# Angioedema with Normal Labs….What Now?

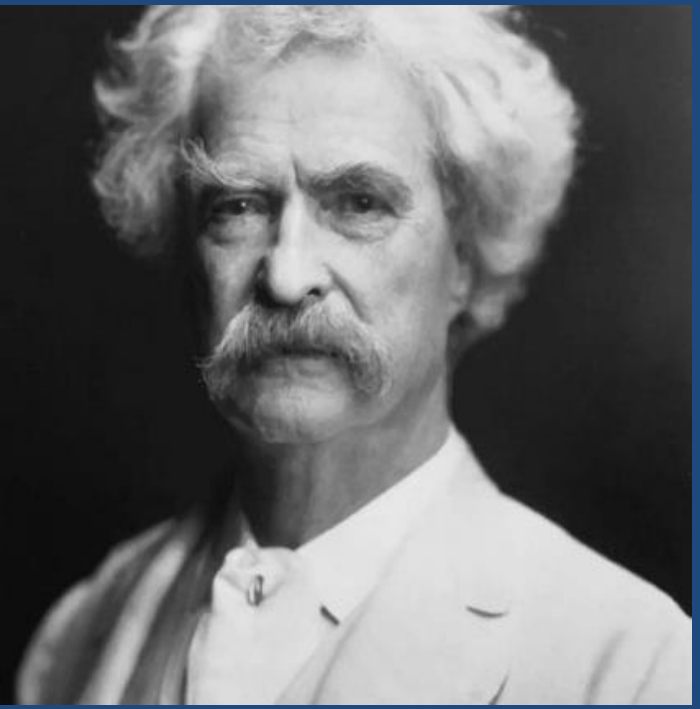
**Marc Riedl, MD MS**
**Professor of Medicine**
**Clinical Director – US HAEA Angioedema Center**
**University of California, San Diego**

# Learning Objectives

- Review data on mechanisms underlying isolated angioedema with normal lab evaluation
- Summarize important clinical features in the assessment of recurrent angioedema
- Develop a management approach for isolated angioedema with normal lab results

It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

*Mark Twain*



# Causes of Angioedema

- IgE-mediated: Foods, drugs, insect stings
- Non-IgE mediated: Radiocontrast media
- Chronic spontaneous urticaria/angioedema
- Physical urticaria/angioedema
- ASA and other NSAIDs

- ACE inhibitor-induced
- C1-INH Deficiency
  - Hereditary - Types I, II
  - Acquired
- Hereditary with normal C1INH
  - Factor XII
  - Angiopoietin-1
  - Plasminogen
  - Kininogen
  - Myoferlin
  - HS3ST6
  - Unknown
- Idiopathic
  - Histaminergic/Mast Cell-mediated
  - Non-histaminergic

Agostoni A. *J Allergy Clin Immunol*. 2004;114:S51-S131.
Cichon S. *Am J Hum Genet*. 2006;79:1098-1104.
Maurer M, et al. Allergy. 2018

# Causes of Isolated Angioedema

**Table 1** *Types of recurrent angioedema diagnosed in 1058 patients examined between 1993 and 2012*

| | Patients, *n* (%) | Male, *n* (%) | Female, *n* (%) | Male : female ratio |
|---|---|---|---|---|
| Hereditary angioedema | 377 (36) | | | |
| ~~C1-INH-HAE~~ | ~~353 (94)~~ | | 202 (57) | 0.75 |
| FXII-HAE | 6 (1) | 1 (17) | 5 (83) | 0.2 |
| U-HAE | 18 (5) | 12 (67) | 6 (33) | 2 |
| AAE | 681 (64) | | | |
| ~~C1-INH-AAE~~ | ~~49 (7)~~ | | 31 (63) | 0.58 |
| ACEI-AAE | 183 (27) | | 76 (42) | 1.4 |
| IH-AAE | 379 (56) | 155 (41) | 224 (59) | 0.69 |
| InH-AAE | 70 (10) | 36 (51) | 34 (49) | 1.06 |
| Total | (100) | 480 (45) | 578 (55) | 0.83 |

4%

68%

84%

16%

11%

C1-INH-HAE, hereditary angioedema (HAE) with C1-inhibitor deficiency; FXII-HAE, HAE with factor XII mutation; U-HAE, HAE of unknown origin; ACEI-AAE, acquired angioedema (AAE) related to angiotensin-converting enzyme inhibitor therapy; IH-AAE, idiopathic histaminergic AAE; InH-AAE, idiopathic nonhistaminergic AAE.

Mansi M, J Intern Med. 2014

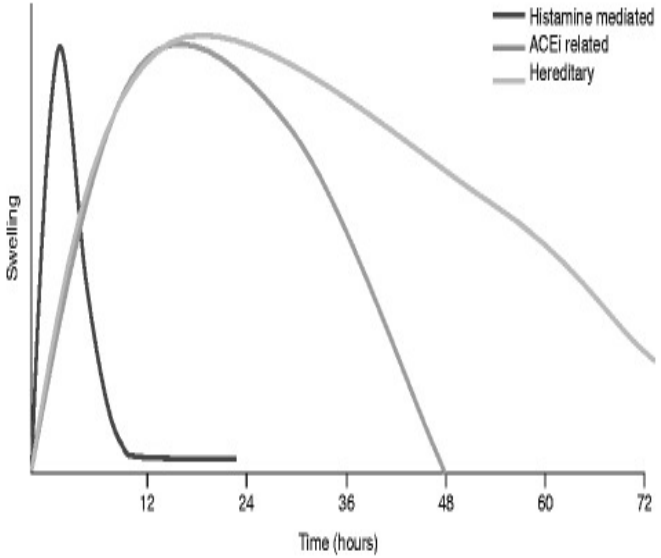
# Complement Testing in Recurrent Angioedema

| Type | C1-INH Level | C1-INH Function | C4 Level | C3 Level | C1q Level |
|---|---|---|---|---|---|
| **HAE Type I** | Low | Low | Low | Normal | Normal |
| **HAE Type II** | Normal-high | Low | Low | Normal | Normal |
| **HAE with normal C1-INH** | Normal | Normal | Normal | Normal | Normal |
| **Acquired C1-INH I/II** | Low | Low | Low | Low-normal | Low |
| **ACE-I associated AE** | Normal | Normal | Normal | Normal | Normal |
| **Idiopathic angioedema** | Normal | Normal | Normal | Normal | Normal |

Zuraw BL, et al. *J Allergy Clin Immunol*. 2013;131:1491-1493.

