Angio-oedeem

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umcg

Angio-oedeem (AE)

Periodiek toenemende vasopermeabiliteit verklaard door een vaso-actieve mediator

Kliniek

- Non-pitting interstitieel oedeem
- Passagère gelokaliseerde zwelling

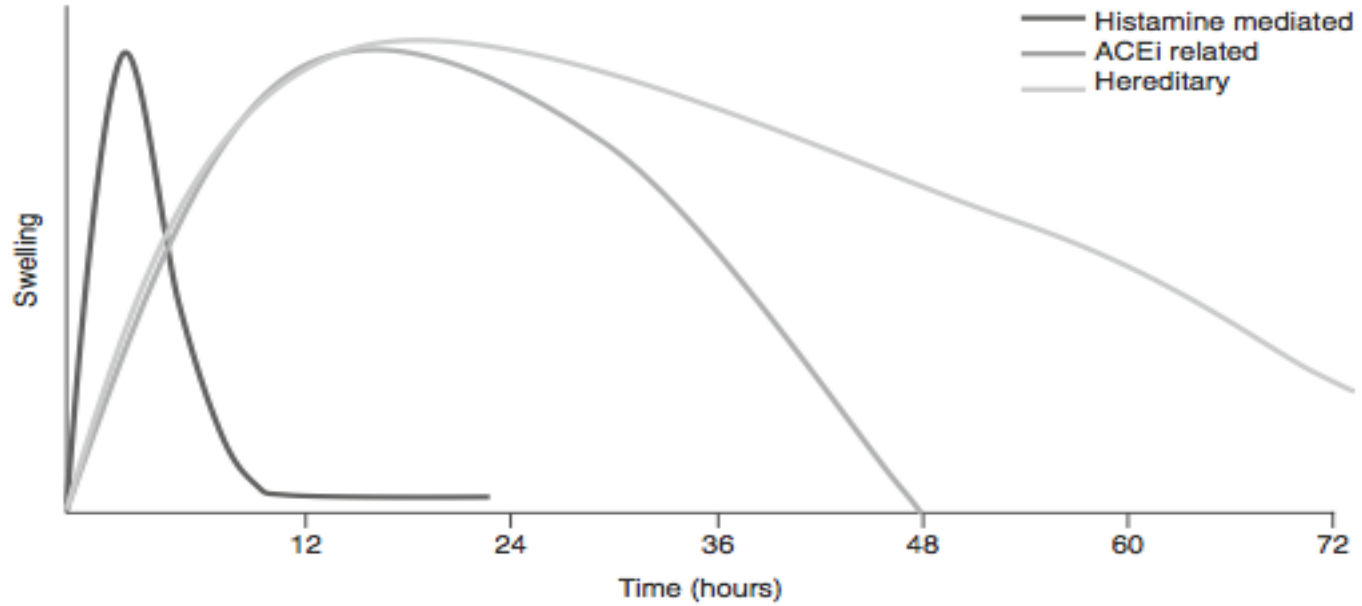
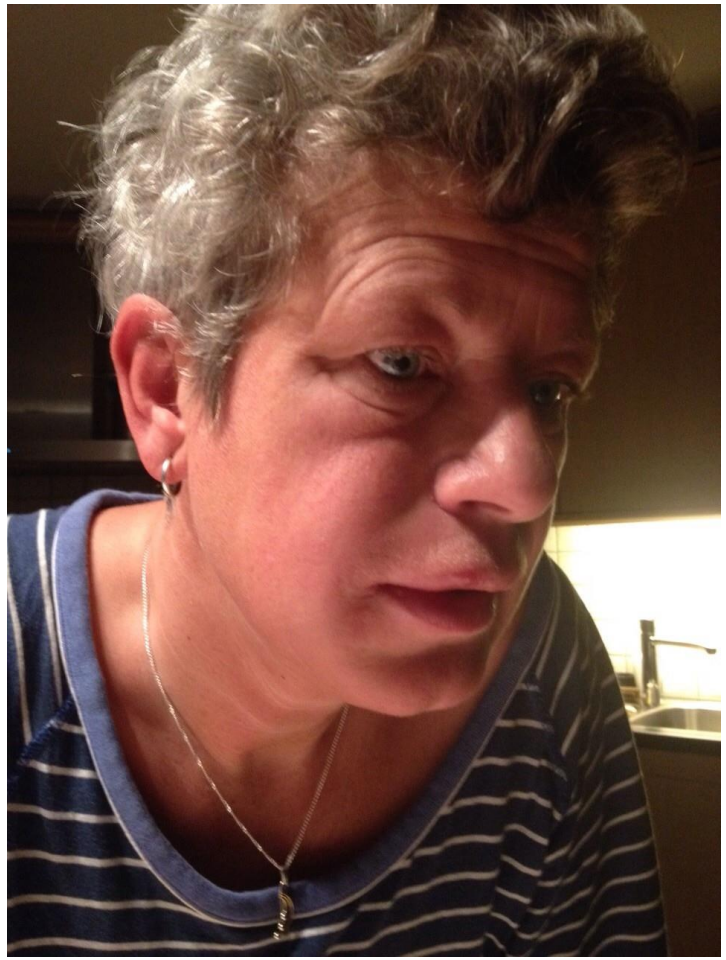
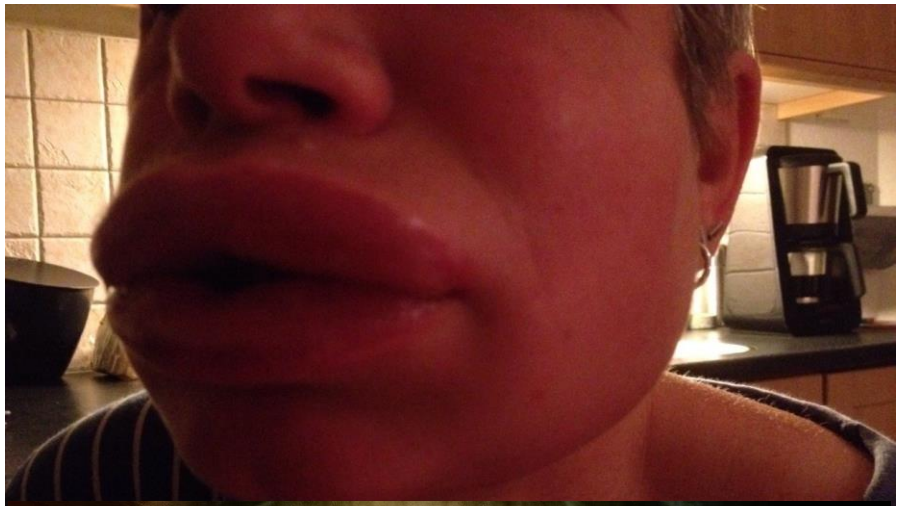


Fig. 4 Schematic representation of angioedema attack onset and duration. Histamine-mediated angioedema attacks tend to have rapid onset and resolution. Bradykinin-mediated angioedema usually develops more slowly and can persist for ≤5 days, although angiotensin-converting enzyme inhibitor (ACEi)–induced angioedema will usually resolve ≤48 h once the drug is discontinued

Casus Mw G.

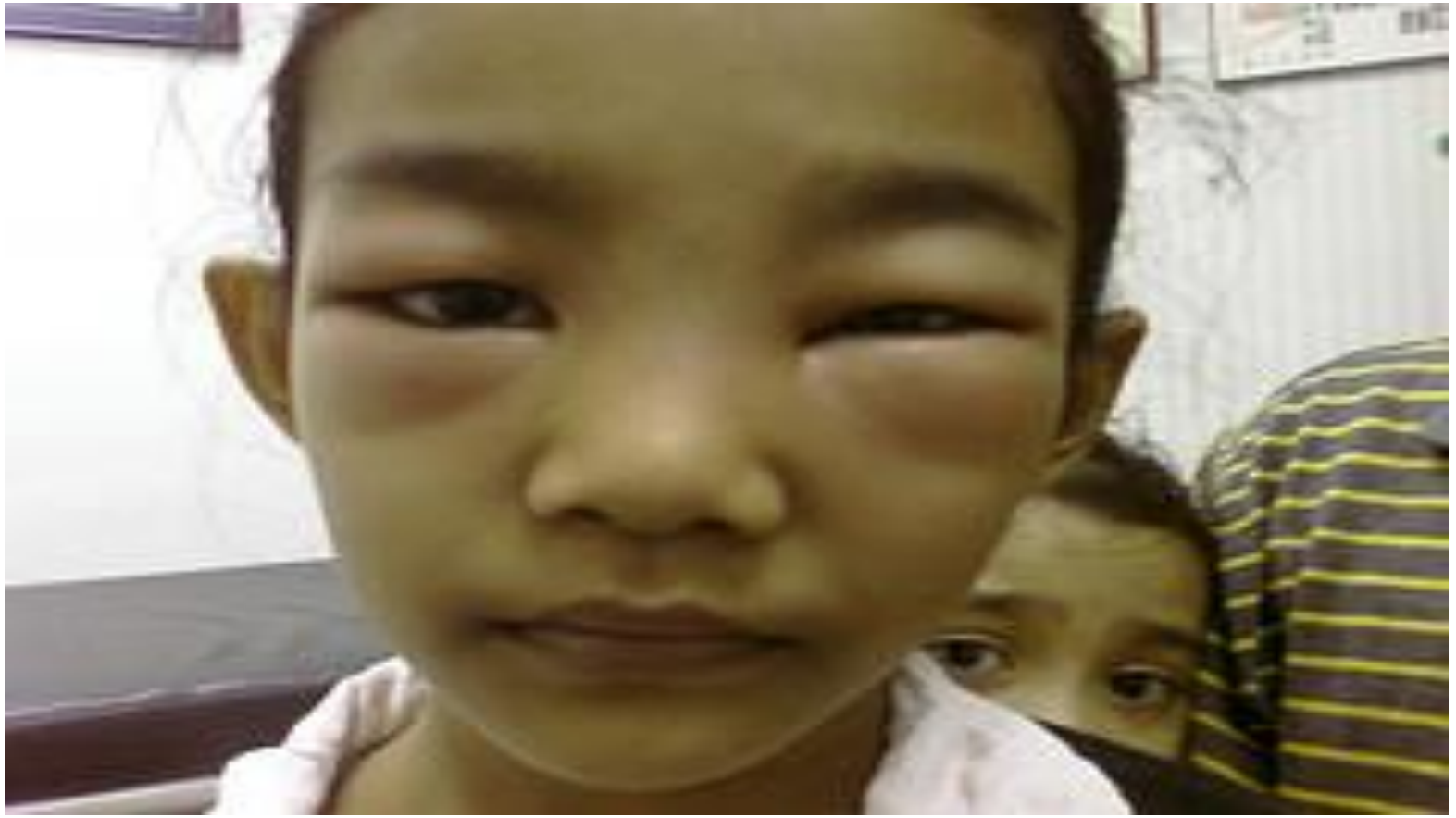




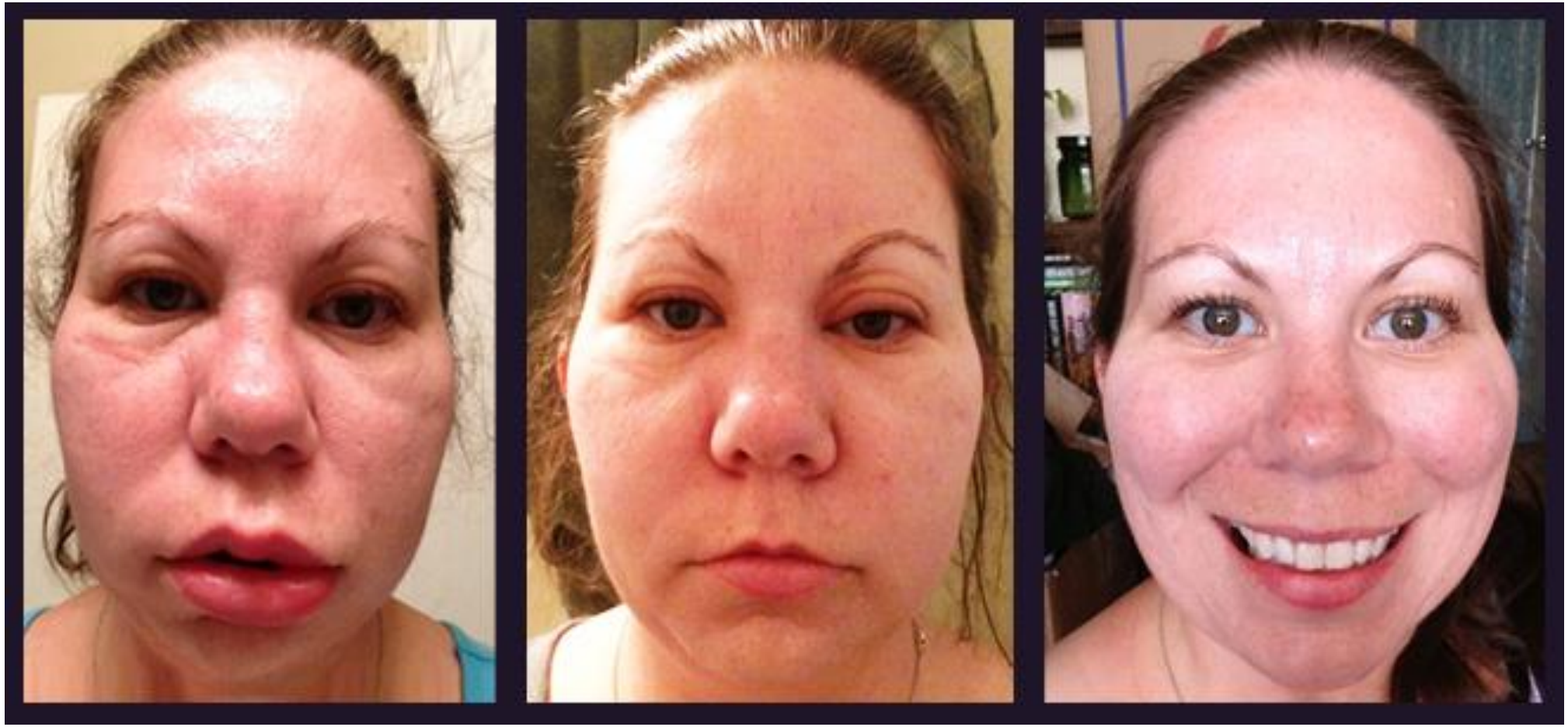
Casus Mw G.

2014	24 feb: Eerste bezoek poli IG / NCIA wgs "Quinckes-oedeem". Lab: Geen HAE-I-II, geen AAE, normaal tryptase, FXII-mutatie neg dus geen HAE-III. D-dimeer 1450 ng/mL. R/ Fexofenadine 180 mg 2xdd1 is dan ineffectief.
2014	17 apr: Op proef desloratidine 5 mg 3xdd1 en ranitidine 300 mg 1xdd1
2014	08 mei: Houdt veel klachten; op proef toevoegen tranexaminzezuur 500 mg 3xdd1.
2014	26 mei: Rapporteert 'geweldig effect van tranexaminezuur toevoeging'. D-dimeer < 500 mg/L. Hierop doorgaan tranexaminezuur en (wgs obstipatie), verlagen desloratidine naar 5 mg 2xdd1.
2014	25 aug: Gaat goed. Heeft het gevoel dat angio-oedeem onder controle is. Bij poging tot verlagen van dosis desloratidine wel meer jeuk. Daaroom nu (weer) als medicatie: - Tranexaminezuur (Cyclokapron) 500 mg 3xdd1, - Desloratidine 5mg 3 of 2xdd1 , - Ranitidine 300 mg 1xdd1.

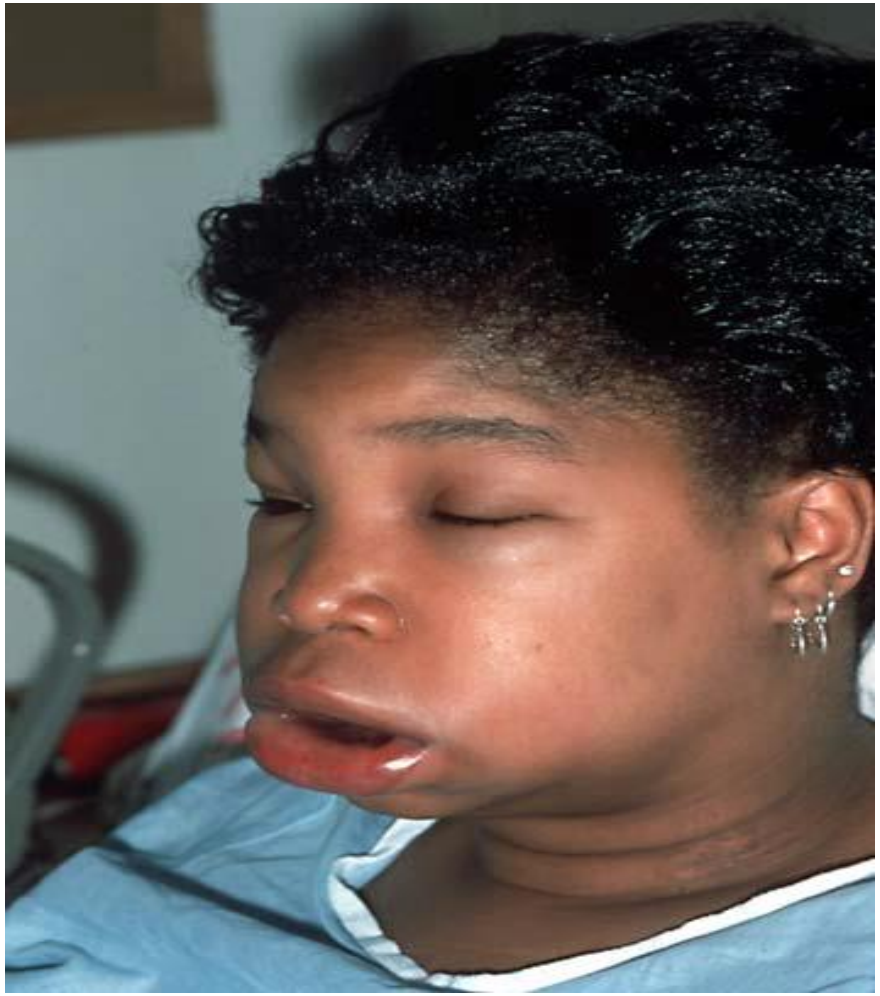
Géén angio-oedeem

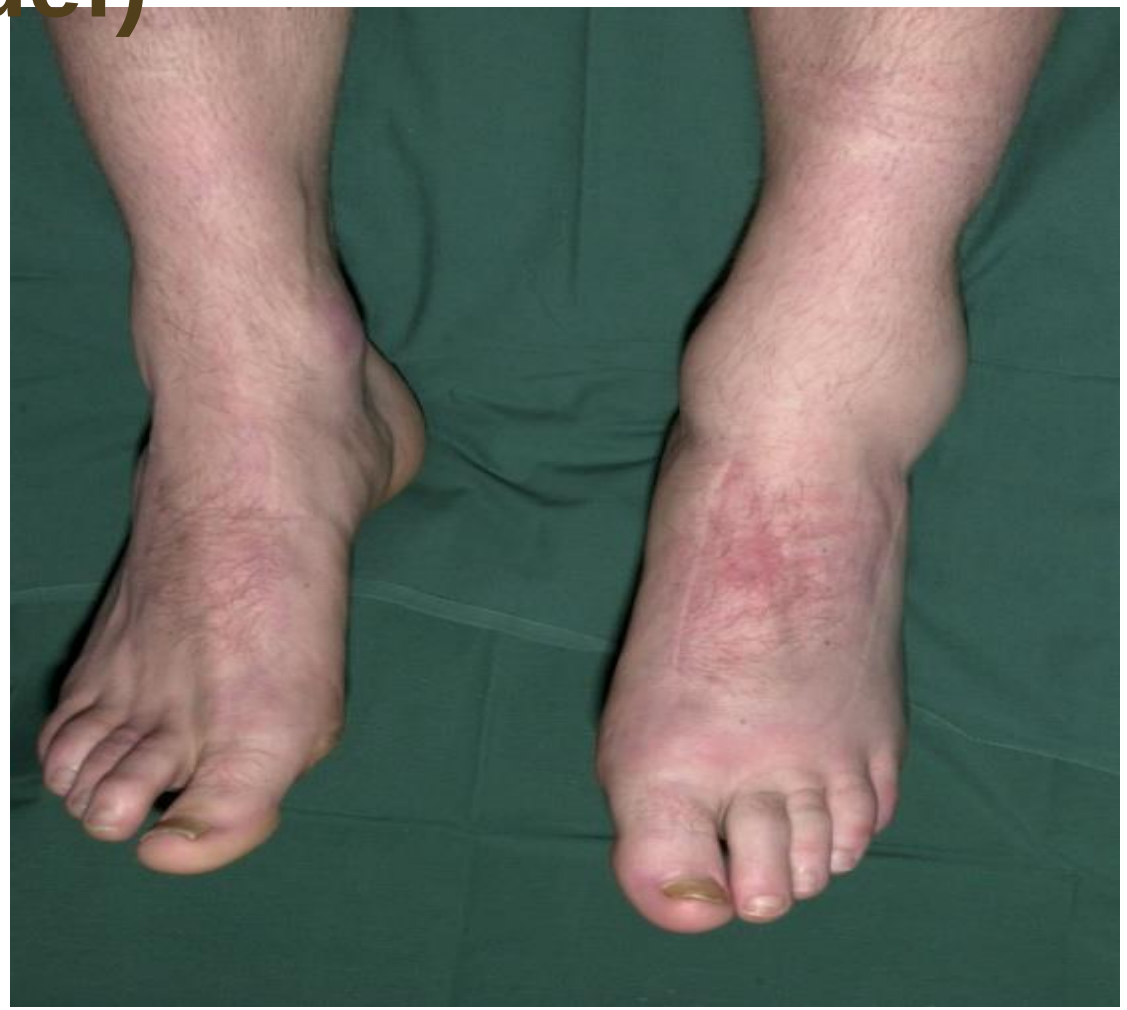


Urticaria en angioedeem



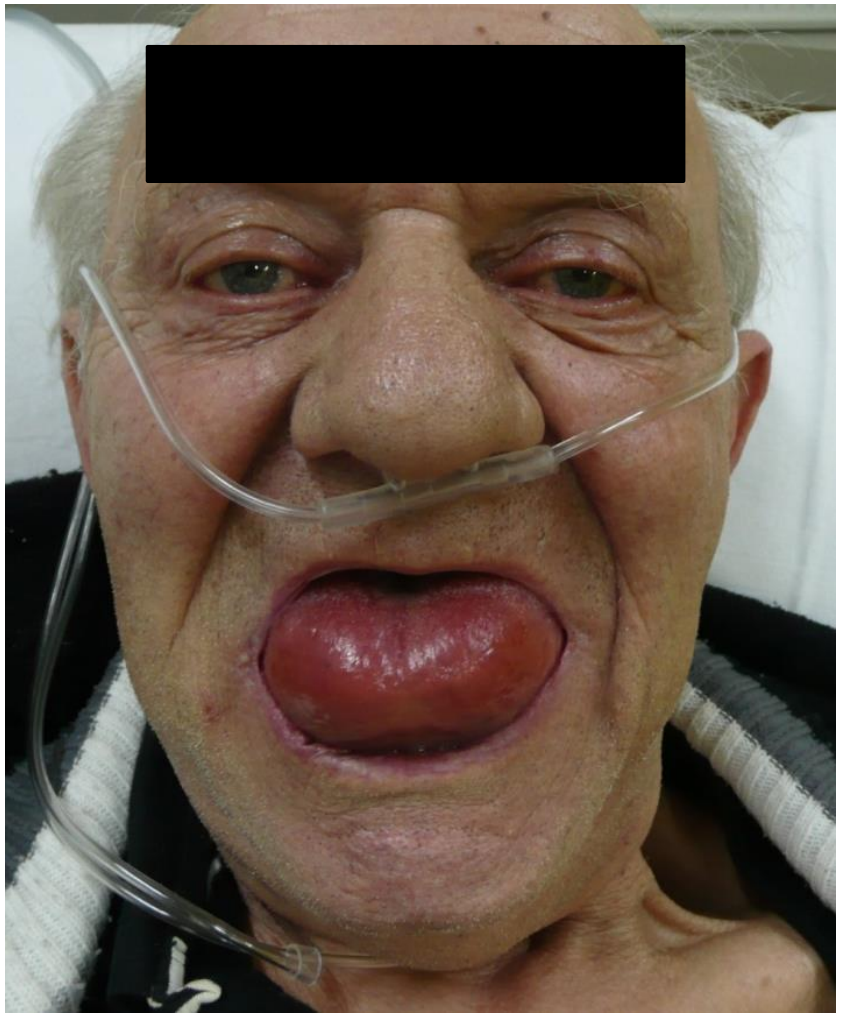
Wel angio-oedeem: Hereditair AE-I (C1-inh def) *

