Angiotensin Converting Enzyme inhibitors (ACEi) and Angioedema

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Overview

- Case study
- Classification of angioedema
- Pathophysiology of angioedema
- ACEi-induced angioedema
- Is this a drug allergy?
- Management and what's new?

Case 1

75/Female/ Caucasian

On fosinopril for many years

Nasoendoscopy: swollen piriform fossa & epiglottic folds

Intubated

Normal complements

Negative sIgE to prawn

Case 2

49/Male/ Aboriginal

Took first dose of perindopril for hypertension and 24 hours later……

He developed gross lower lip and facial swelling

↑ vascular permeability

localised & self-limiting

subcutaneous & submucosal oedema

Classification of angioedema

Category	Bradykinin mediated					
	C1INH deficiency/ defect		Normal C1INH			
	Positive inheritance	Negative inheritance	Positive inheritance	Negative inheritance		
Disease	HAE1 HAE2	ACID	HAE (normal C1INH)	Drug (ACEi) Nonclassified		
Wheals	Negative					

Classification of angioedema

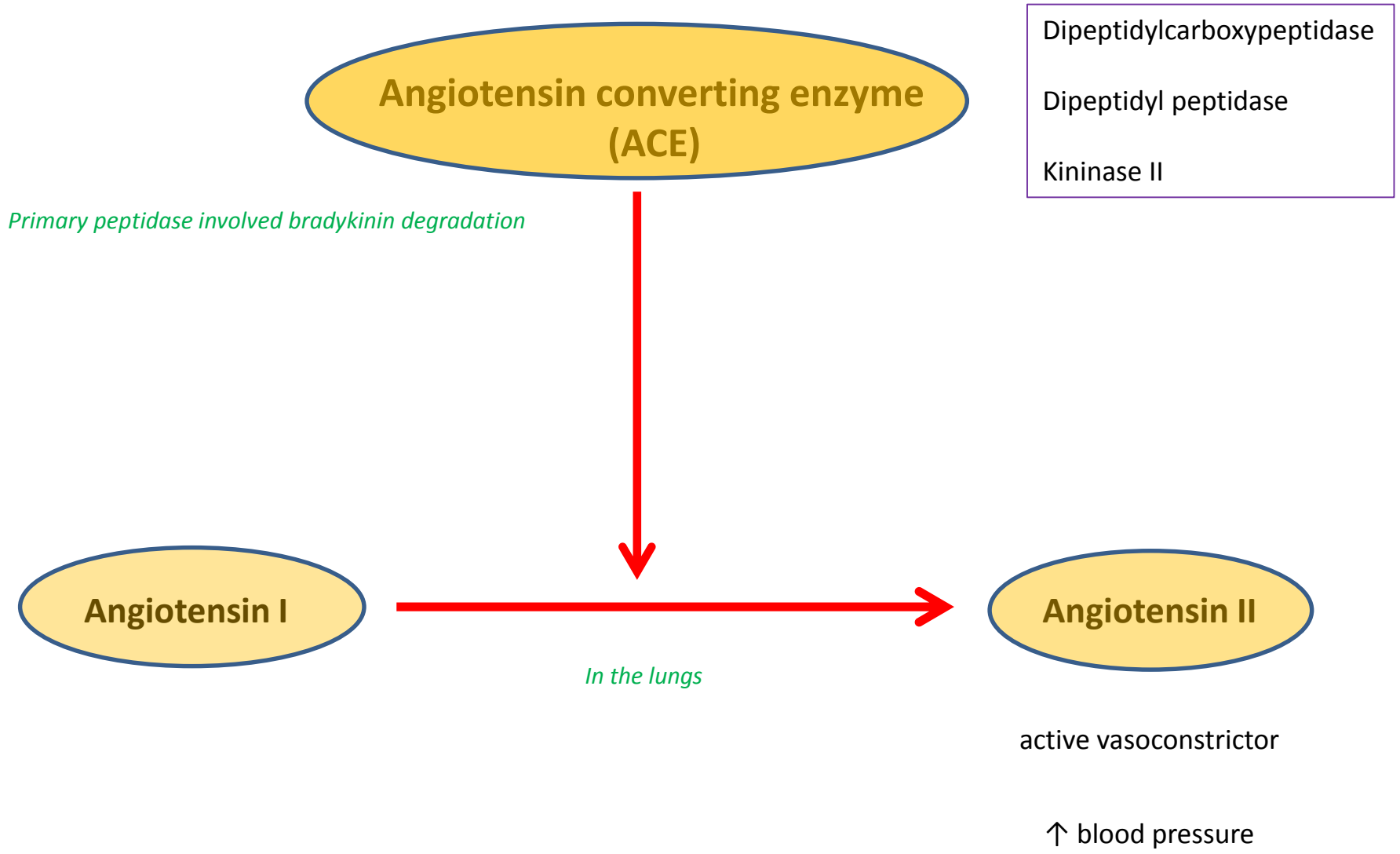
Category	Bradykinin mediated				Mast cell mediated		
	C1INH deficiency/ defect		Normal C1INH		Normal C1INH		
	Positive inheritance	Negative inheritance	Positive inheritance	Negative inheritance	IgE mediated	Non-IgE mediated	
Disease	HAE1 HAE2	ACID	HAE (normal C1INH)	Drug (ACEi) Nonclassified	Anaphylaxis IgE-mediated urticaria	Chronic sp urticaria Inducible urticaria Nonclassified AE	
Wheals	Negative				Positive/Negative	Positive/Negative	