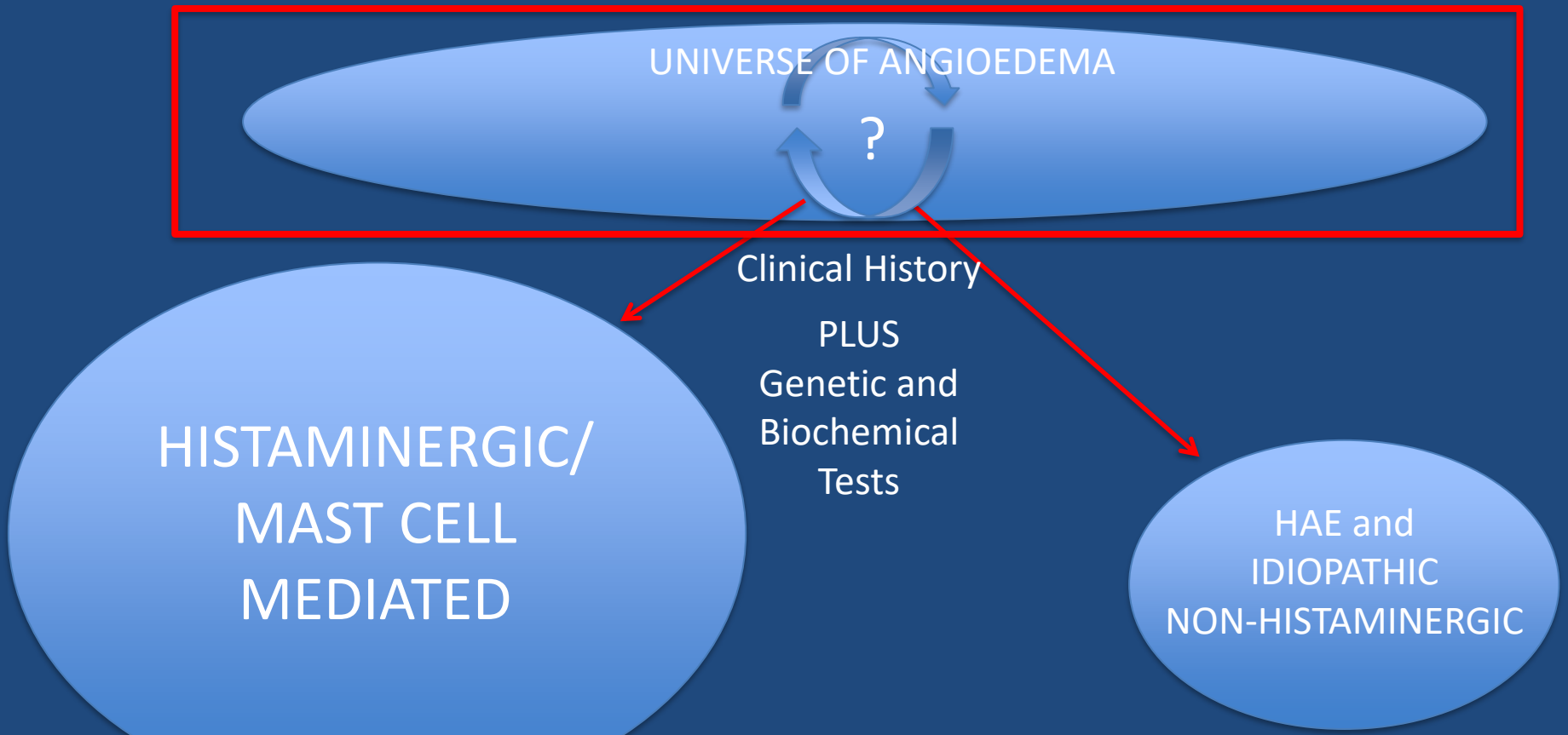
# Major Types of Angioedema

| | Histaminergic/ Mast-cell Mediated | Non-histaminergic/Kinin-mediated |
|---|---|---|
| **Onset/Duration ("Trajectory")** | Minutes to hours | Hours |
| **Urticaria** | + | - |
| **Pruritis** | + | - |
| **Pain/burning** | - | May be present |
| **Response to antihistamine** | + | - |
| **Response to steroids** | + | - |



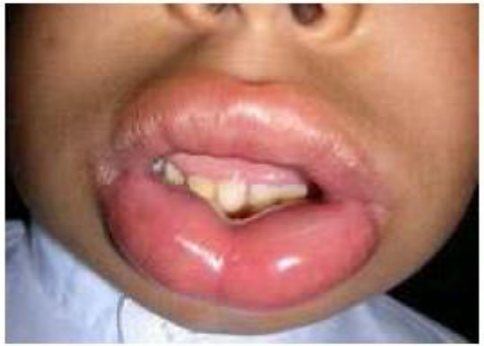

Maurer M, et al. Clin Rev Allergy Immunol. 2021
Bernstein JA, et al. Int J Emerg Med. 2017

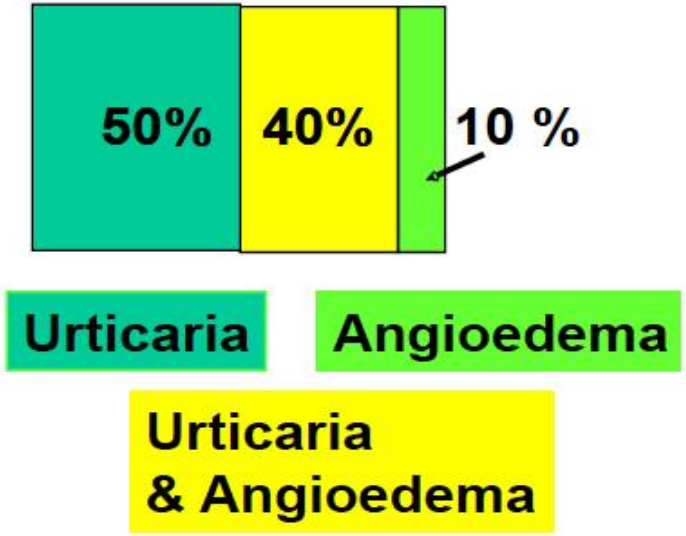
# Improved Diagnostic Testing to Targeted Therapy



# Mast-Cell Mediated Angioedema is Common

- Angioedema is often co-expressed with urticaria
  - Deeper dermal and subcutaneous layers.
  - Pruritic or burning quality
  - Consider hereditary angioedema in isolated angioedema