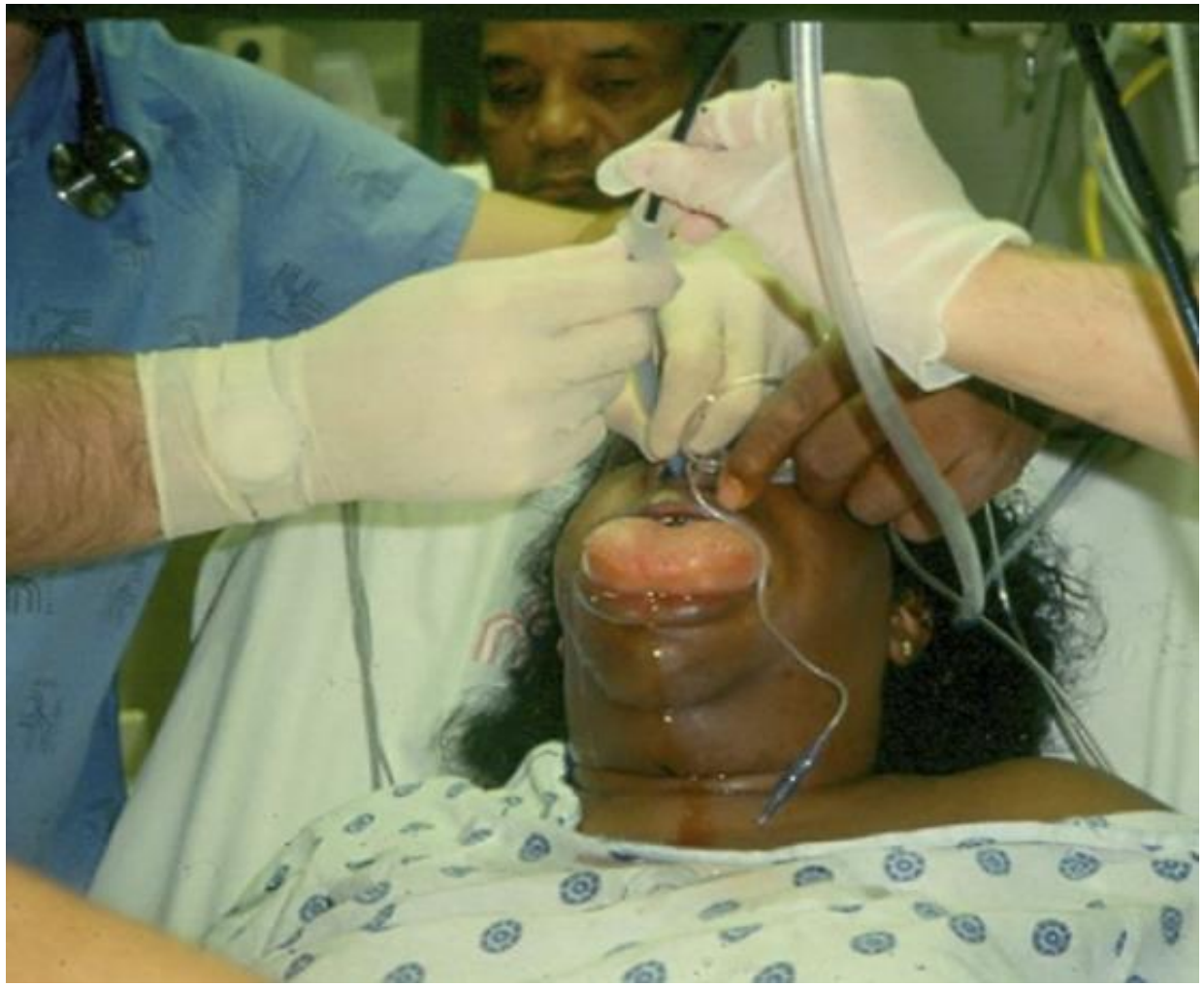




* Met toestemming van betrokkene

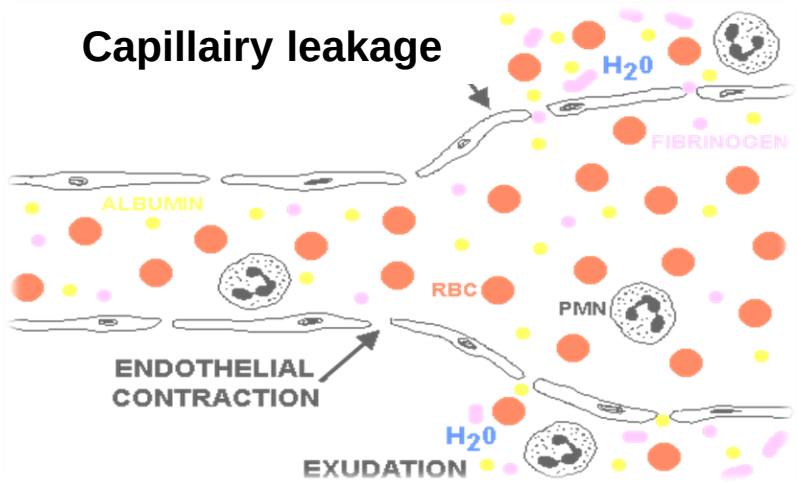
Wel angio-oedeem: ACE-remmer geassocieerd AE





AE – Mediatoren

Histamine
Mestcel-afhankelijk



Bradykinine
Zymogeen-afhankelijk

"Cytokine"
MacroØ/T-cel(?)-afhankelijk

AE – Klinische kenmerken

jeuk ⟷ geen jeuk

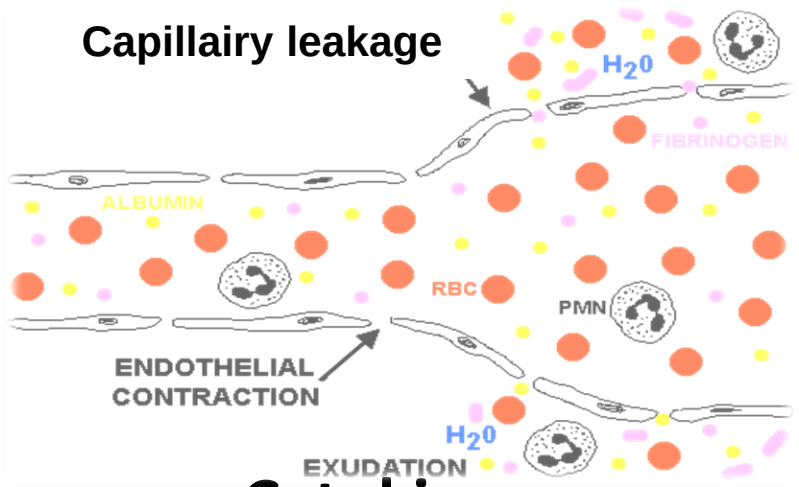
lokaal ↕ gegeneraliseerd

geen koorts ↕ koorts

urticae ⟷ geen urticae

Histamine

Mestcel-afhankelijk



Bradykinine

Pro-enzym(Zymogeen)-afhankelijk

"Cytokine"

MacroØ/T-cel(?)-afhankelijk

M. Van Deuren

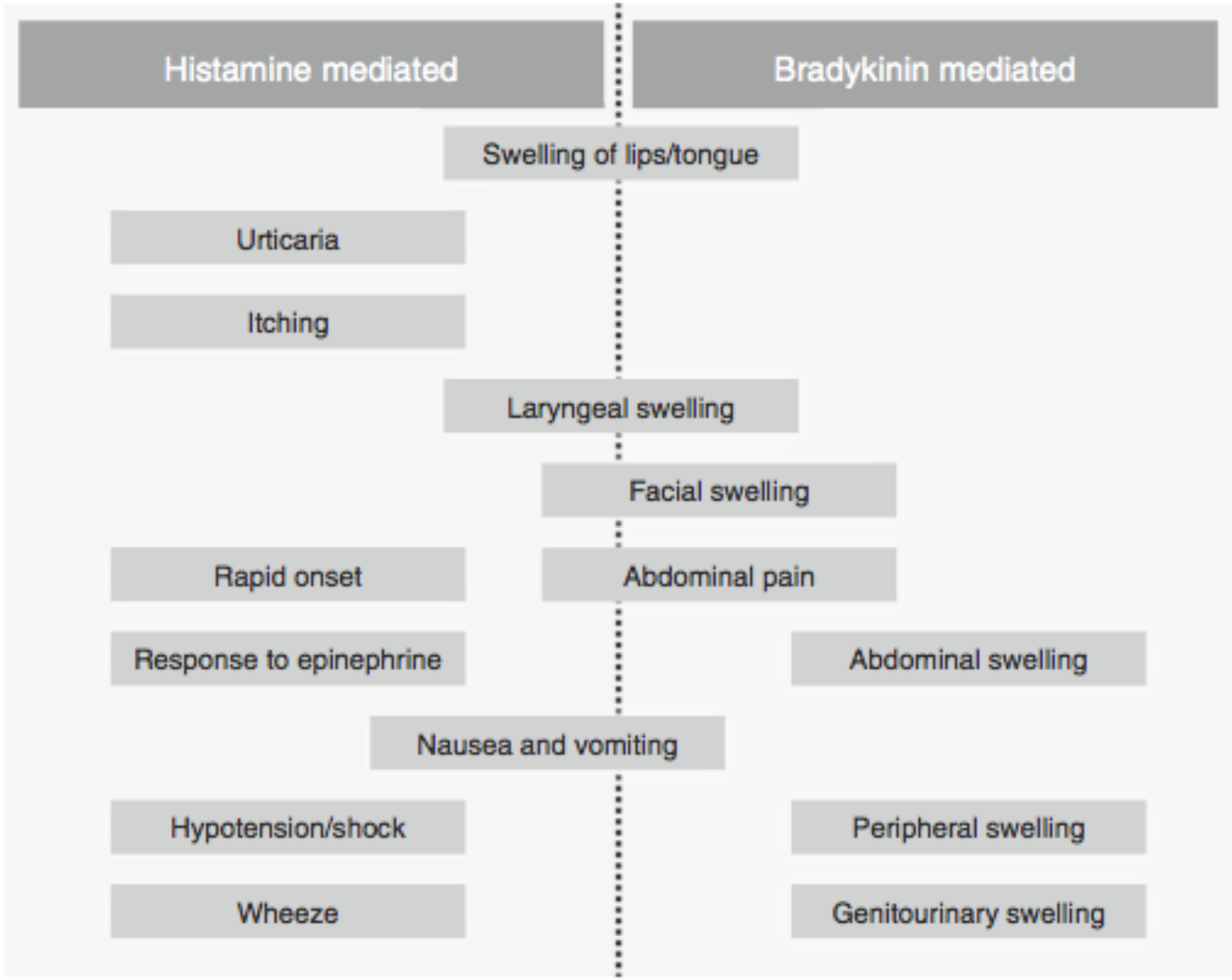
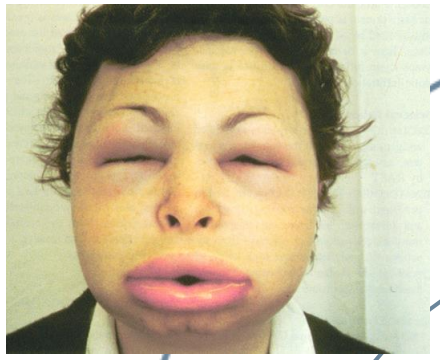


Fig. 3 Distinguishing histamine- versus bradykinin-mediated angioedema

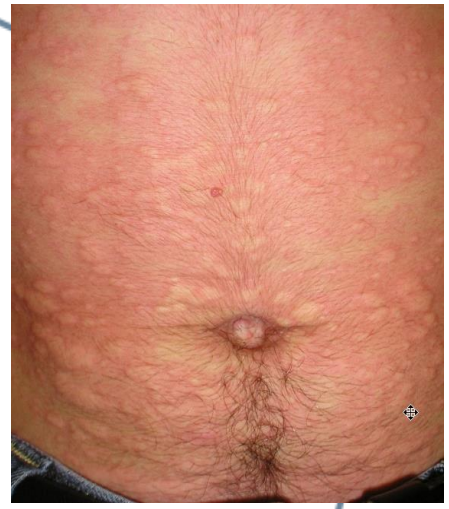
Angioedeem / urticaria

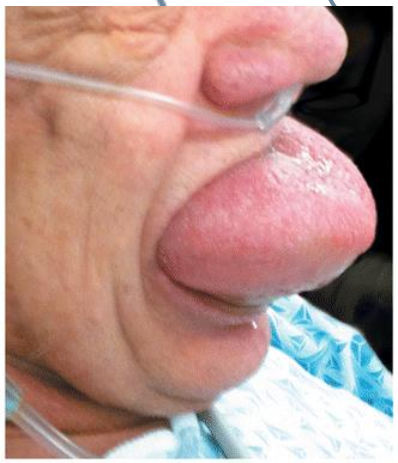


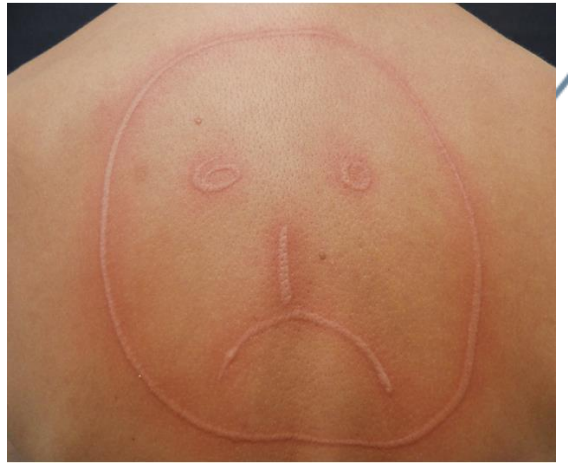
10

50

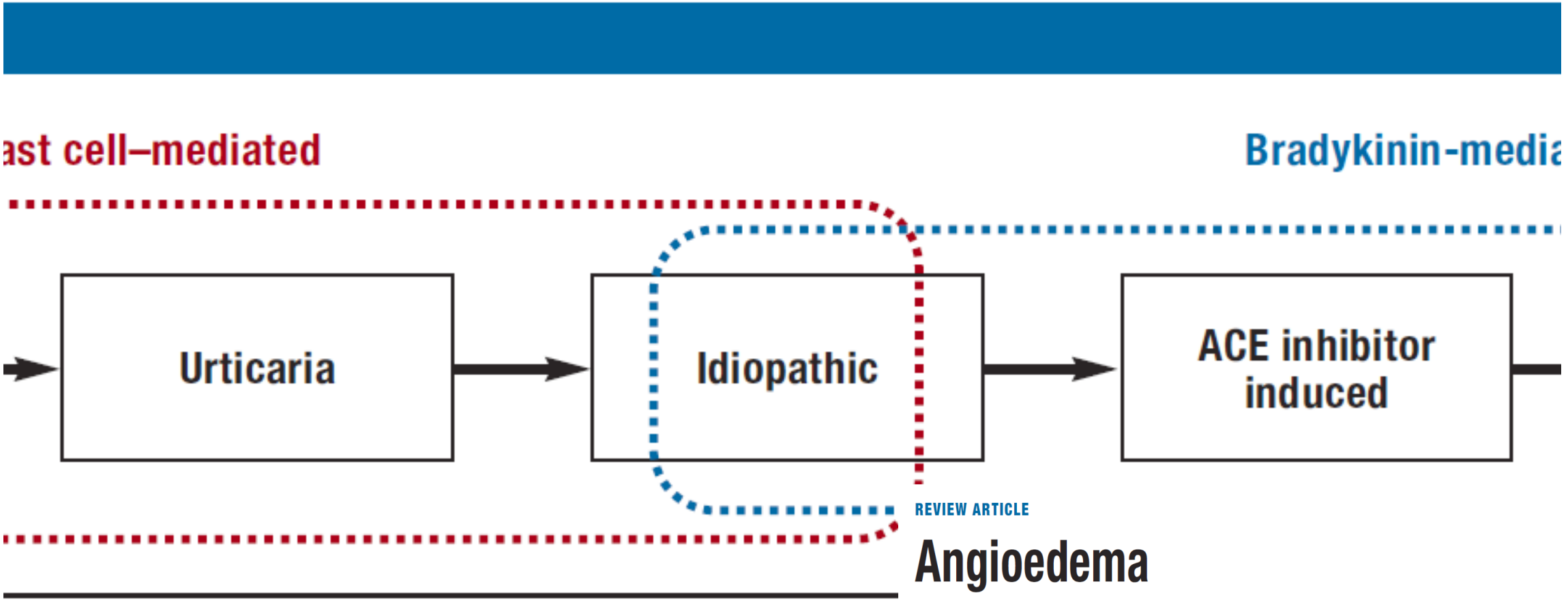
40







Angioedeem - mechanisme

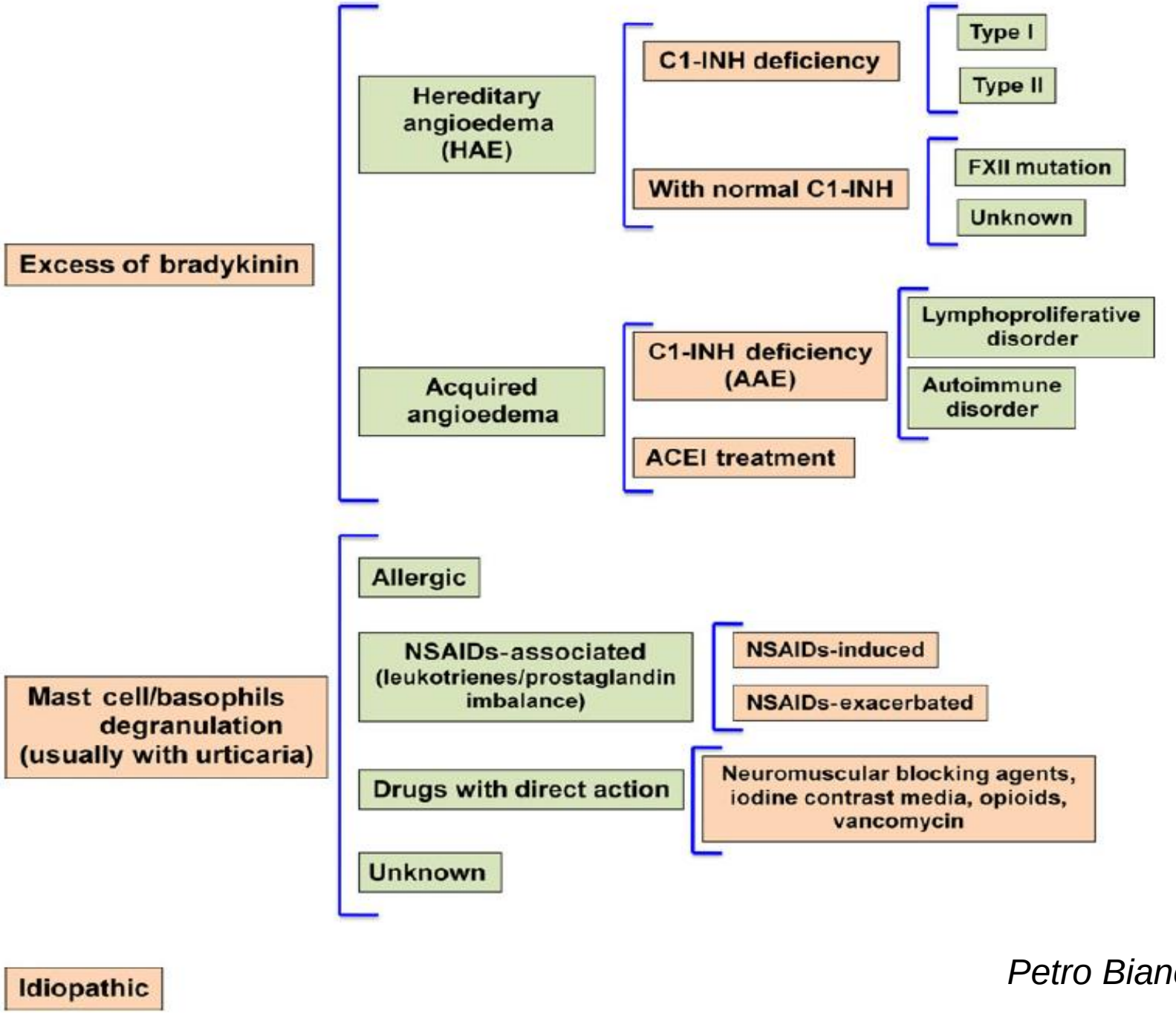


REVIEW ARTICLE

Angioedema

An Interdisciplinary Emergency

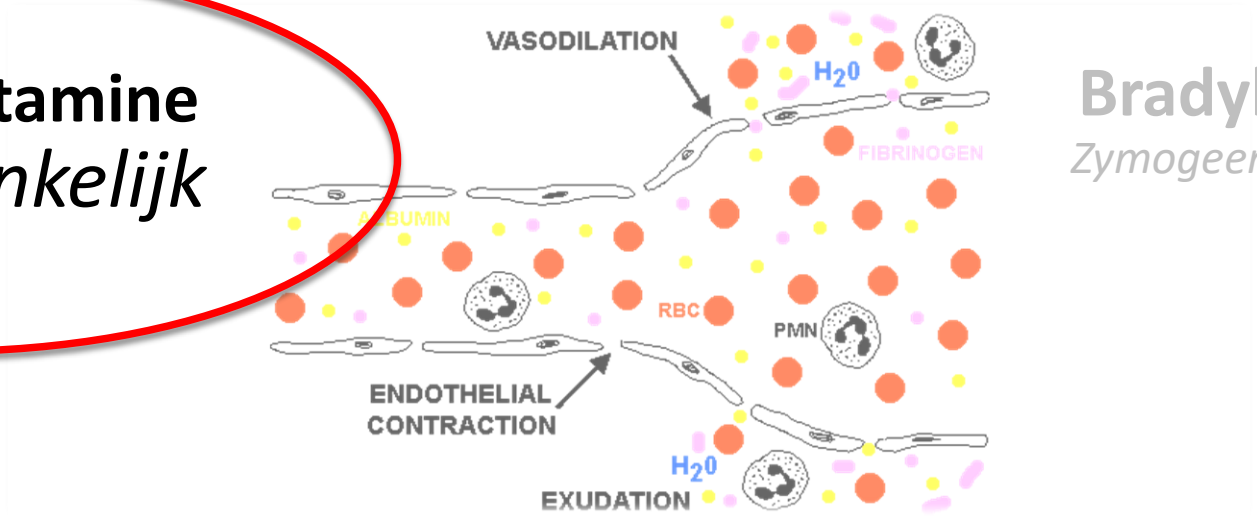
Janina Hahn, Thomas K. Hoffmann, Bastian Bock, Melanie Nordmann-Kleiner, Susanne Trainotti, Jens Greve



