

L'ANGIOEDEMA IN PRONTO SOCCORSO

Dott Luca Dutto

MCAU ASO S. Croce e Carle - Cuneo



XI congresso nazionale

simeu

ROMA 24-26 MAGGIO 2018

Disclosure of Conflicts of Interest

Non-financial conflicts of interest

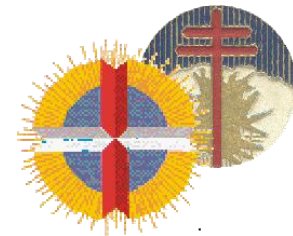
Luca Dutto MD



XI congresso nazionale

simeu

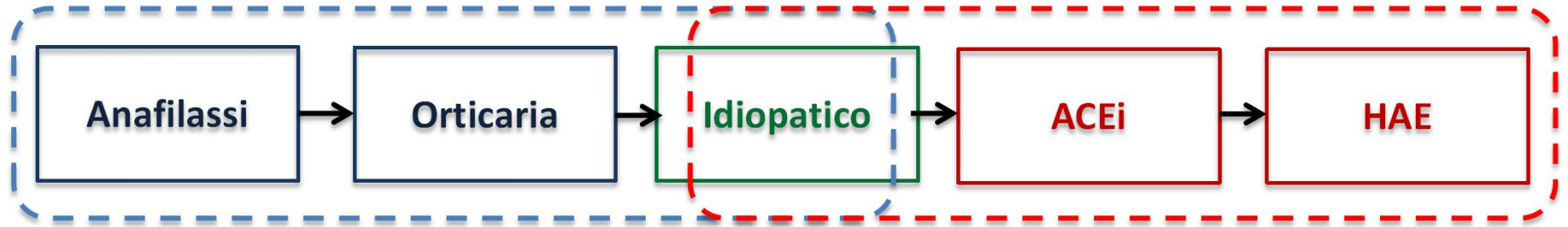
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ANGIOEDEMA - Definizione

Improvviso e transitorio rigonfiamento di una zona limitata di derma, tessuto sottocutaneo, mucosa e sottomucosa, accompagnato o meno da orticaria

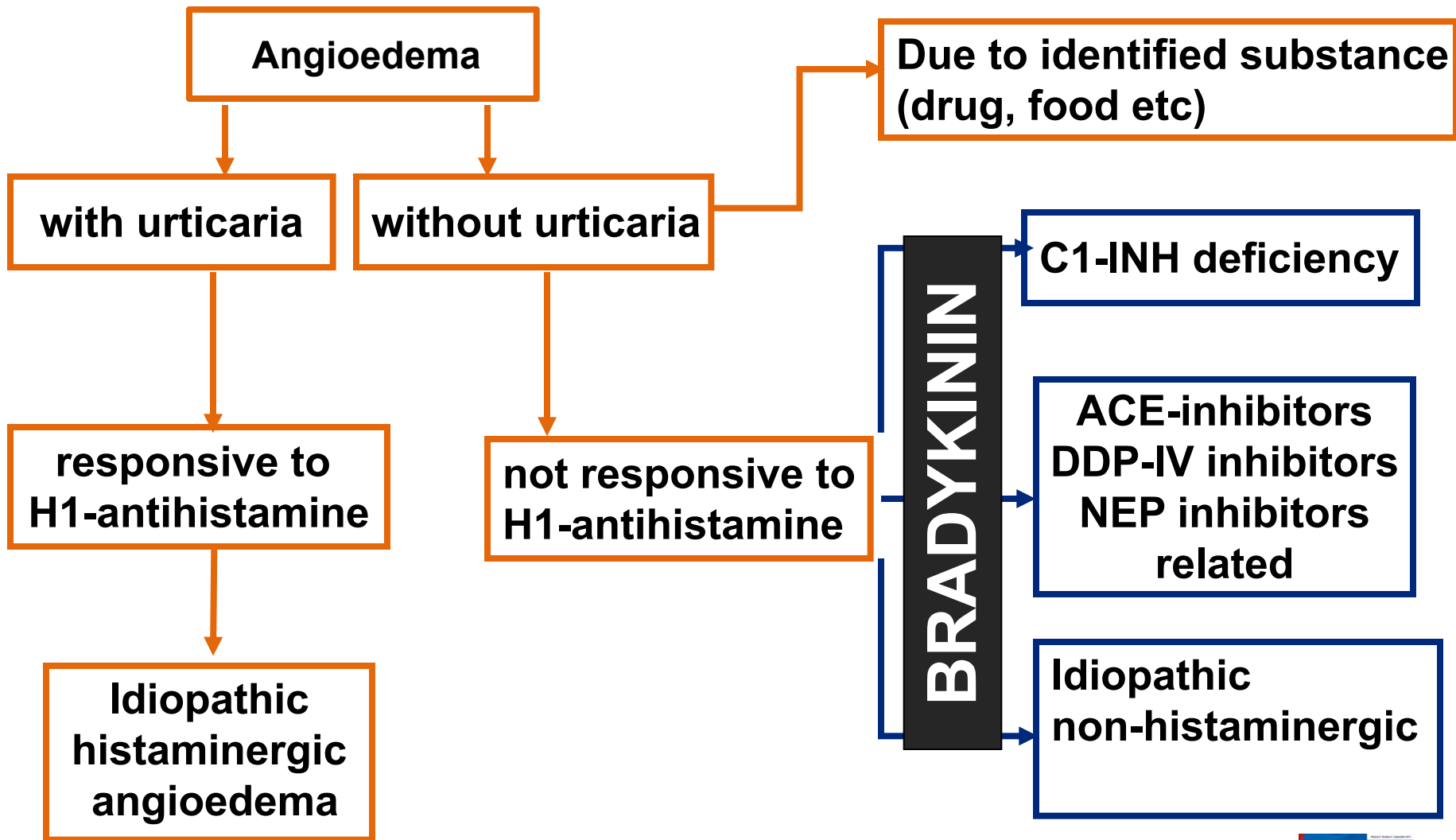
Angioedema – Diagnosi differenziale



Mast- cell mediato

Bradikinino-mediato

Classificazione Angioedema



Istamino-mediato

Bradikinino-mediato

Edema labbra/lingua

Edema laringeo

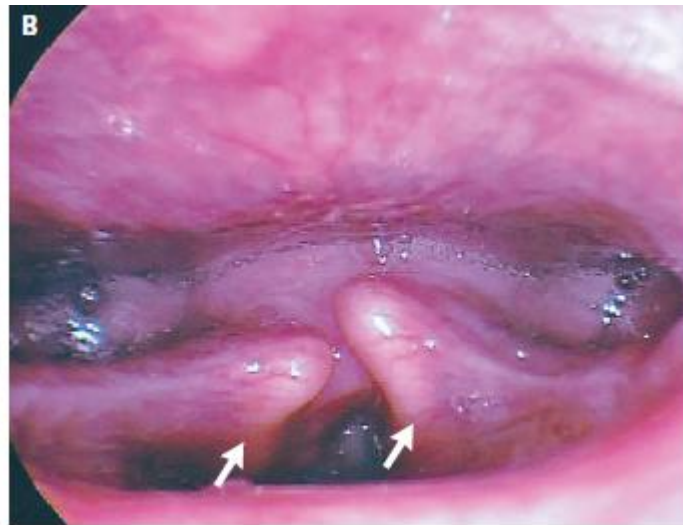
Edema volto

Dolore addominale

Nausea e vomito



Angioedema of the Arytenoids



Istamino-mediato

Bradikinino-mediato

Edema labbra/lingua

Prurito

Orticaria

Edema laringeo

Edema volto

Rapida insorgenza

Dolore addominale

Adrenalina

Nausea e vomito

Ipotensione/shock

Wheezing

Orticaria



Istamino-mediato

Bradikinino-mediato

Edema labbra/lingua

Prurito

Orticaria

Edema laringeo

Edema volto

Rapida insorgenza

Dolore addominale

Adrenalina

Gonfiore addominale

Nausea e vomito

Ipotensione/shock

Edemi periferici

Wheezing

Edemi genito-urinari

Attacchi addominali

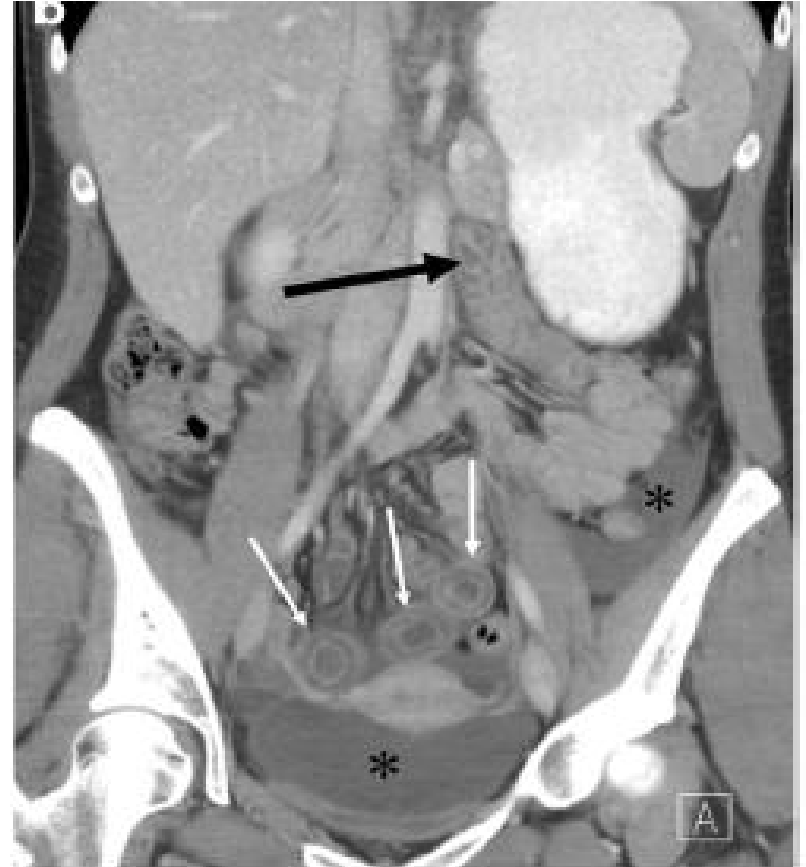
- Rigonfiamento della mucosa intestinale descritto nell'70-80% dei pazienti affetti
- Subocclusione intestinale e addome acuto
- Interventi chirurgici inappropriati
- Radiologia utile nella diagnosi

Abdominal Swelling



Post-abdominal Swelling





Attacchi cutanei



- Edema cutaneo sintomo frequente nell' HAE
- I pazienti percepiscono dapprima formicolio e stiramento della cute
- Alcuni presentano un rash non pruriginoso chiamato eritema marginato

US Hereditary Angioedema Association. www.haeimages.com.



- Angioedema si sviluppa per ore
- Il gonfiore provoca limitazione funzionale
- Risoluzione dell'edema in 2-3 giorni ma può durare di più

Binotto MS, et al. *Images Paediatr Cardiol.* 2002;11:12-31.
<http://www.health.gov.mt/impaedcard/issue/issue11/1231/1231.htm>.

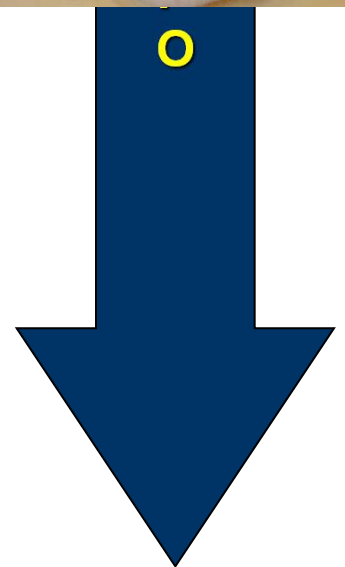
Sindrome Orale Allergica (SOA)

Cross reazione tra antigeni inalanti e proteine vegetali

Cavità orale e faringe (gusto metallico, prurito ed edema delle labbra e mucose).

Edema laringeo (tosse secca ed abbaiante, disfonia e disfagia)

Nausea, dolore addominale colico, vomito, diarrea





Everything You Need to Know About:

ORAL ALLERGY SYNDROME

JAXALLERGY.COM
@JAXALLERGY



BETULLA



Birch



Apple Peach Plum Pear Cherry Apricot Almond
Rosaceae



Carrot Celery Parsley Caraway Fennel Coriander Aniseed
Apiaceae



Soybean Peanut
Fabaceae (old Leguminosae)



Hazelnut
Betulaceae

AMBROSIA



Ragweed



Cantaloupe Honeydew Watermelon Zucchini Cucumber
Cucurbitaceae



Banana
Musaceae

ARTEMISIA



Mugwort



Celery Carrot Parsley Caraway Fennel Coriander Aniseed
Apiaceae



Bell pepper
Solanaceae



Black pepper
Piperaceae



Mustard Cauliflower Cabbage Broccoli Garlic Onion
Brassicaceae **Liliaceae**

GRAMINACEE



Orchard



Cantaloupe Honeydew Watermelon
Cucurbitaceae



Peanut
Fabaceae (old Leguminosae)



White potato Tomato
Solanaceae

CODA DI GATTO



Timothy



Swiss chard
Amaranthaceae



Orange
Rutaceae



Natural rubber latex

35 percent risk of reaction to at least one food*



11 percent risk of reaction to latex*



Kiwi



Banana



Peach



Avocado



Chestnut



Fig



Bell pepper



Tomato



White potato

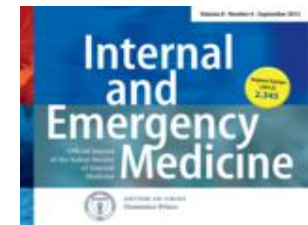


Cross-reactivity between aeroallergens and food allergens. World J of Methodology. June 2015

ANGIOEDEMA Valutazione primaria

Table 1 Criteria for the initial evaluation of angioedema severity at presentation to the emergency department

Triage tag	Symptoms
Red Life-threatening condition	Swelling of face, oral cavity, or neck with one of the following: Dysphonia Retraction or stridor Respiratory distress Oxygen desaturation
Yellow Not life-threatening	One of the following: Swelling of face, oral cavity, pharynx, or neck Recurrent angioedema and abdominal pain Dysphagia Perception of swollen throat
Green Mild severity	Swelling of extremities and genitals