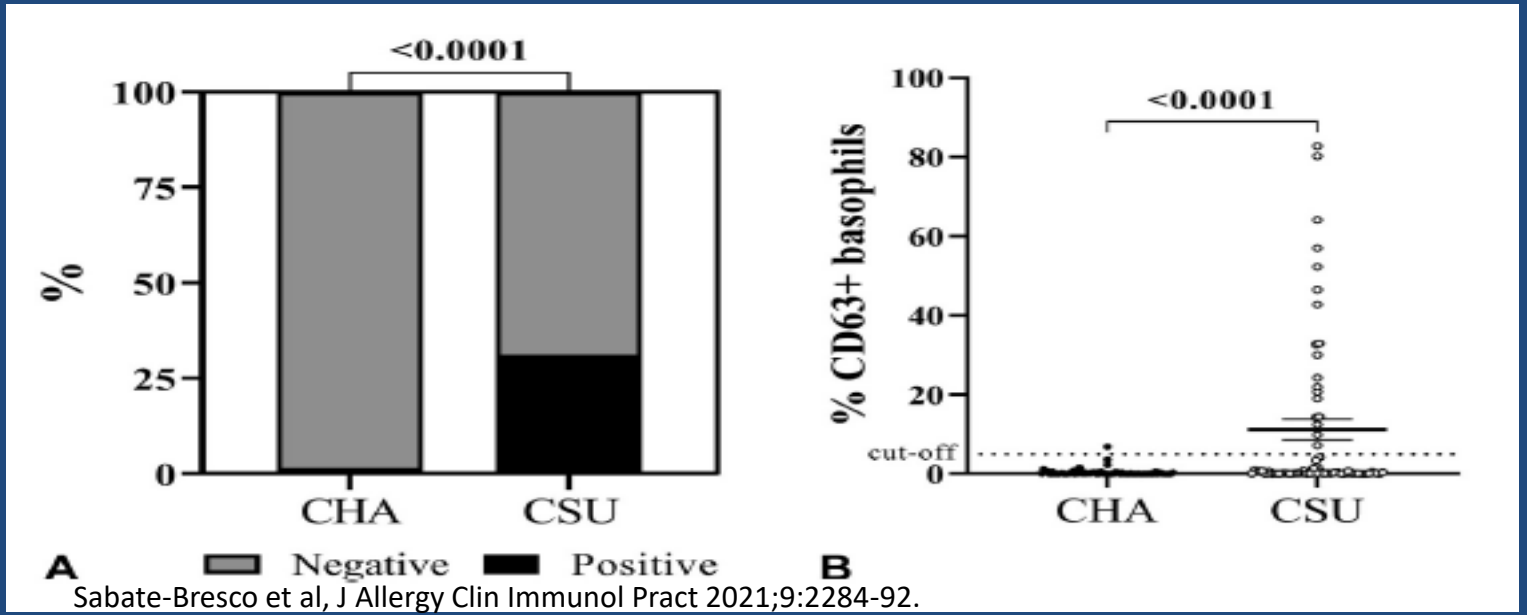





Sabroe et al, J Am Acad Dermatol 1999

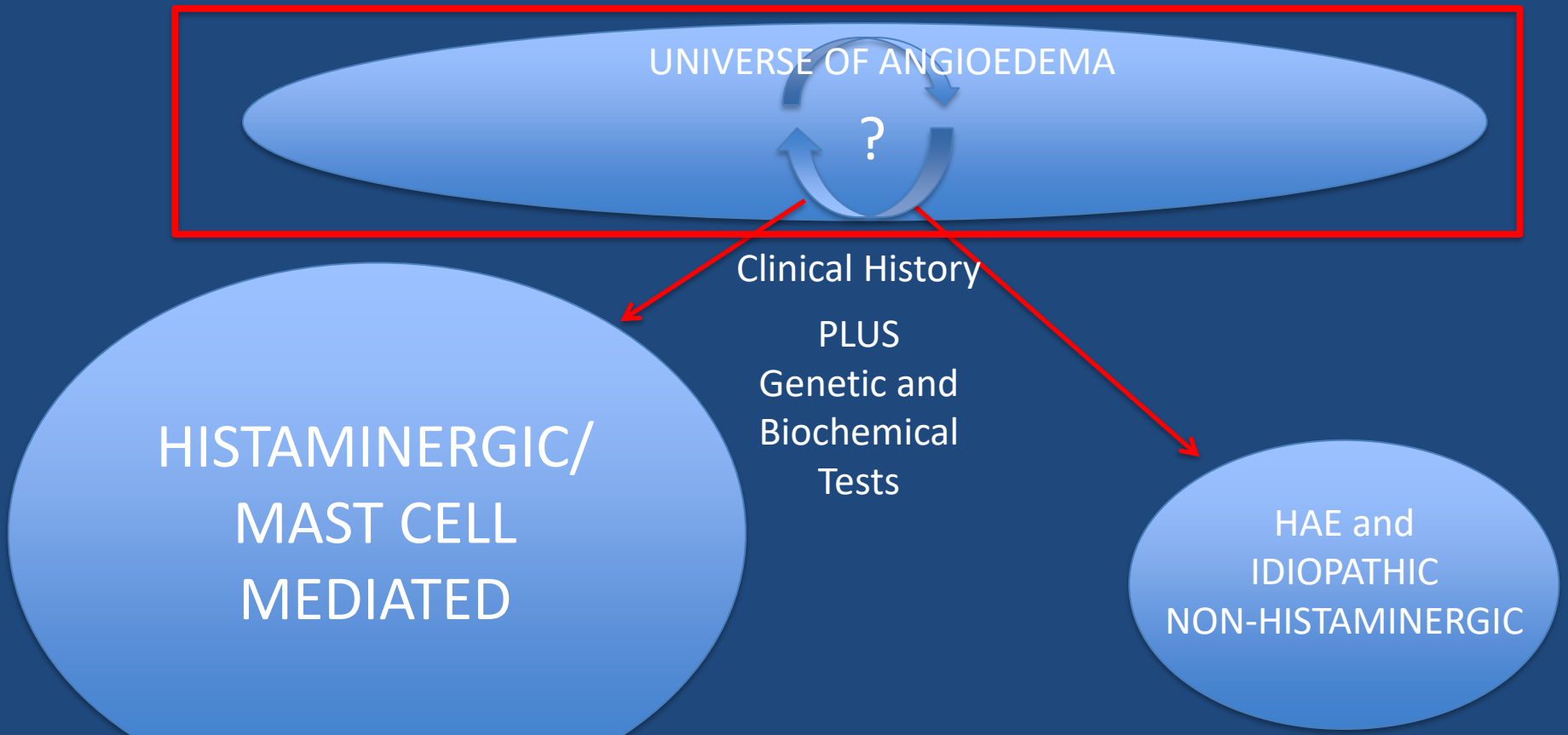
# Angioedema without Urticaria: Evaluation for Mast Cell Activity

- Serum tryptase
- Basophil activation studies



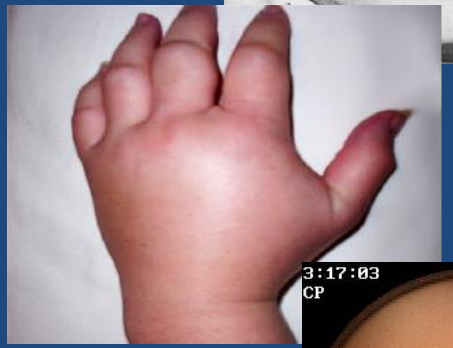

Sabate-Bresco et al, J Allergy Clin Immunol Pract 2021;9:2284-92.

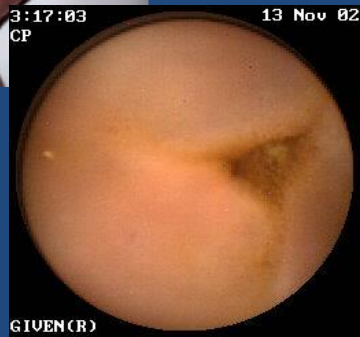
# Improved Diagnostic Testing to Targeted Therapy



# Hereditary Angioedema with Normal C1-INH

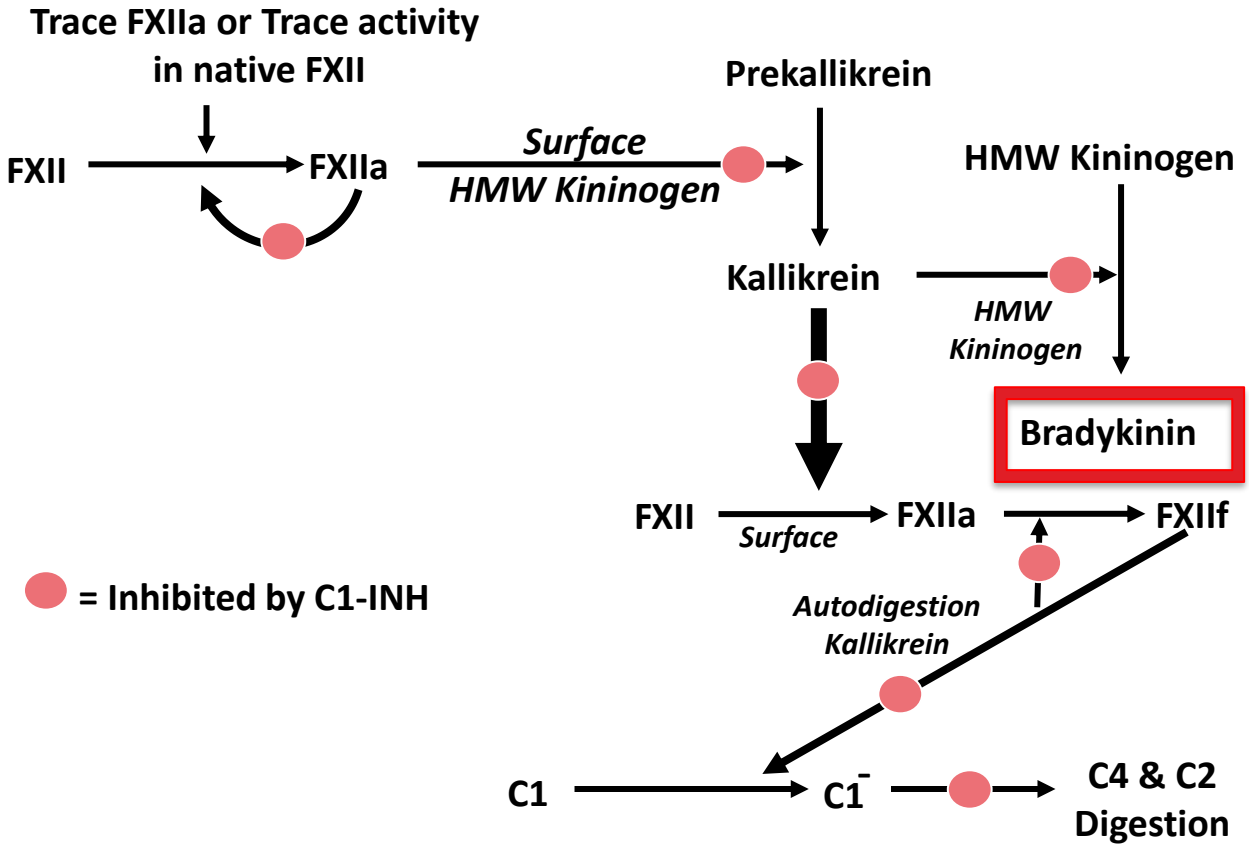
- **Familial condition**
- Clinical diagnosis + exclusion of other causes
- Pathophysiology poorly defined
- **Does not respond to treatment for histaminergic/mast cell-mediated angioedema**
- **Appears kinin-mediated**
- Striking predominance in women
  - Estrogen role in regulating phenotypic expression
- Facial and lip swelling frequent
- **Recurrent tongue swelling a cardinal symptom**
- Many patients have only skin swelling, with **infrequent GI angioedema**
- **Asphyxiation due to airway involvement occurs**