Petro Bianchi CEA 2015

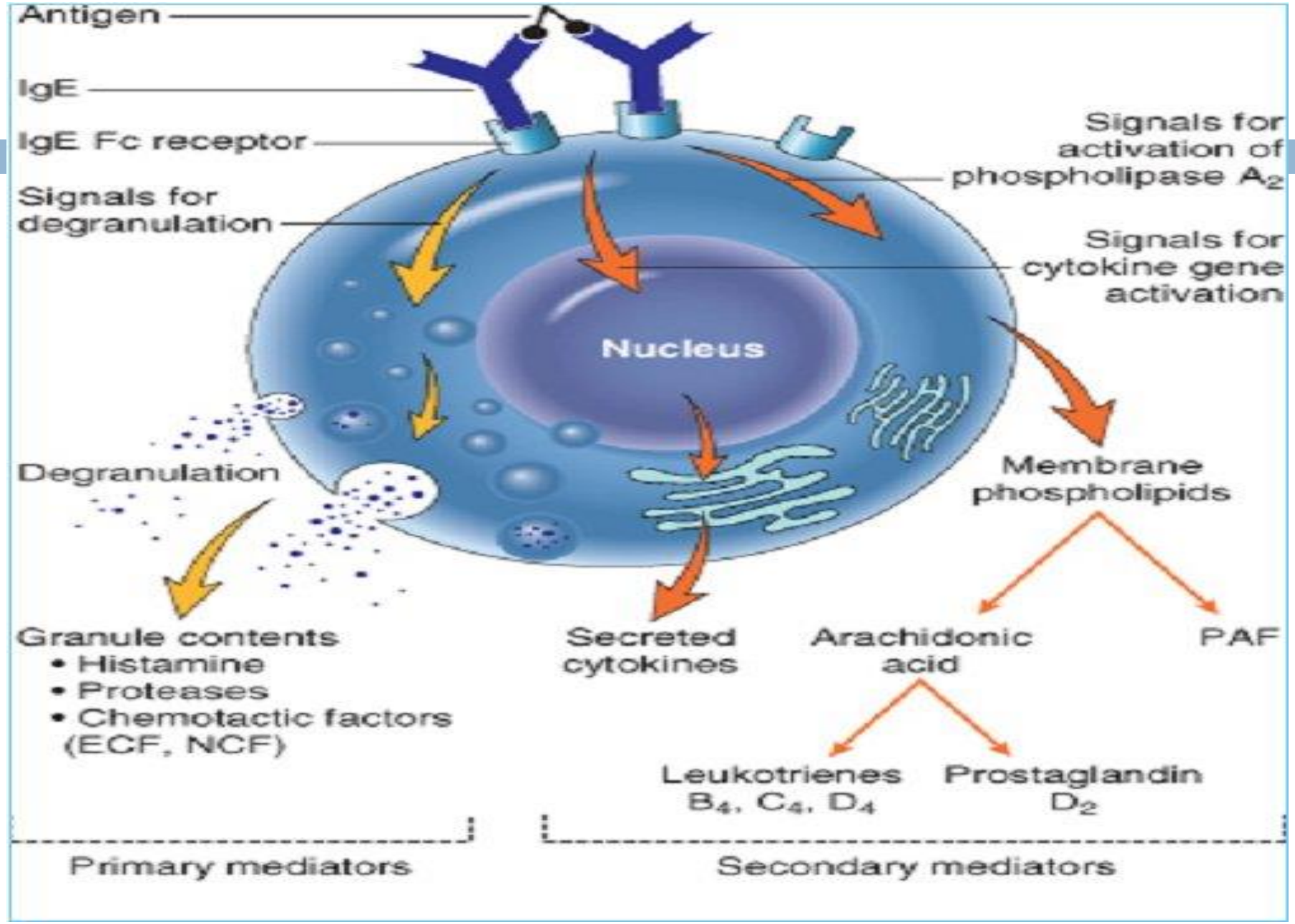
Angioedeem - mediatoren

Histamine
Mestcel-afhankelijk

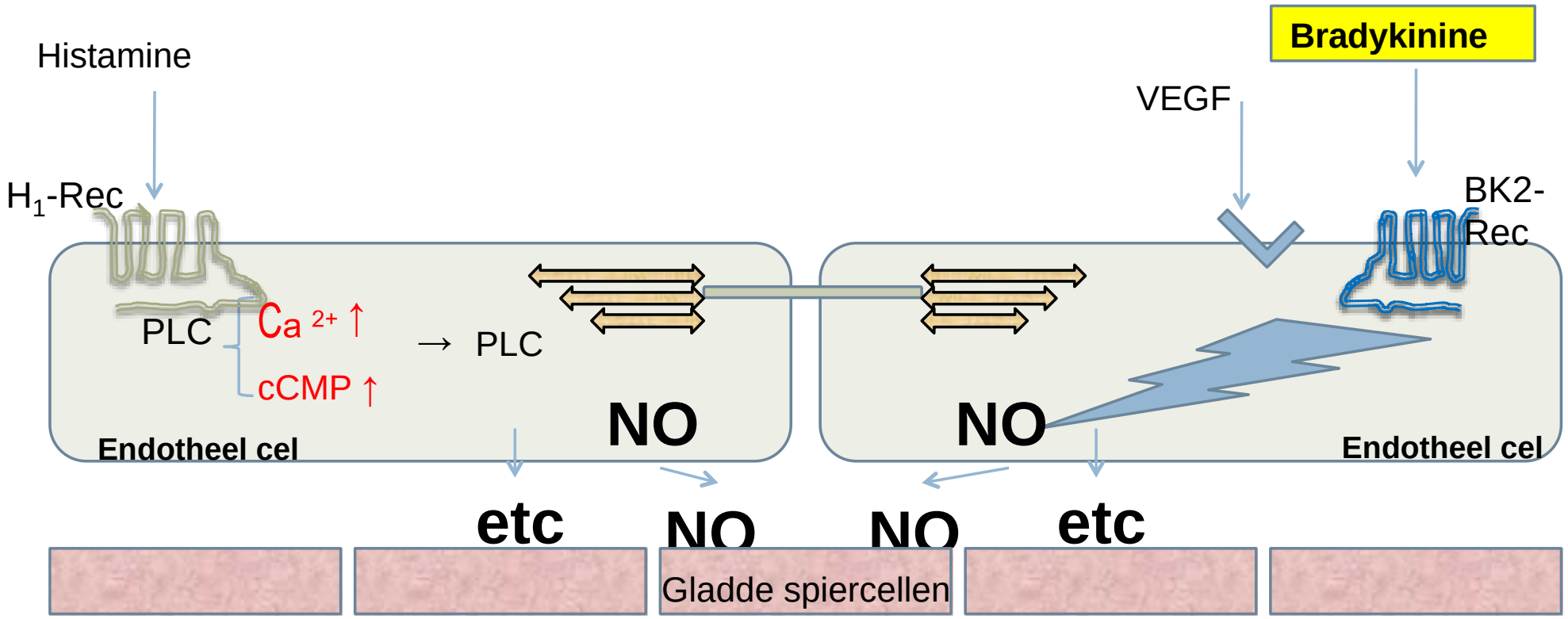


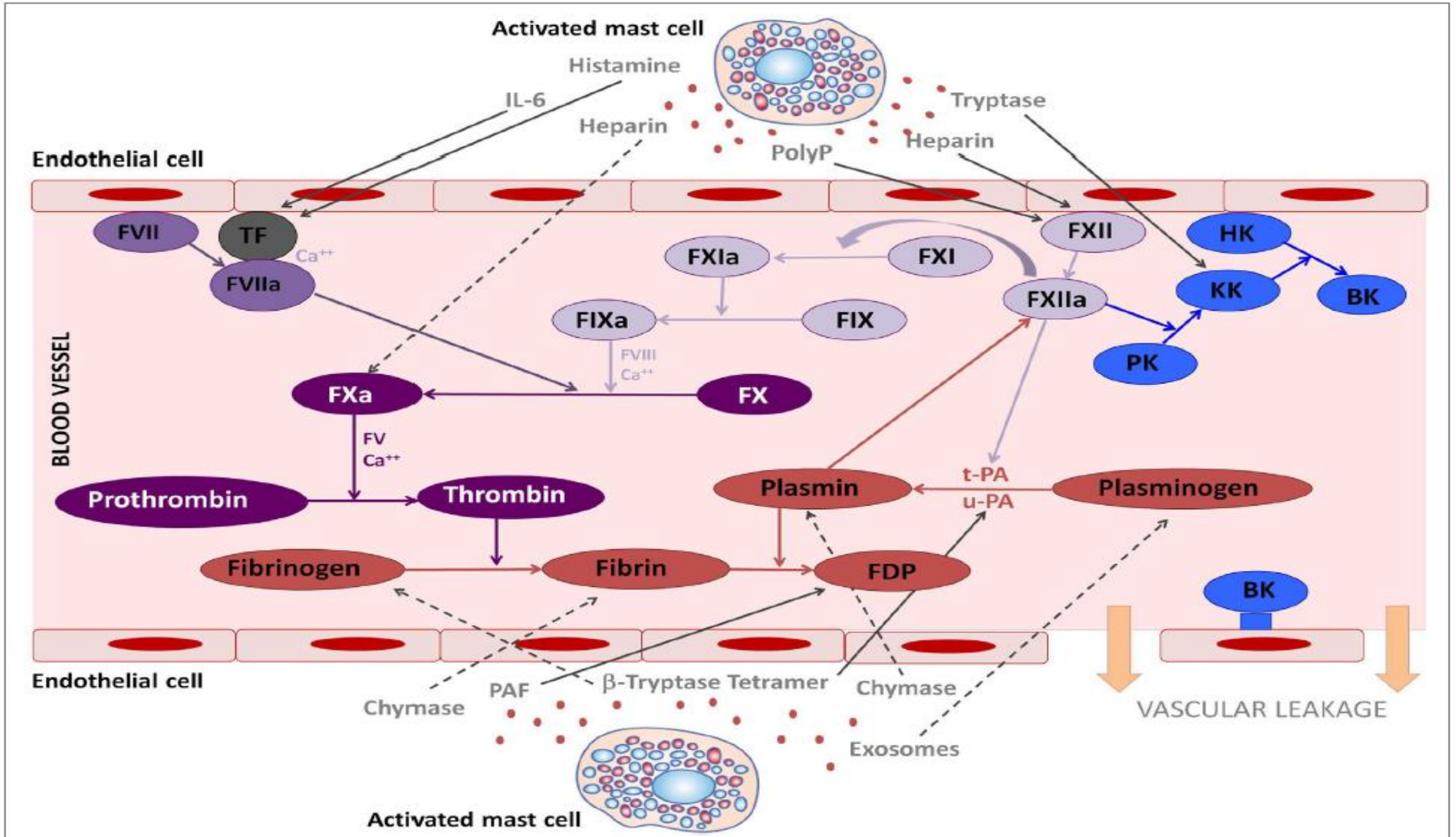
Bradykinine
Zymogeen-afhankelijk

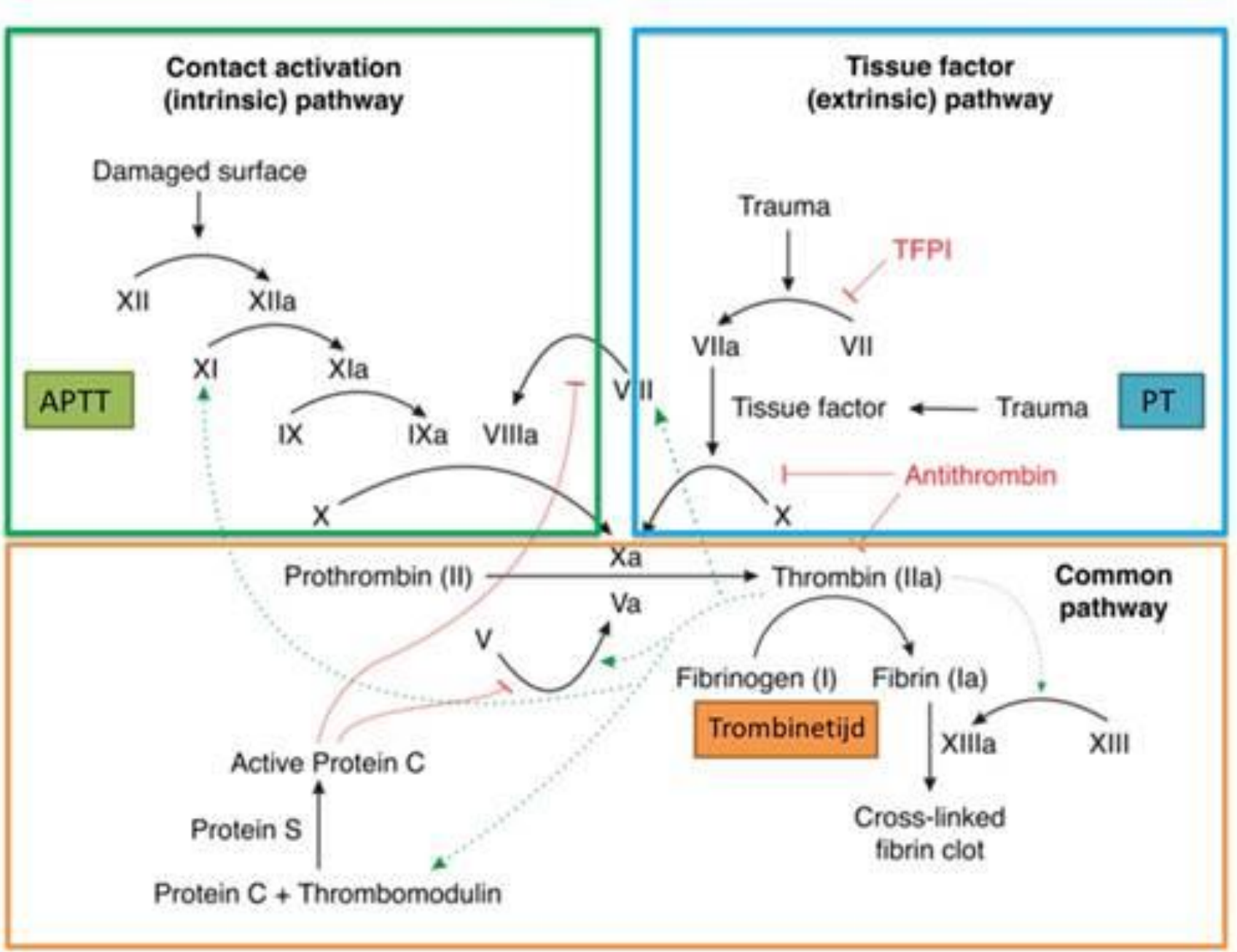
“Cytokine”
MacroØ/T-cel(?)-afhankelijk


Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for activation of phospholipase A_2
Signals for cytokine gene activation
Nucleus
Degranulation
Membrane phospholipids
Granule contents
• Histamine
• Proteases
• Chemotactic factors (ECF, NCF)
Secreted cytokines
Arachidonic acid
PAF
Leukotrienes B_4, C_4, D_4
Prostaglandin D_2
Primary mediators
Secondary mediators

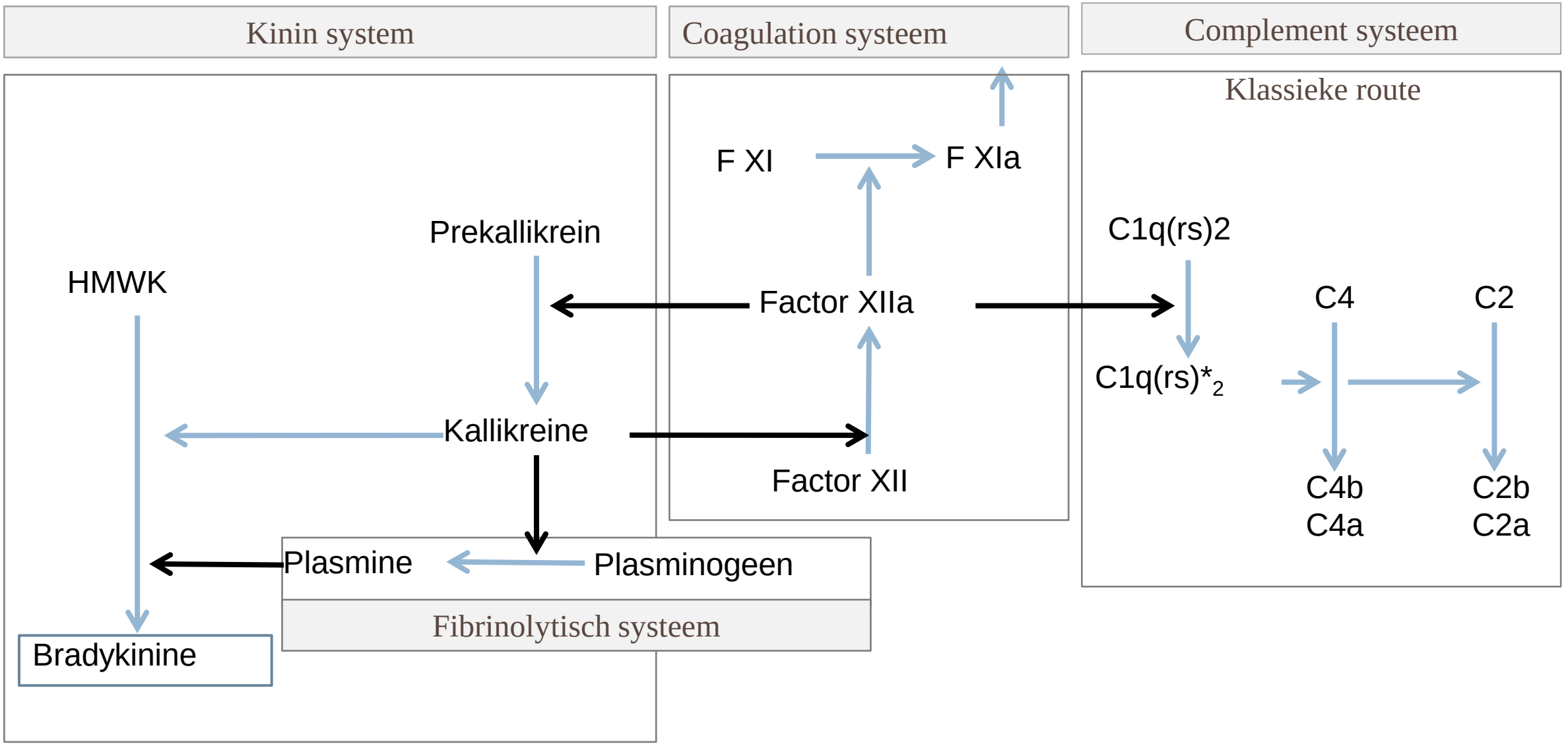
Werking histamine

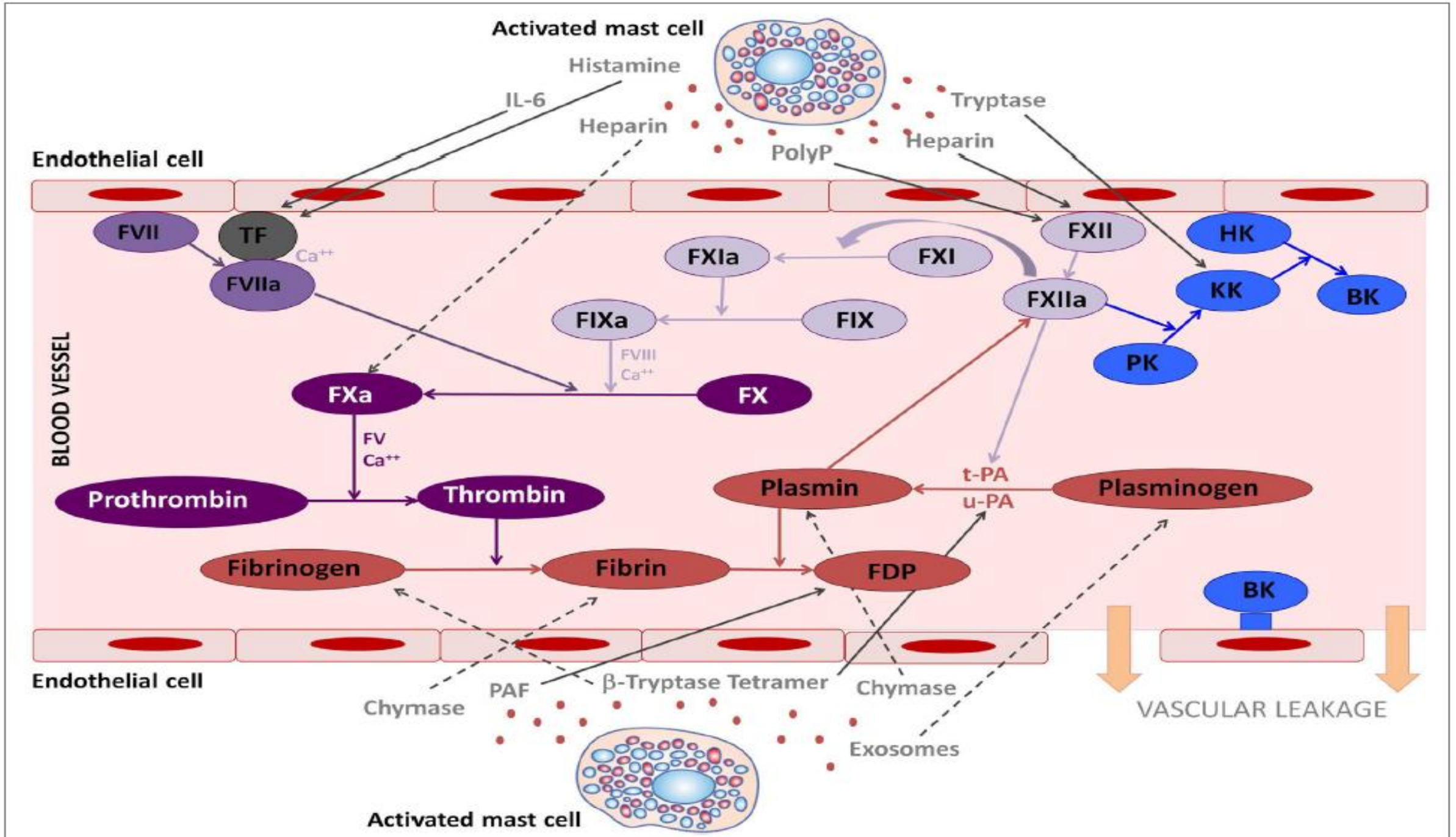



Activated mast cell
Histamine
IL-6
Heparin
Tryptase
Heparin
PolyP
Endothelial cell
FVII
TF
Ca++
FVIIa
FXIa
FXI
FXII
HK
KK
BK
FXIIa
FIXa
FIX
PK
FVIII
Ca++
BLOOD VESSEL
FXa
FX
FV
Ca++
Prothrombin
Thrombin
Plasmin
t-PA
u-PA
Plasminogen
Fibrinogen
Fibrin
FDP
BK
Endothelial cell
Chymase
PAF
β-Tryptase Tetramer
Chymase
VASCULAR LEAKAGE
Exosomes
Activated mast cell


Contact activation
(intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
APTT
Tissue factor
(extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
PT
Antithrombin
X
VII
Xa
Prothrombin (II)
Thrombin (IIa)
Common
pathway
Va
V
Fibrinogen (I)
Fibrin (Ia)
Trombinetijd
XIIIa
XIII
Cross-linked
fibrin clot
Active Protein C
Protein S
Protein C + Thrombomodulin

Diverse cascades




Activated mast cell
Histamine
IL-6
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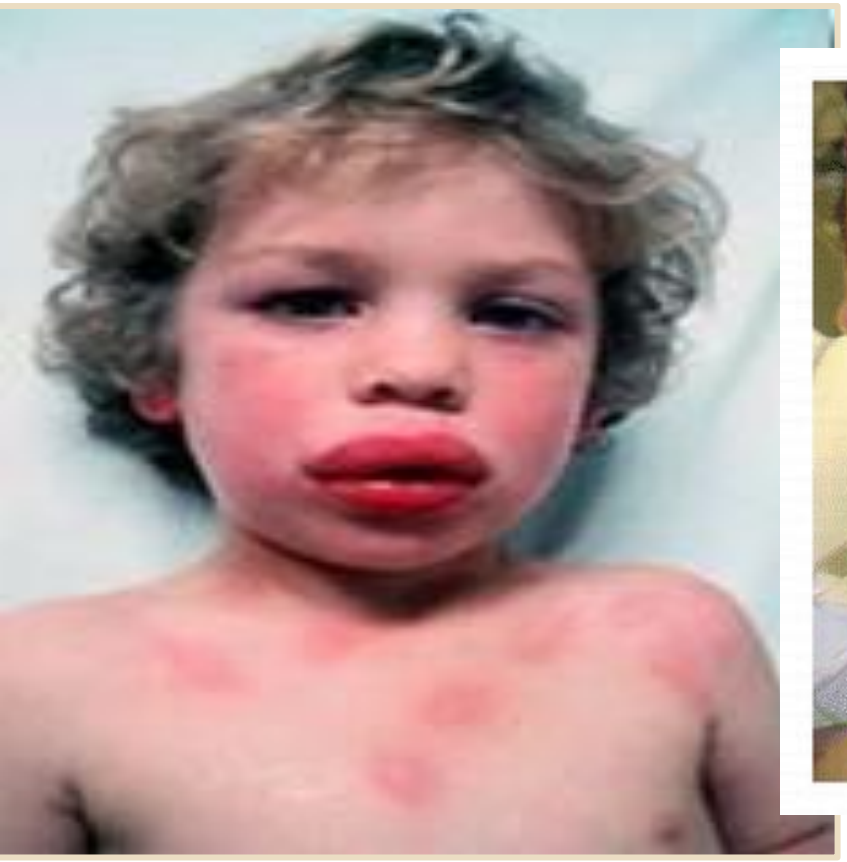
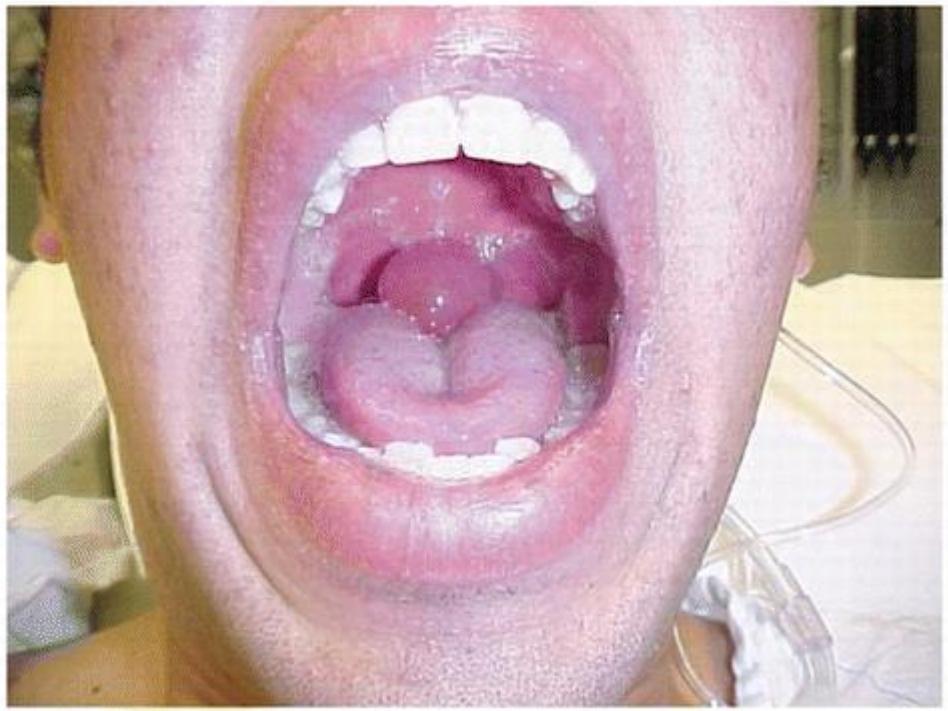
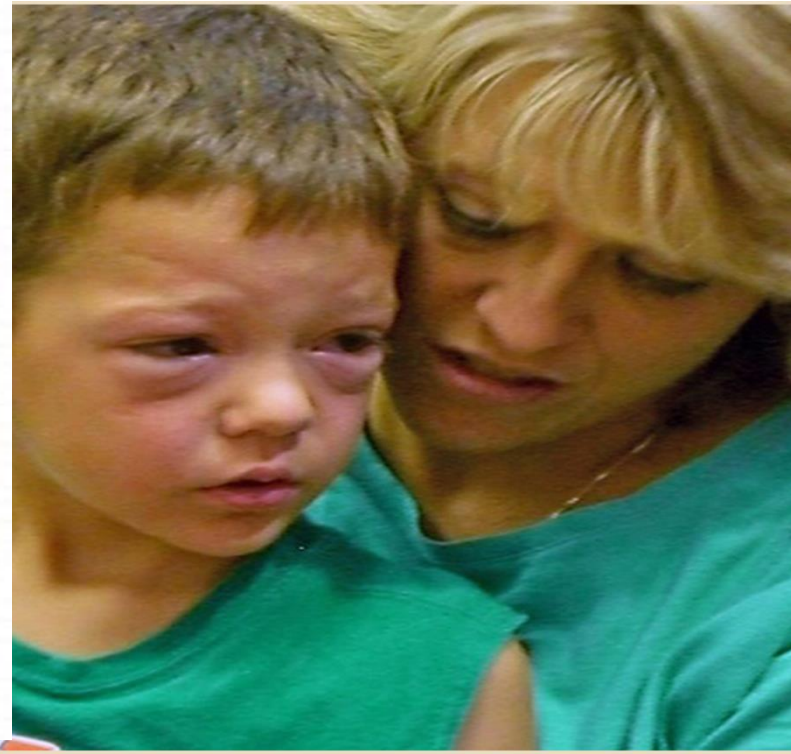
FXIIa
FIXa
FIX
PK
FVIII
Ca++
BLOOD VESSEL
FXa
FX
FV
Ca++
Prothrombin
Thrombin
Plasmin
t-PA
u-PA
Plasminogen
Fibrinogen
Fibrin
FDP
BK
Endothelial cell
Chymase
PAF
β-Tryptase Tetramer
Chymase
VASCULAR LEAKAGE
Exosomes
Activated mast cell