Cicardi M et al IEM 2014

Vie aeree prossimali



Lingu



e

Angioedema in DEA





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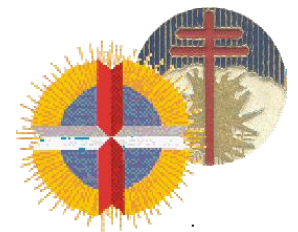
2013-2015



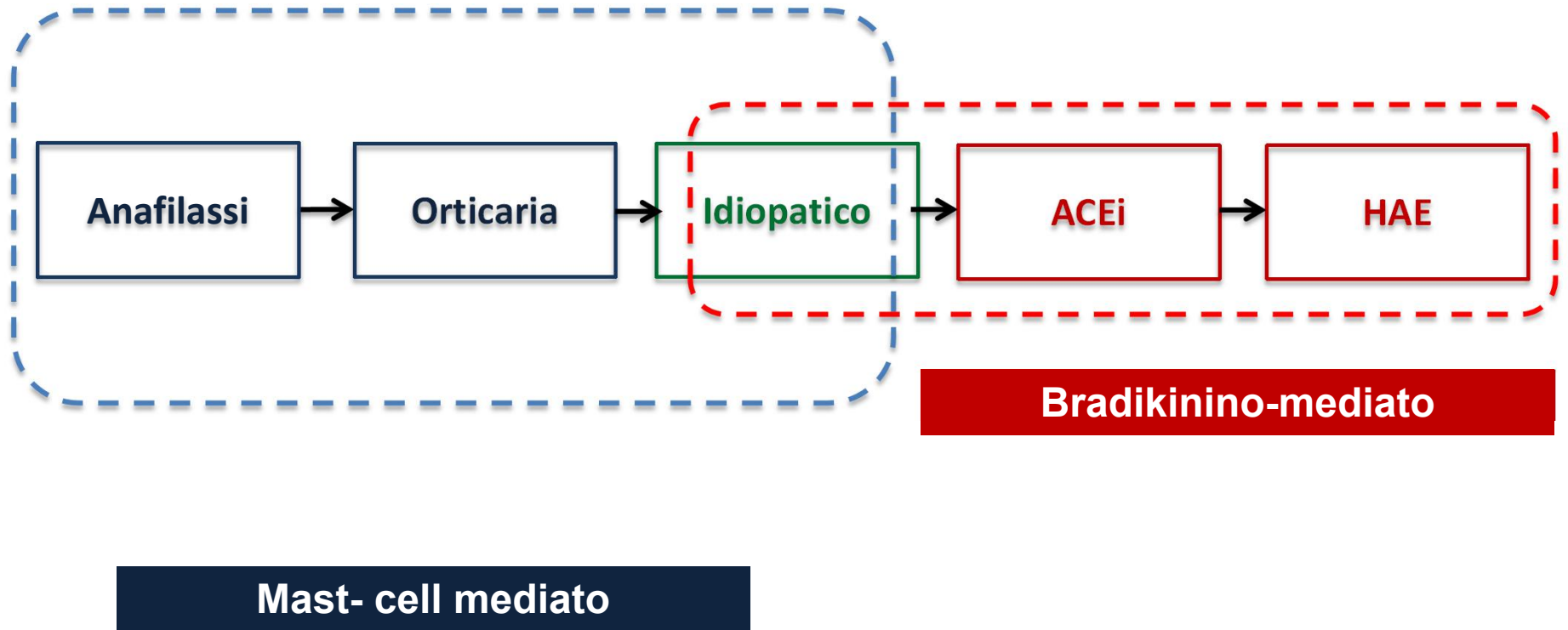
Angioedema senza orticaria

N° (%)

Codice Bianco		1 (1.6)
Codice Verde		27 (45.0)
Codice Giallo		29 (48.3)
Codice Rosso		3 (5.0)
		60



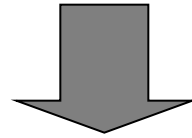
Angioedema – Diagnosi differenziale



ANAFILASSI Trattamento

ADRENALINA

1/1000 1 mg/ml



VIA INTRAMUSCOLARE

Dose 0.3 - 0.5 mg

RIPETIBILE DOPO 5-15 MINUTI SE INEFFICACE

ANAFILASSI Trattamento

SOMMINISTRAZIONE DI FLUIDI

CRISTALLOIDI/COLLOIDI

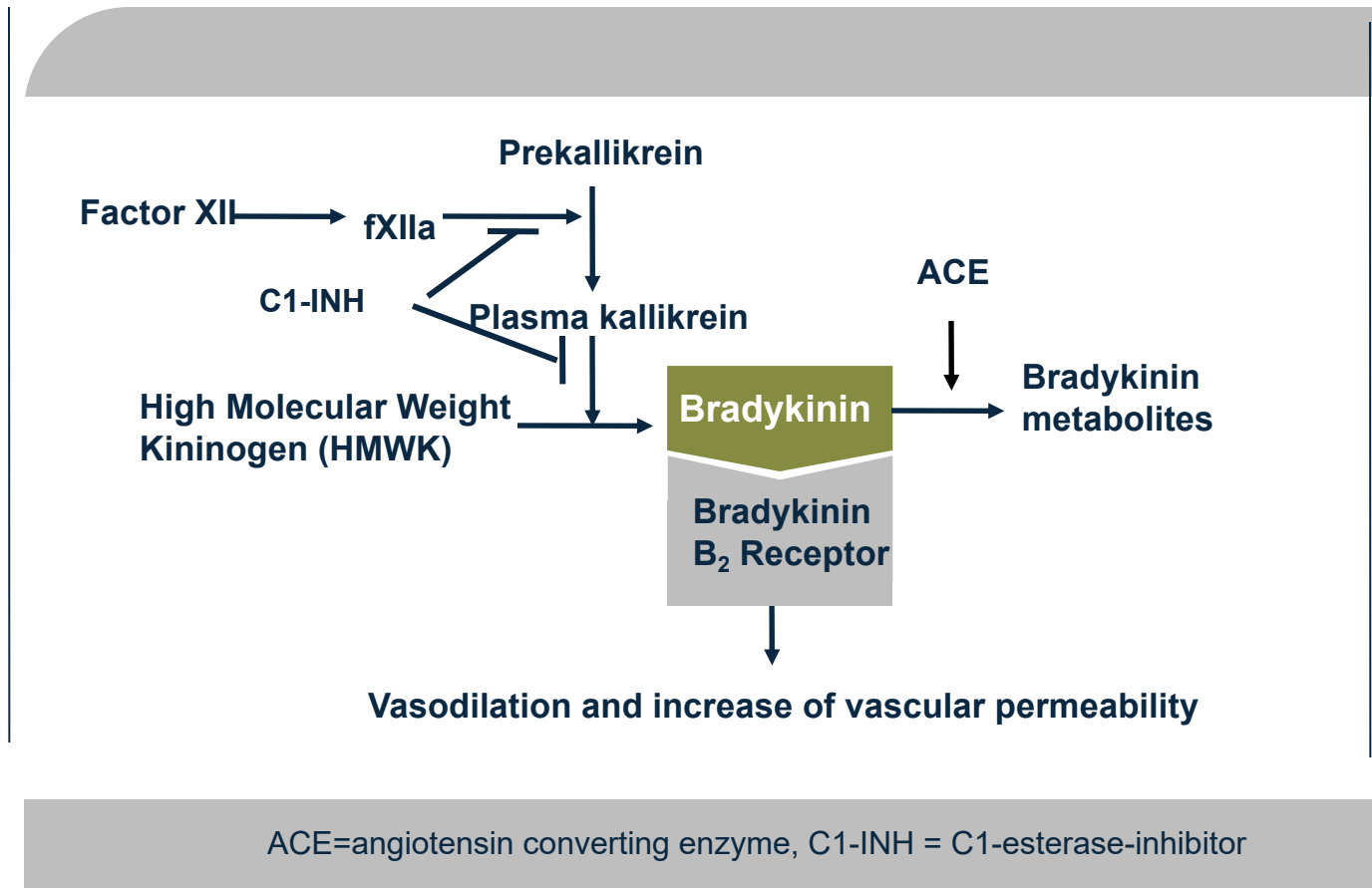
1000 cc in bolo rapido (10 min)

ripetibili se necessario



Angioedema bradichinino-mediato

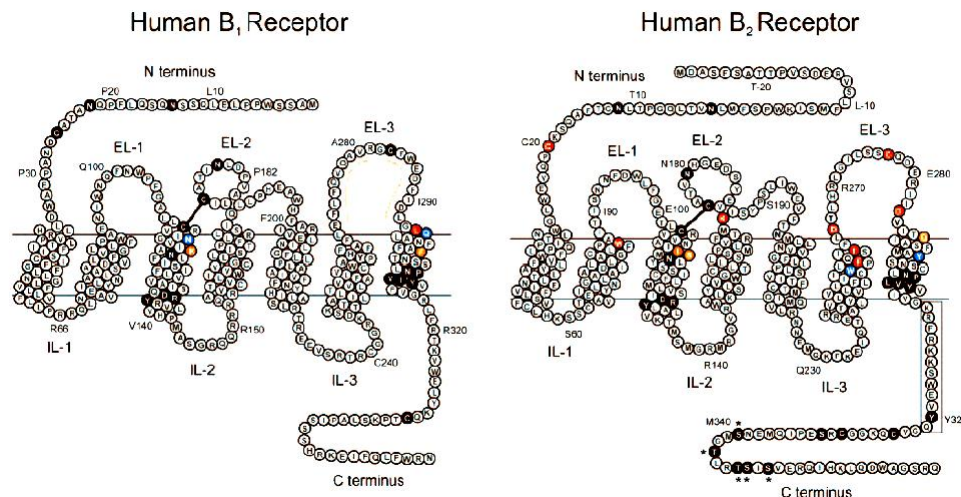
Angioedema provocato dall'accumulo di plasmatico di **BRADICHININA**



Bradichinina

- Nanopeptide ad azione vasodilatatrice
- Incremento della permeabilità vascolare
- Generato dall'attivazione del sistema di contatto

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg



Hereditary Angioedema

Bruce L. Zuraw, M.D.

1 caso ogni 50000 persone

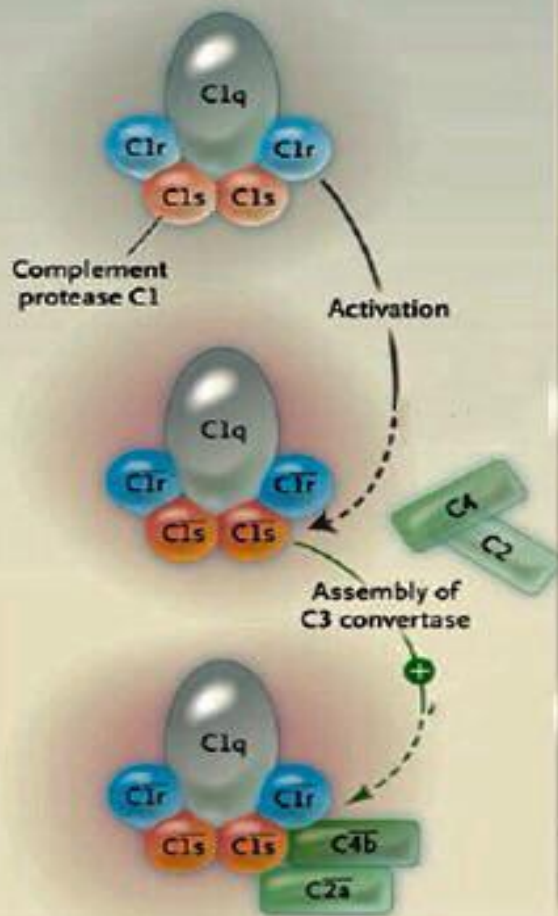
Esordio in età infantile

Media di attacchi 7-14 giorni

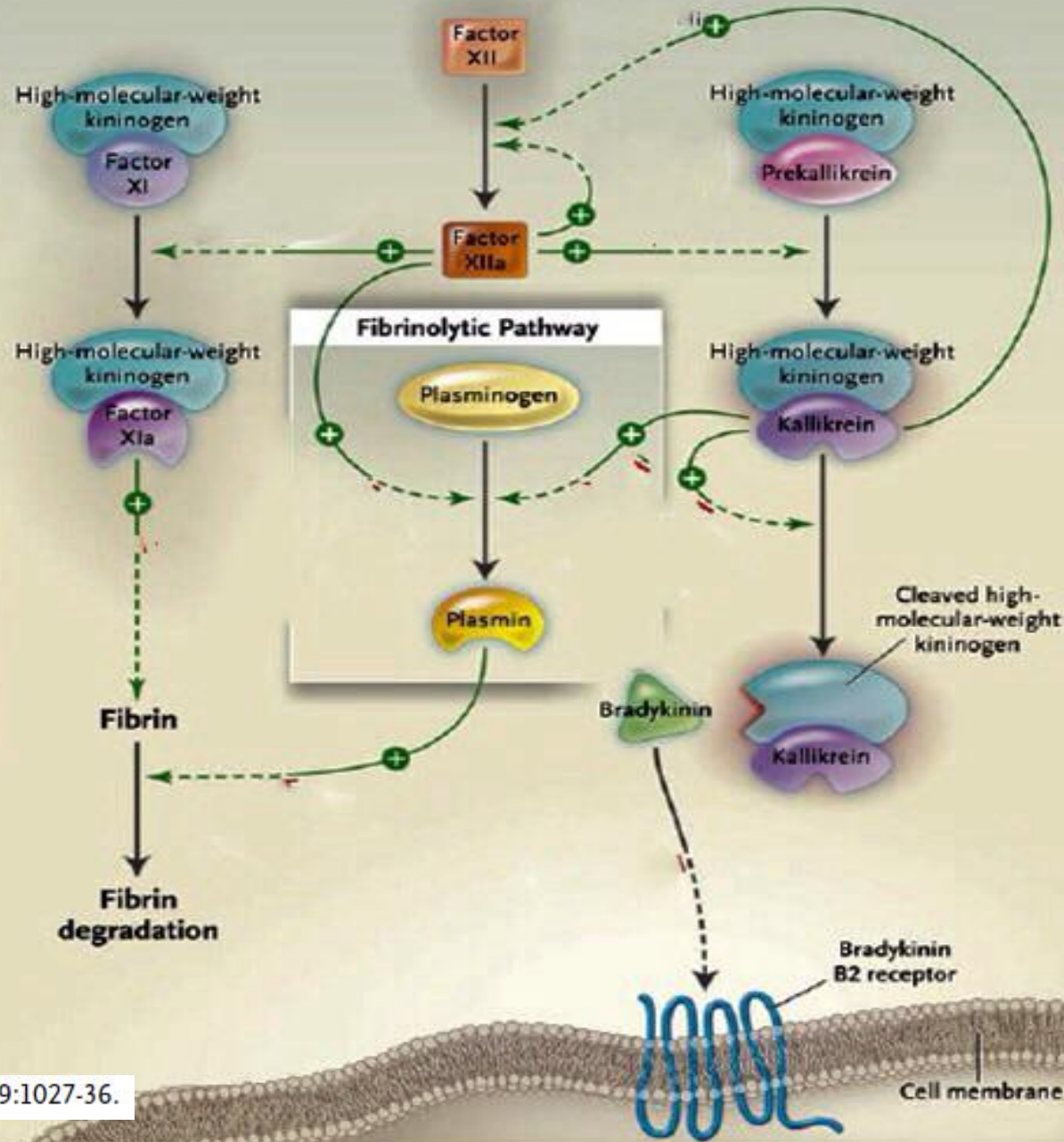
C1- inibitore (C1ihn)