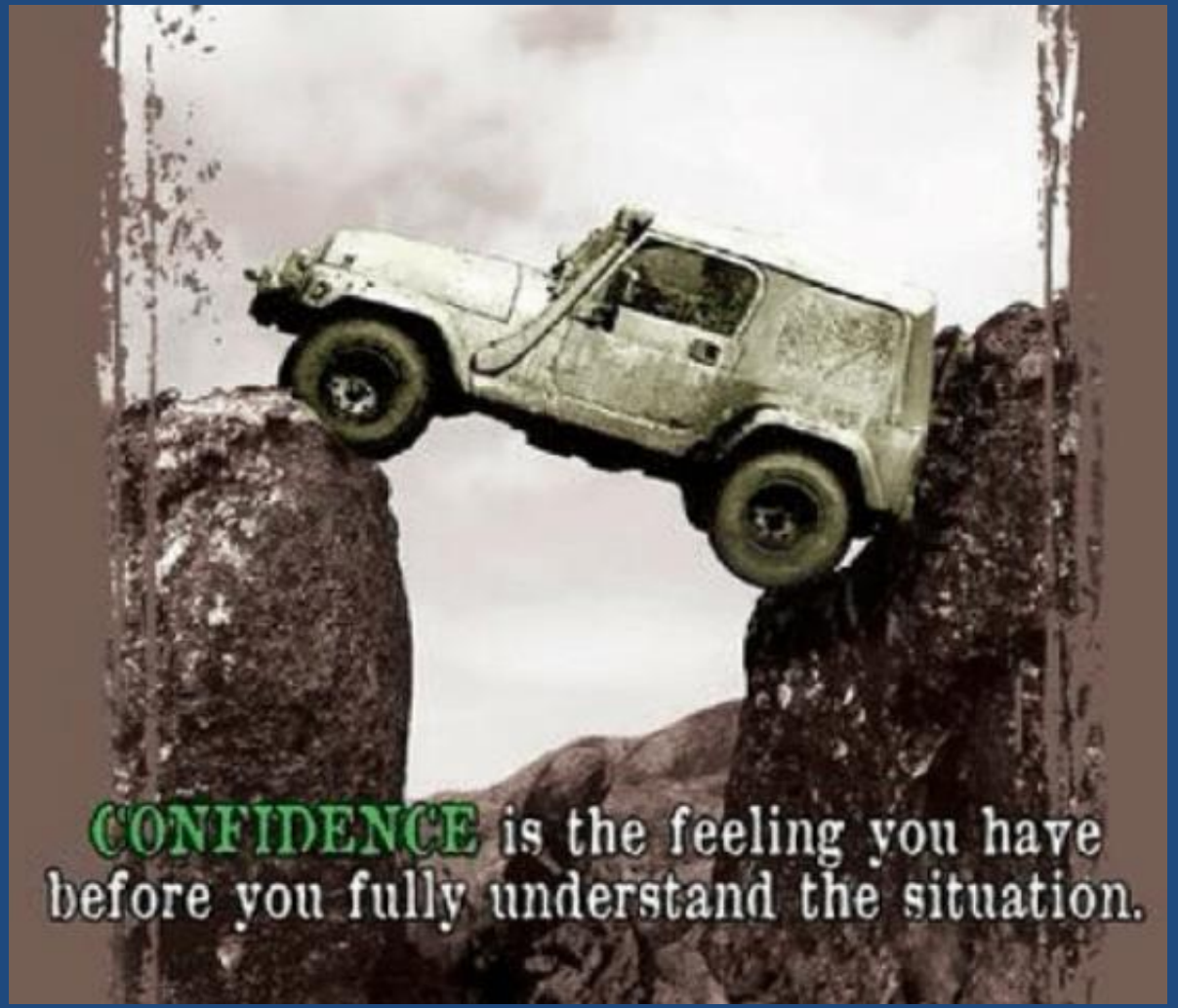




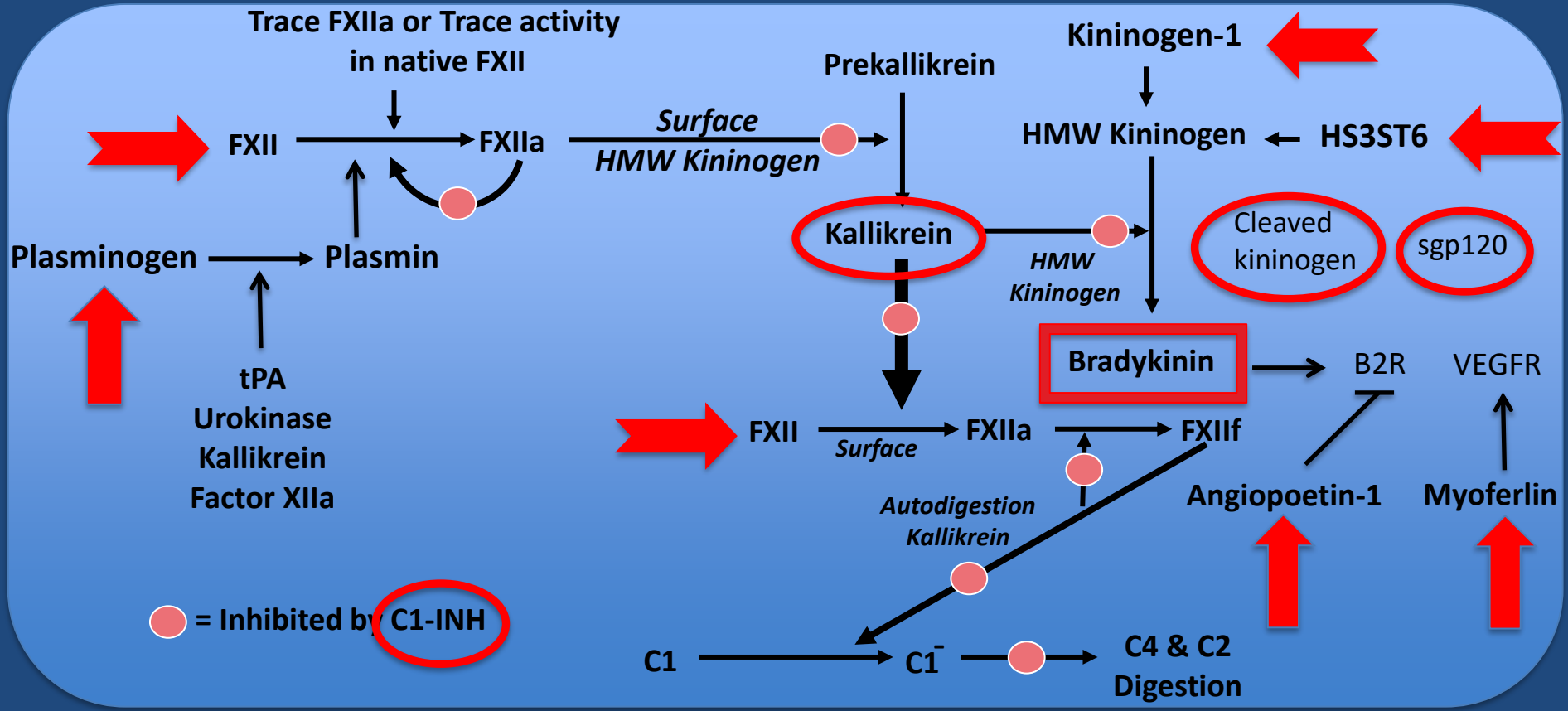

Bork K. *AJM* 2007;120:987-92.