Classification of angioedema

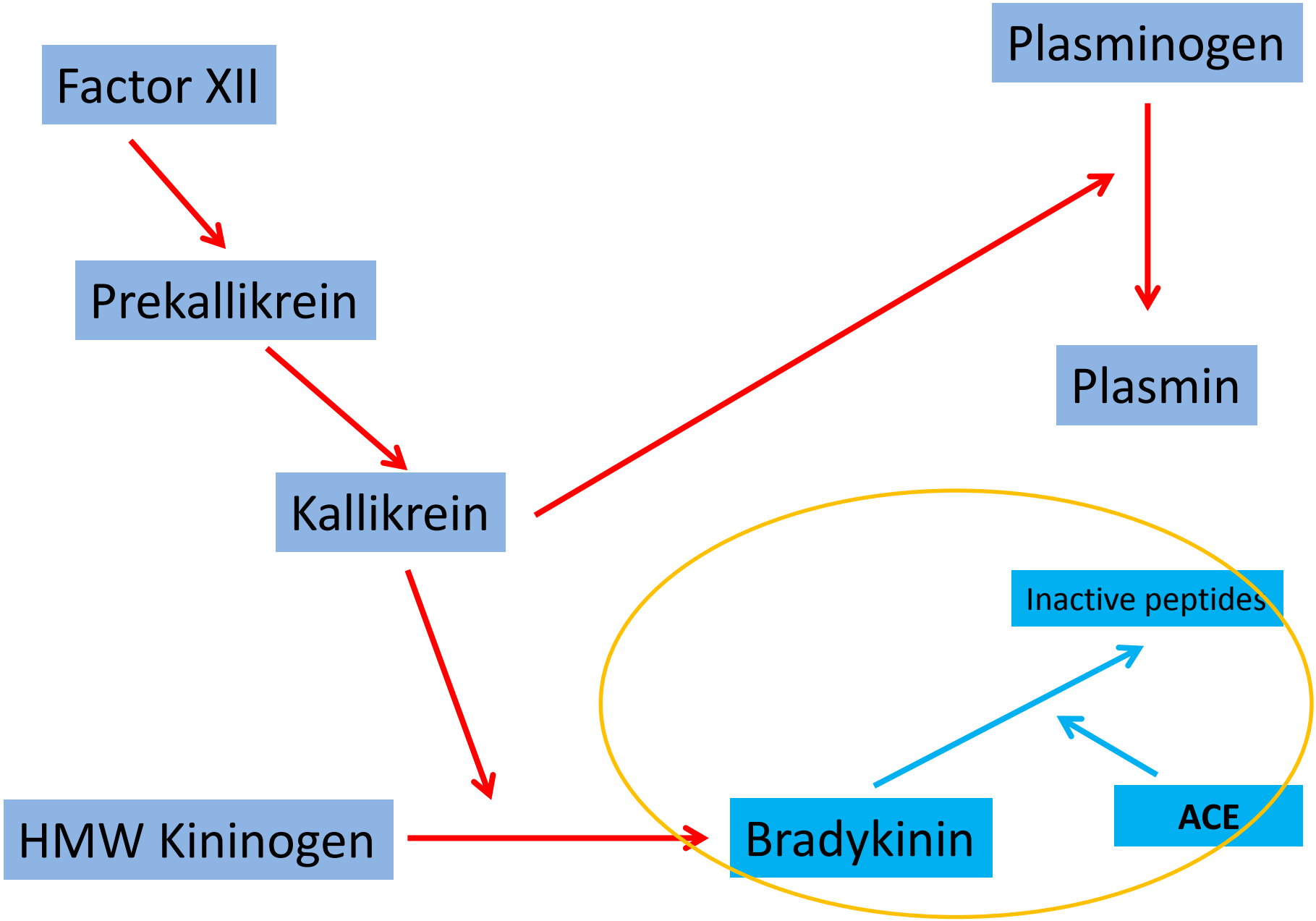
Category	Bradykinin mediated				Mast cell mediated		Idiopathic
	C1INH deficiency/ defect		Normal C1INH		Normal C1INH		Normal C1INH
	Positive inheritance	Negative inheritance	Positive inheritance	Negative inheritance	IgE mediated	Non-IgE mediated	Negative inheritance
Disease	HAE1 HAE2	ACID	HAE (normal C1INH)	Drug (ACEi) Nonclassified	Anaphylaxis IgE-mediated urticaria	Chronic sp urticaria Inducible urticaria Nonclassified AE	Nonclassified AE
Wheals	Negative				Positive/Negative	Positive/Negative	Negative