- **Inibitore di proteasi del Complemento**
- **Inibitore delle proteasi del sistema di contatto**
- **Inibitore della plasmina**
(azione anti-fibrinolitica)

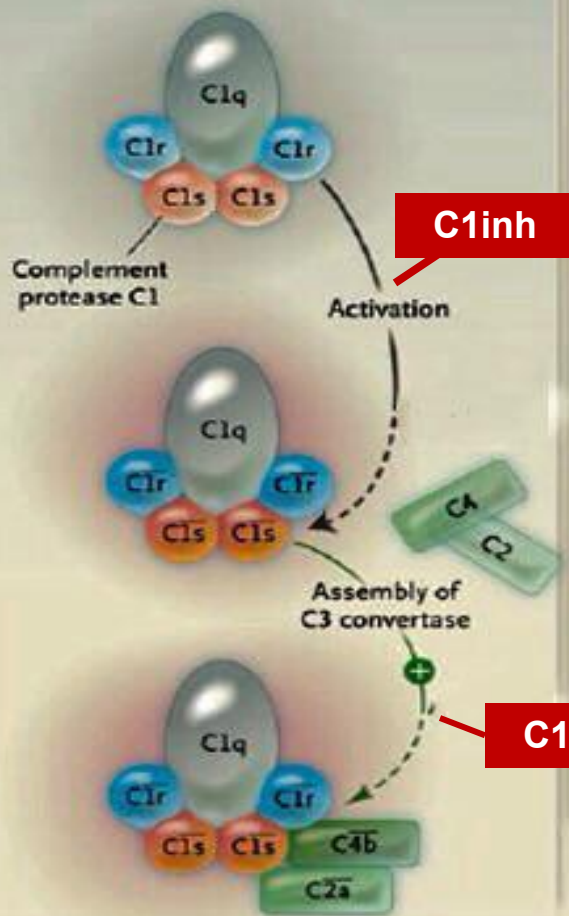
Complement Pathway



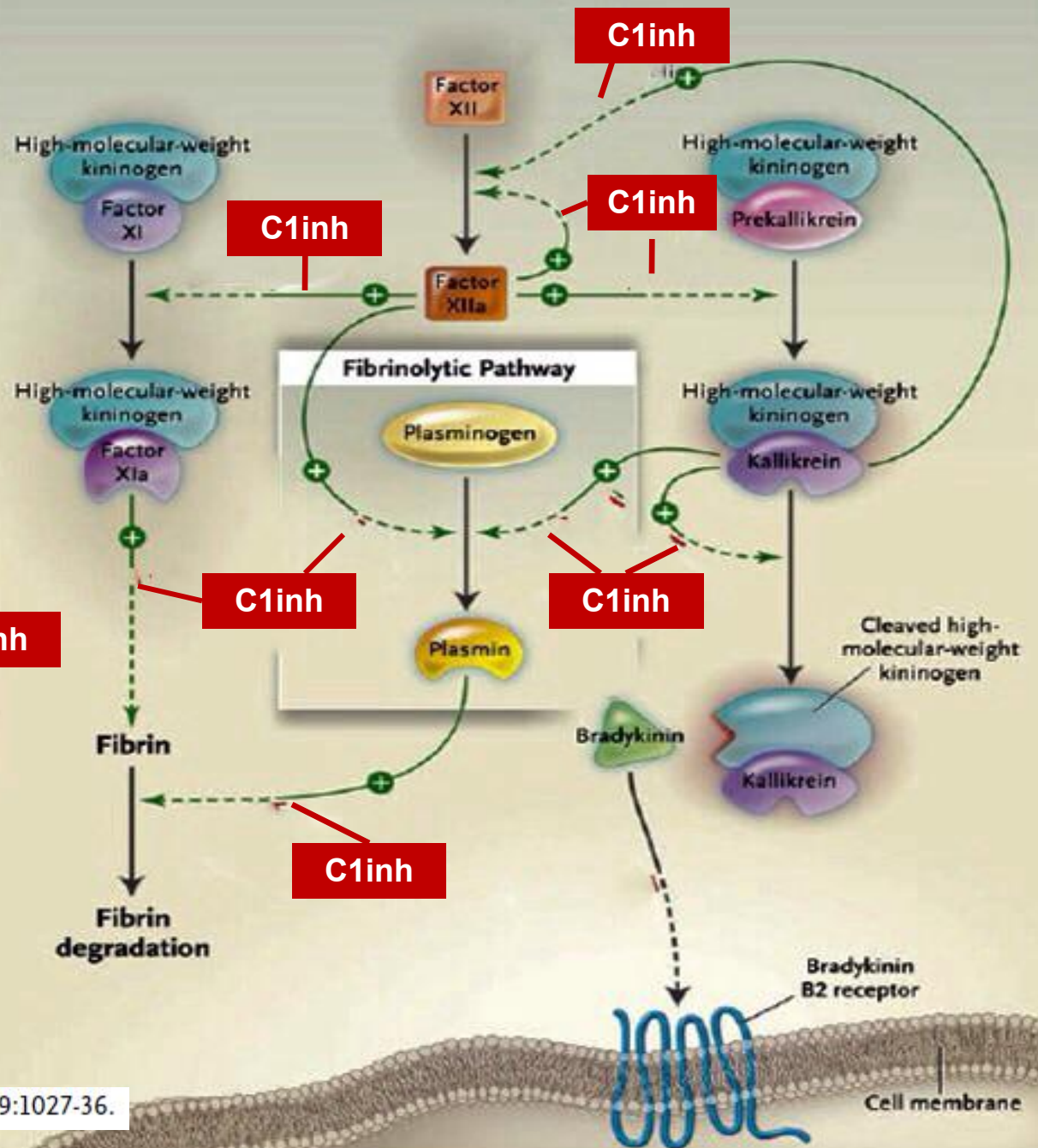
Contact Activation Pathway



Complement Pathway



Contact Activation Pathway



Angioedema bradichino-mediato

ACE-inibitori

Inibitori Dipeptidilpeptidasi 4

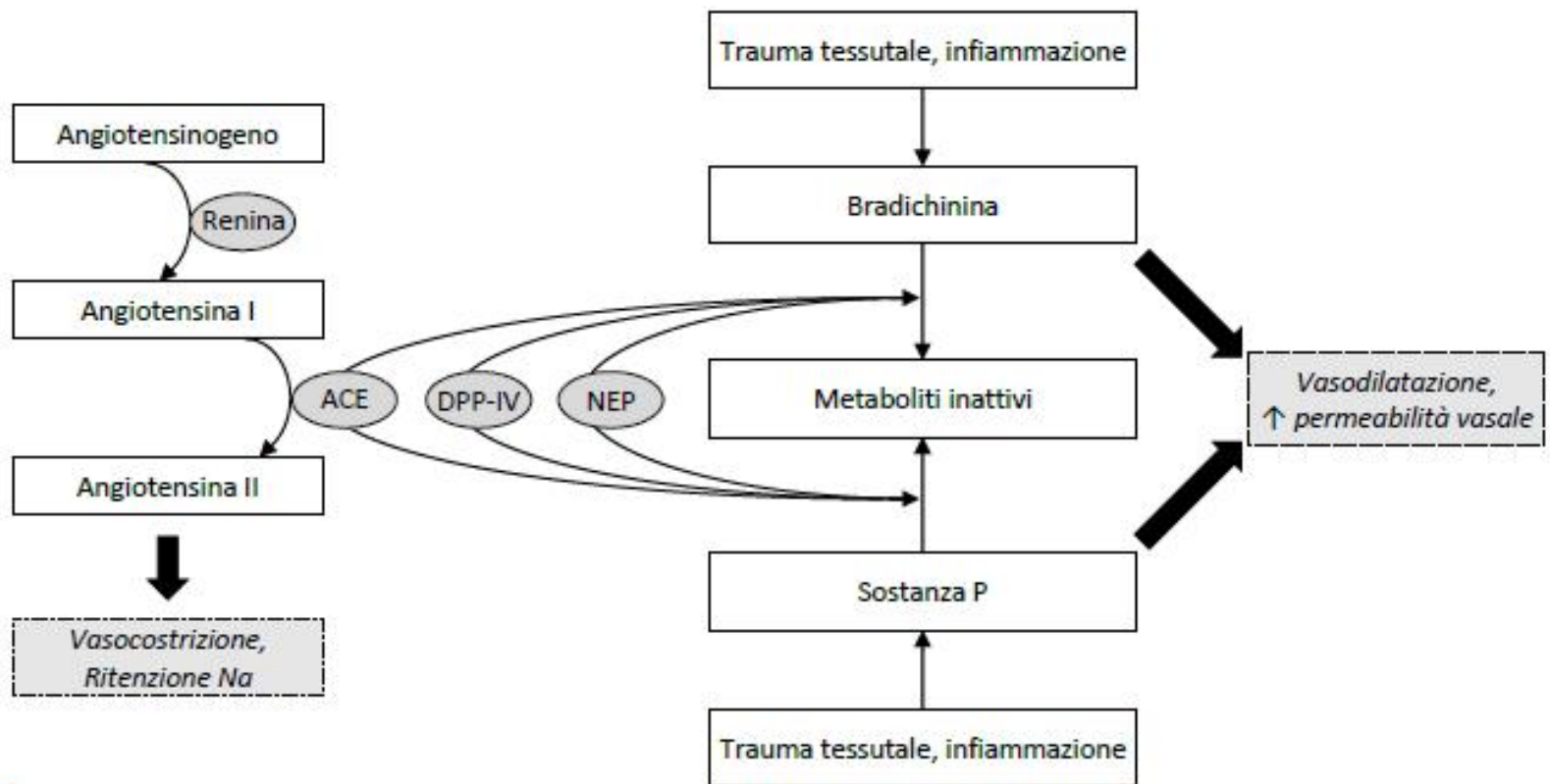
Inibitori della Neprilisina

rTPa nella trombolisi ictus ischemico



Bradichinina e Sostanza P

Catabolismo



Angioedema bradichino-mediato

ACE-inibitori

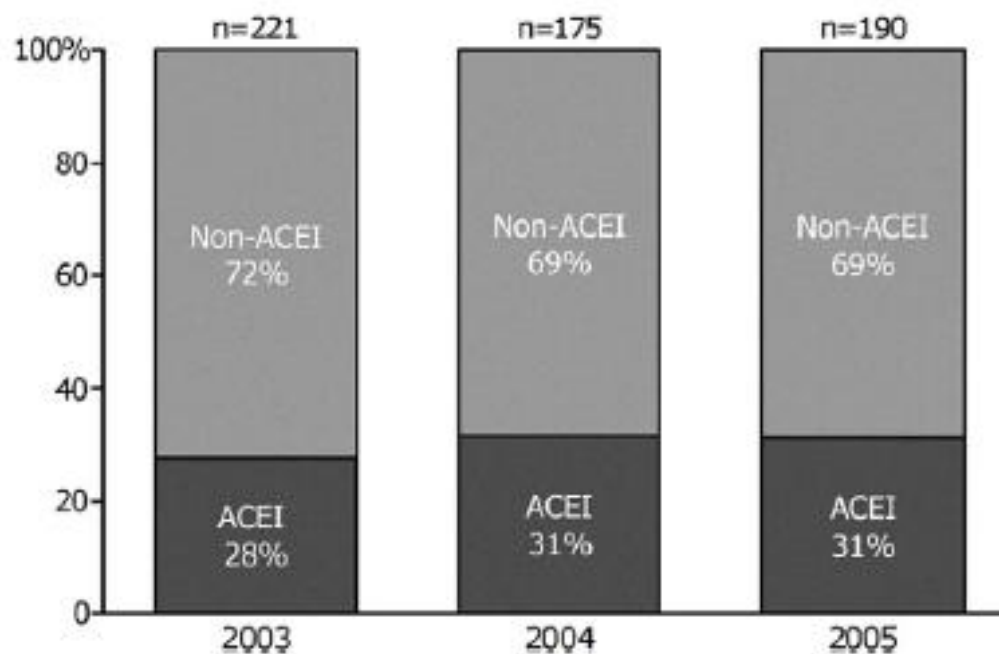
Inibitori Dipeptidilpeptidasi 4

Inibitori della Neprilisina

rTPa nella trombolisi ictus ischemico

Multicenter study of patients with angiotensin-converting enzyme inhibitor–induced angioedema who present to the emergency department

Aleena Banerji, MD*; Sunday Clark, MPH, ScD†; Michelle Blanda, MD‡; Frank LoVecchio, DO§; Brian Snyder, MD||; and Carlos A. Camargo Jr, MD, DrPH¶



Angioedema in DEA

ASO S. Croce e Carle Cuneo
2013-2015



Angioedema senza orticaria

N° (%)