# Hereditary Angioedema Pathophysiology




CONFIDENCE is the feeling you have
before you fully understand the situation.

# Bradykinin-mediated Angioedema with Normal C1INH: Various Mechanisms

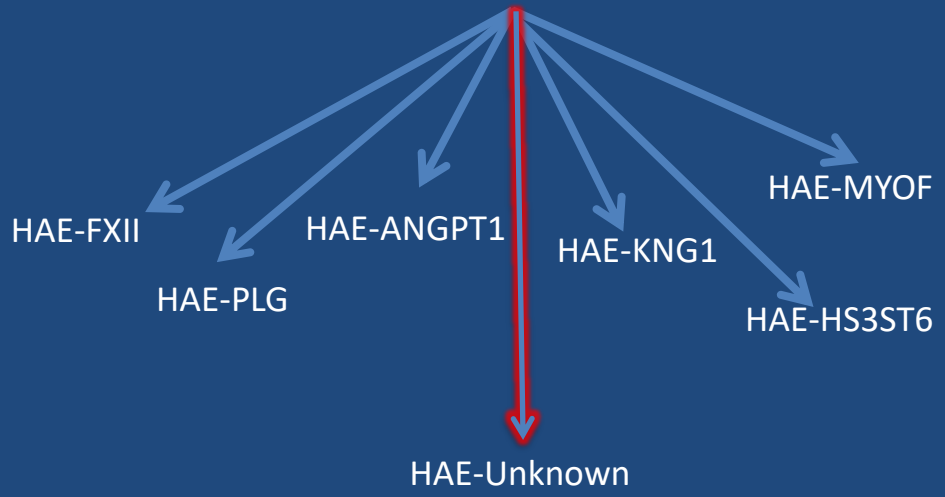



Adapted from Chen M, et al. *Immunol Allergy Clin North Amer* 2017

# Identification of Genetic Markers for HAE-normal C1INH

| | HAE-Normal C1INH |
|---|---|
| Percent of all HAE | Rare |
| C4 Level | Normal |
| C1-INH antigenic level | Normal |
| C1-INH antigenic function | Normal |

? HAE-Normal ?




Veronez CL, et al. J Allergy Clin Immunol Pract. 2021

# Biomarkers Assessing Contact System Activity

**A novel assay to diagnose hereditary angioedema utilizing inhibition of bradykinin-forming enzymes**

Joseph K. *Allergy*. 2015 Jan;70(1):115-119.

**Threshold-stimulated kallikrein activity distinguishes bradykinin- from histamine-mediated angioedema**

Lara-Marquez M. *Clin Exp Allergy* 2018. Jun 29.

J Allergy Clin Immunol. 2017 Aug 3. pii: S0091-6749(17)31268-X. doi: 10.1016/j.jaci.2017.07.012. [Epub ahead of print]

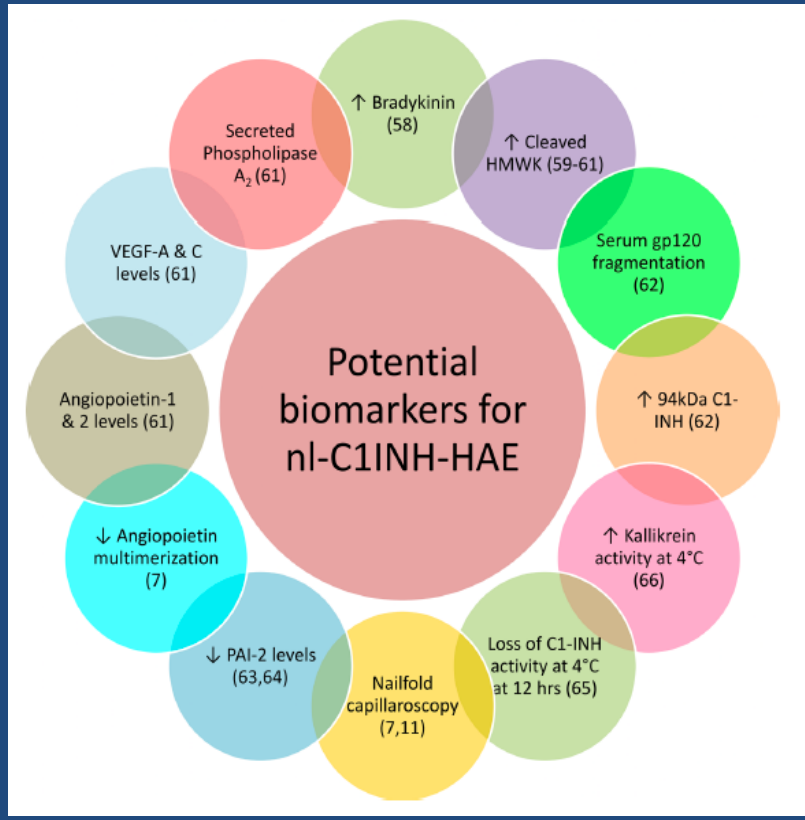
**Cleaved kininogen as a biomarker for bradykinin release in hereditary angioedema.**

Hofman ZLM. *J Allergy Clin Immunol*. 2017 Aug 4. pii: S0091-6749.

Mol Immunol. 2020 Jan 16;119:27-34. doi: 10.1016/j.molimm.2020.01.003. [Epub ahead of print]