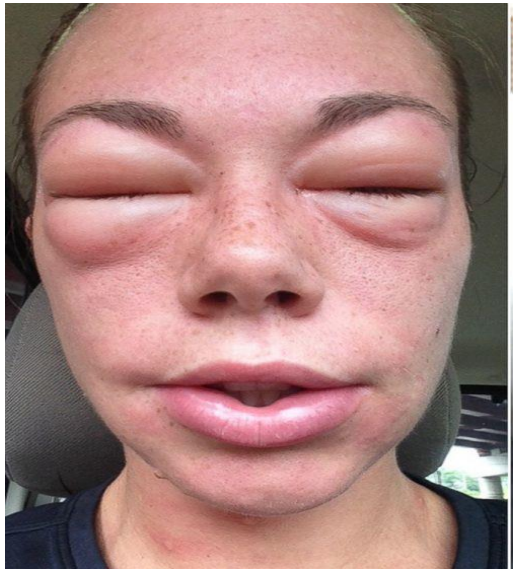
IgE gemedieerd

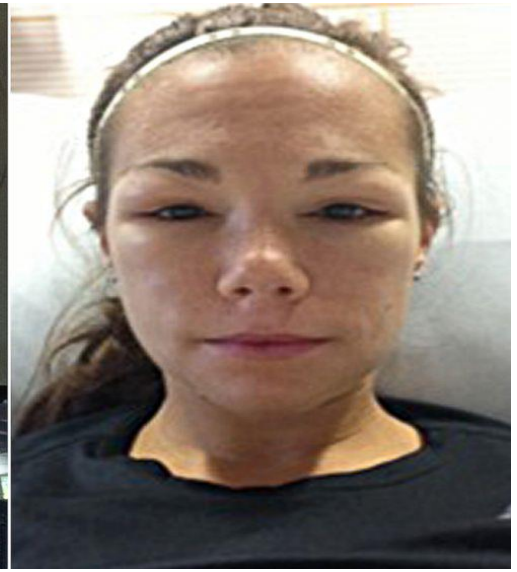






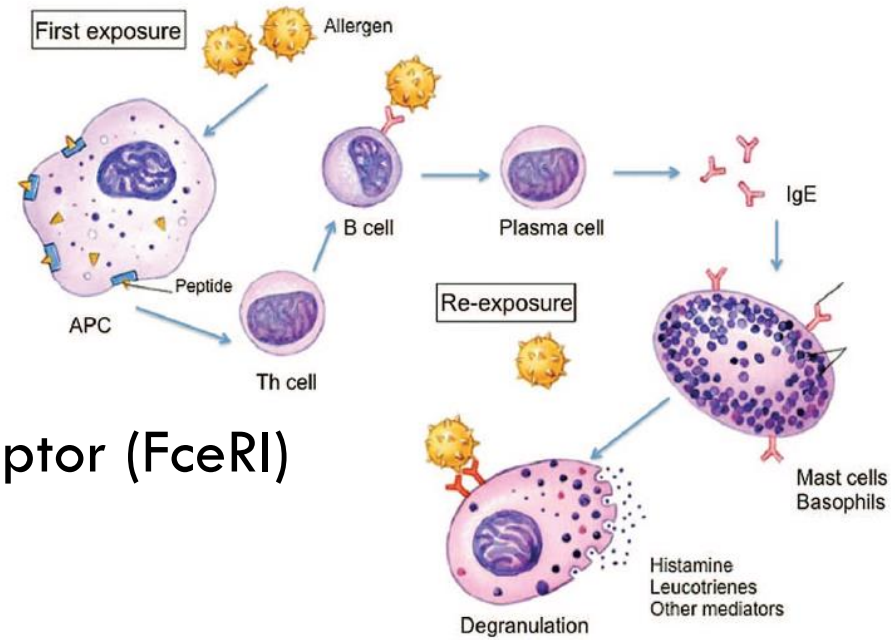
IgE gemedieerd; omega-5-gliadine





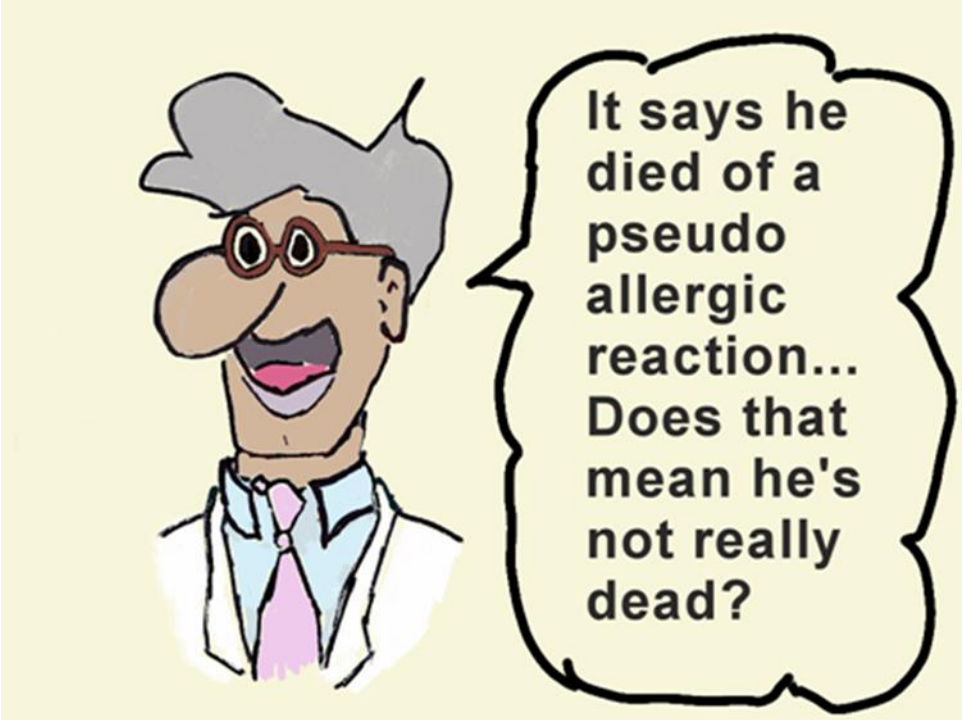
1. Mestcel/Histamine mediated angioedema

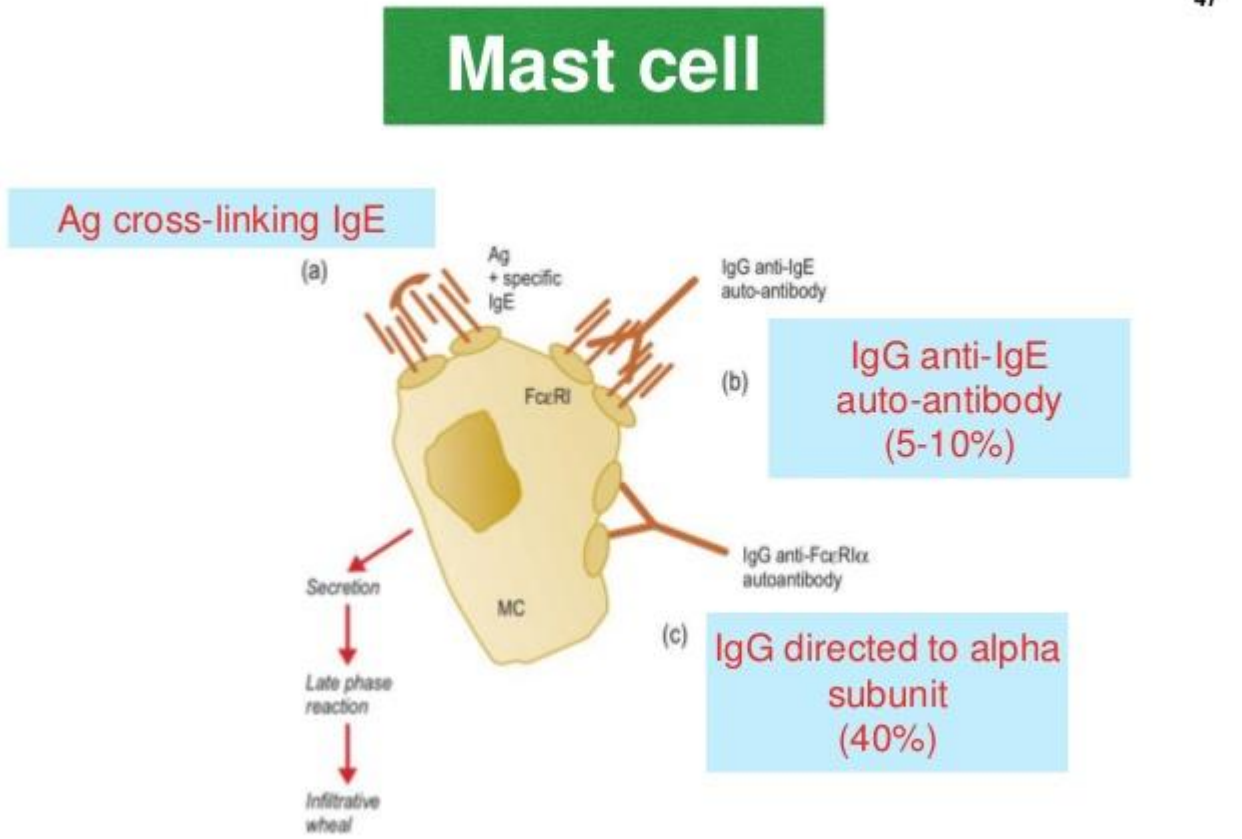
- Type I / IgE mediated



- Autoantibodies against mast cell IgE receptor (FceRI)
- Complement
- IgG mast cell receptors
- Non-immunological triggers (physical factors, opioids, ethanol)

Autoantibodies against mast cell IgE receptor (FceRI)





Sarbjit S. Saini. Middleton's 8th edition.
Lajos Kemeny. Hindawi Publishing Corporation Dermatology Research and Practice Volume 2014.

Cross talk tussen kallikreine en complementsysteem

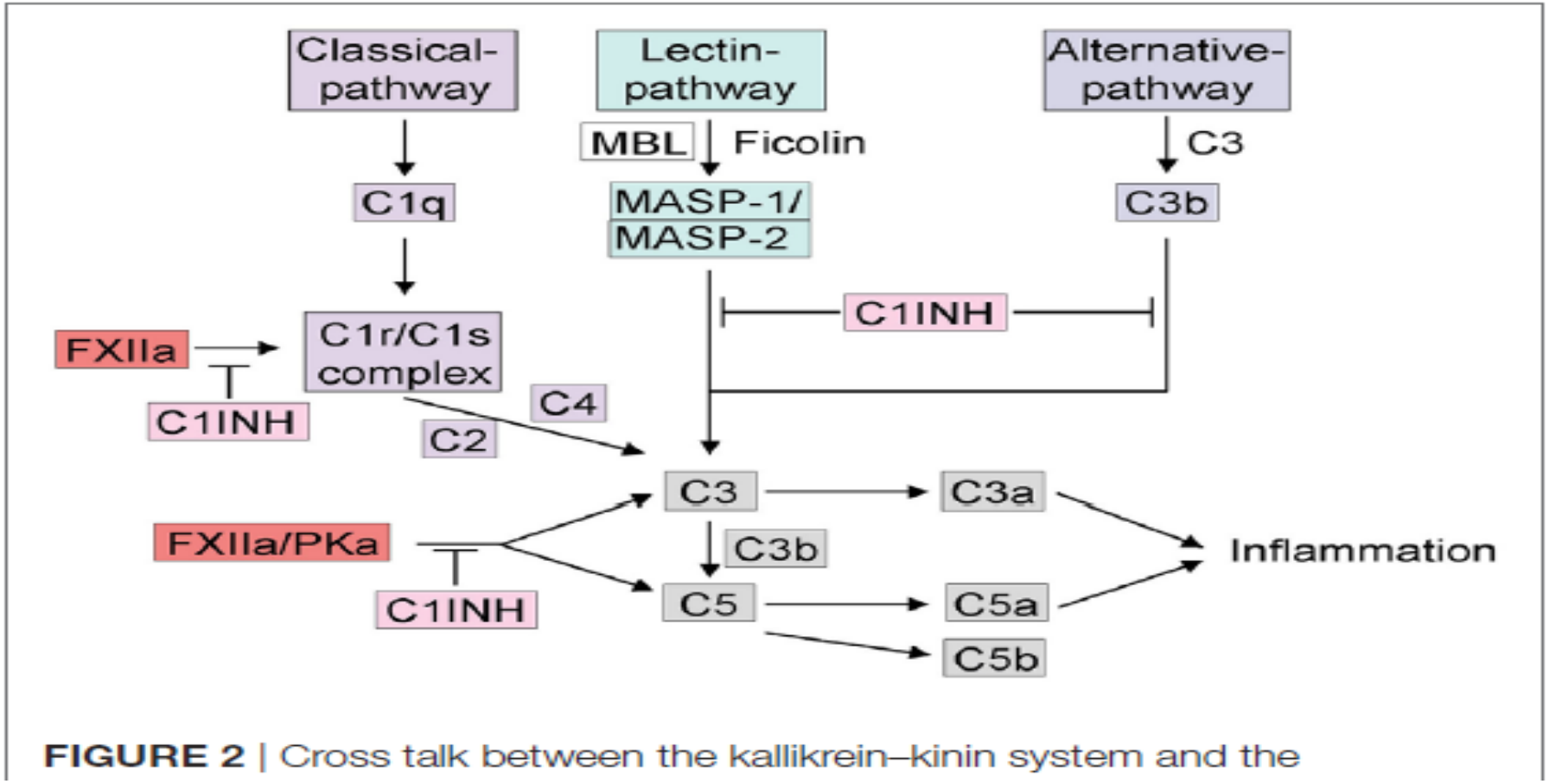
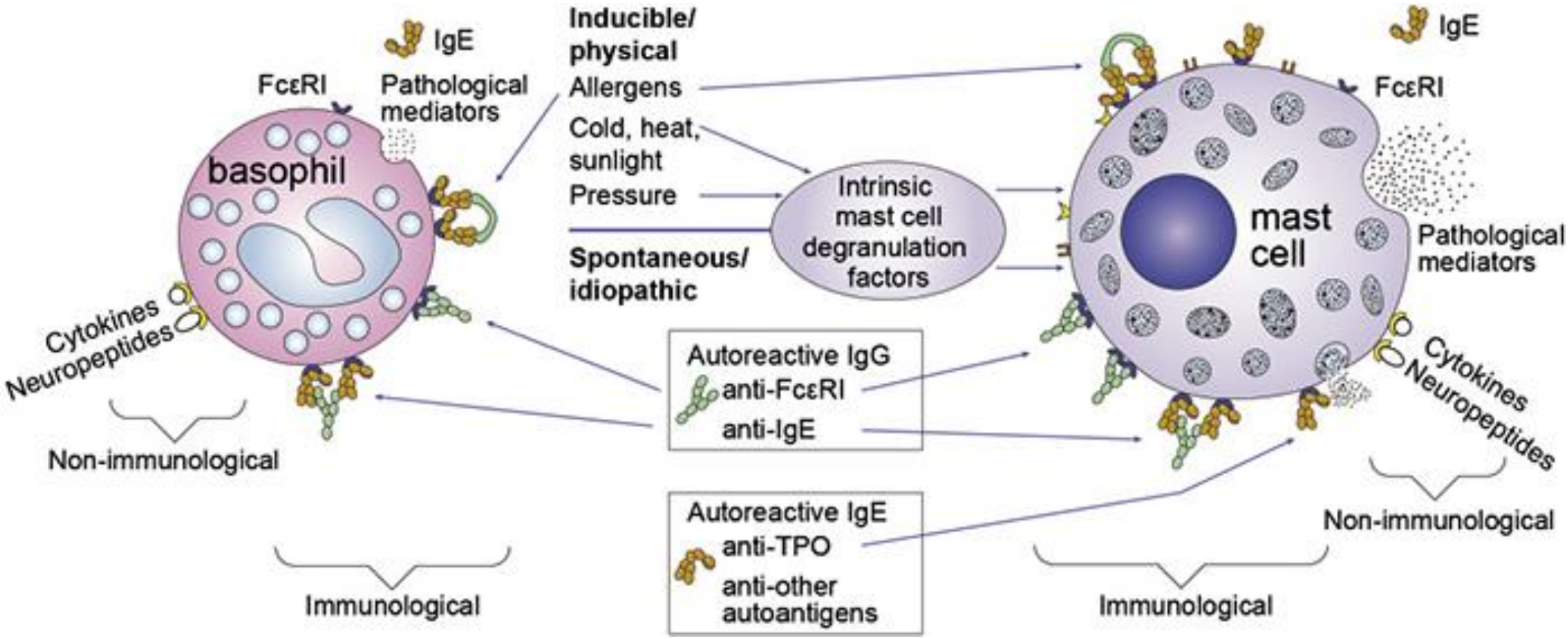
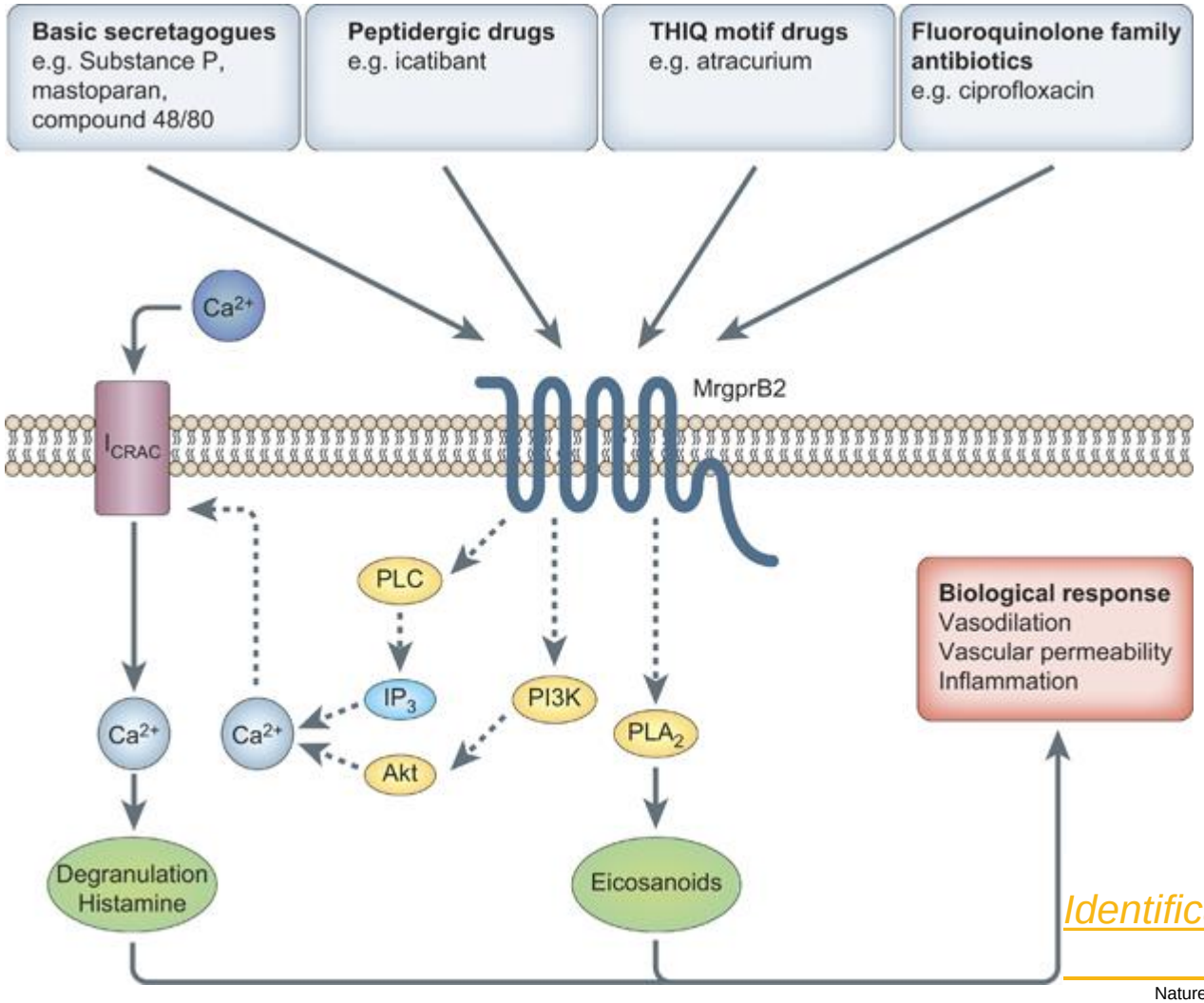


FIGURE 2 | Cross talk between the kallikrein–kinin system and the

IgG en niet-immunologisch



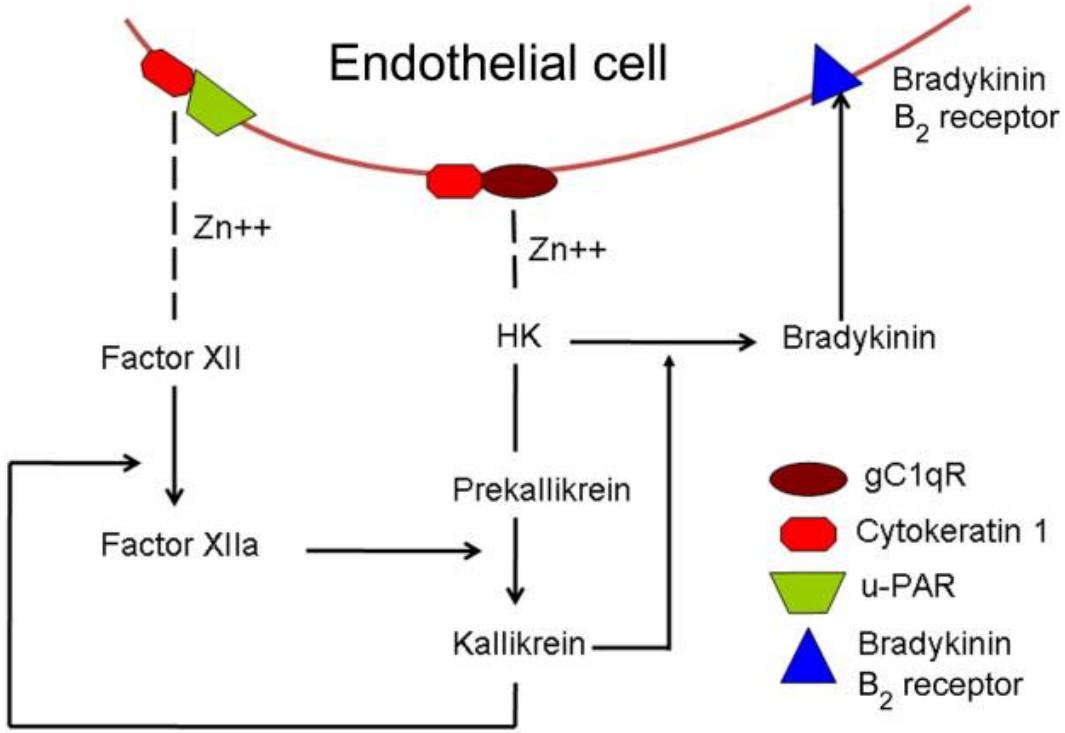
MRG PRX2 receptor



Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Nature519,237–241(12 March 2015)doi:10.1038/nature14022

2. Bradykinin-mediated angioedema

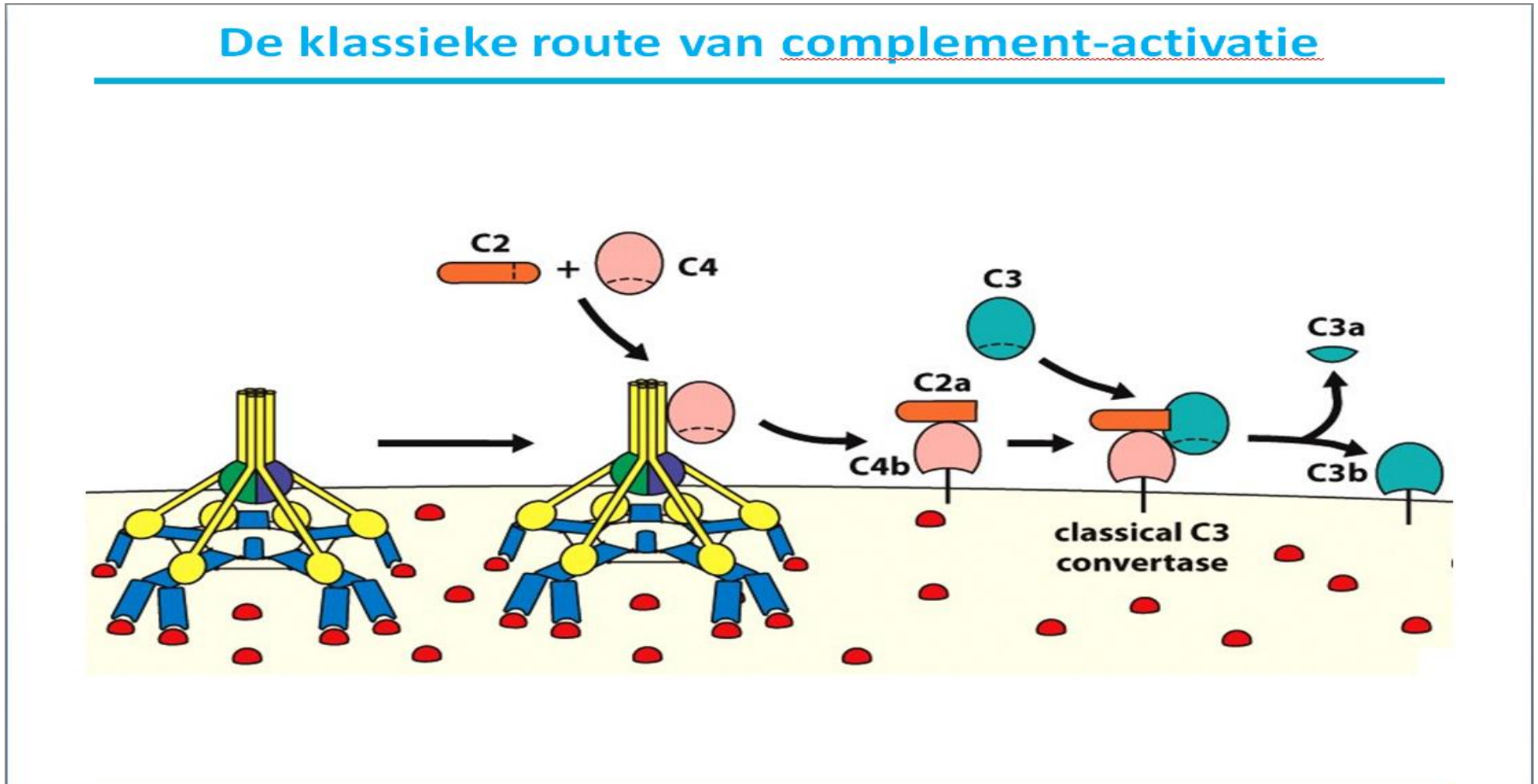


2. Bradykinin-mediated angioedema

- Hereditary and acquired angioedema with C1-inhibitor deficiency
  - HAE type I and II
  - AAE type I and II
- Hereditary angioedema without C1-inhibitor deficiency (HAE type III)
  - Defective glycosylation of FXII (1)
  - Diverse nieuwe mutaties (oa plasminogeen) (2)
- Angiotensin-converting enzyme (ACE) inhibitor-induced angioedema
- Idiopathic bradykinin-mediated angioedema