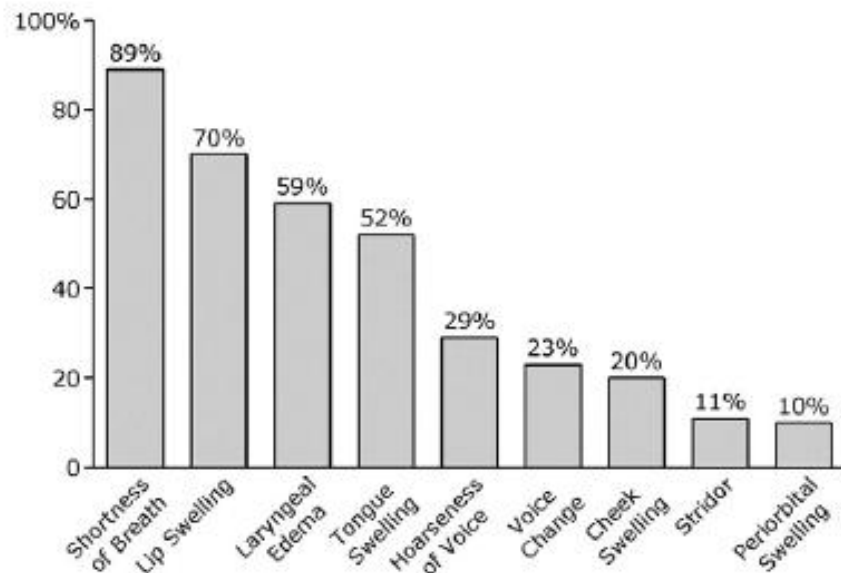
ACE-Inibitori	24 (40.0)
Sartani	3 (5.0)
FANS	2 (3.3)
Idiopatici	19 (31.6)
Altri farmaci	10 (16.6)
HAE	2 (3.3)

60



Multicenter study of patients with angiotensin-converting enzyme inhibitor–induced angioedema who present to the emergency department

Aleena Banerji, MD*; Sunday Clark, MPH, ScD†; Michelle Blanda, MD‡; Frank LoVecchio, DO§; Brian Snyder, MD||; and Carlos A. Camargo Jr, MD, DrPH¶



- Edema labbra e lingua 90 %
- Dispnea 90 %
- Stridore 29 %
- Disfagia 20 %
- Tosse 11 %
- Scialorrea 18 %
- Prurito 13 %

MANCA L'ORTICARIA

Angioedema da ACE inibitori

Incidenza 0.1- 0.2% dei pazienti trattati

Latenza da 1 giorno a 5 anni

**Nella metà dei casi si manifesta entro 1 mese
dall'inizio della terapia**

Nei 3/4 dei casi dopo 2 mesi

Nel 25 % dei casi tra 6 mesi e 5 anni

Angioedema bradichino-mediato



ACE-inibitori

Inibitori Dipeptidilpeptidasi IV (Incretine)

Inibitori della Neprilisina

rTPa nella trombolisi ictus ischemico

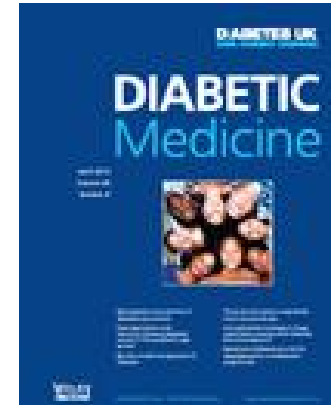
Dipeptidil peptidasi IV (DPP-IV)

- Inattiva Glucagone-like peptide 1 (GLP-1)
- Inattiva il polipeptide insulinotropo glucosio-dipendente (GIP)

Inibitori DPP-IV

- } Aumentano la concentrazione di GLP-1 e GIP
- } Stimolazione secrezione insulinica e soppressione rilascio di glucagone
- } Riduzione glicemia nel diabete tipo 2

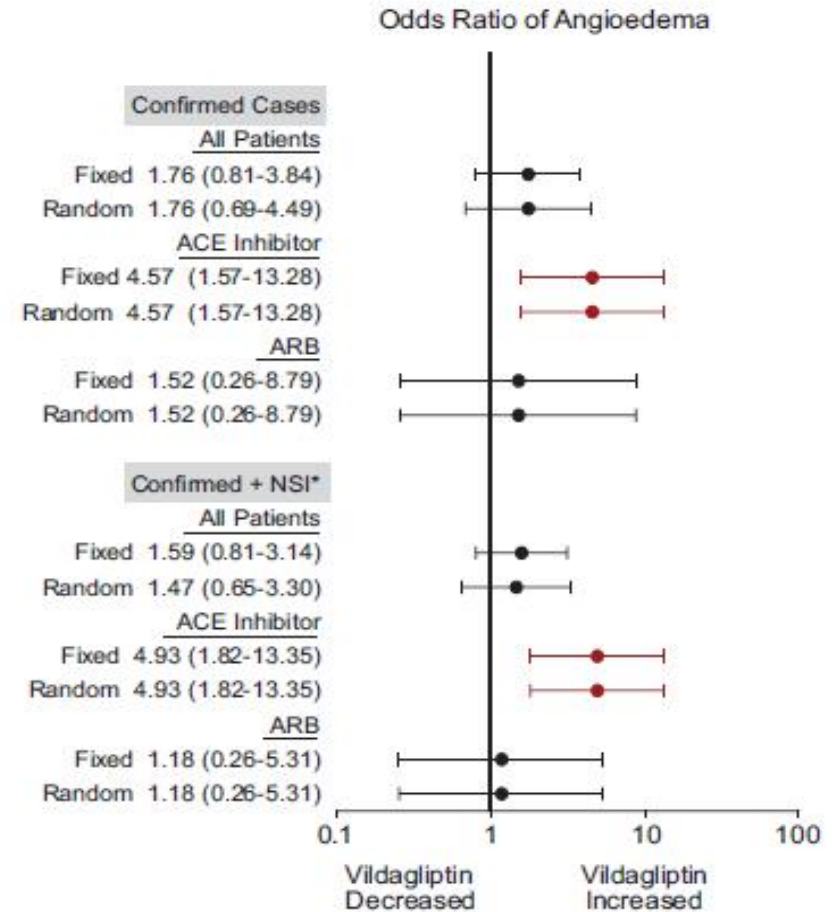
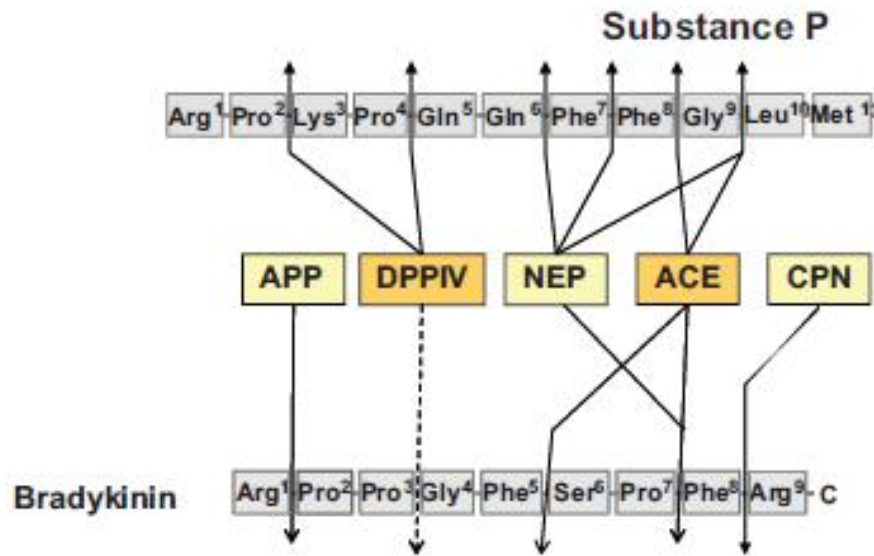
Dipeptidyl peptidase-4 inhibitors and angioedema: a class effect ? Saisho Y et al



DPP-IV inhibitor use may be associated with an increased risk of angioedema in diabetic patients who take an ACE inhibitor concurrently

Dipeptidyl Peptidase-IV Inhibitor Use Associated With Increased Risk of ACE Inhibitor-Associated Angioedema

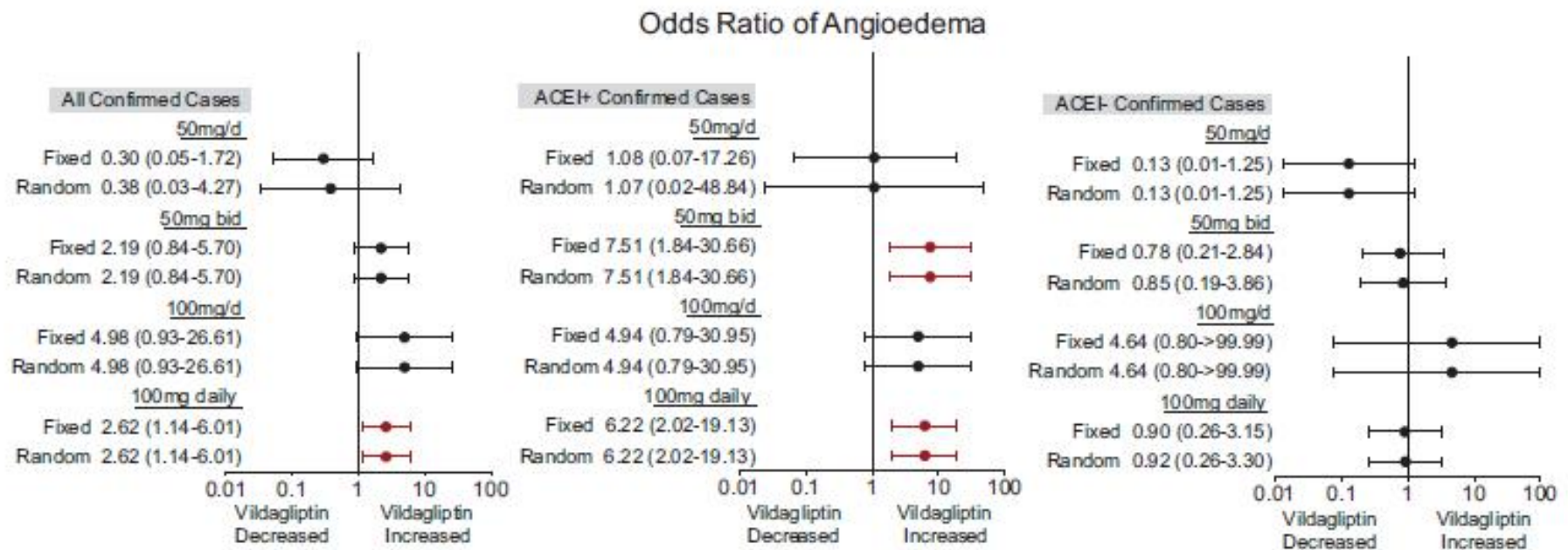
Nancy J. Brown, Stuart Byiers, David Carr, Mario Maldonado, Barbara Ann Warner



(Hypertension. 2009;54:516-523.)

Dipeptidyl Peptidase-IV Inhibitor Use Associated With Increased Risk of ACE Inhibitor-Associated Angioedema

Nancy J. Brown, Stuart Byiers, David Carr, Mario Maldonado, Barbara Ann Warner



(Hypertension. 2009;54:516-523.)