Lang DM, Aberer W, Bernstein JA, Chng HH, Grumach AS, Hide M, Maurer M, Weber R, Zuraw B. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012; 109:395-402.

Renin-angiotensin-aldosterone System



Kinin-kallikrein System



Bradykinin → Inactive peptides

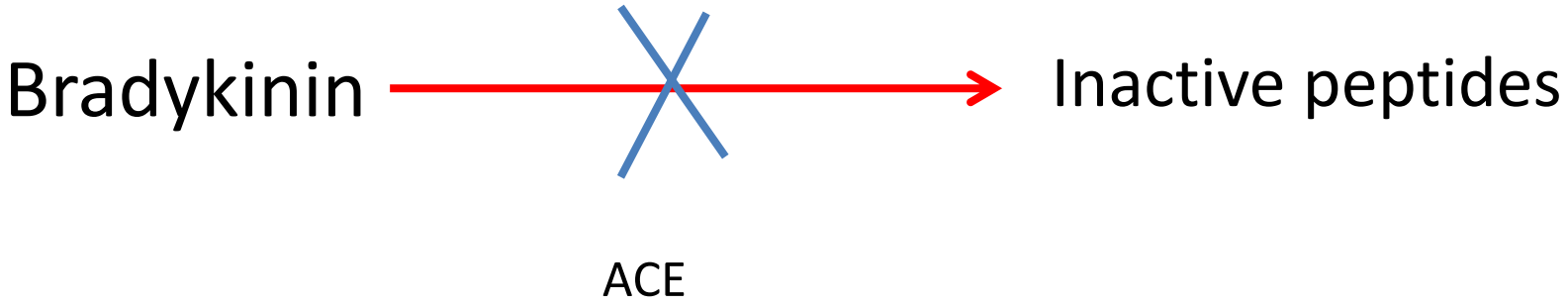
ACE

Short $t_{1/2}$ 17 sec

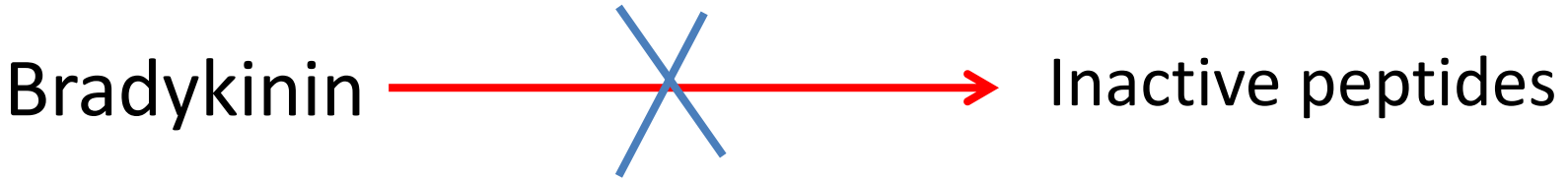
Metabolised primarily by ACE (kininase II)
neutral endopeptidase (NEP)
aminopeptidase P (APP)
secondarily by dipeptidyl peptidase IV (DPPIV)
kininase I

Des-Arg9-BK is an active metabolite of bradykinin formed primarily due to the kininase I enzyme (also degraded by DPPIV)

**decreased activity of DPPIV correlated to a prolonged half life of substance P, only in the presence of ACE inhibition – a requirement for multiple enzymes defects to inhibit degradation*



ACE inhibitor



Bradykinin degradation prolonged

ACE inhibitor

Vasodilation

↑ vascular permeability
(postcapillary venules)

Plasma extravasation into submucosal tissue

This is the result from defective degradation of at least three vasoactive peptides:
- Bradykinin *(level increase – may be 10 fold)*
- des-Arg9-BK (a metabolite of bradykinin)
- substance P (can increase vascular permeability)

ACE inhibitors (ACEi) and Angioedema

- Commonly prescribed for hypertension, cardiac failure, myocardial infarct and diabetic nephropathy
- About 35 to 40 million people worldwide are taking ACEi
- Angioedema reported to occur in 0.1-2.5% of patients taking ACEi

Warner KK et al. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000;34:526-8.

Miller DR et al. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension* 2008;51:1624-30.

Kostis JB et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med* 2005;165:1637-42.

- Potentially life-threatening when it involves the airway
- Fatalities reported

Kim S et al. Angioedema deaths in the United States. 1979-2010. *Ann Allergy Asthma Immunol* 2014;113:630-4.