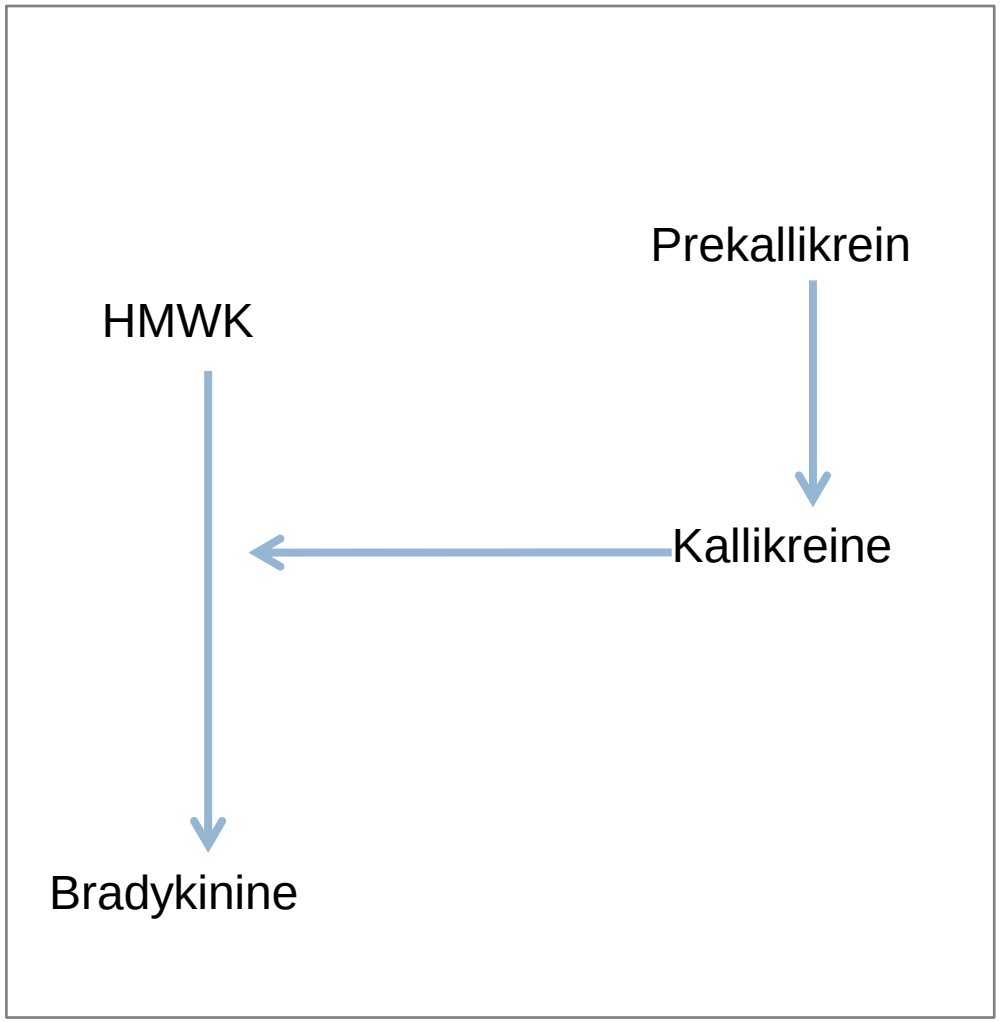
1. *Bjorkqvist et al. J Clin Invest 2015*
2. *Bork et al Allergy 2017*

Prototype van bradykinerg AE: C1-inh deficiëntie

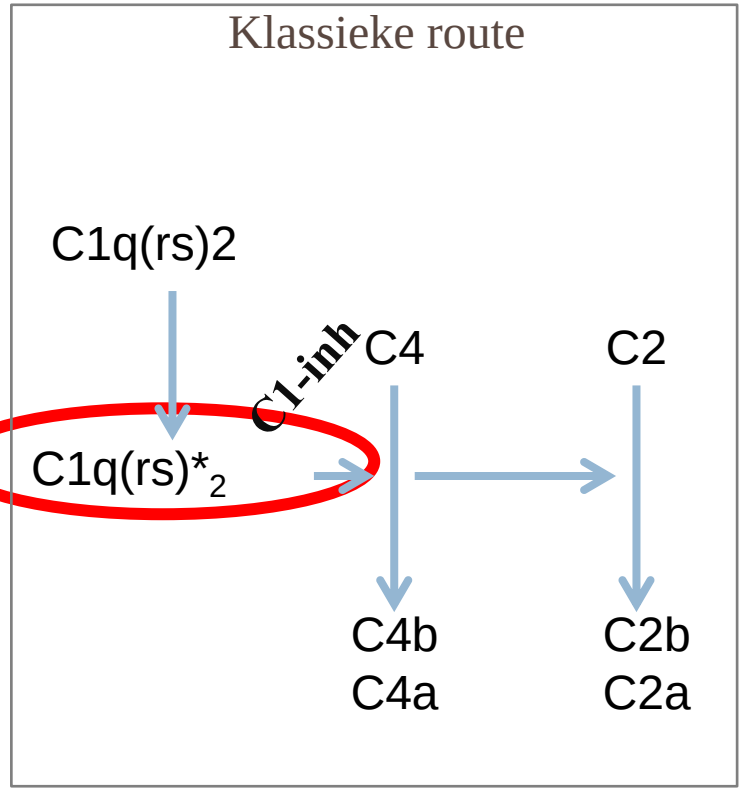


C1 esterase remmer

Kinin system



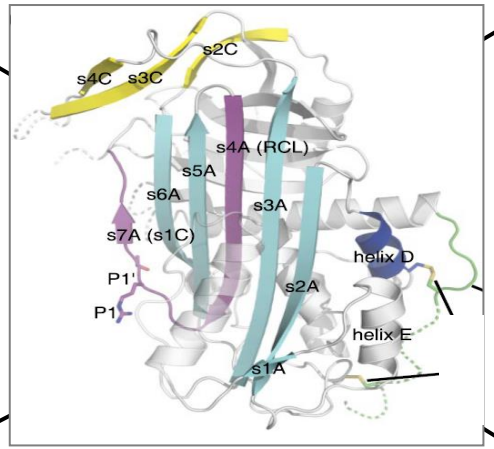
Complement systeem



C1-esteraseremmer is eigenlijk een verkeerde naam

Complementsysteem
C1r,s, MASP-1,-2

“C1-inh”



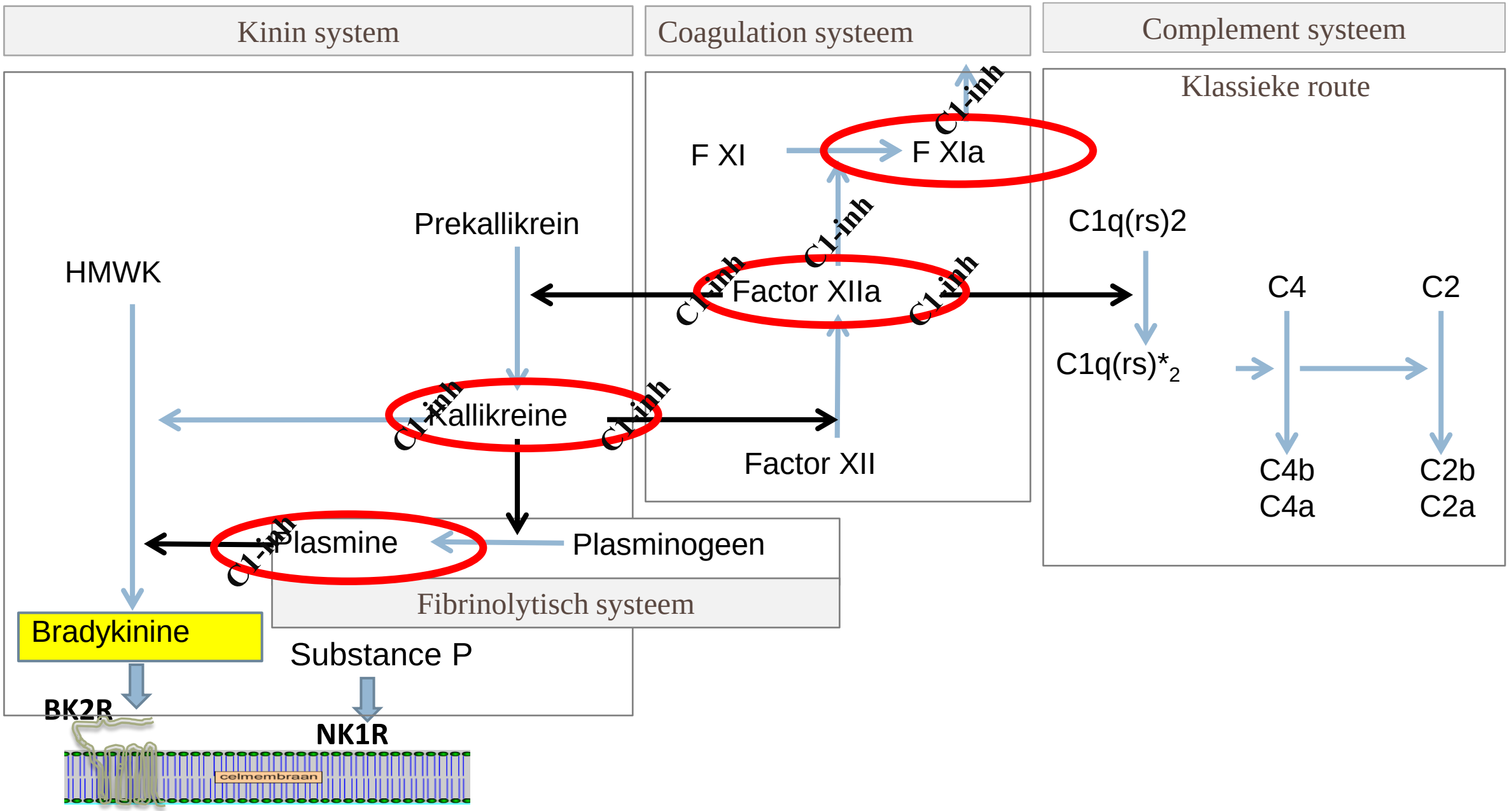
Stollings systeem
FXIa, thrombine

Contactsysteem /
Kallikreine-kinine systeem
FXIIa, (90%) kallikreïne (50%)

Fibrinolytisch systeem
Plasmine, t-PA

Bos, Hack, Abrahams. Immunobiology 2002;205(4-5):518-33
Gettins. Chem Rev 2002; 102: 4751-4803

C1-inh remt (ook) FXII/kallikreine activiteit



Hereditary Angioedema Classification

- Autosomal dominant inheritance
- Multiple mutations

Three types:

- I Low levels of C1 INH
- II Inactive protein
- III C1 INH normal

- Type I:
  - 80%-85%
  - Caused by a decreased synthesis of C1-INH
- Type II:
  - 15%-20%
    - Characterized by normal or elevated levels of a functionally impaired C1-INH protein
- Type III:
  - rare
    - Normal C1-INH levels and activity
    - Factor XII (Hageman factor) mutation involved in some patients ,nieuwe mutaties
    - Affects mainly women; estrogen-associated

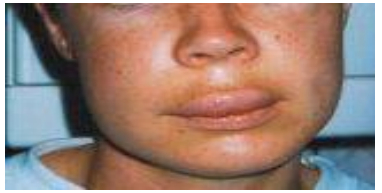
Verworven angioedeem (AE)

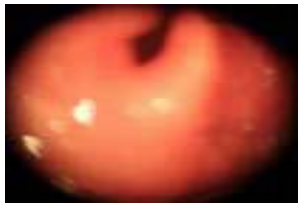
- Antistoffen tegen C1 esteraseremmer of verhoogde consumptie
- Ernstige of chronische ziekten: bv.
  - Maligniteit (B-cel lymfoom)
  - auto-immuun aandoening

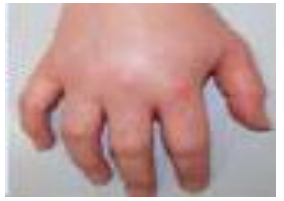
HAE:Clinical Features

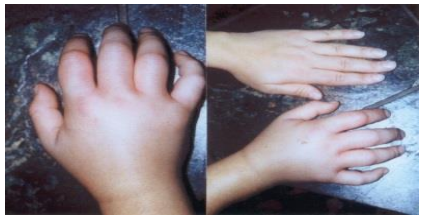
A rare but potentially life-threatening disease

- HAE is characterized by spontaneous and recurrent attacks of edema in various parts of the body
- Attacks can be life-threatening, painful and debilitating
- Approx. 30% of untreated patients have >1 attack per month, 40% have 6-11 swellings per year, and the remaining 30% are infrequently symptomatic or symptom-free
- Symptoms of edema usually subside in 2-5 days









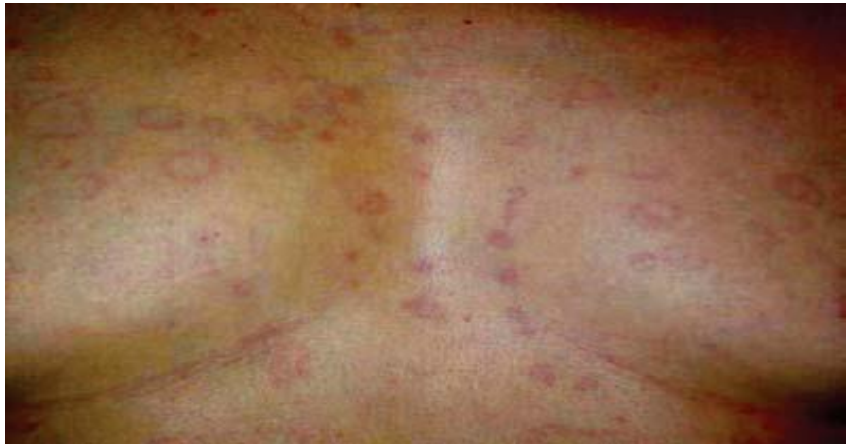
Agostoni A et al. J Allergy Clin Immunol 2004;114(3):S51-131.
Bork K et al. Am J Gastroenterol 2006;101:619-627.
Bowen T et al. Ann Allergy Astma Immunol 2008;100(Suppl 2):S3-40.

Signs and Symptoms, prodromes

Erythema marginatum

An erythematous, non-pruritic rash that may precede an attack

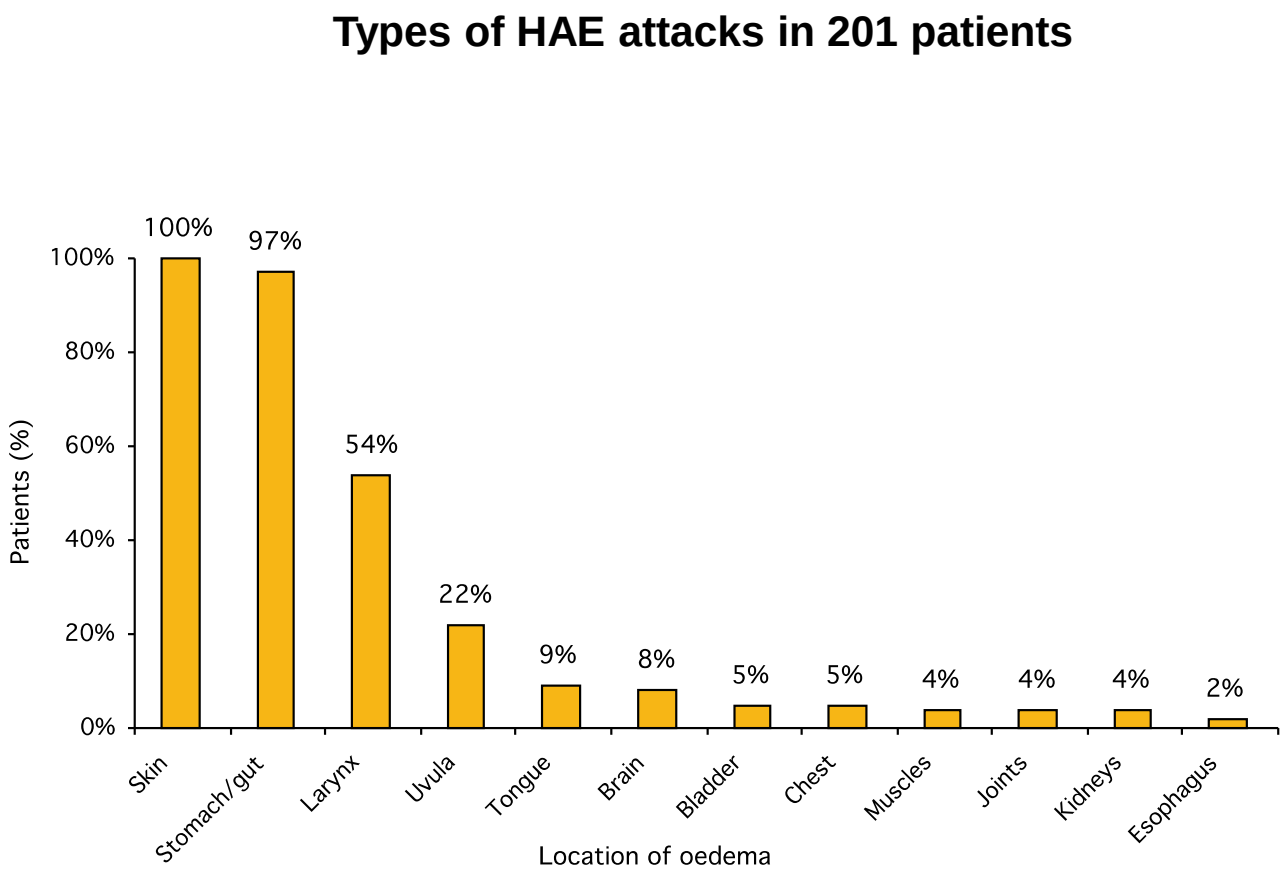
Reported in up to 25% of patients



Bork K et al. Am J Gastroenterol 2006;101:619-627.

Signs and Symptoms

Frequency and location of affected organs

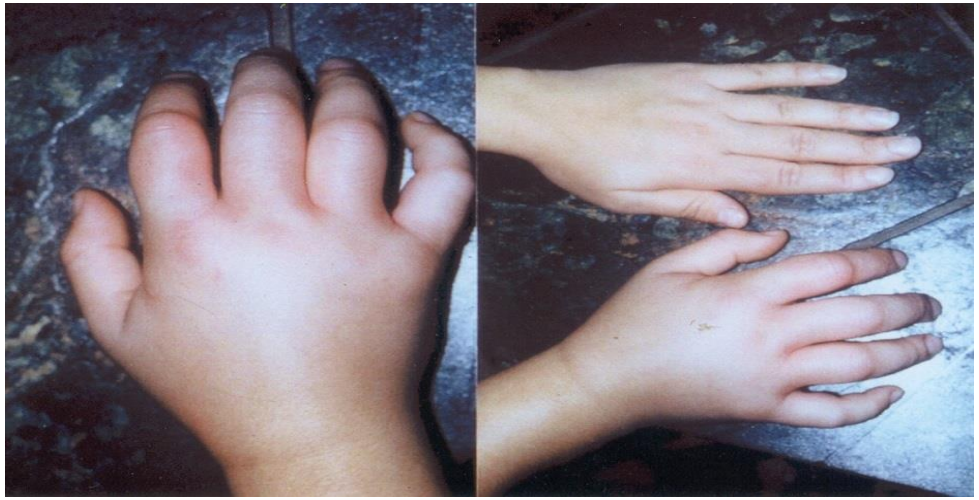


Bork K et al. Am J Med 2006;119:267-274.

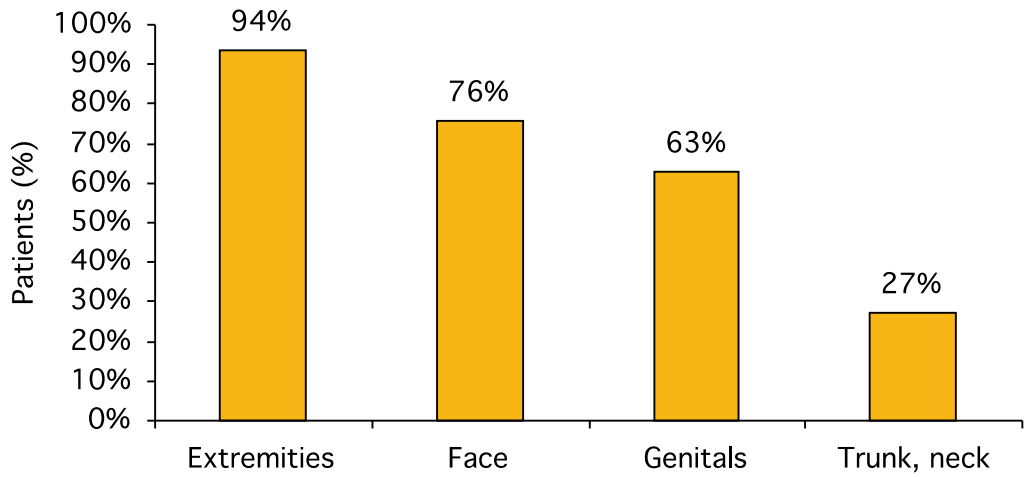
Signs and Symptoms

Cutaneous attacks

- Cutaneous edema is the most common and noticeable symptom of HAE
- Patients experience a tightness of the skin or tingling
- Patients may also report pain in joints

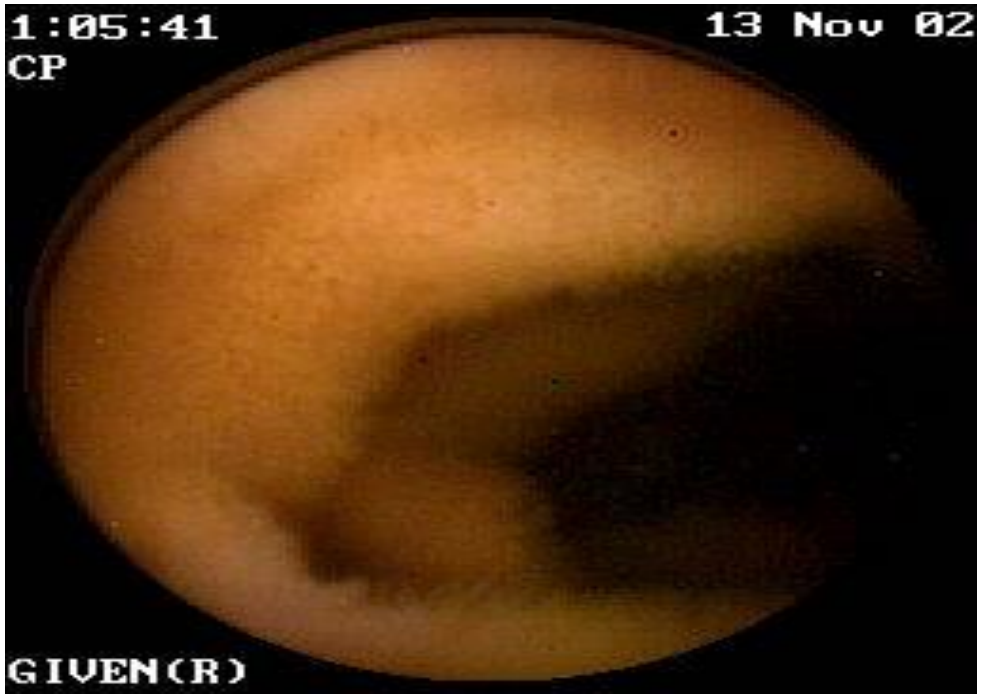


*Frequency and location of **cutaneous** attacks*

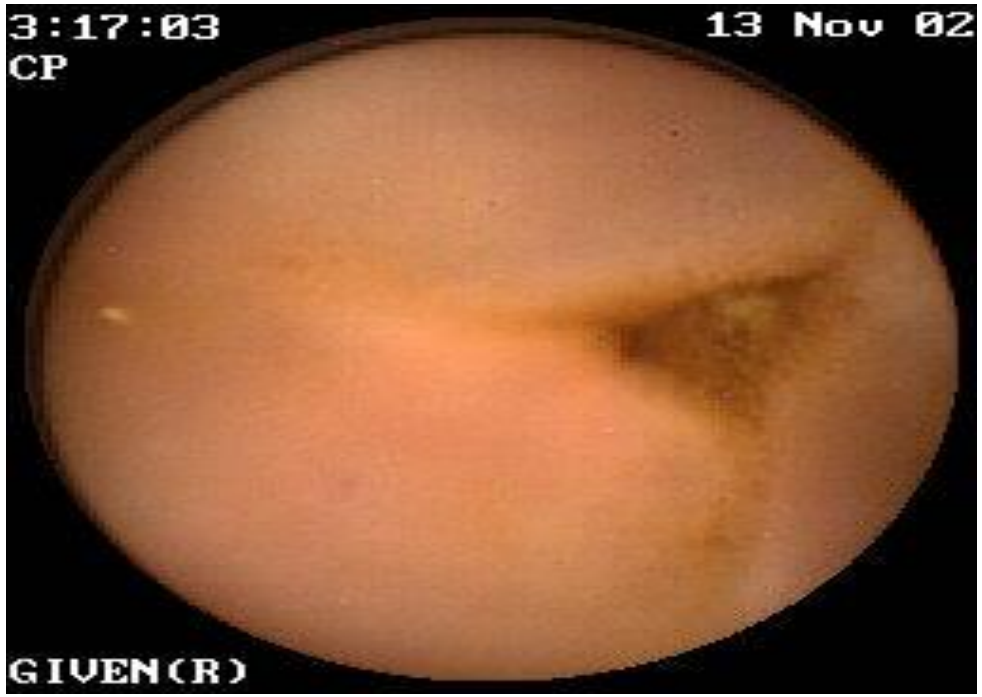


Agostoni A et al. J Allergy Clin Immunol 2004;114(3):S51-131.
Bork K et al. Am J Med 2006;119:267-274.