Angioedema bradichino-mediato

ACE-inibitori

Inibitori Dipeptidilpeptidasi 4

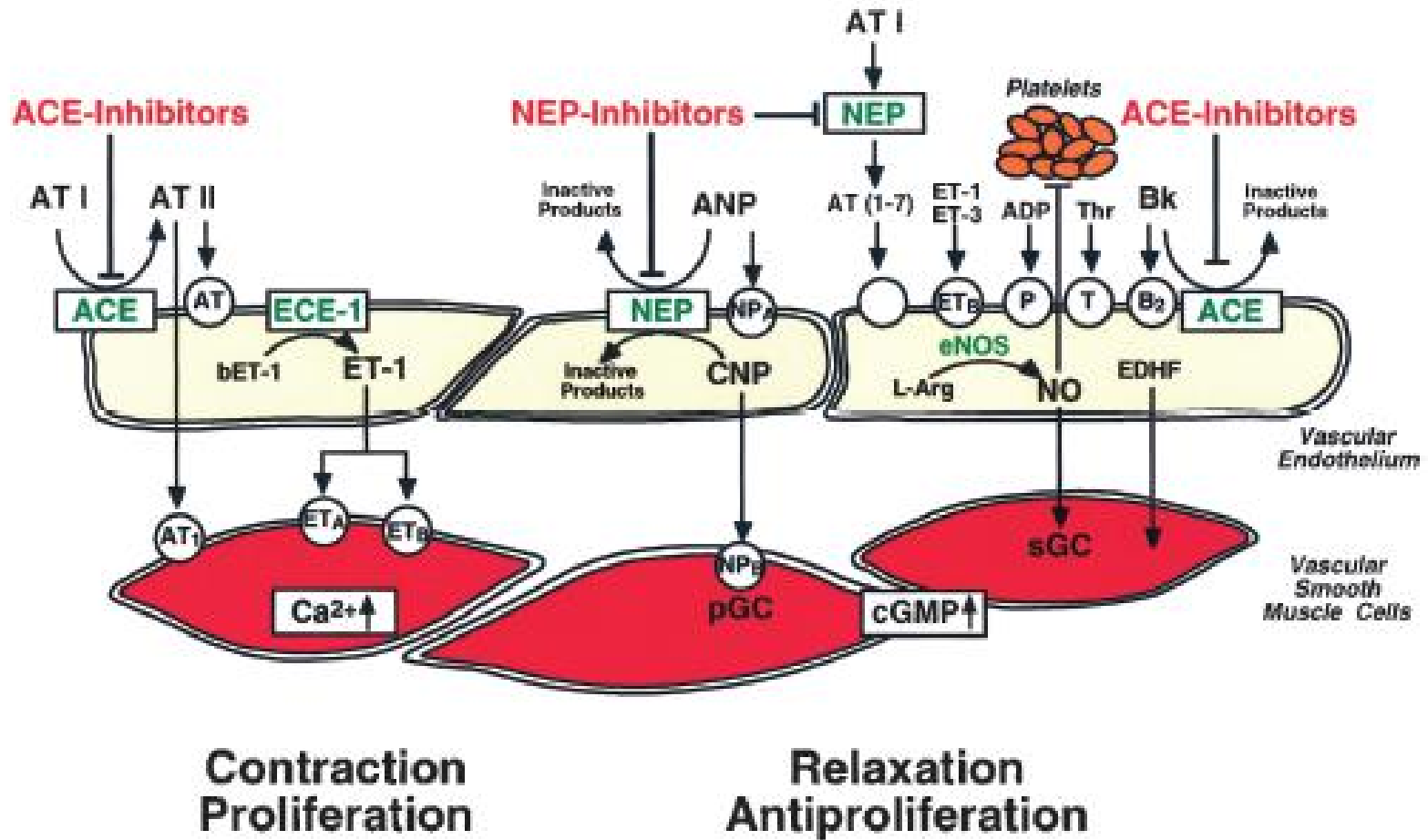
Inibitori della Neprilisina

rTPa nella trombolisi ictus ischemico

Vasopeptidase Inhibitors

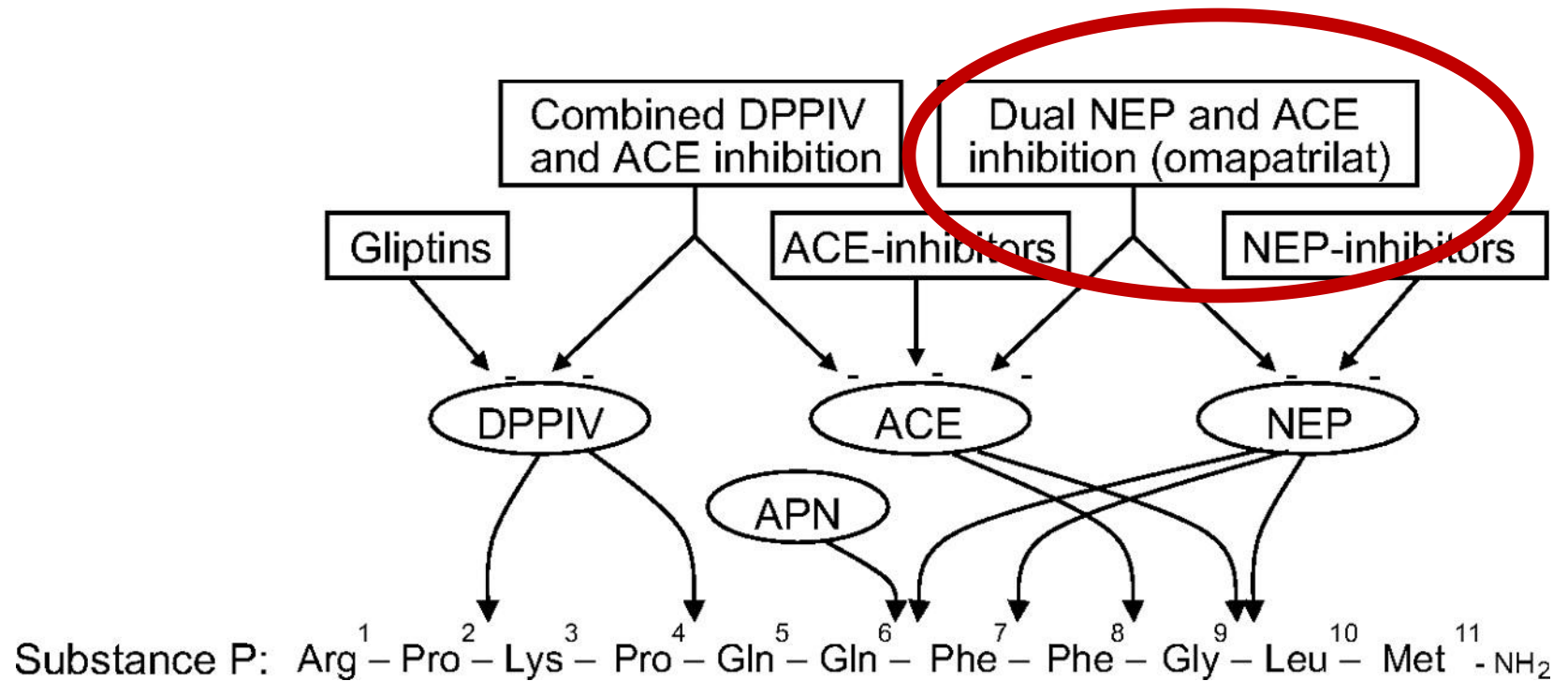
A New Therapeutic Concept in Cardiovascular Disease?

Roberto Corti, MD; John C. Burnett, Jr, MD; Jean L. Rouleau, MD;
Frank Ruschitzka, MD; Thomas F. Lüscher, MD



(*Circulation*. 2001;104:1856-1862.)

Figure. Schematic showing cleavage of substance P by peptidases.



Grouzmann E et al. Hypertension. 2009;54:468-470

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 11, 2014

VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

Valsartan + Sacubitril

- LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.
- The LCZ696 group had higher proportions of patients with hypotension and ***nonserious angioedema*** but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.



The NEW ENGLAND
JOURNAL of MEDICINE

Angioedema bradichino-mediato

ACE-inibitori

Inibitori Dipeptidilpeptidasi 4

Inibitori della Neprilisina

rTPa nella trombolisi ictus ischemico

Angioedema after Administration of tPA for Ischemic Stroke: Case Report

Maertins M et al. Air Medical J



Angioedema lingua 20 min dopo R-TPA.

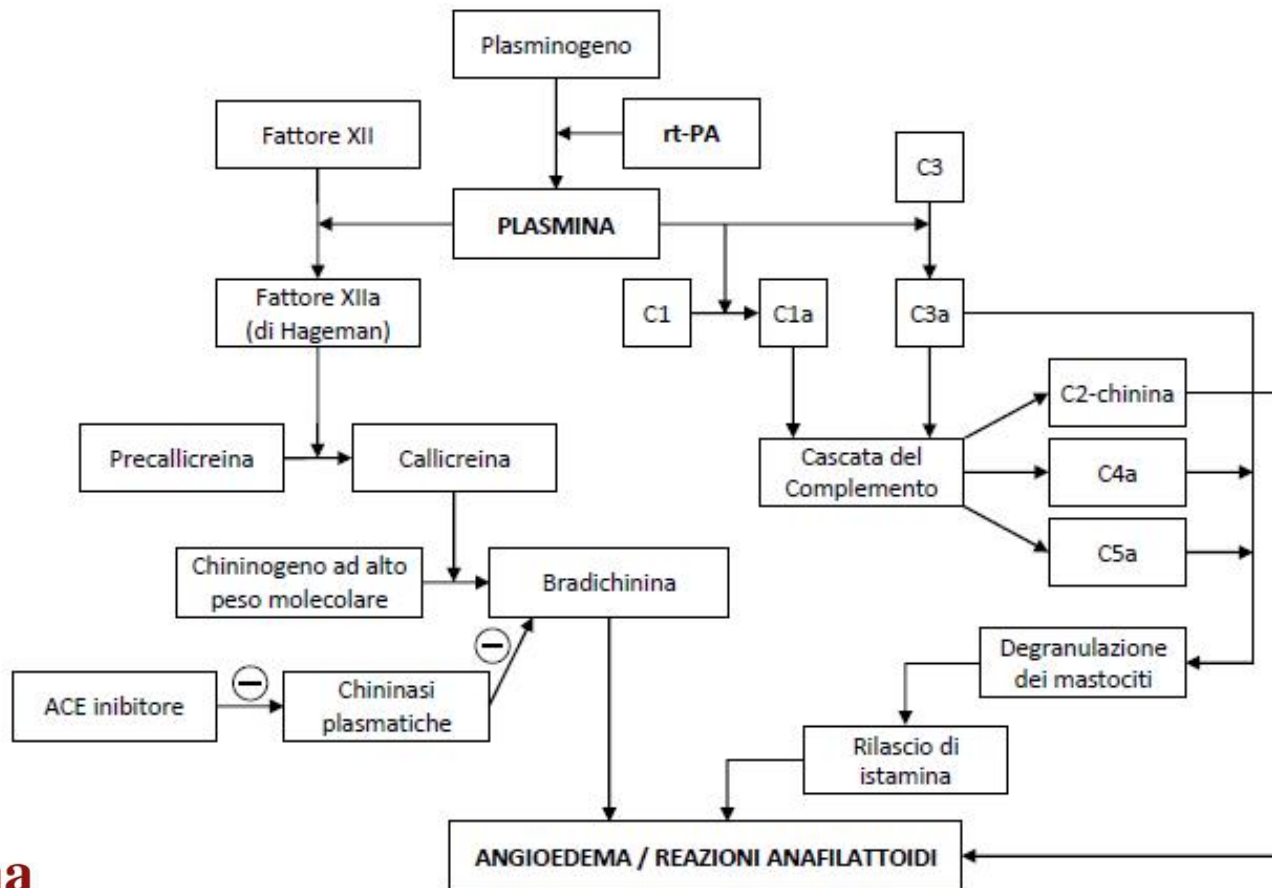
Trattato con antistaminico e CS con
risoluzione in 2 ore circa

Complica l'1-2 % delle trombolisi per ictus,
maggior rischio in chi assume ACE
inibitori

Meccanismo misto istaminergico /
bradichinergico + disautonomia correlata
all'ictus (spesso coinvolge l'emilingua
opposta al lato della trombosi)

Meccanismo dell'AE da fibrinolisi

Rolla G, Raie A



Angioedema – Terapia “classica”

- Adrenalina im/aerosol
- Steroidi sistemici ed inalatori
- Antistaminici

Efficacia nell'angioedema associato ad orticaria

Scarsa efficacia nelle altre forme

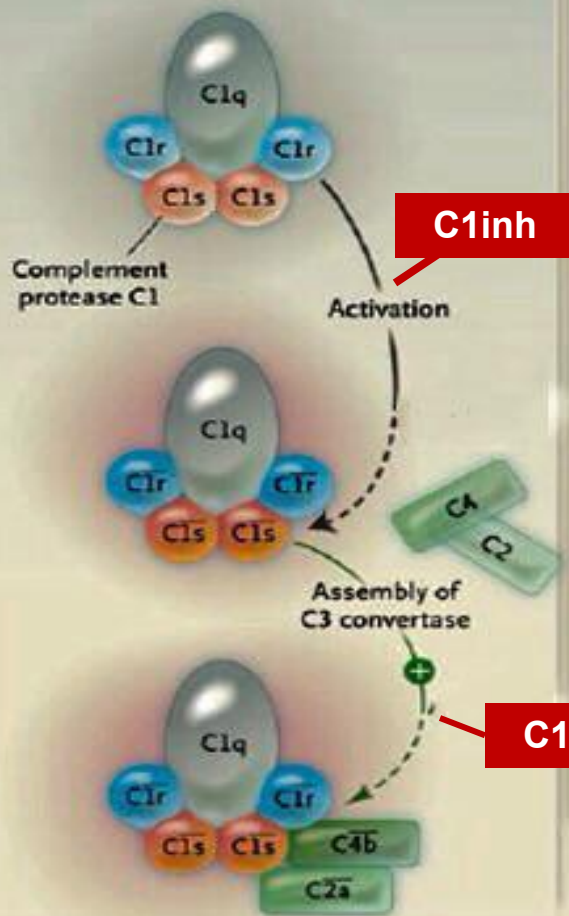
Terapia attacco acuto HAE

TABLE 2

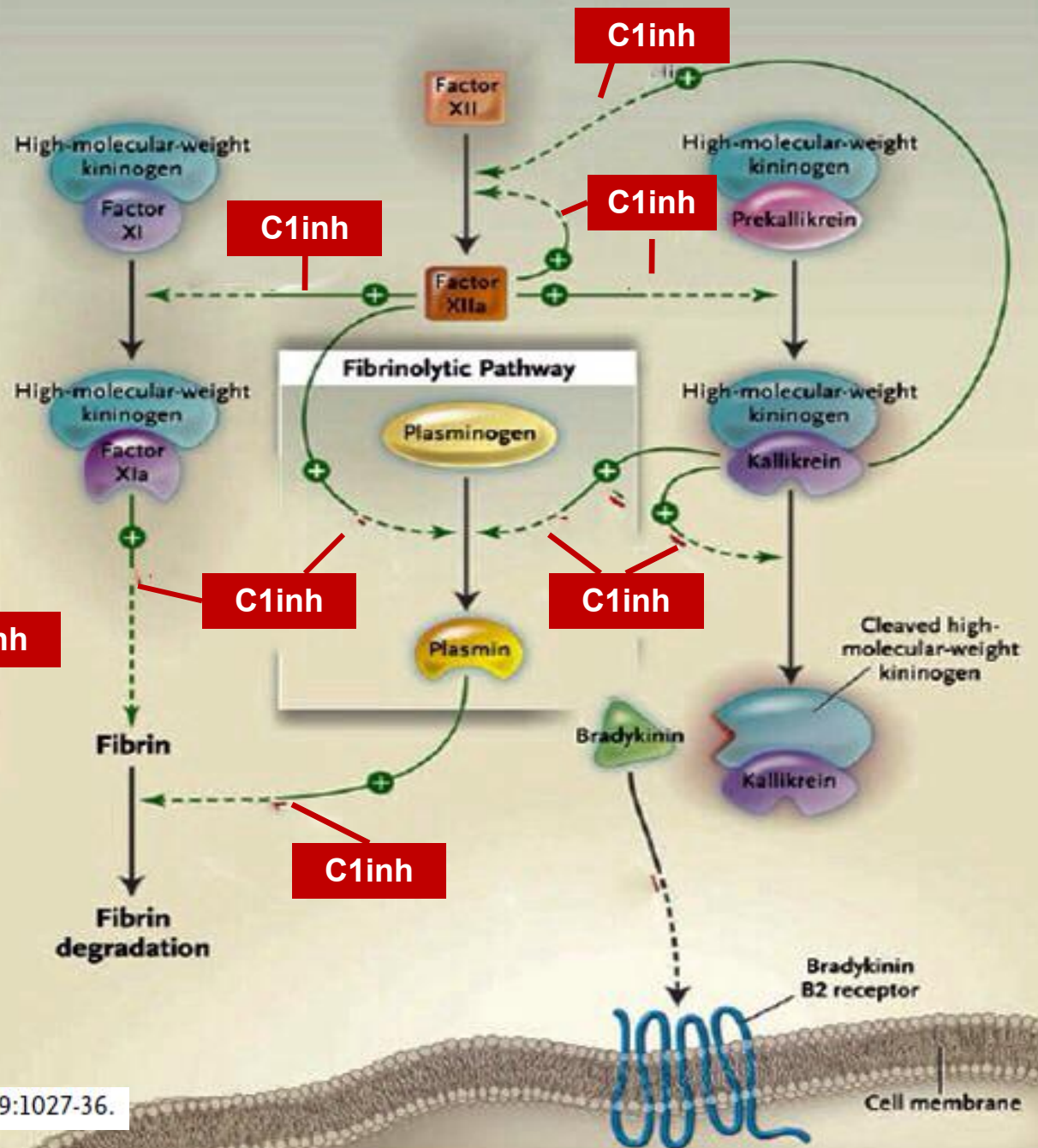
Medications for acute attacks of hereditary angioedema

