (6.9)	1 (3.7)	6 (7.1)
Dizziness	0 (0.0)	1 (3.6)	3 (10.3)	1 (3.7)	5 (6.0)

The most common AEs were local injection site reactions, viral upper respiratory tract infection, headache, and dizziness

Treatment-emergent adverse events that were reported at the Preferred Term level in ≥5% of patients in the total lanadelumab-treated group and excludes HAE attack events.
AE = adverse event; HAE = hereditary angioedema; q2wks = every 2 weeks; q4wks = every 4 weeks
Banerji A, et al. JAMA 2018;320:2108–21

Safety: Treatment-related Adverse Events Reported in ≥5% of Lanadelumab-treated Patients

	Placebo, N=41 n (%)	Lanadelumab			
		150 mg q4wks, N=28 n (%)	300 mg q4wks, N=29 n (%)	300 mg q2wks, N=27 n (%)	Total, N=84 n (%)
Any treatment-related AE*	14 (34.1)	17 (60.7)	14 (48.3)	19 (70.4)	50 (59.5)
Injection site pain	11 (26.8)	12 (42.9)	9 (31.0)	14 (51.9)	35 (41.7)
Injection site erythema	1 (2.4)	4 (14.3)	2 (6.9)	2 (7.4)	8 (9.5)
Injection site bruising	0 (0.0)	2 (7.1)	2 (6.9)	1 (3.7)	5 (6.0)
Headache	1 (2.4)	1 (3.6)	2 (6.9)	3 (11.1)	6 (7.1)

The most common treatment-related AEs were injection site reactions and headache

*Adverse events that were judged by the investigator to be related to the use of the investigational product.
Includes adverse events that were reported at the Preferred Term level in ≥5% of patients in the total lanadelumab-treated group and excludes HAE attack events.
AE = adverse event; HAE = hereditary angioedema; q2wks = every 2 weeks; q4wks = every 4 weeks
Banerji A, et al. JAMA 2018;320:2108–21

Safety: Serious Adverse Events*

Preferred term	Placebo, N=41 n (%)	Lanadelumab		
		150 mg q4wks, N=28 n (%)	300 mg q4wks, N=29 n (%)	300 mg q2wks, N=27 n (%)
Any SAE	0 (0.0)	0 (0.0)	3 (10.3)	1 (3.7)
Catheter site infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)
Meniscus injury	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)
Bipolar II disorder	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)

Four SAEs were reported during the study, but none was considered to be related to treatment

*These data are reported in the Supplementary Online Content.
q2wks = every 2 weeks; q4wks = every 4 weeks; SAE = serious adverse event
Banerji A, et al. JAMA 2018;320:2108–21

Safety: Adverse Events of Special Interest

- A total of 8 AESIs were reported in 5 patients, all treated with lanadelumab:[1]
  - 2 events of injection site induration in 1 patient receiving lanadelumab 150 mg q4wks
  - 2 events of injection site erythema in 1 patient receiving lanadelumab 300 mg q4wks
  - 4 events in 3 patients receiving lanadelumab 300 mg q2wks:
    - 2 related hypersensitivity events in 1 patient, 1 mild and 1 moderate in severity
      - Symptoms of pruritus, itching, and tingling of the tongue were reported for both events; the events resolved within 1 day without interruption of lanadelumab treatment and the patient continued in the study without further reactions
    - 1 event of injection site reaction in 1 patient
    - 1 mild event of microcytic anemia in 1 patient that was not considered related to treatment

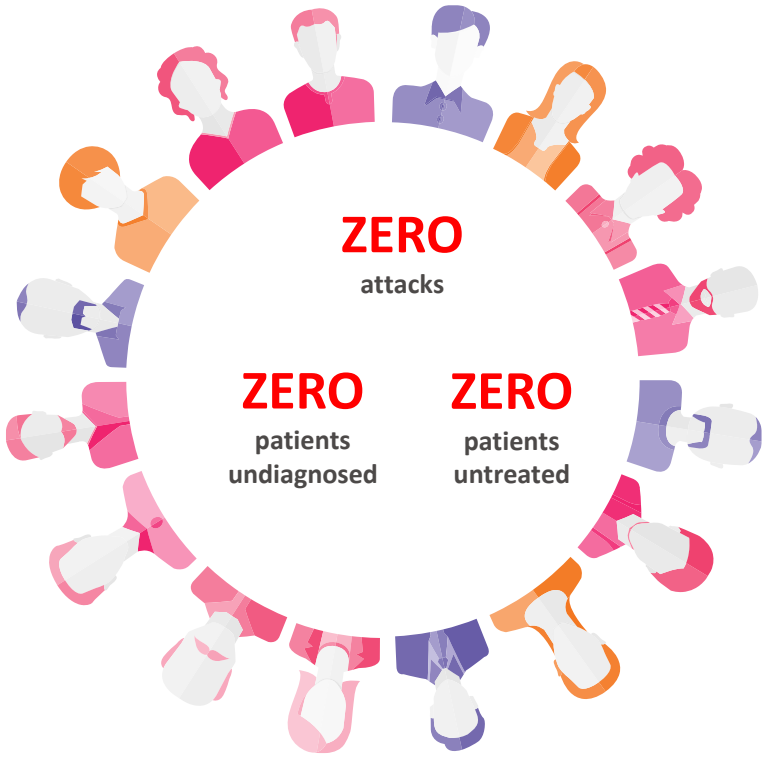
None led to treatment discontinuation[2]

AESIs = adverse events of special interest; q2wks = every 2 weeks; q4wks = every 4 weeks

1. Johnston DT, et al. Presented at the American College of Allergy, Asthma and Immunology (ACAAI) Annual Scientific Meeting, November 15–19, 2018, Seattle, WA; Poster P166;
2. Clinical Study Report: DX-2930-03, Shire, September 2017; pp. 2491, 2492, 2519, 2521, 2524, 2527

Strategic portfolio vision:

Enable every patient to Aim for ZERO



1. Elevate prophylaxis standard of care
2. Drive awareness, diagnosis and treatment of HAE
3. Continuously innovate to improve patient care

Thank you for your attention

Better Health, Brighter Future