- Increased use of ACEi; substantial proportion of angioedema cases presenting to the Emergency Department
- May occur with any ACEi
- Diagnosis may be missed unless drug history is taken
- Perindopril accounted for the majority of cases in our experience → reflection of prescribing patterns

  (perindopril – 54% of all ACEi prescriptions in Australia in 2012-2013)

Triggers and nature

- Seldom identified
- May occur as early as within 24 hours of the first dose, or as long as 20 years

Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. *Int Med J* 2015;45(8):821-7.

Andrew N, Gabb GM, Del Fante M. ACEi associated angioedema: a case study and review. *Aust Fam Physician* 2011;40:985-8.

- Incidence highest during the 1st month of treatment, but majority of cases occur after 1 month of treatment; about 1/3 of cases after 6 months

Kostis JB, Kim HJ, Rusnak J et al. Incidence and characteristics of angioedema associated with enelapril. Arch Intern Med 2005;165(14):1637-42.

Slater EE, Merrill DD, Guess HA et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. JAMA 1988;260(7):967-70.

Gabb GM, Ryan P, Wing LM et al. Epidemiological study of angioedema and ACE inhibitors. Aust N Z J Med 1996;26(6):777-82.

Brown NJ, Ray WA, Snowden M et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60(1):8-13.

- Higher incidence in African-Americans (4-5 times) compared to white Americans

Brown NJ, Ray WA, Snowden M et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60(1):8-13.

Gibbs CR, Lip GY, Beevers DG. Angioedema due to ACE inhibitors: increased risk in patients of African origin. Br J Clin Pharmacol 1999;48(6):861-5

- Susceptibility may be genetically determined

Duan QL et. A variant in XPNPEP2 is associated with angioedema induced by angiotensin converting enzyme inhibitors. *Am J Hum Genet* 2005;77:617-26.

Cilia La Corte AL et al. A functional XPNPEP2 promoter haplotype leads to reduced plasma aminopeptidase P and increased risk of ACE inhibitor-induced angioedema. *Hum Mutat* 2011;32:1326-31.