Drug	Approved	Self-dosing	Dosage
Plasma-derived nanofiltered C1 inhibitor (Berinert)	United States: adolescents and adults Europe: all ages	Yes	20 U/kg intravenously
Plasma-derived nanofiltered C1 inhibitor (Cinryze, Cetor)	Europe: adolescents and adults	Yes	1,000 U intravenously, with possibility of second dose of 1,000 U after 60 minutes
Ecallantide (Kalbitor)	United States: ≥ 16 years old	No	30 mg subcutaneously
Icatibant (Firazyr)	United States and Europe: ≥ 18 years old	Yes	30 mg subcutaneously
Recombinant human C1 inhibitor (Rhucin)	Europe: adults United States: pending	No	50 U/kg or 4,200 U intravenously, whichever dose is higher

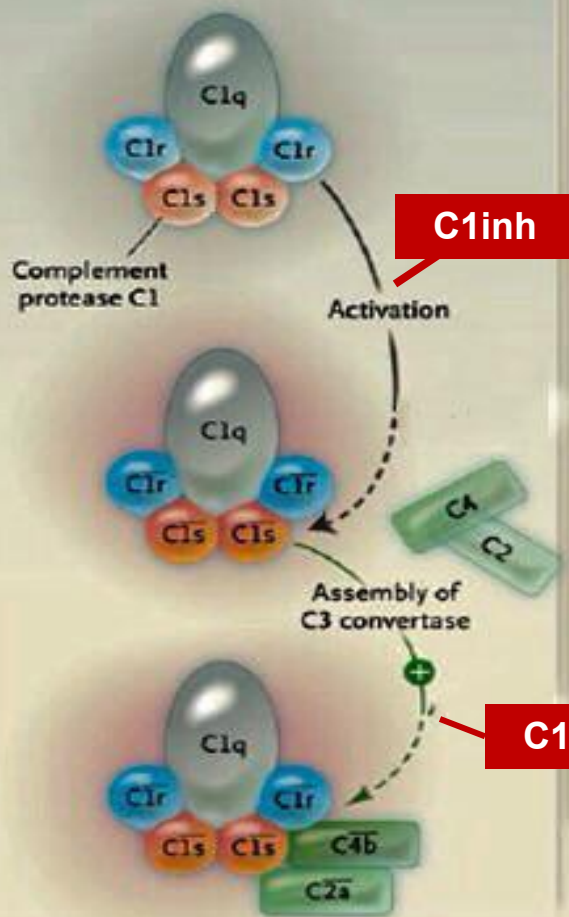
Complement Pathway



Contact Activation Pathway



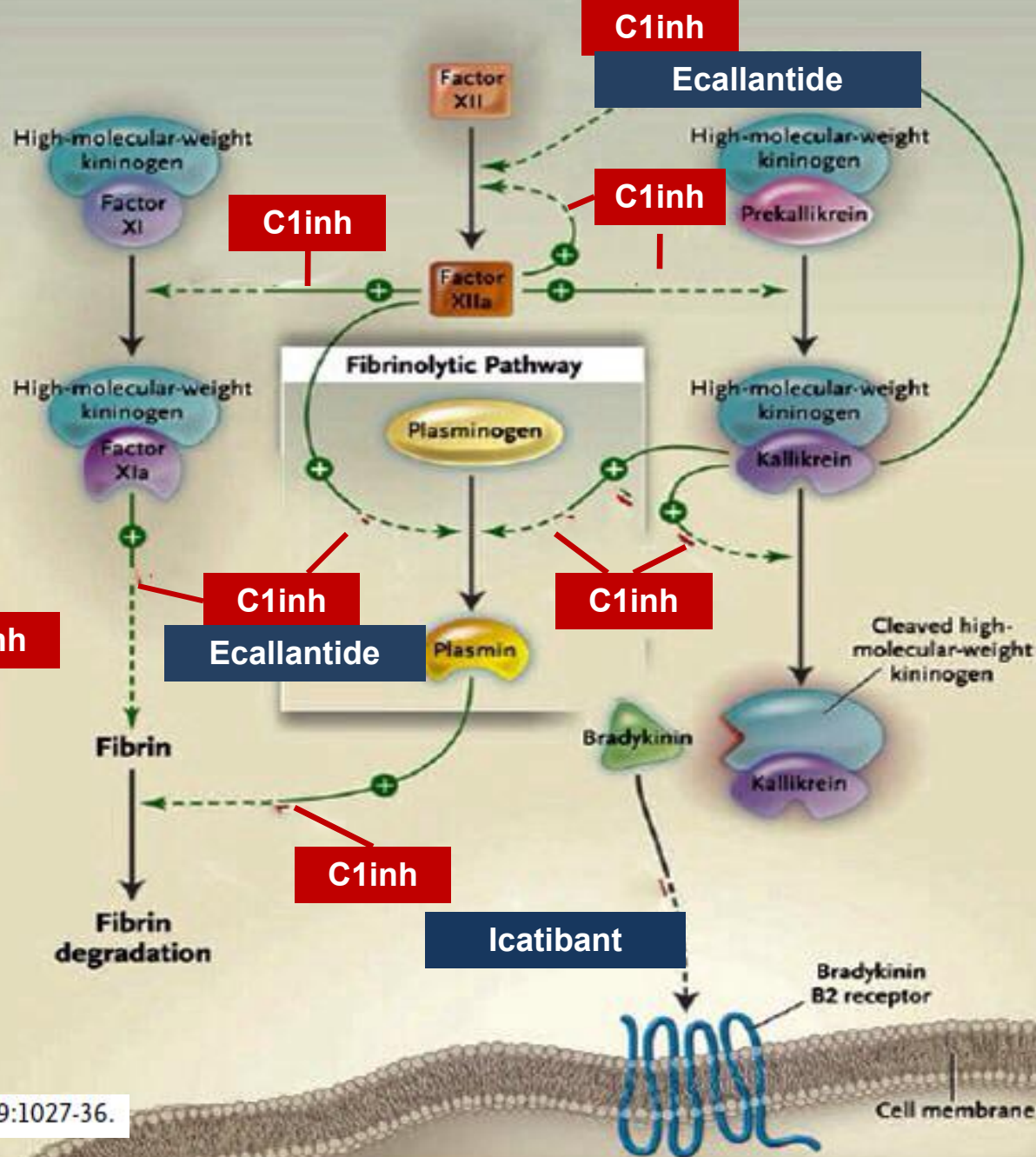
Complement Pathway



C1inh

C1inh

Contact Activation Pathway



C1inh

Ecallantide

C1inh

C1inh

Fibrinolytic Pathway

C1inh

Ecallantide

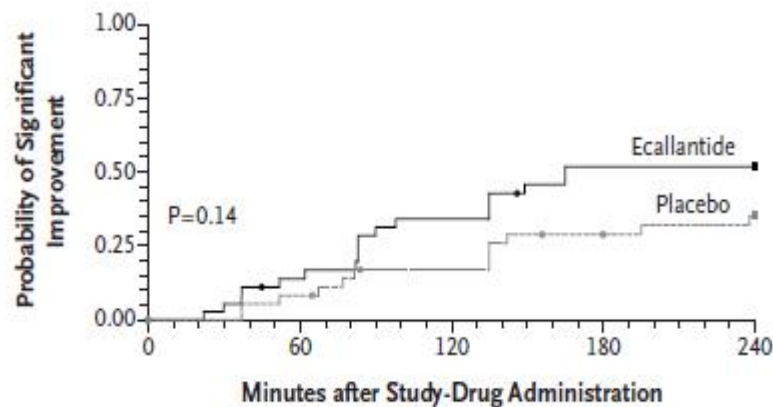
C1inh

C1inh

Icatibant

Ecallantide for the Treatment of Acute Attacks in Hereditary Angioedema

Marco Cicardi, M.D., Robyn J. Levy, M.D., Donald L. McNeil, M.D.,
H. Henry Li, M.D., Ph.D., Albert L. Sheffer, M.D.,
Marilyn Campion, M.S., Patrick T. Horn, M.D., Ph.D.,
and William E. Pullman, M.B., B.S., Ph.D., F.R.A.C.P.



No. of Patients

Ecallantide	36	29	22	15	15
Placebo	36	32	27	22	19

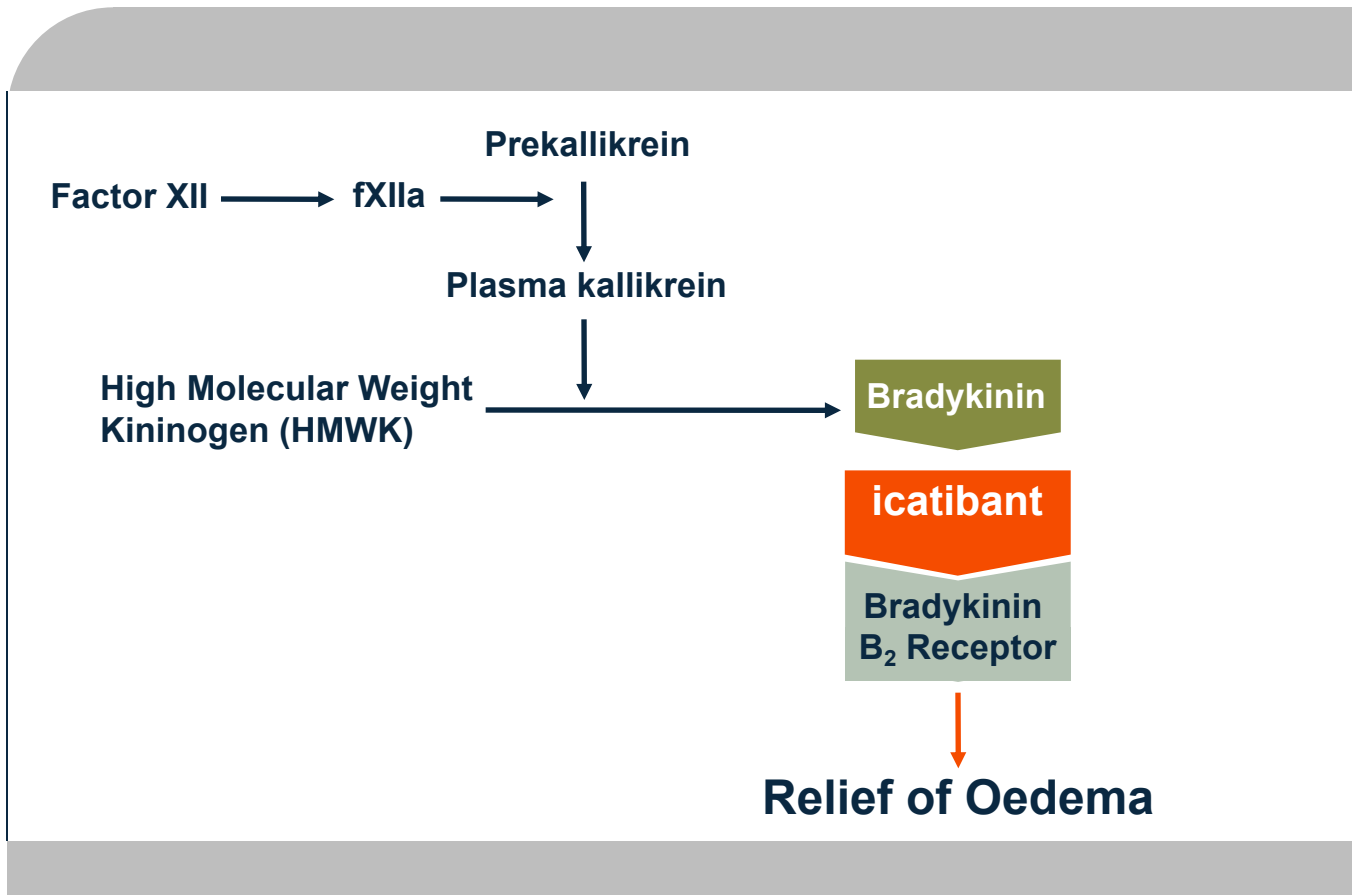
In summary, we compared the effect of the recombinant plasma kallikrein inhibitor ecallantide with that of placebo in treating acute attacks of angioedema in patients with hereditary angioedema. At 4 hours after study-drug administration, the treatment outcome score, a patient-reported outcome measure, was significantly better with ecallantide than with placebo.

N Engl J Med 2010;363:523-31.

Copyright © 2010 Massachusetts Medical Society.