Capsule endoscopy during an abdominal attack in a patient with HAE



Normal bowel



Edematous bowel

Signs and Symptoms

Abdominal attacks

- Abdominal attacks are associated with edema of the gastrointestinal wall
- Symptoms may include colic-like pain, nausea, vomiting and diarrhea
- The non-specific symptoms of abdominal attacks may result in misdiagnosis and unnecessary surgery

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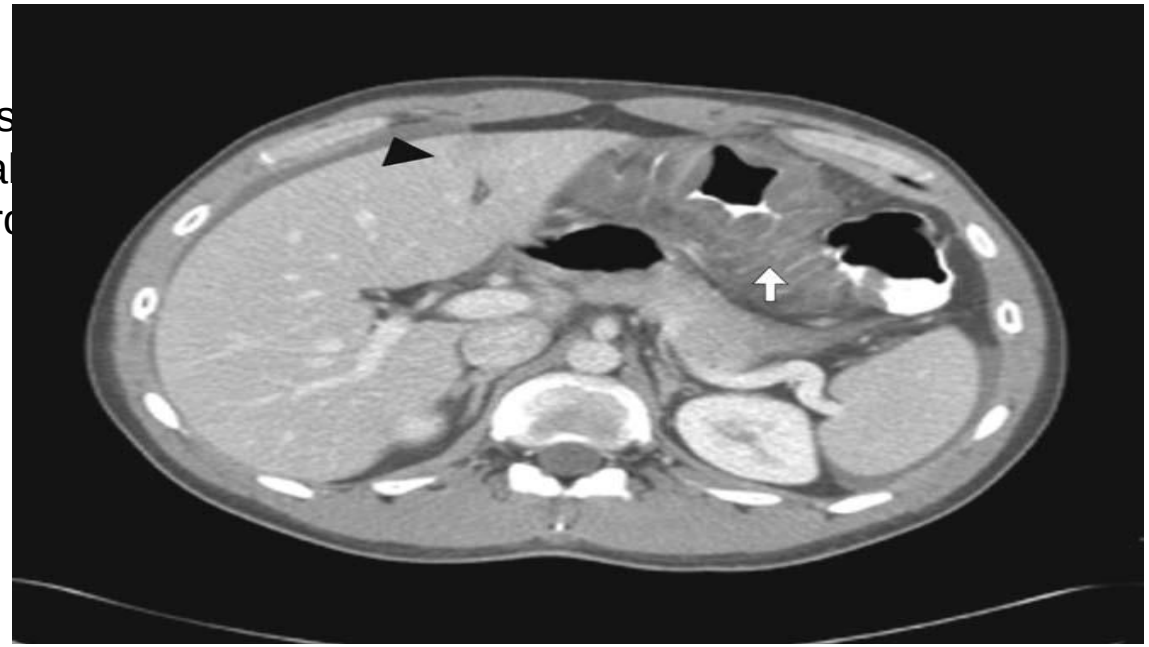
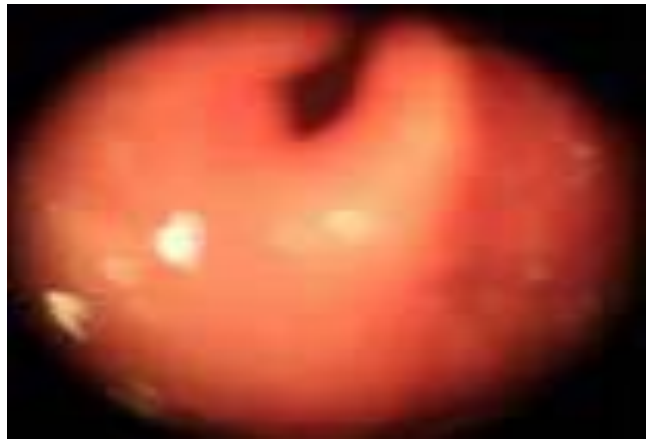


Agostoni A et al. J Allergy Clin Immunol 2004;114(3):S51-131.
Bork K et al. Am J Gastroenterol 2006;101:619-627.
Koruth JS et al. Gastrointest Endosc 2005; 61(7):907-911.

Signs and Symptoms

Laryngeal attacks

- Laryngeal edema can be life-threatening
- More than 50% of HAE patients have experienced laryngeal angioedema
- Laryngeal edema can develop rapidly into complete airway obstruction in less than 4 h
- Patients with laryngeal edema may eventually require emergency intubation or a tracheotomy

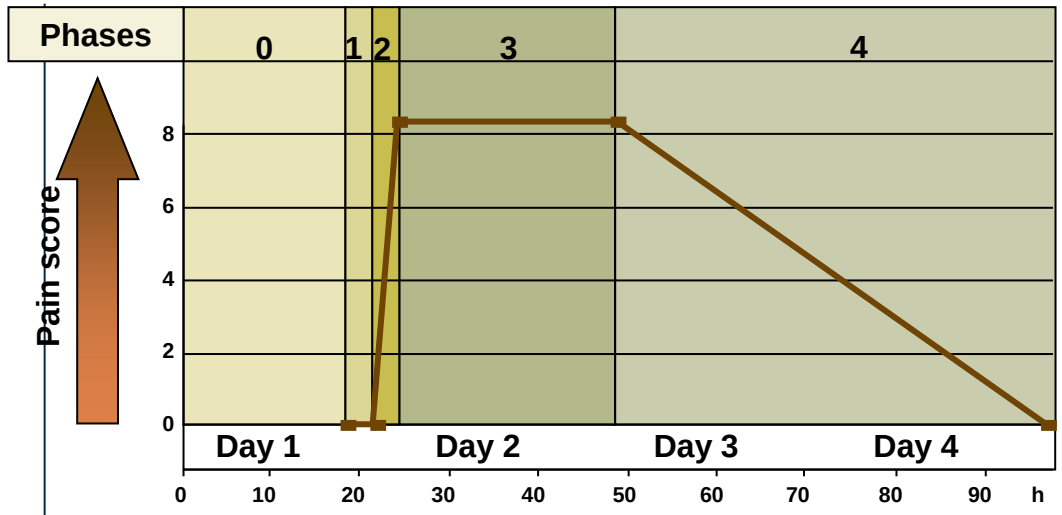


Agostoni A et al. J Allergy Clin Immunol 2004;114(3):S51–131.
Bork K et al. Am J Med 2006;119:267-274.
Bas M et al. Allergy 2006;61(12):1490-492.

Clinical Feature: Course of Attack

Course of an average abdominal attack

Time course of abdominal pain during an attack



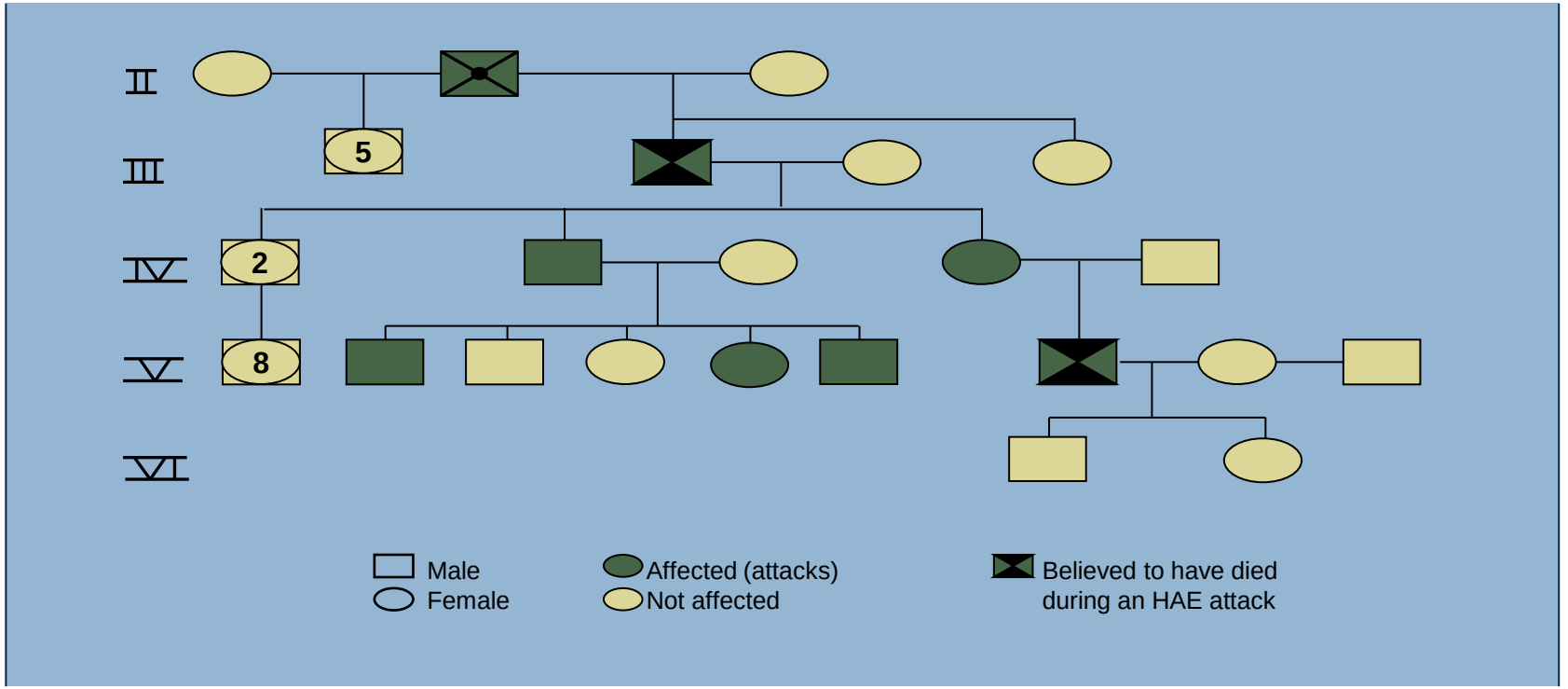
- Pre-phase
- Early abdominal phase
- Crescendo phase
- Maximum phase
- Decrescendo phase

Bork K et al. Am J Gastroenterol 2006;101:619-627.

Genetics of HAE

Patterns of inheritance

HAE may be passed on to 50% of offspring



Female and male offspring are equally affected
Family counselling is important to educate patients about disease inheritance

Donaldson VH, Evans RR. Am J Med 1963;35:37–44.
Heiner DC, Blitzer JR. Pediatrics 1957;20(5, Part1):782-793.

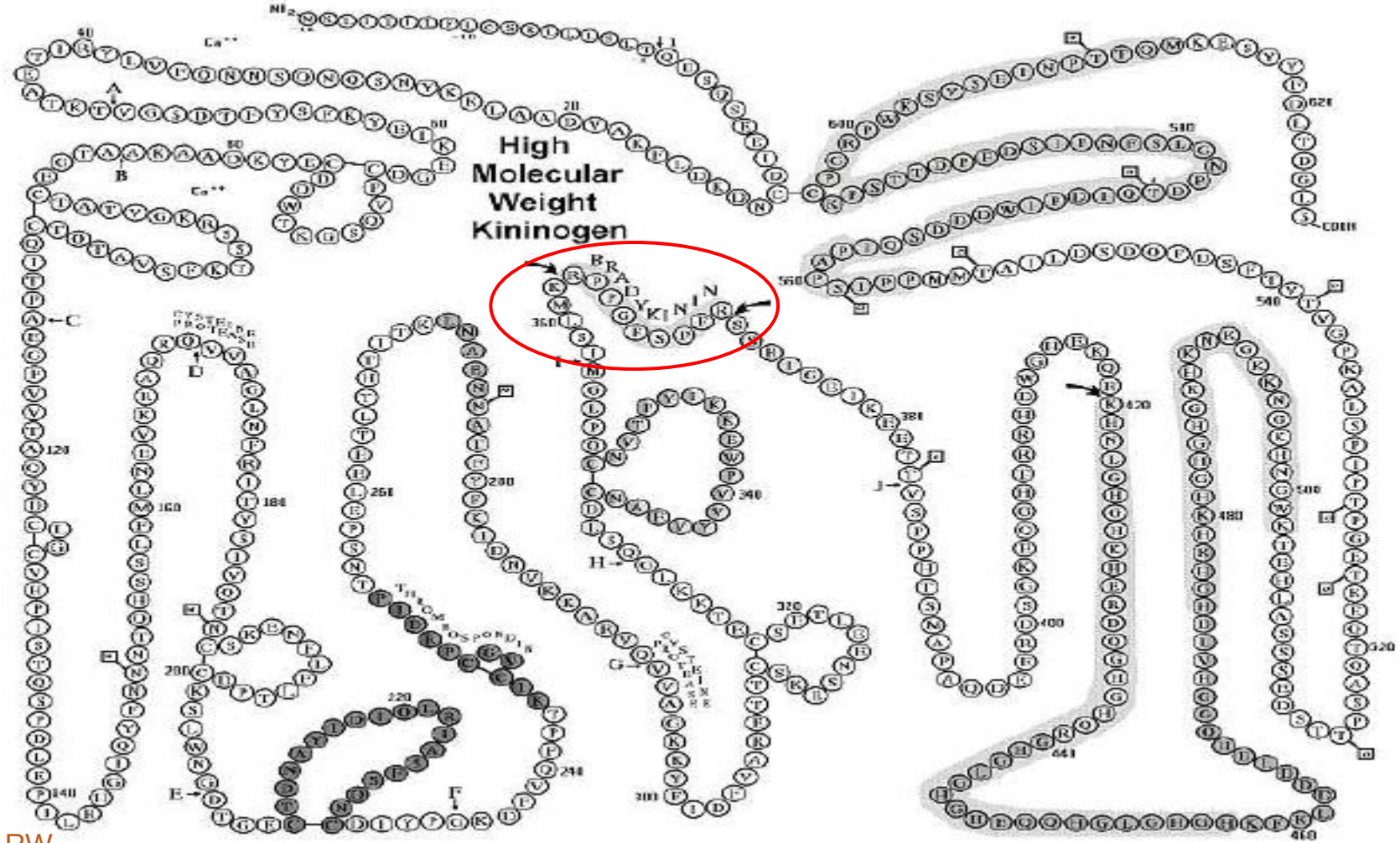
Genetics of HAE

- HAE is inherited in an **autosomal dominant** manner
- The ***de novo*** mutation rate is approximately 25%
- More than **180** different C1-INH **gene mutations** have been reported to date
- Regardless of the type of mutation present, there is a high degree of **variability** in the **frequency and severity of attacks**

Agostoni A et al. J Allergy Clin Immunol 2004;114(3):S51-131.
HAEdb-C1 inhibitor gene mutation database: http://hae.enzim.hu/stat.php

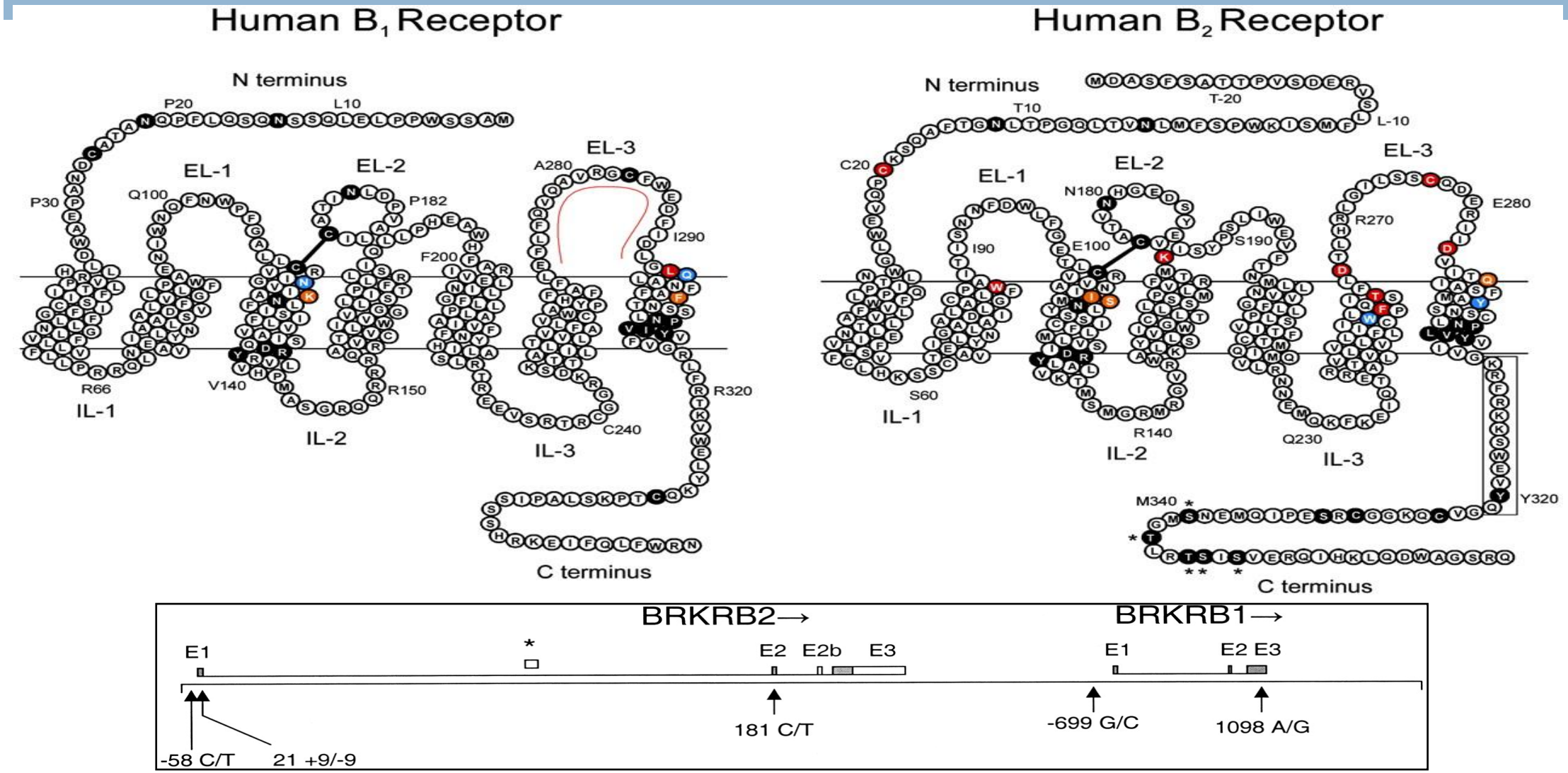
Medicatie geassocieerd Angioedeem

Bradykinine wordt (door kallikreine) vrijgemaakt uit HMWK

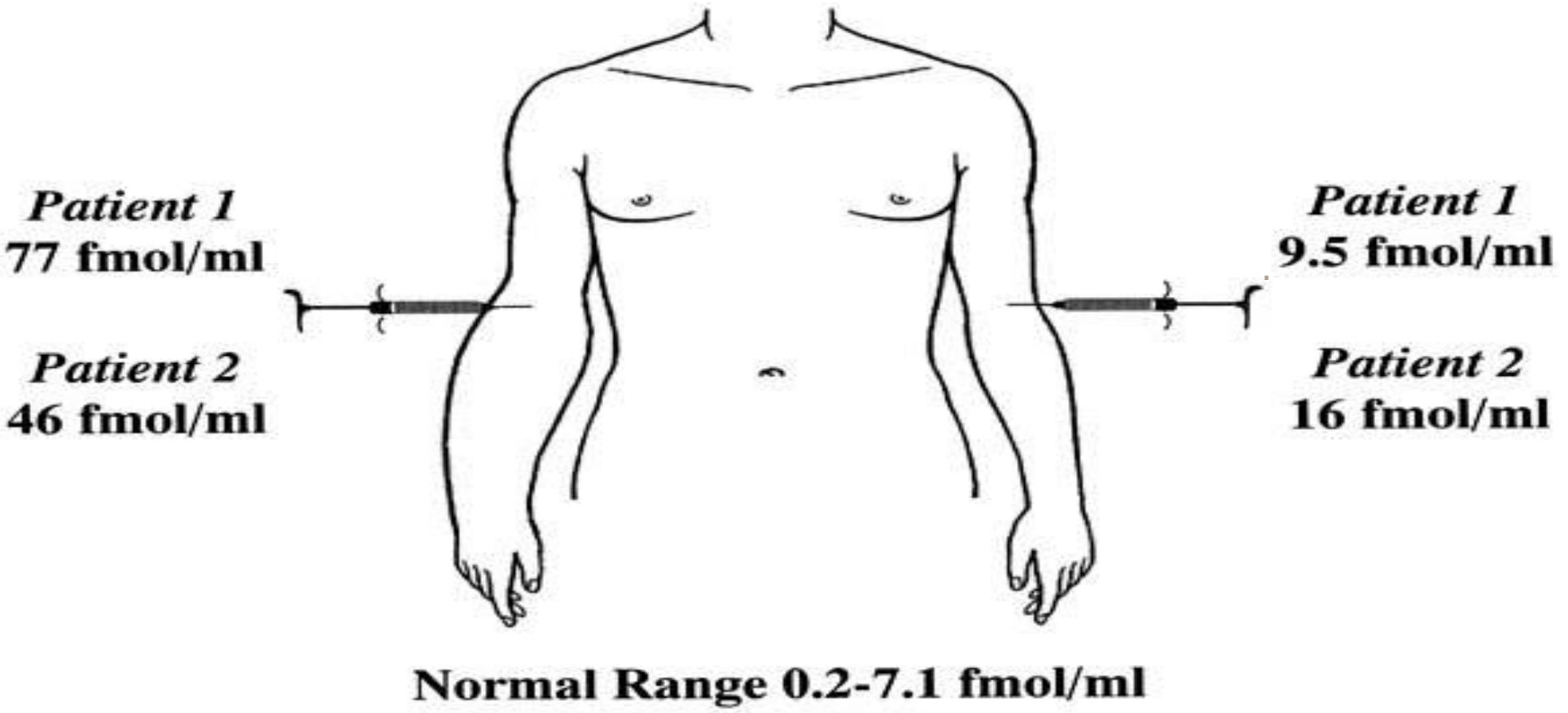


Sainz IM, Pixley RA, Colman RW.
Fifty years of research on the plasma kallikrein-kinin system: From protein structure and function to cell biology and in-vivo pathophysiology.
Thromb Haemost 2007; 98:77-83.