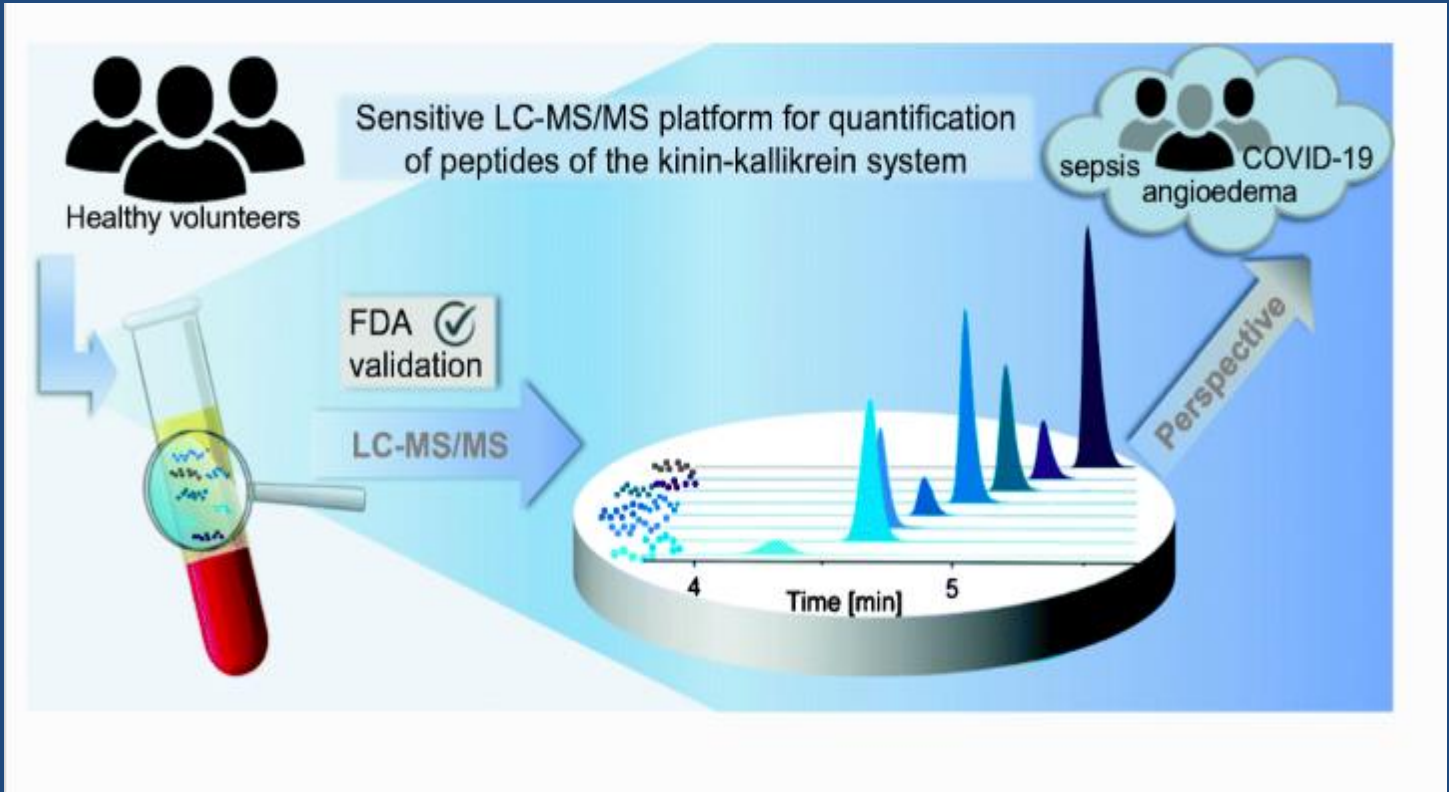
**sgp120 and the contact system in hereditary angioedema: A diagnostic tool in HAE with normal C1 inhibitor.**

Larrauri B[1], Hester CG[2], Jiang H[2], Miletic VD[2], Malbran A[2], Bork K[3], Kaplan A[4], Frank M[2].



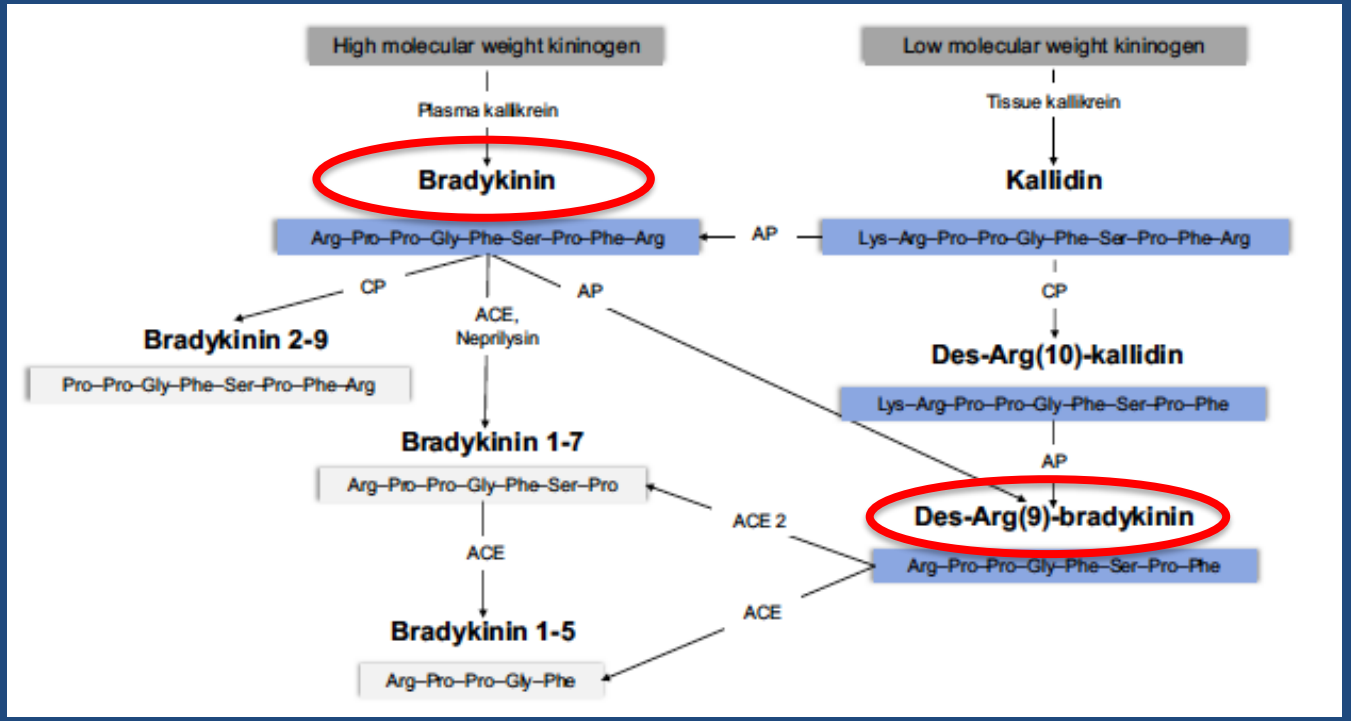

Sharma J, et al. Clin Rev Allergy Immuno 2021
Porebski G, et al. Clin Rev Allergy Immuno 2021