Meccanismo d'azione dell'icatibant



Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema

M. Cicardi, A Banerji, et al. N Engl J med 2010;363:532-41

FAST-1
56 Pazienti

FAST-2
74 Pazienti

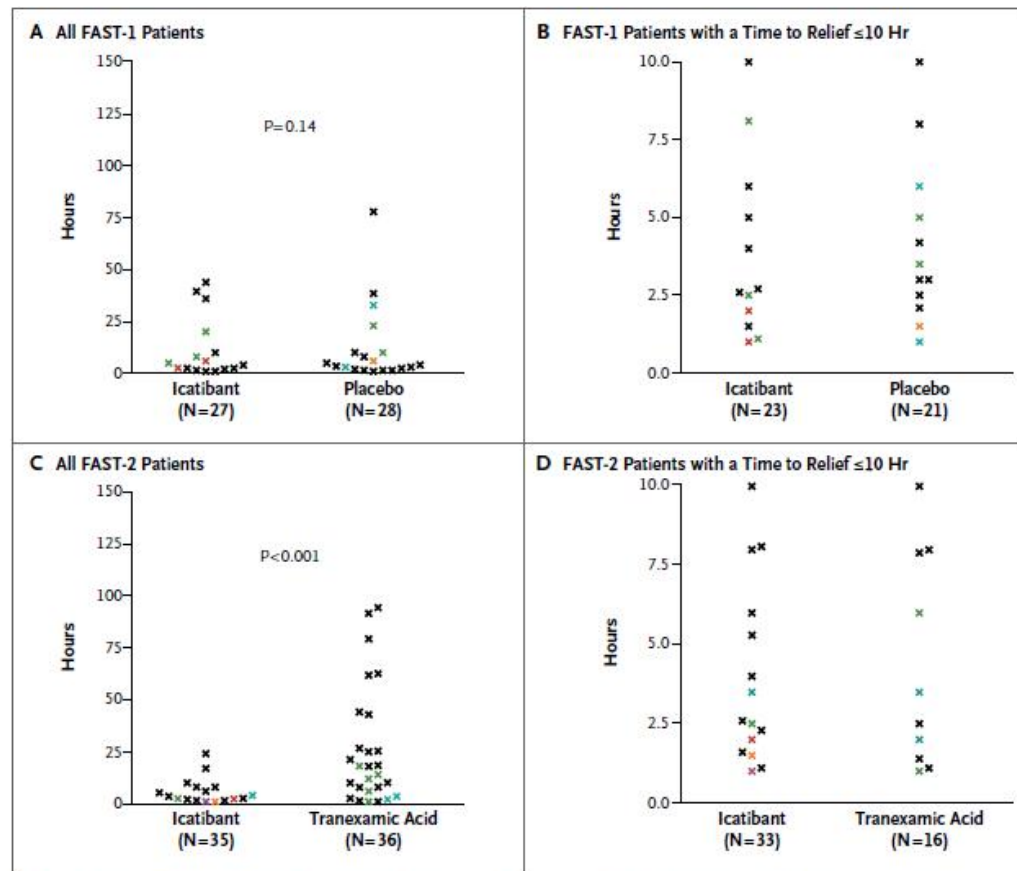


Figure 1. Time to Clinically Significant Relief of the Index Symptom in the FAST-1 and FAST-2 Trials, According to Study Group.

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637 THIS WEEK IN THE JOURNAL

ORIGINAL ARTICLE

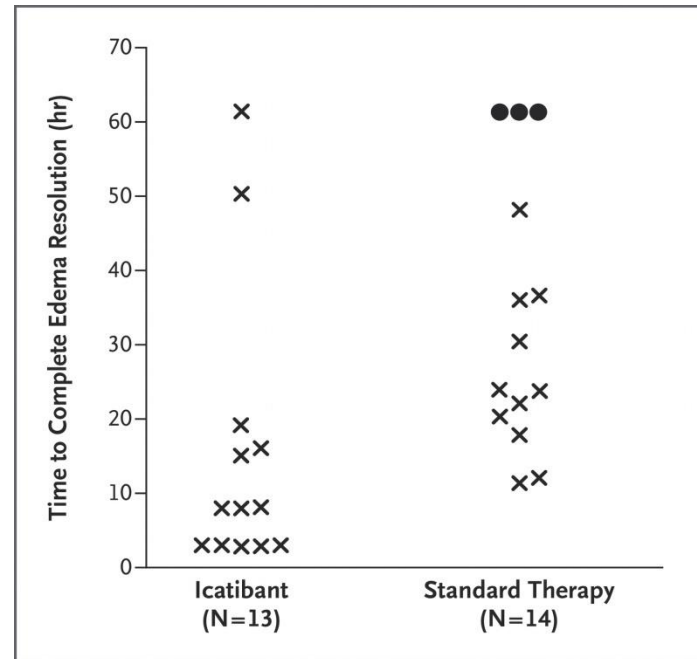
A Randomized Trial of Icatibant in
ACE-Inhibitor–Induced Angioedema

N Engl J Med 2015;372:418-25

A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

27 patients with ACE-inhibitor–induced angioedema were assigned to receive icatibant or standard therapy with intravenous prednisolone plus clemastine.

The median time to complete resolution of edema was 8.0 hours with icatibant and 27.1 hours with standard therapy



Clinical Outcomes (Icatibant 30 mg sc)

Table 2. Clinical Outcomes.*

Outcome	Icatibant (N=13)	Standard Therapy (N=14)	P Value
Median (IQR) time to complete resolution of edema: primary end point — hr	8.0 (3.0–16.0)	27.1 (20.3–48.0)	0.002†
Patients with complete resolution of edema at 4 hr after treatment — no. (%)	5 (38)	0	0.02‡
Median (95% CI) time to onset of symptom relief — hr§			
According to composite investigator-assessed symptom score	2.0 (1.0–8.1)	11.7 (8.0–18.0)	0.03¶
According to composite patient-assessed VAS score	2.0 (2.0–6.3)	7.9 (1.2–11.8)	0.36¶
According to composite investigator-assessed angioedema score	2.0 (2.0–12.0)	12.0 (11.3–NE)	0.003¶

* Clinical outcomes were assessed in the per-protocol population. CI denotes confidence interval, IQR interquartile range, and NE not estimable.

† The P value was calculated with the use of the Wilcoxon rank-sum test.

‡ The P value was calculated with the use of Fisher's exact test.

§ The time to the onset of symptom relief was defined as the time to the first improvement (i.e., decrease) of at least 1 point in the composite score.

¶ The P value was calculated with the use of the Peto–Peto–Prentice test.

Adverse Events and Injection-Site Reactions.

Table 3. Adverse Events and Injection-Site Reactions.*

Outcome	Icatibant (N = 15)	Standard Therapy (N = 15)
	<i>no. of patients (%)</i>	
Any adverse event	1 (7) [†]	4 (27)
Drug-related adverse event	1 (7)	1 (7)
Serious adverse event	0	1 (7)
Injection-site reaction [‡]		
Redness	12 (80)	4 (27)
Swelling	8 (53)	3 (20)
Pain	7 (47)	2 (13)
Itching	4 (27)	1 (7)
Sensation of warmth	4 (27)	0

* These analyses were performed in the as-treated population, which included all patients who received at least one dose of either study medication, with results attributed to the treatment they actually received.

[†] The only patient-reported adverse event in the icatibant group was “pain at the administration site (local pain).”

[‡] Injection-site reactions were assessed by the investigators.

**Randomized Trial of Icatibant for Angiotensin-
Converting Enzyme Inhibitor–Induced Upper
Airway Angioedema**



Studio FASE III randomizzato controllato

ICATIBANT vs PLACEBO

121 pazienti provenienti da 31 Centri USA

Terapia steroidea ed antistaminica consentita

Forme lievi e gravi escluse

Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor–Induced Upper Airway Angioedema

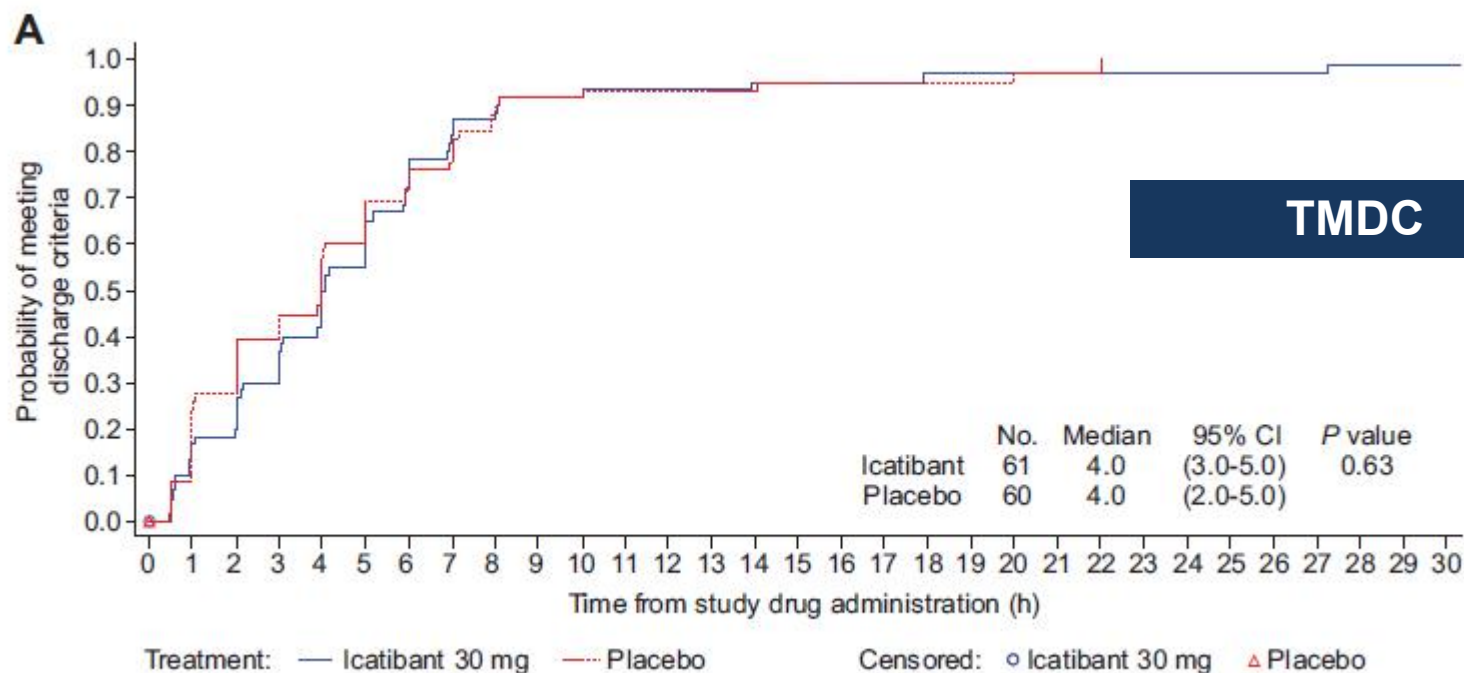


Symptom	Rating	Description of rating
Difficoltà respiratoria	0 = absence of symptoms	Normal breathing
	1 = mild	Mild additional effort required for breathing by subject, but no audible wheezing or no stridor heard with stethoscope
	2 = moderate	Audible wheezing and/or stridor heard with stethoscope only, with uncomfortable breathing and moderate additional effort required for breathing by subject
	3 = severe	Audible wheezing and/or stridor audible without stethoscope, with subject in moderate distress
	4 = very severe	Audible severe wheezing and audible marked stridor, with subject in severe distress and tripod posturing (sitting or standing, leaning forward and supporting the upper body with hands on the knees or on another surface)
Turbe deglutorie	0 = absence of symptoms	Normal swallowing
	1 = mild	Mild sensation of difficulty swallowing (fullness in throat), but can swallow solids and liquids
	2 = moderate	Marked difficulty or unable to swallow solids, but can swallow liquids
	3 = severe	Unable to swallow solids or liquids, but can swallow saliva
	4 = very severe	Unable to swallow solids, liquids, or saliva (drooling)
Cambio voce	0 = absence of symptoms	Normal voice
	1 = mild	Audible speech, but mild disruption of normal voice (hoarseness)
	2 = moderate	Audible speech, but moderate disruption of normal voice (muffled voice)
	3 = severe	Very difficult to hear speech or for subject to articulate
	4 = very severe	Unable to speak at all
Edema della lingua	0 = absence of symptoms	No swelling
	1 = mild	Mild anterior or lateral tongue swelling, uvula completely visible
	2 = moderate	Moderate anterior or lateral tongue swelling, uvula only partially visible
	3 = severe	Severe diffuse swelling of tongue, soft palate and uvula not visible at all
	4 = very severe	Very severe diffuse tongue swelling that completely fills mouth orifice

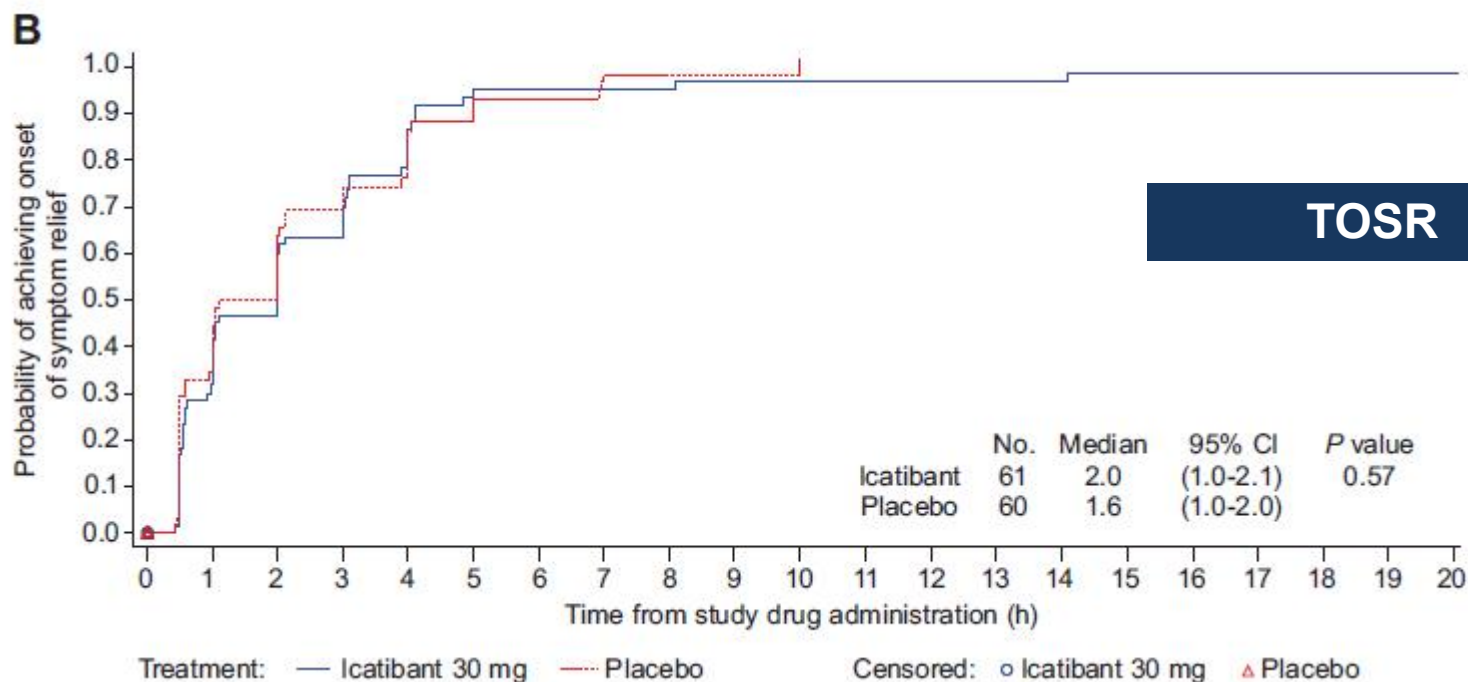
Time to meeting discharge criteria (TMDC)

- **Il tempo minimo per raggiungere:**
 - **Assenza di disturbi respiratori e deglutitori (grade 0)**
 - **Assenza o lieve edema lingua o alterazione voce (grade 0-1)**

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Icatibant e Angioedema da ACE-inibitori PRO

- **Elevata biodisponibilità + picco plasm. 0.5 h**
- **Pochi effetti collaterali**
- **Nessun rischio biologico**
- **Potenziabilmente utile in circa 30-40% casi senza orticaria**
- **In teoria efficace anche negli AE da incretine e post trombolisi**

Icatibant e Angioedema da ACE-inibitori

CONTRO



- **Inefficace vs placebo in studio di fase III**
- **Uso off label del farmaco**
- **Costi ancora eccessivi del farmaco**

E se non abbiamo risorse?