- Smoking
- Female sex
- Age >65
- Seasonal allergies
- Concomitant use of mTOR inhibitors (sirolimus, everolimus) in renal transplant recipients

  **effects of immunosuppressants on decreasing the activity of circulating levels of dipeptidyl peptidase IV (DPPIV)

- A predilection for the lips, tongue, face and upper airway

**Bradykinin receptors are expressed in the tongue, laryngeal areas and parotid gland

- Lip and anterior tongue being the most common sites of involvement in a series

Grant NN et al. Clinical experience with angiotensin-converting enzyme inhibitor-induced angioedema. Otolaryngol Head Neck Surg 2007;137:931-5.

- May rarely involve the bowel wall

Schmidt TD, McGrath KM. Angiotensin-converting enzyme inhibitor angioedema of the intestine: a case report and review of the literature. Am J Med Sci 2002;324(2):106-8.

So, is this a drug allergy?

Fok JS et al

Mario, 71, presented with an episode of gross swelling of the lower face. He had a similar milder swelling of the lip a month ago. Three months ago he commenced perindopril for hypertension.

Allergy!!

So, is this a drug allergy?

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Health profession	Type of reaction N (%)		Severity of reaction N (%)			Level of contraindication N (%)		
	Allergy	Intolerance	Mild	Moderate	Severe	Absolutely	Relatively	Used with caution
Medical (n=160)	109 (68.1)	48 (30.0)	14 (8.8)	82 (51.3)	63 (39.4)	110 (68.8)	45 (28.1)	4 (2.5)
Nurse (n=50)	38 (76.0)	11 (22.0)	4 (8.0)	30 (60.0)	16 (32.0)	29 (58.0)	18 (36.0)	3 (6.0)
Pharmacist (n=96)	73 (76.0)	23 (23.9)	1 (1.0)	30 (31.3)	65 (67.7)	87 (90.6)	9 (9.4)	0
Medical student (n=88)	74 (84.1)	14 (15.9)	9 (10.2)	51 (58.0)	28 (31.8)	36 (40.9)	46 (52.3)	6 (6.8)
Overall (n=394)	294 (74.6)	96 (24.4)	28 (7.1)	193 (49.0)	172 (43.7)	262 (66.5)	118 (29.9)	13 (3.3)

Majority = Allergy!!

Management

Recognition of problem

- Lack of reliable history in a patient presenting acutely
- Lack of knowledge of the association of ACEi with angioedema
- Misattribution to an allergic cause
- Poor understanding of the time course of angioedema in those taking ACEi

ACEi cessation

- Stop the culprit medication
- Not to be replaced with other ACEi ***(class effect)***
- If clinically indicated, an angiotensin receptor blocker (ARB) may be tried in the future
- For unclear reason, angioedema has been reported in association with the use of ARB but the rate is substantially lower