Bradykinine-1 en Bradykinine-2 receptor

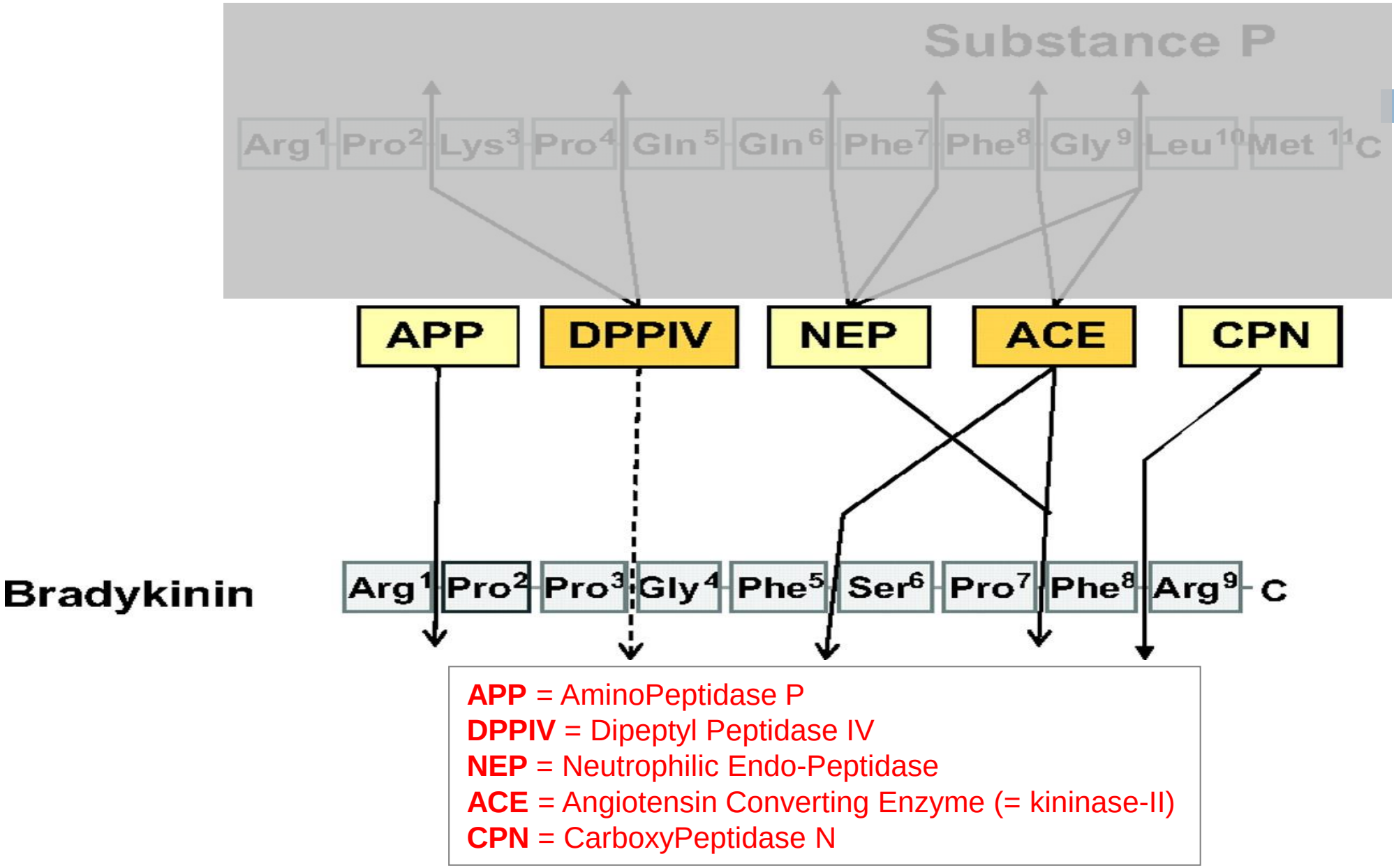


Locaal oedeem zonder systemische verspreiding



Nussberger J, M Cugno and M Cicardi. Bradykinin mediated angioedema. NEJM 2002; 347:621.
Nussberger J, M Cugno, M Cicardi, A Agostini. Local bradykin generation in hereditary angioedema. J All Clin Immun 1999;104:1321-22.

Afbraak van bradykinine, door….



APP = AminoPeptidase P
DPPIV = Dipeptyl Peptidase IV
NEP = Neutrophilic Endo-Peptidase
ACE = Angiotensin Converting Enzyme (= kininase-II)
CPN = CarboxyPeptidase N

Brown et al. Dipeptidyl Peptidase-IV Inhibitor Use Associated with Increased Risk of ACE-inhibitor-Associated Angioedema. Hypertension 2009; 54: 516-23.

ACE-remmer geassocieerd AE*
- vaker bij lage APP-activiteit

RESEARCH LETTERS

Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors

Albert Adam, Massimo Cugno, Giuseppe Molinaro, Melissa Perez, Yves Lepage, Angelo Agostoni

Angio-oedema is a rare but potentially life threatening side-effect of angiotensin-converting-enzyme (ACE) inhibitor treatment. Identification of individuals at risk of this adverse effect is not possible. Angio-oedema is associated with raised concentrations of bradykinin, which is mainly inactivated by ACE. We assessed the plasma activity of two other enzymes that catabolise bradykinin (aminopeptidase P and carboxypeptidase N) in 39 hypertensive patients with a history of angio-oedema during ACE inhibitor treatment and in 39 hypertensive patients who had never had ACE inhibitor associated side-effects. Patients with previous angio-oedema had a lower plasma activity of aminopeptidase P than did those who never presented with angio-oedema (p=0·003). Our data suggest that low plasma concentrations of aminopeptidase P could be a predisposing factor for development of angio-oedema in patients treated with ACE inhibitors.

Lancet 2002; **359:** 2088–89

Genetische aanleg en lage APP

4)

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

A Functional *XPNPEP2* Promoter Haplotype Leads to Reduced Plasma Aminopeptidase P and Increased Risk of ACE Inhibitor-Induced Angioedema

Amy L. Cilia La Corte,[1,2] Angela M. Carter,[2] Gillian I. Rice,[1†] Qing Ling Duan,[3] Guy A. Rouleau,[4] Albert Adam,[5] Peter J. Grant,[2] and Nigel M. Hooper[1*]

[1] Institute of Molecular and Cellular Biology, University of Leeds, Leeds, UK; [2] Division of Cardiovascular and Diabetes Research, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK; [3] Department of Human Genetics, McGill University, Montréal, Québec, Canada; [4] Centre for Excellence in Neuromics, University of Montreal, and the Centre Hospitalier de l'Université de Montréal and Ste-Justine Hospital, Montreal, Canada; [5] Faculté de Pharmacie, Université de Montréal, H3T 1J4 Montréal, Canada

- Plasma APP is derived from GPI-anchored membrane bound APP
- *XPNPEP2* gene on chromosome Xq25-26.1
- Screening of all exons plus 3-kb upstream of the initiator ATG-codon
- Identification of 25 SNPs
- Genetic factors contribute tot 47% of the variation in plasma APP activity
- Three of them associated with APP-activity: **c.-2399C>A**, c.-1612G>T, c.-393G>A
- Explain 10.8% of the transcriptional regulation of XPNEP2 and cellular expression

Duan et al. Am J Hum Genet 2005; 77: 617-26.
Woodard-Grice et al. Pharmacogenetics and Genomocs 2010; 20: 532-6.
La Corte et al. Human Mutation 2011 32(11): 1326-31.dmic. A. J. Cardiol 2012;109:774-777.

ACEi-AE vaker bij gebruik DPP-IV-remmer (Vidagliptine)

Clinical Treatment

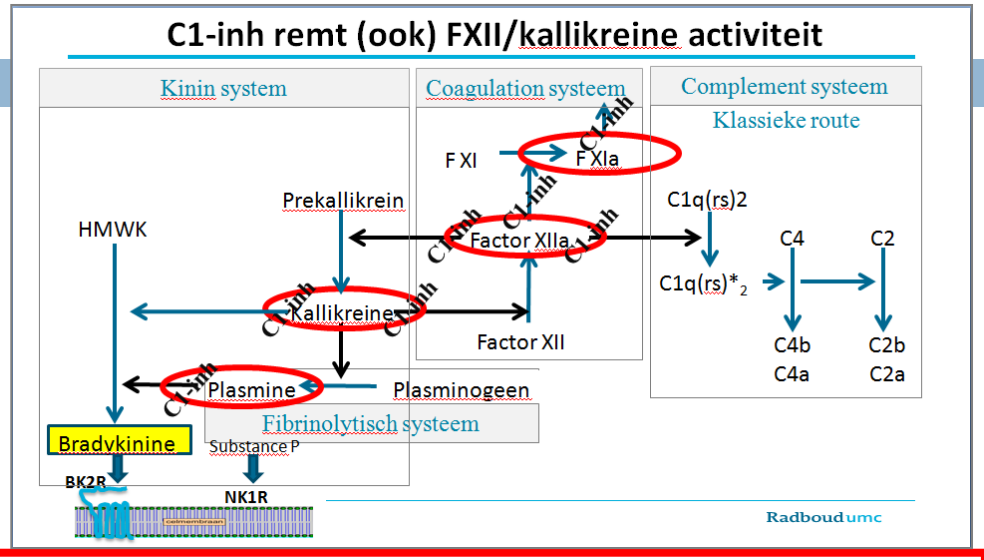
Dipeptidyl Peptidase-IV Inhibitor Use Associated With Increased Risk of ACE Inhibitor-Associated Angioedema

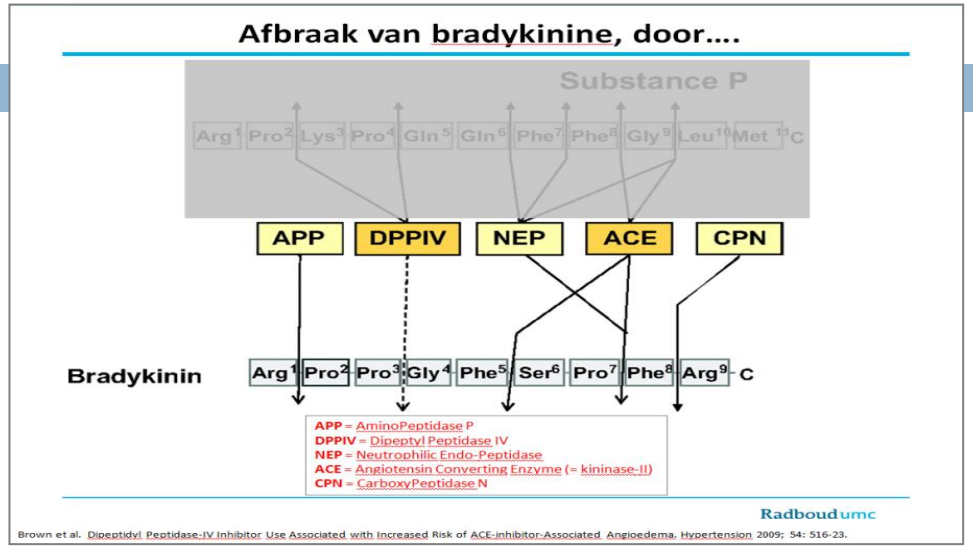
Nancy J. Brown, Stuart Byiers, David Carr, Mario Maldonado, Barbara Ann Warner

Abstract—Dipeptidyl peptidase-IV (DPP-IV) inhibitors decrease degradation of the incretins. DPP-IV inhibitors also decrease degradation of peptides, such as substance P, that may be involved in the pathogenesis of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. This study tested the hypothesis that DPP-IV inhibition affects risk of clinical angioedema, by comparing the incidence of angioedema in patients treated with the DPP-IV inhibitor vildagliptin versus those treated with comparator in Phase III randomized clinical trials. Prospectively defined angioedema-related events were adjudicated in a blinded fashion by an internal medicine adjudication committee and expert reviewer. Concurrent ACE inhibitor or angiotensin receptor blocker exposure was ascertained from case report forms. Study drug exposure was ascertained from unblinded data from phase III studies. Odds ratios and 95% confidence intervals comparing angioedema risk in vildagliptin-treated and comparator-treated patients were calculated for the overall population and for patients taking ACE inhibitors or angiotensin receptor blockers, using both an analysis of pooled data and a meta-analysis (Peto method). Overall, there was no association between vildagliptin use and angioedema. Among individuals taking an ACE inhibitor, however, vildagliptin use was associated with an increased risk of angioedema (14 confirmed cases among 2754 vildagliptin users versus 1 case among 1819 comparator users: odds ratio 4.57 [95% confidence interval 1.57 to 13.28]) in the meta-analysis. Vildagliptin use may be associated with increased risk of angioedema among patients taking ACE inhibitors, although absolute risk is small. Physicians confronted with angioedema in a patient taking an ACE inhibitor and DPP-IV inhibitor should consider this possible drug–drug interaction. (*Hypertension*. 2009;54:516-523.)

Key Words: angioedema ■ angiotensin-converting enzyme inhibitor ■ hypertension ■ antihypertensive agents ■ type 2 diabetes

Welke condities geven bradykinerg AE?





Meer aanmaak van bradykinine:

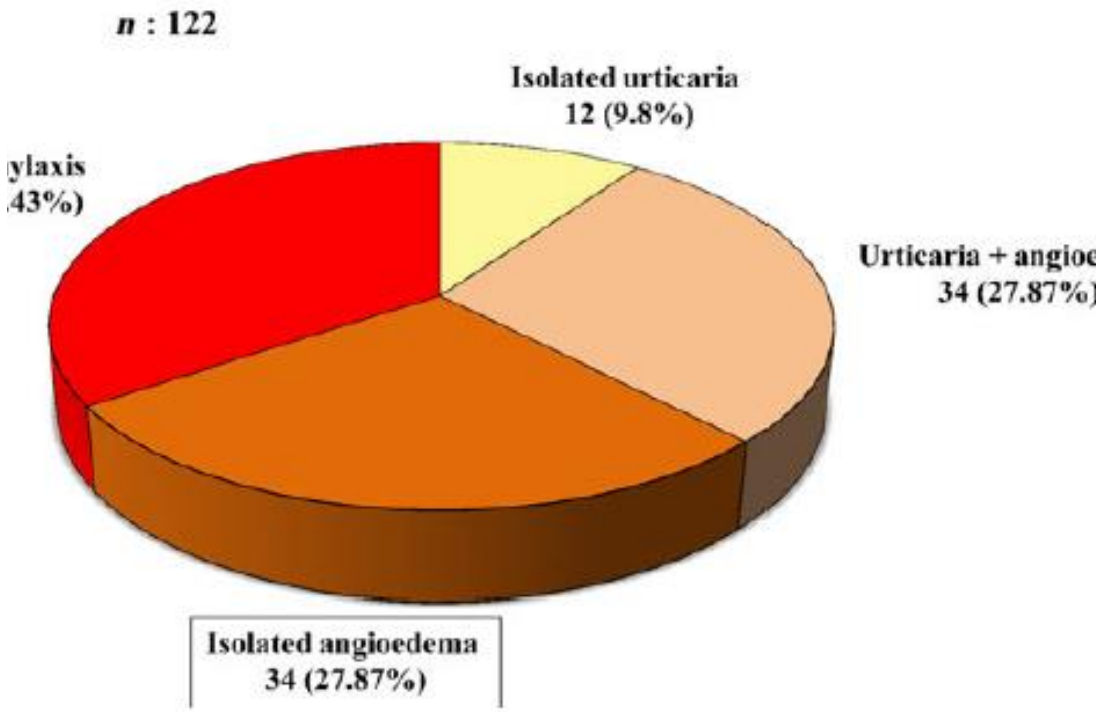
- Verlaagde C1-inh activiteit
  - genetisch (HAE-I, HAE-II)
  - verworven (AAE)
- Verhoogde FXII activiteit (genetisch) (HAE-III)
- Medicatie:
  - rtPA*

Minder afbraak van bradykinine:

- Genetisch verlaagde APP-activiteit
- Medicatie:
  - ACE-remmers
  - DPPIV-remmers

* Molinaro G., et al. Biochemical Basis of Angioedma Associated With Recombinant Tissue Plasminogen Activator Treatment. Stroke 2002;33:1712-6.

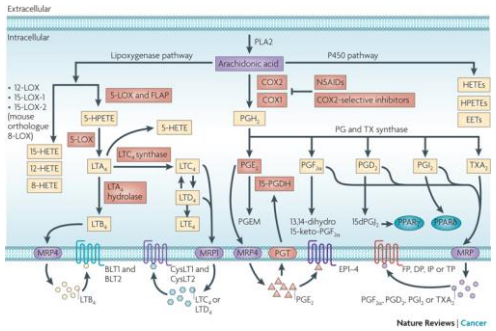
3. Non-histaminerg non-bradykinin



l. Clinical manifestations of hypersensitivity reactions to
dal anti-inflammatory drugs with cutaneous involvement.

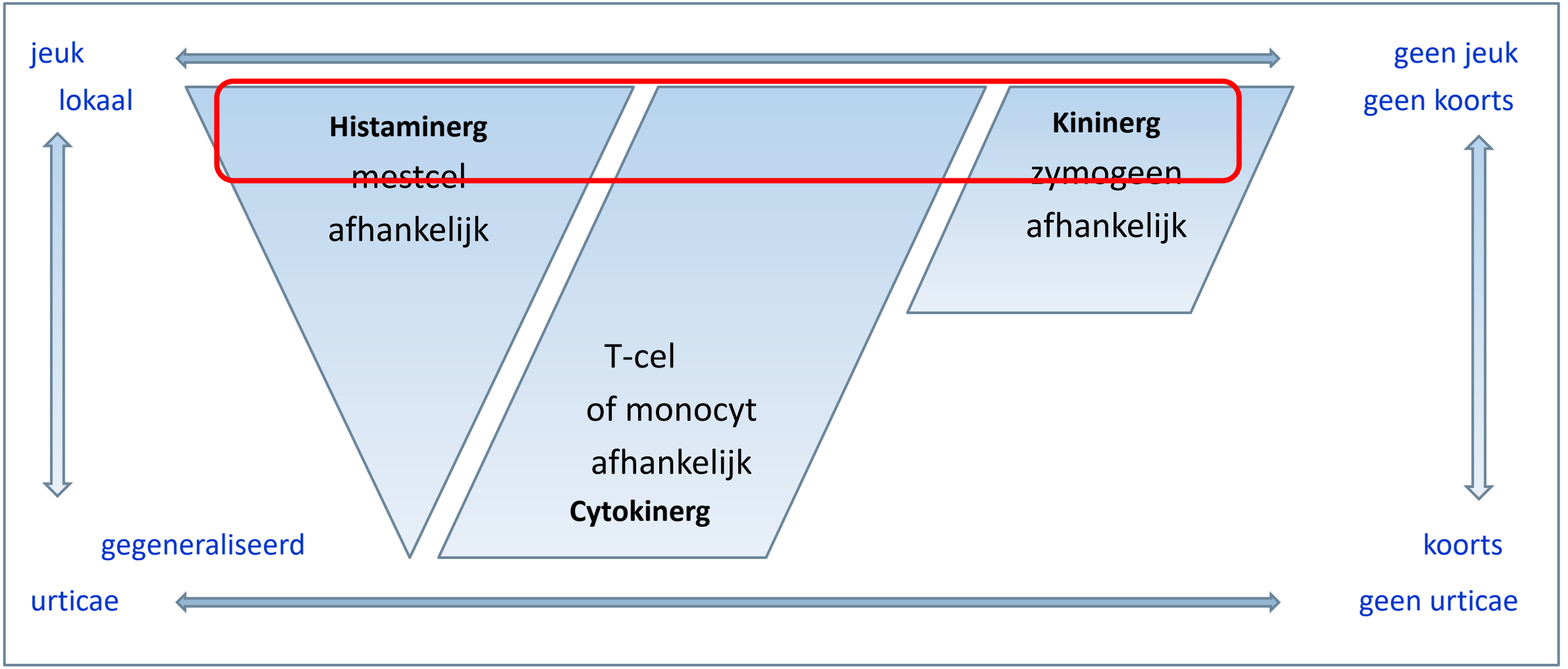
Intolerance for

- ASA
- NSAID's



- Prostaglandins
- leukotriens

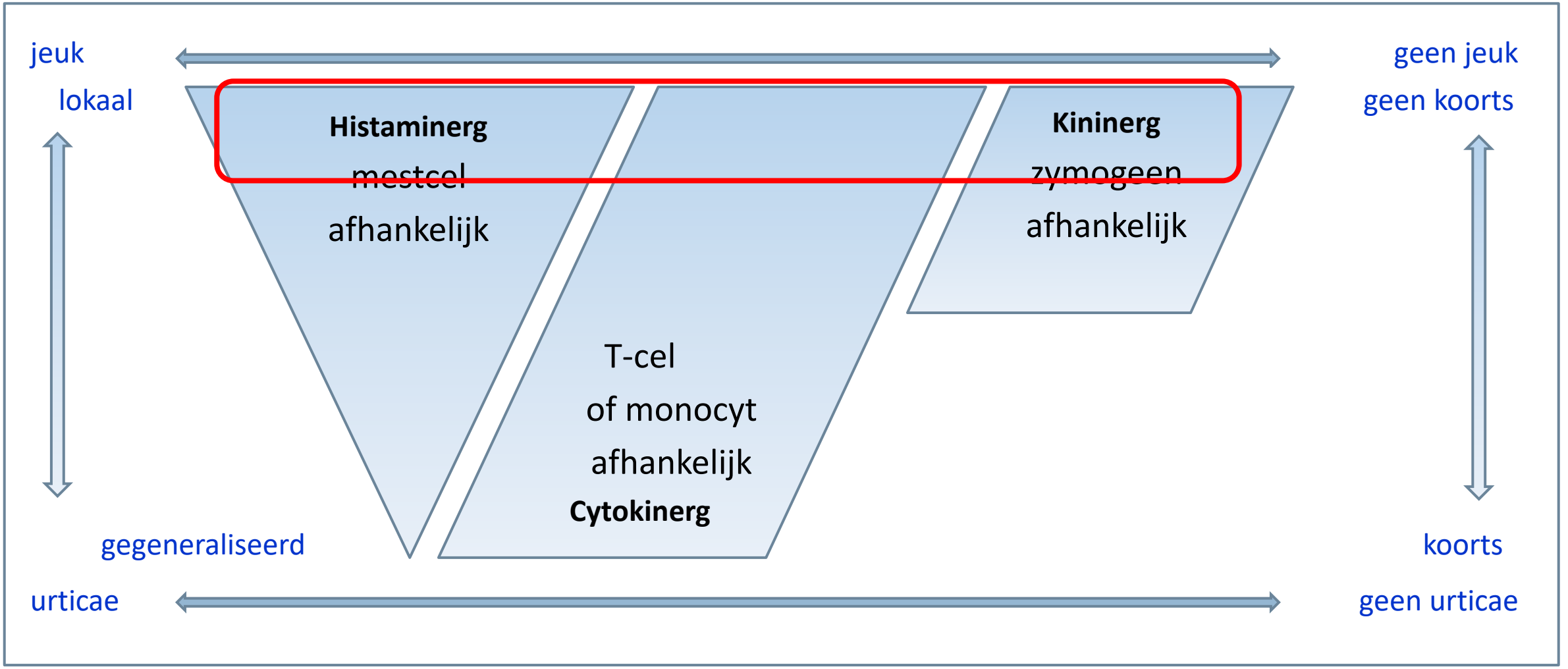
Conclusie
AE: niet steeds óf dit óf dat



Angioedeem

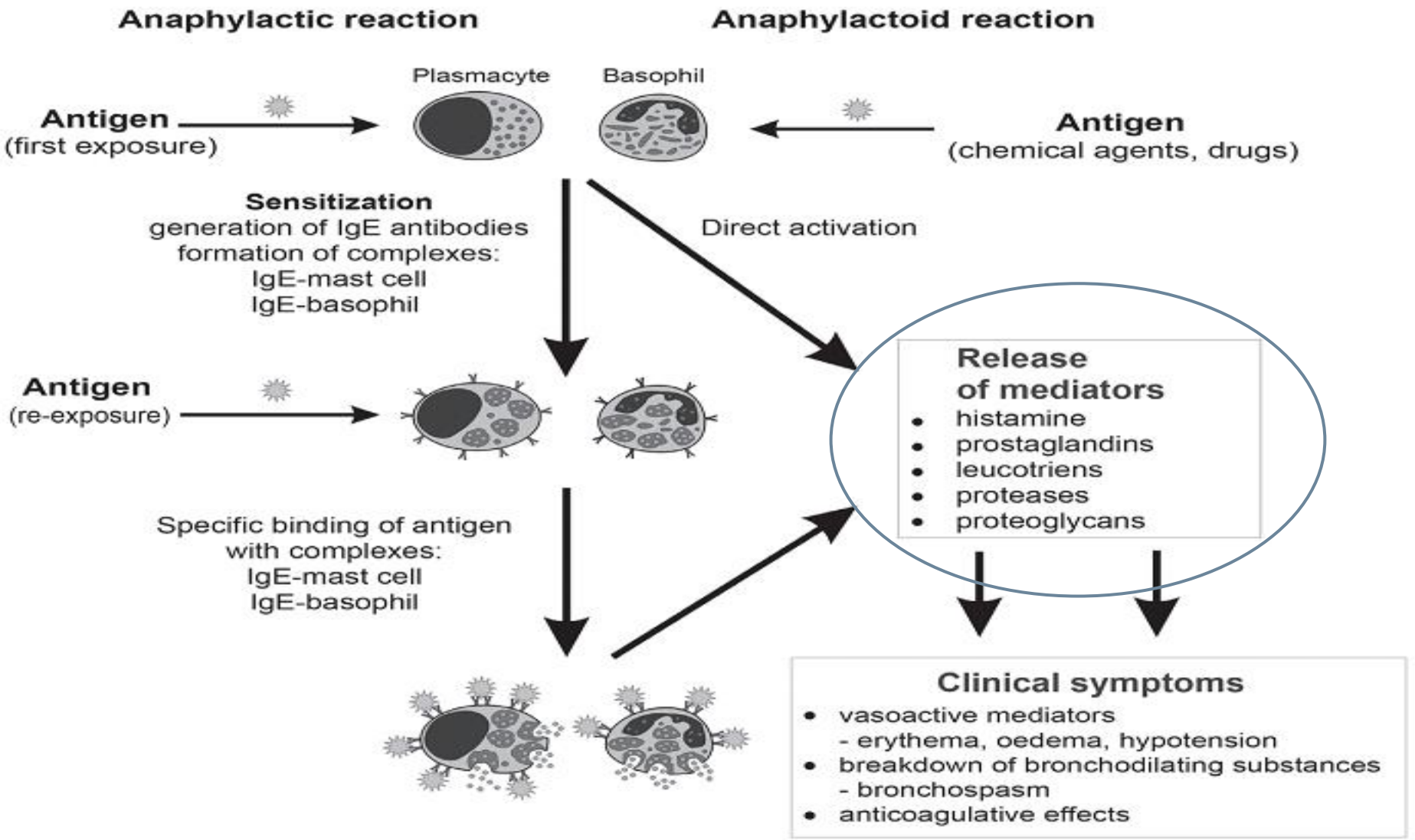
Biomarkers en behandeling

Conclusie
AE: niet steeds óf dit óf dat



Biomarkers

Potential markers



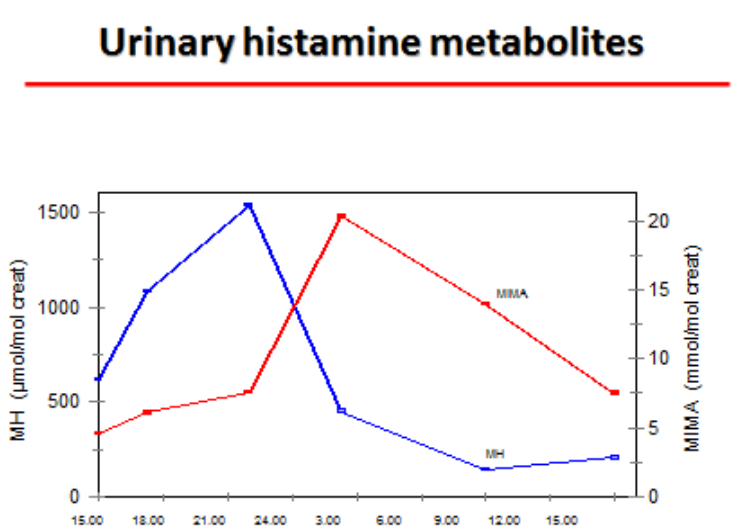
Objectiveren! Parameters in de acute situatie