# COVID and Renewed Interest in Kinins



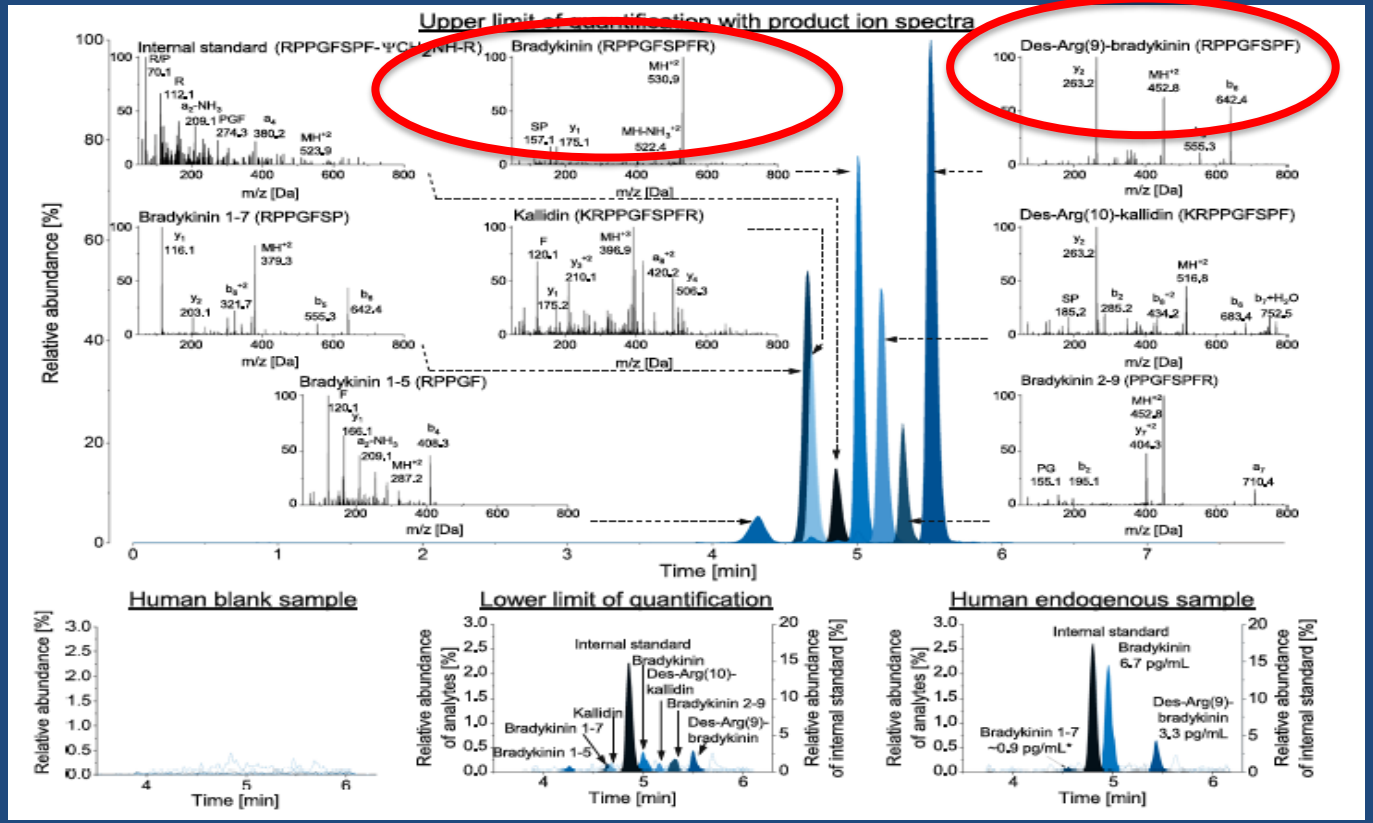

Gangnus T, et al. An Bioanal Chem. 2021 May;413(11):2971-2984.

# Targets for Measurement




Gangnus T, et al. An Bioanal Chem. 2021 May;413(11):2971-2984.

# Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)




Gangnus T, et al. An Bioanal Chem. 2021 May;413(11):2971-2984.

# Back to the Current Day…..

# “ALL SYSTEMS REPORT NORMAL, CAPTAIN”

# Management Approach

- 1) History, history, history
  - Assess trajectory, duration, characteristics of symptoms, associated findings, response to therapies
  - Family history

UNKNOWN OR UNRELIABLE

VARIABLE PENETRANCE

DE NOVO MUTATIONS?

Busse P, et al.
*J Allergy Clin Immunol Pract.* 2020:

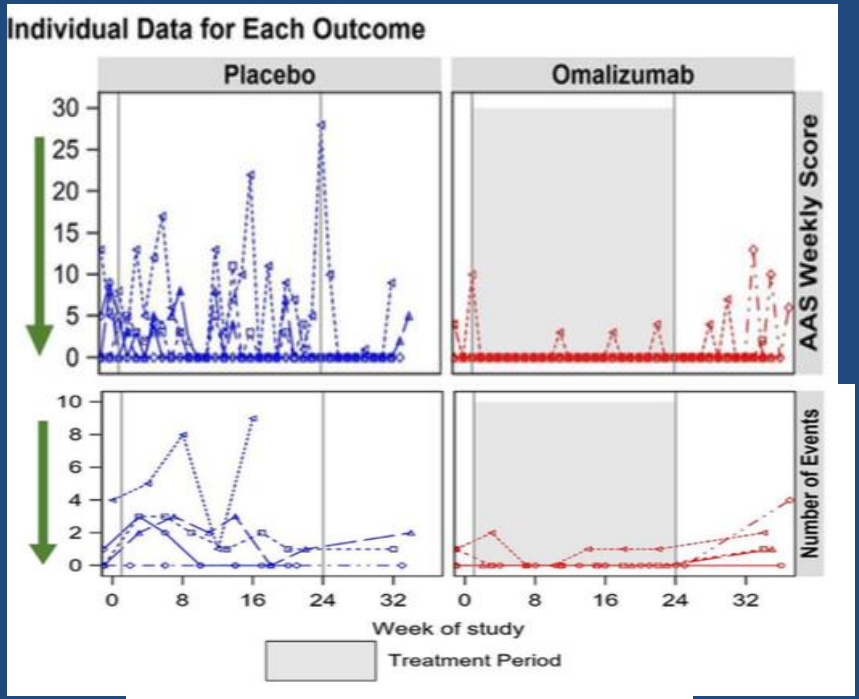
# Management Strategy

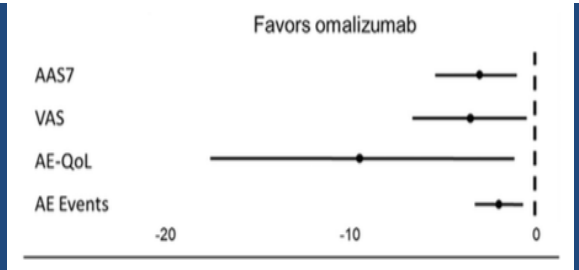
- 2) Implement and document response to aggressive mast-cell targeted therapy
  - Acute: antihistamines, corticosteroids, epinephrine
  - Preventative: high-dose antihistamines (4x labeled-dose of 2nd generation H1-antagonist), montelukast, omalizumab?

Akenroye AT, et al. J Allergy Clin Immunol Pract. 2018
Goswamy VP, et al. Ann Allergy Asthma Immunol. 2022 Jul

# Omalizumab for Isolated Idiopathic Angioedema

- Randomized, placebo-controlled trial of omalizumab in adults with 2 or more episodes of idiopathic angioedema in the past 6 months
- 10 patients randomized to omalizumab 300 mg or placebo every 4 weeks for 24 weeks with 12-week follow-up
- Significant improvement in omalizumab group vs placebo:
  - Angioedema Activity Score (p = .003)
  - Angioedema QoL (p = .03)
  - Number of angioedema episodes per month (p = .005)




Goswamy VP, et al. Ann Allergy Asthma Immunol. 2022 Jul

# Management Strategy

- 3) If steps 1 and 2 supportive, consideration of contact-system targeted therapy based on longitudinal clinical symptoms and clinical judgment
  - Acute treatment with targeted therapy EARLY in course of angioedema attack with consistent documented significant improvement within expected response time (1-2 hours)

Busse P, et al.
*J Allergy Clin Immunol Pract.* 2020:

# Hereditary Angioedema with Normal C1-INH

## Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel

Bruce L. Zuraw, M.D.,[1,2] Konrad Bork, M.D.,[3] Karen E. Binkley, M.D.,[4] Aleena Banerji, M.D.,[5] Sandra C. Christiansen, M.D.,[1,6] Anthony Castaldo, M.P.A.,[7] Allen Kaplan, M.D.,[8] Marc Riedl, M.D.,[9] Charles Kirkpatrick, M.D.,[10] Markus Magerl, M.D.,[11] Christian Drouet, Ph.D.,[12] and Marco Cicardi, M.D.[13]

Allergy Asthma Proc 33:S145–S156, 2012

**Table 2. Diagnosis of Hereditary Angioedema with Normal C1 Inhibitor Levels.**

**Consensus criteria***

History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
Normal or near-normal C4 level and C1 inhibitor antigen level and function
Documented lack of response to high-dose antihistamines (e.g., second-generation antihistamines given 4 times/day)
Either a known genetic mutation (factor XII, angiopoietin-1, plasminogen, or kininogen-1) or a family history of angioedema†

**Supportive data**

History of no response to epinephrine and glucocorticoids
History of prompt and durable responses to a bradykinin-targeted medication‡
Documented, visible angioedema or, in patients with predominantly abdominal symptoms, evidence of bowel-wall edema identified by computed axial tomography or magnetic resonance imaging§

**Emerging biomarkers**

Threshold-stimulated kallikrein activity¶

Busse and Christiansen, NEJM 2020

# Hereditary Angioedema with Normal C1INH

- Treatment data limited; No controlled trials to date
- Acute treatment of attacks
  - Icatibant
  - Ecallantide
  - C1INH concentrates