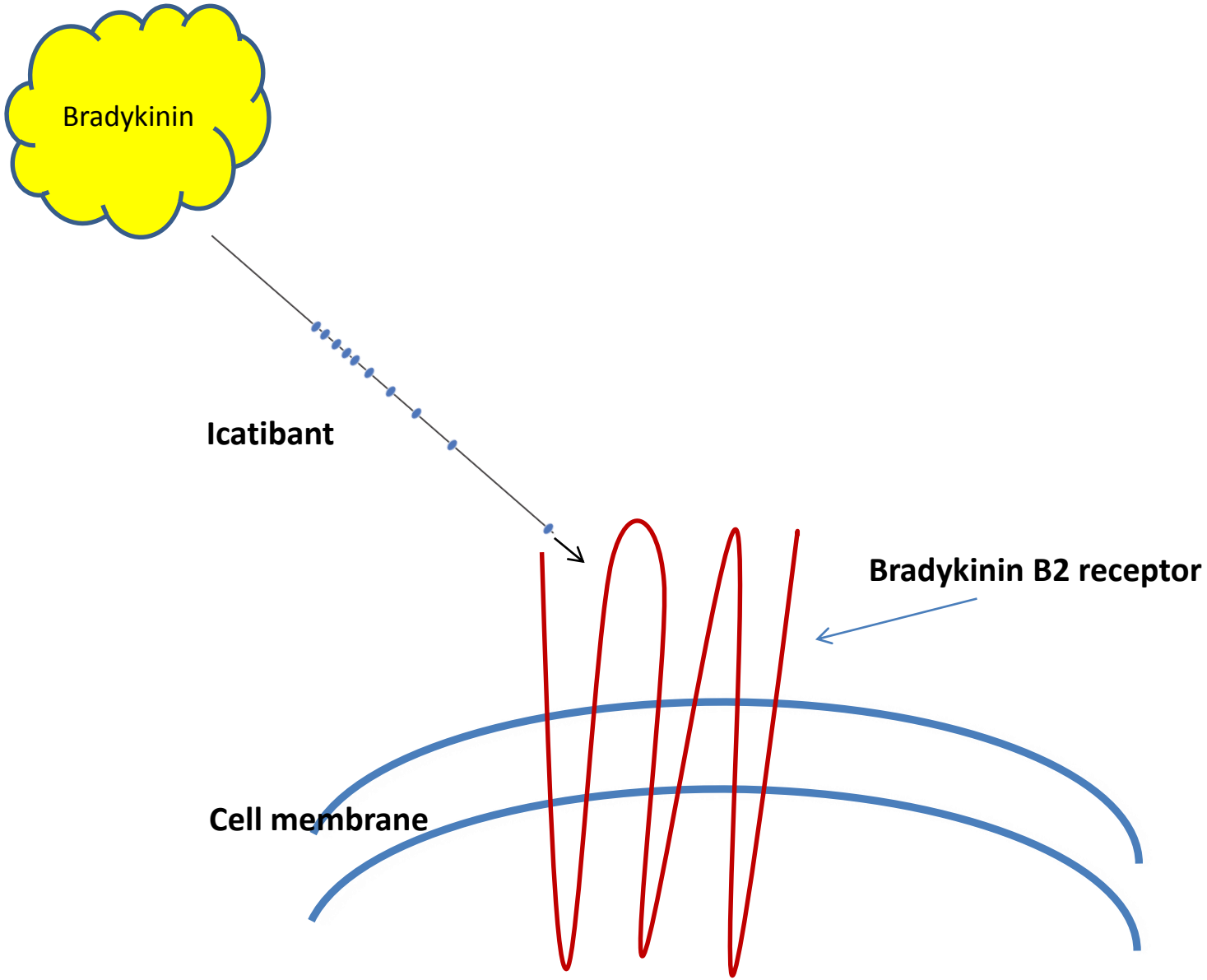
Pharmacological therapy

- Antihistamines
- Corticosteroids
- Adrenaline

Usually ineffective
More for allergic, histamine-mediated angioedema

- Intubation (if airway compromise)

Type 1 angioedema	Lip & anterior tongue involvement
Type 2 angioedema	Floor of mouth, palatal or oropharyngeal oedema
Type 3 angioedema	Laryngeal or hypopharyngeal oedema


Bradykinin
Icatibant
Bradykinin B2 receptor
Cell membrane

- Bradykinin B2 receptor antagonist
- Approved for HAE acute attacks
- Most likely effective if given in the first few hours of attacks
- Usually only one dose required (subcutaneously; 30mg)
- Well tolerated; pain at injection site
- Efficacy recognised and documented in literature

An RCT involving 27 adults with ACEi angioedema

Bas M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, Veit J, Schossow B, Hapfelmeier A, Kehl V, Kojda G, Hoffman TK

N Eng J Med 2015;372(5):418-25

An observational study involving 13 adults with ACEi angioedema

Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. *Intern Med J*. 2015;45(8):821.

- We treated 13 consecutive emergency department patients, who had not improved with adrenaline and /or corticosteroids, with icatibant 30mg subcutaneously for ACEi-associated upper respiratory tract angioedema according to an agreed protocol

An observational study involving 8 adults with ACEi angioedema

Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK, Kojda G. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. *Ann Emerg Med*. 2010 Sep;56(3):278-82.

Summary

ACEi-induced angioedema

- is bradykinin mediated

- reflects intolerance instead of allergy

Icatibant appears to be effective in relieving symptoms