UMAN COMPLEX D.I. 500 IU

Powder for solution for infusion
Human plasma prothrombin complex concentrate
(factors II - IX - X), lyophilised
Reconstitute with 20 ml of solvent
Only by intravenous use

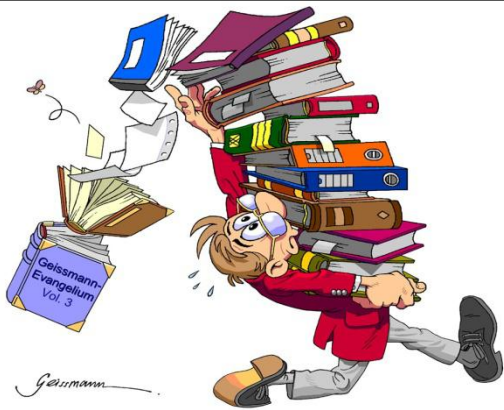
 

Batch n° Prep date Expiry date

8095078 - Rev. 00 06/01



1-2 grammi ev



Take home messages..

- **Adrenalina e antistaminici se AE con orticaria**
- **Anamnesi farmacologica (non solo ACEi!!)**
- **Icatibant nell'HAE**
- **Icatibant *off label* nell' AE non responsivo ad antistaminici (ma solo nei casi gravi)**
- **FFP se non disponibile C1inh o icatibant**



**GRAZIE
PER
L'ATTENZIONE**

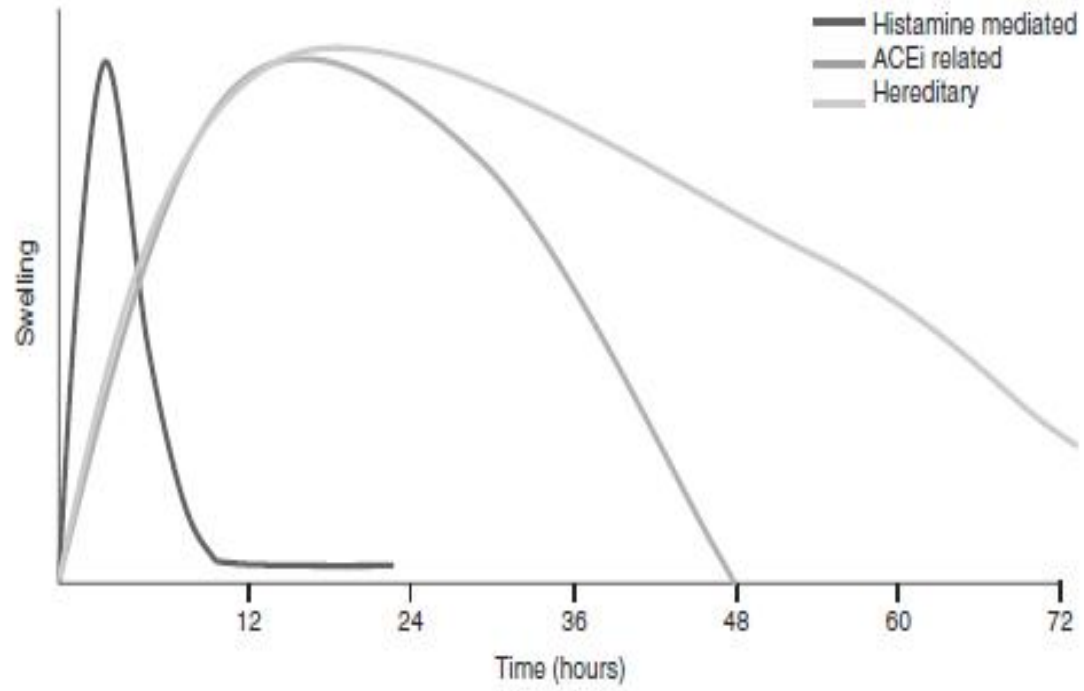


Laboratorio e HAE

	C1-INH Level	C1-INH Function	C ₄ Level	C1 _q Level
85%				
HAE type I	<30%	<30%	Low	Normal
HAE type II	Normal/High	<30%	Low	Normal
15%				
HAE type III	Normal	Normal	Normal	Normal

C1_q=component of complement protein C1.

Agostoni A, et al. *J Allergy Clin Immunol.* 2004;114(3 suppl):S51-S131.



Clinica dell' HAE

Courtesy of Murat Bas, MD



Courtesy of Murat Bas, MD



Cutaneous edema can affect the face, extremities, and genitals¹

Edema of the mucous membranes can affect the larynx and GI tract²

Courtesy of Murat Bas, MD

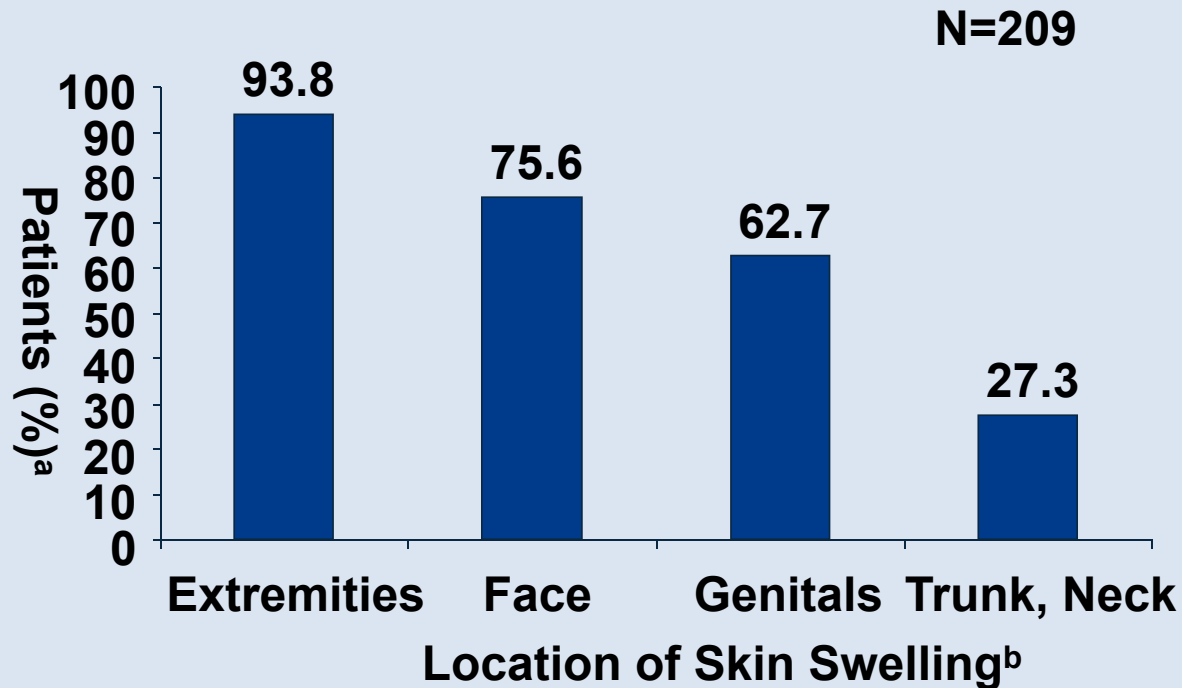


US Hereditary
Angioedema Association
www.haeimages.com



1. Agostoni A, et al. *J Allergy Clin Immunol.* 2004;114(3 suppl): S51-S131.
2. Bork K, et al. *Am J Med.* 2006;119(3):267-274.

Distretti cutanei coinvolti



- A retrospective study of 209 patients with clinical symptoms of HAE
- This population accounted for 131,110 total episodes of edema
- 65,102 of all episodes were skin swellings, occurring in 201 patients

Attacchi del volto

Pre-facial Swelling

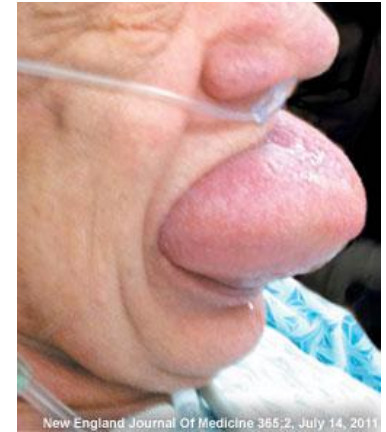


Facial Swelling

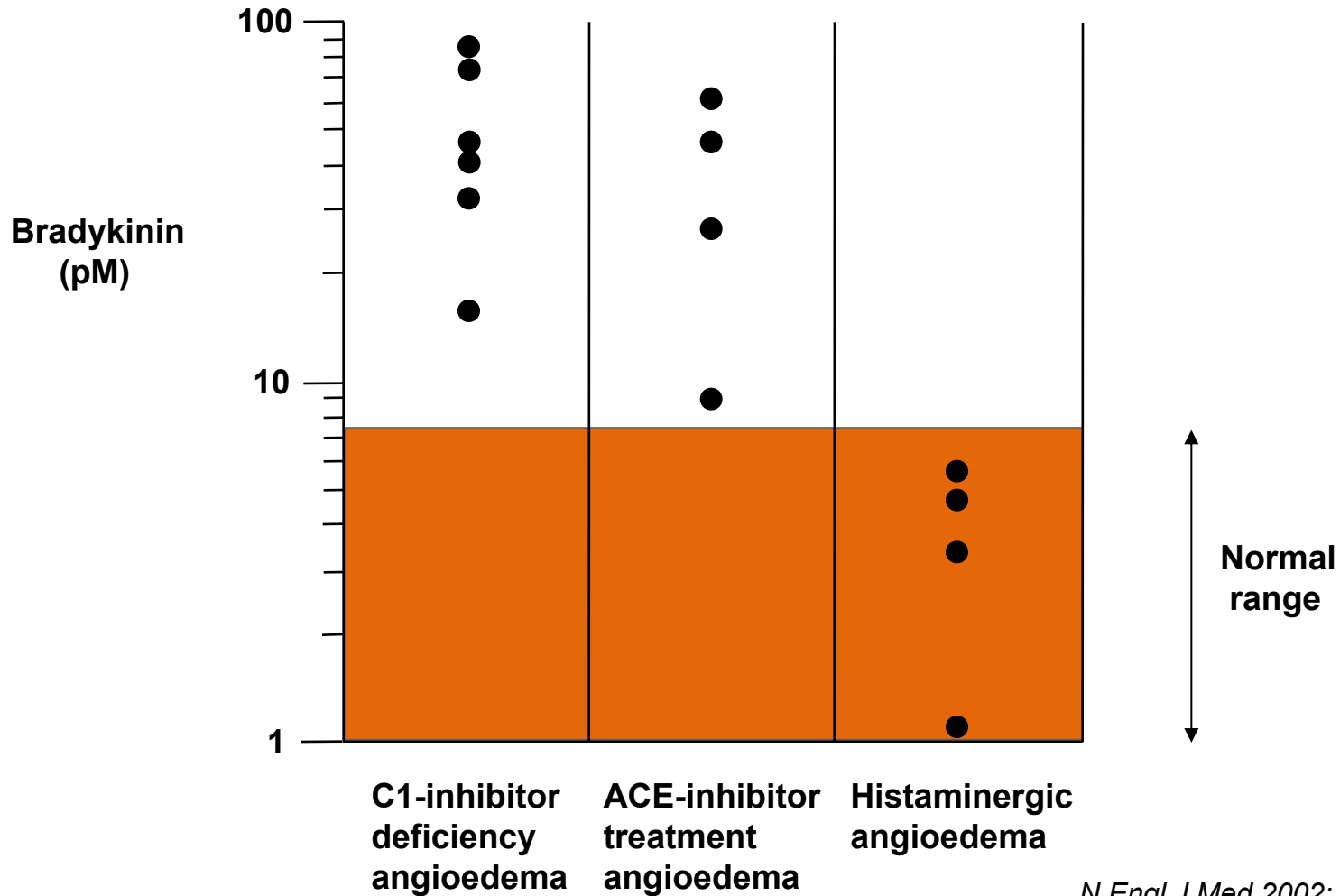


- **Edema del volto spesso associato ad ostruzione delle vie aeree prossimali**
- **“Disfiguring attacks” con compromissione funzionale (impossibilità ad alimentarsi, difficoltà a respirare)**

Esempi di angioedema



Livelli plasamtici di Bradichinina



Meccanismo della fibrinolisi