  **Data limited to case series, case reports**
- Prophylaxis
  - Tranexamic Acid
  - Progestins

  **Most Data Currently**
  - Lanadelumab*
  - Berotralstat
  - C1INH concentrates
  - Androgens

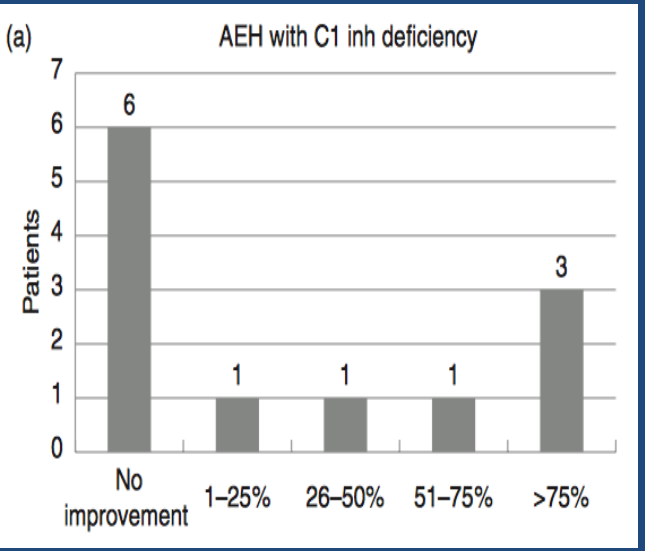
  **Case reports, Case series reporting benefit**

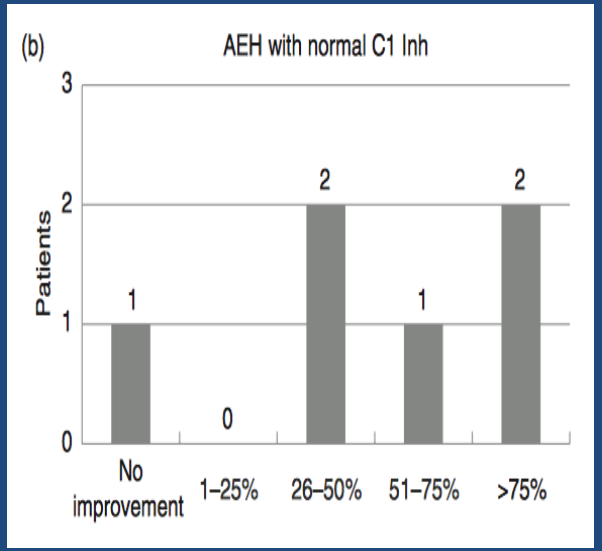
**Clinical Trials to Validate Biomarkers and Investigate Treatment Efficacy**

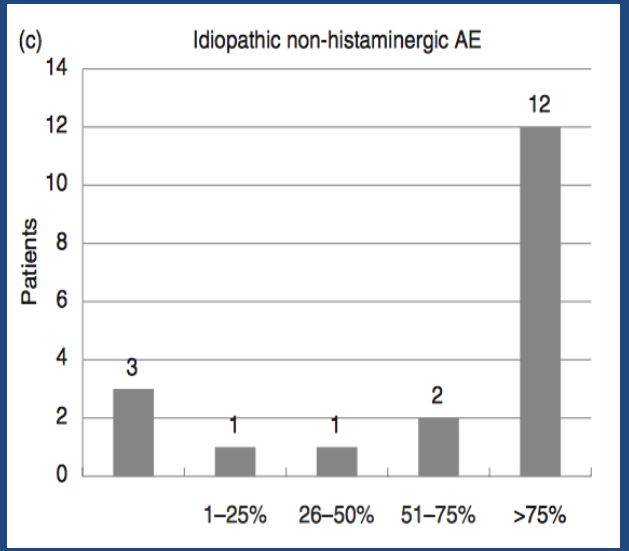
Bork K. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):15.
Boccon-Gibod I,et al. Clin Exp Immunol. 2012 Jun;168(3):303-7

*Phase III study enrollment completed

# Tranexamic Acid Effects




Wintenberger C et al, Clin Exp Immunol. 2014

# Progestin Effects

Table 4. Efficacy of progestin according to type of HAE

| | | POP | AGP |
|---|---|---|---|
| AE types I/II | Improvement | 5 | 6 |
| | No modification | 2 | 1 |
| | Worsening | 1 | 0 |
| AE type III | Improvement | 10 | 13 |
| | No modification | 1 | 2 |
| | Worsening | 2 | 0 |
| IdiopathicAE | Improvement | 4 | 15 |
| | No modification | 2 | 1 |
| | Worsening | 4 | 0 |

POP, Low dose progestin-only pills; AGP, antigonadotropic progestin agents; HAE, Hereditary angioedema.

77% improved

40% improved

Saule C, et al. Clin Exp Allergy. 2013

# Our Patients' Perspective

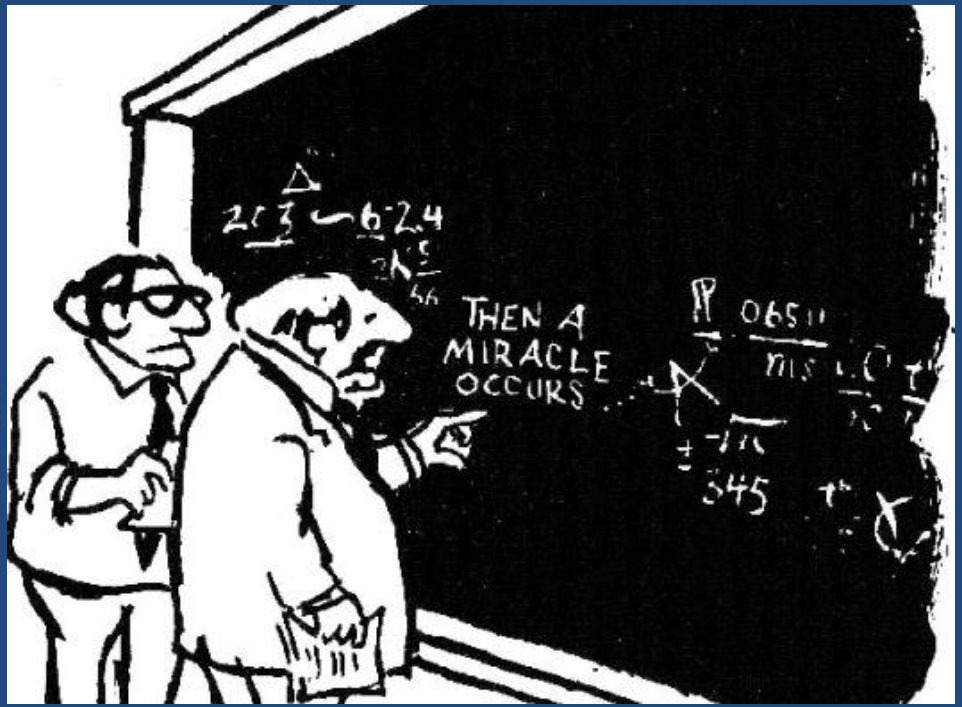
- Recurring troubling symptoms
- Disfiguring
- Disabling
- Frightening – fear of asphyxiation
- Secondary depression and anxiety
- Concern about a hereditary condition passed to children
- HAE-normal C1INH is both overdiagnosed and underdiagnosed; results in overtreatment (costs and side effects) and undertreatment (morbidity and disability)

- SYSTEMATIC APPROACH – Enables gradual move to an effective management plan

# Takeaways

- Evaluation of angioedema relies heavily on detailed clinical history
- Diagnostic testing is currently limited to markers of mast cell activity, C1INH evaluation, genetic testing; ongoing investigation of additional biomarkers
- Most isolated recurrent angioedema with normal lab evaluation is mast cell mediated/histaminergic
- A small subset of isolated angioedema is non-histaminergic/kinin mediated
- Longitudinal clinical follow-up and documented response to targeted treatments remain important in the diagnosis and management of angioedema with normal labs

# THANK YOU




"Medicine is a science of uncertainty and an art of probability"

– *William Osler*