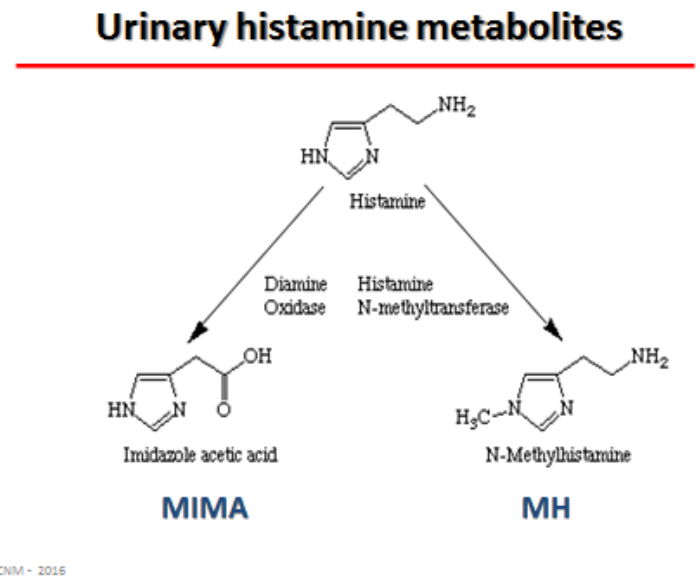
Mediator(cel)

- Mestcel

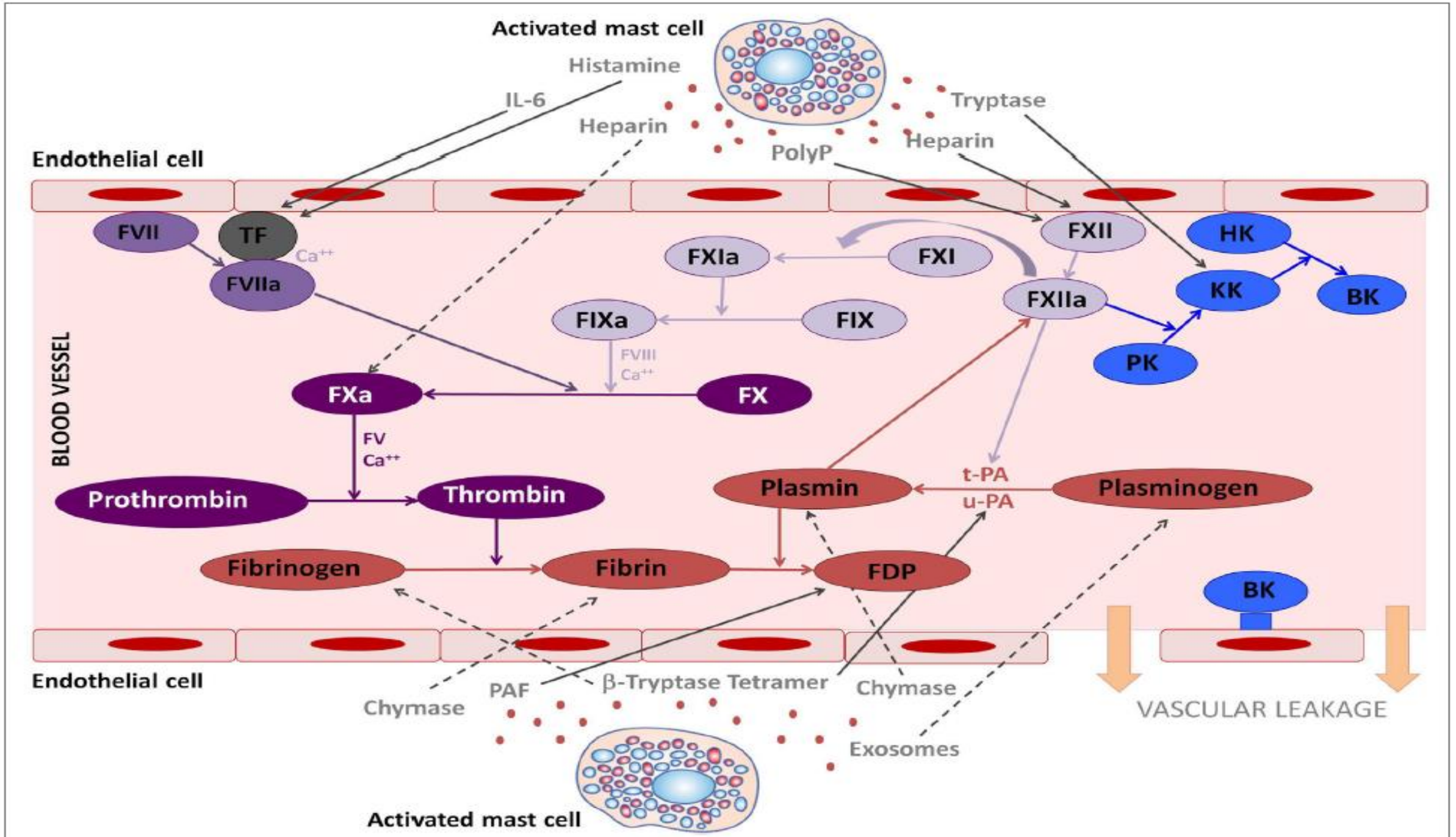
Parameter

- Tryptase (serum)
- Histamine metabolieten (urine)





ECNM - 2016


Activated mast cell
Histamine
IL-6
Heparin
Tryptase
Heparin
PolyP
Endothelial cell
FVII
TF
Ca++
FVIIa
FXIa
FXI
FXII
HK
KK
BK
FXIIa
FIXa
FIX
PK
FVIII
Ca++
BLOOD VESSEL
FXa
FX
FV
Ca++
Prothrombin
Thrombin
Plasmin
t-PA
u-PA
Plasminogen
Fibrinogen
Fibrin
FDP
BK
Endothelial cell
Chymase
PAF
β-Tryptase Tetramer
Chymase
VASCULAR LEAKAGE
Exosomes
Activated mast cell

Veronderstelde productie D-dimeer bij AE-aanval

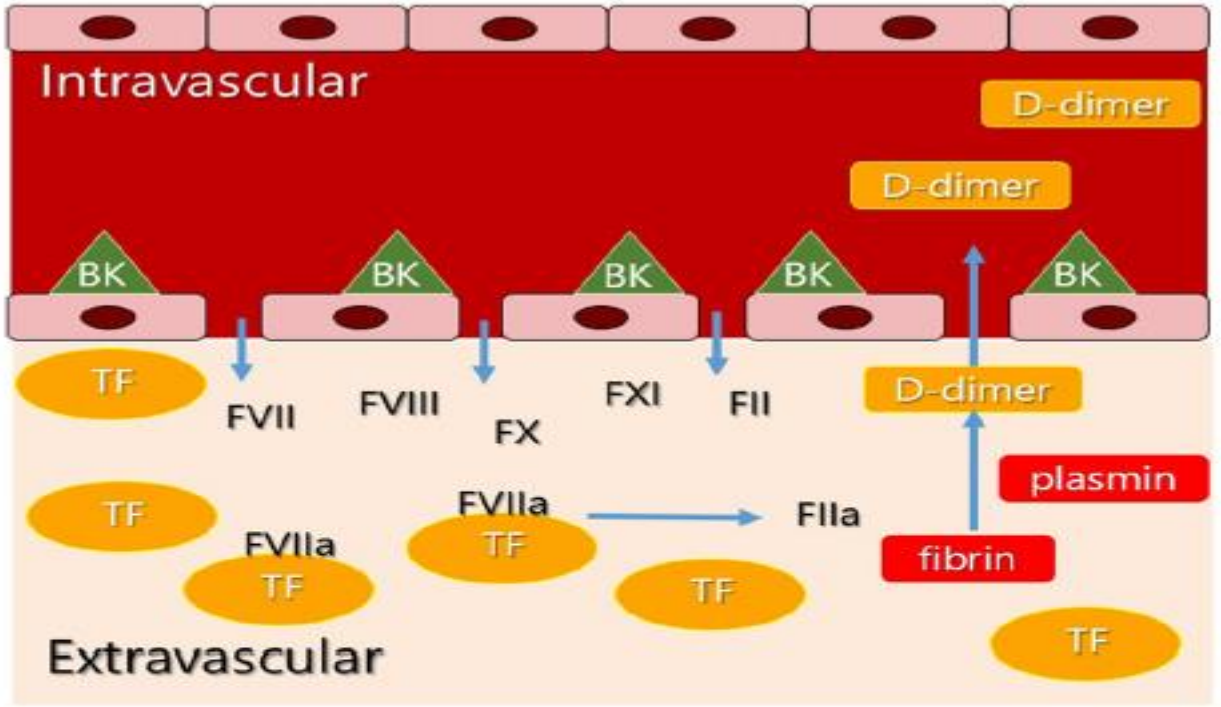
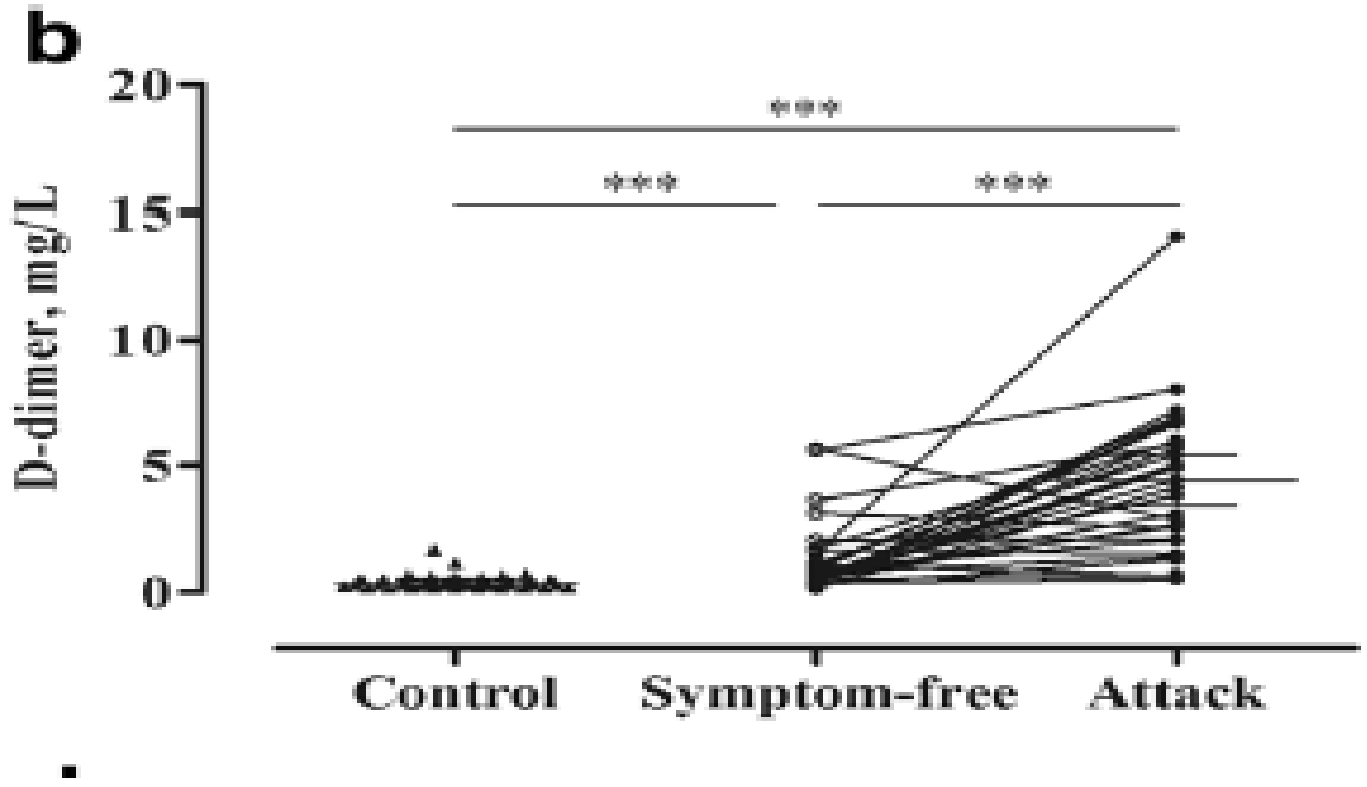


Fig. 2 Proposed model: increased plasma coagulation parameters secondary to increased vascular permeability and extravascular coagulation. *Bradykinin* binds to its receptors on endothelial cells. Increased vascular permeability allows extravasation of coagulation factors. Tissue factor expressed in the extravascular space can initiate coagulation. In the absence of any injury, the forming *fibrin* lattice is continuously degraded by *plasmin*. Subsequently, *D-dimer* formed in the extra vascular space dissipates into the blood stream. Abbreviations: *TF tissue factor, FII factor II, BK bradykinin*

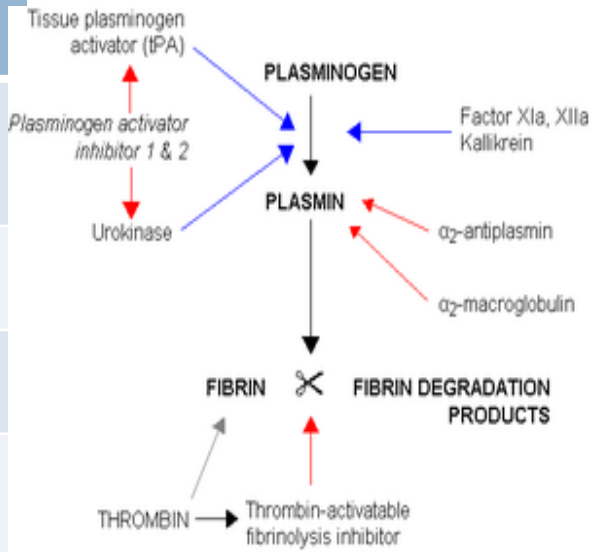
Hoffman Z, de Maat S, Hack CE, Maas C. Bradykinin: Inflammatory Product of Coagulation System. Clin Rev Allerg Immunol. 2016;51:152-61.

HAE, verhoogd D-dimeer tijdens aanval



Lab-parameters bij (H)AE
buiten en tijdens aanval

Systeem	Activatie	Parameters	Klinische betekenis
Complement	Baseline én bij aanval	C4, C2↓C4bc↑	Onbekend, rol C2a?
Stolling	Bij aanval (?)	F1+2, TAT↑	Onbekend
Fibrinolyse	Bij aanval	PAP, ***D-dimeer***↑	Speelt ws rol
Contact	Bij aanval	FXII, PK, HMWK↓ BK en cleaved HMWK↑	Oorzakelijke rol in AE-genese



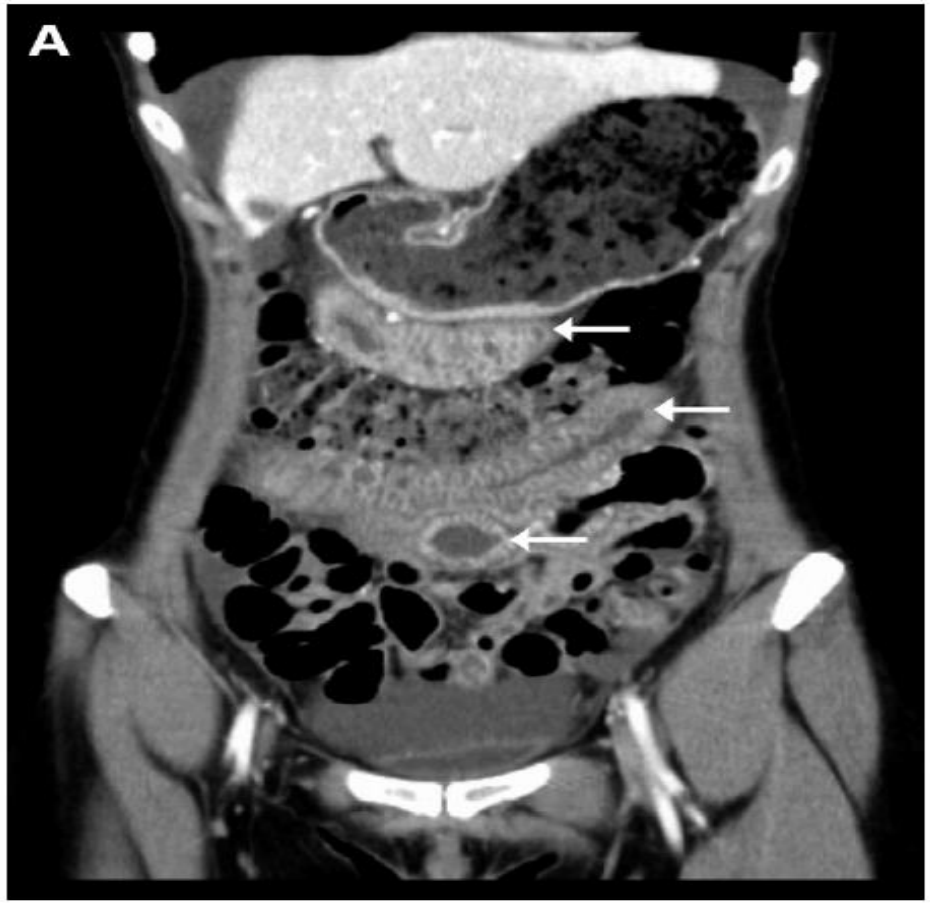
Herkennen kliniek HAE (en AAE)

- Uitlokkend moment (?):
  - meestal niet gekend
  - klein trauma (tandheelkundige ingreep), infectie, emotionele stress,
  - geneesmiddelen (zwangerschap, OAC, ACE-remmers).
- Begint met tintelend gevoel 1-2 uur vóór oedeem
- Soms (30% ?) serpigineuze roodheid (*erythema marginatum*)
- Zwelling: niet pijnlijk, niet jeukend, in 12-36 uur
- Bij 25% aanval op meerdere plekken vaak achtereenvolgens
- Verdwijnt spontaan na 1-2 dagen

AE-aanval in buik: darmwand-oedeem

Clinical Challenges and Images in GI *continued*

Abdominal Pain Beyond IBS



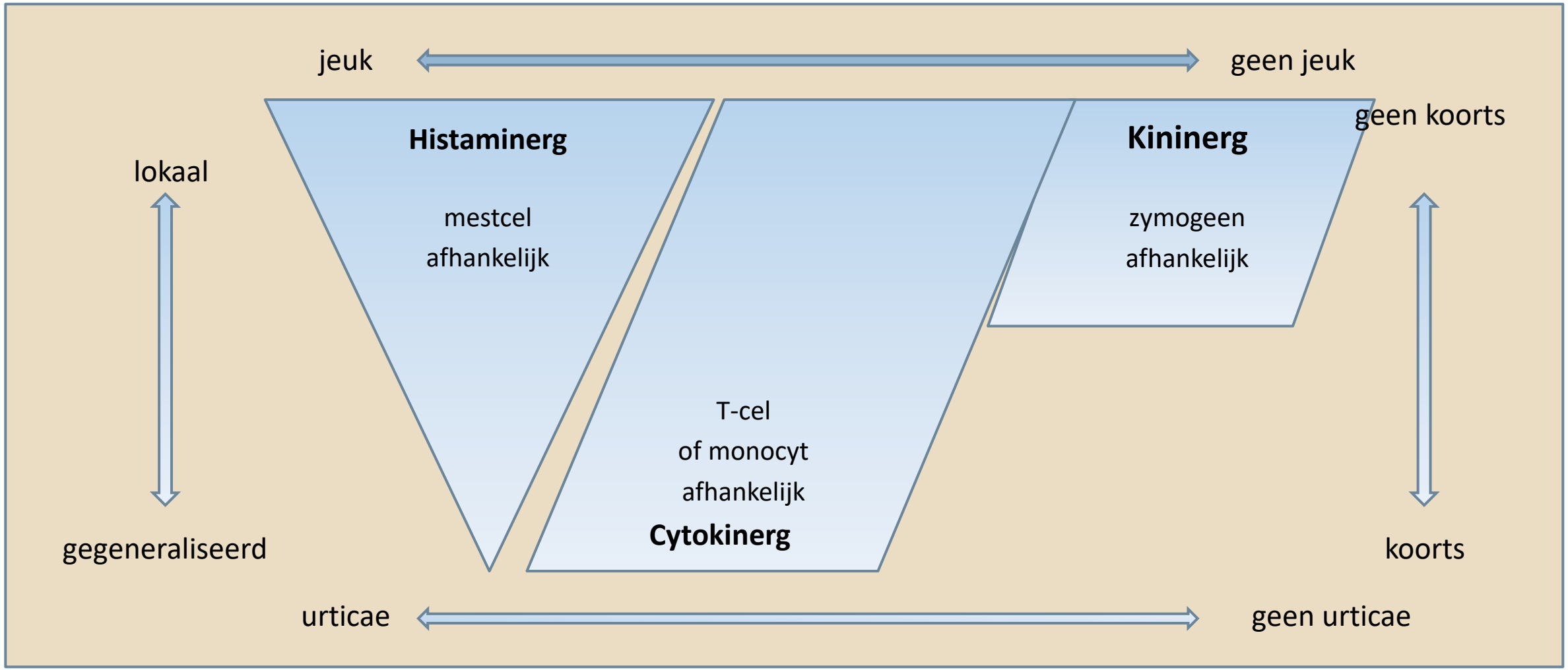
Vogetseder W, Tilg H. Abdominal pain Beyond IBS. Gastroenterology 2011;140:34,371.

Behandeling

Acuut

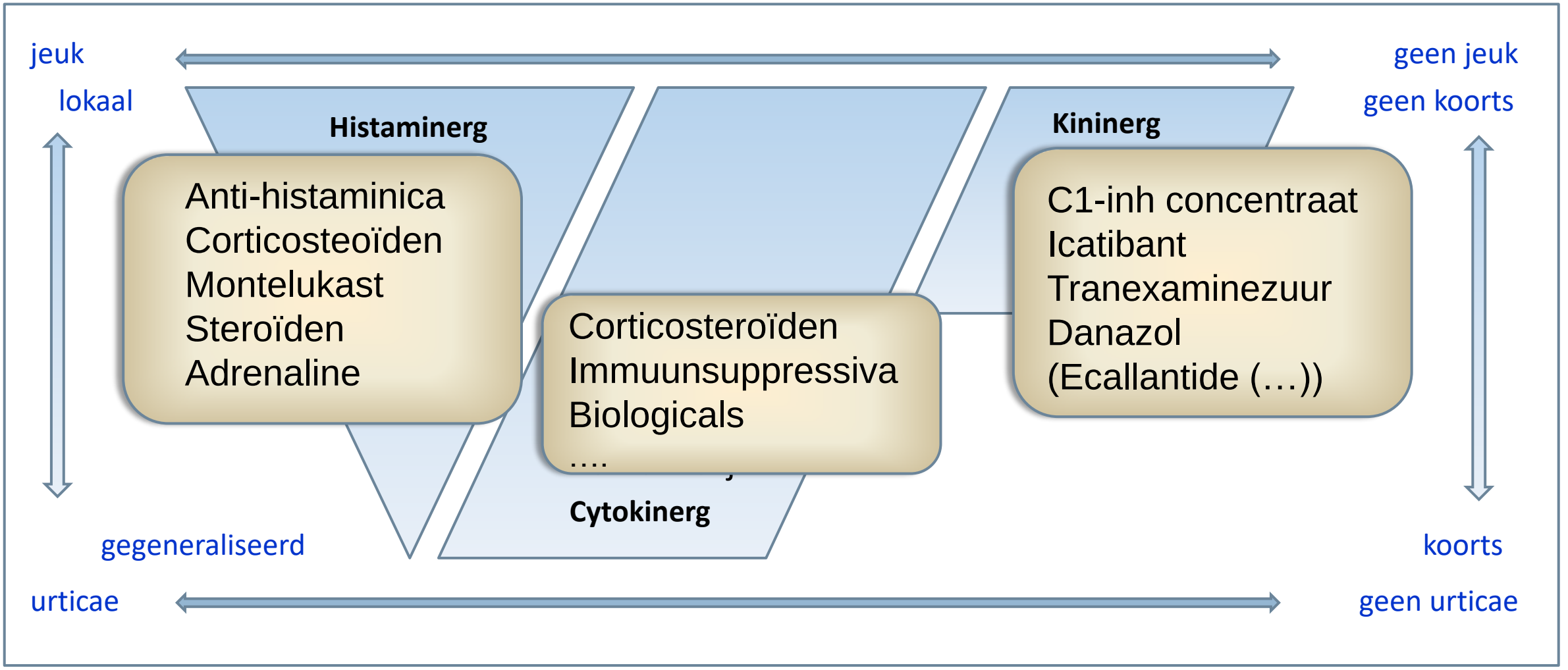
Preventief

Angioedeem



M. van Deuren

AE – schema met therapie



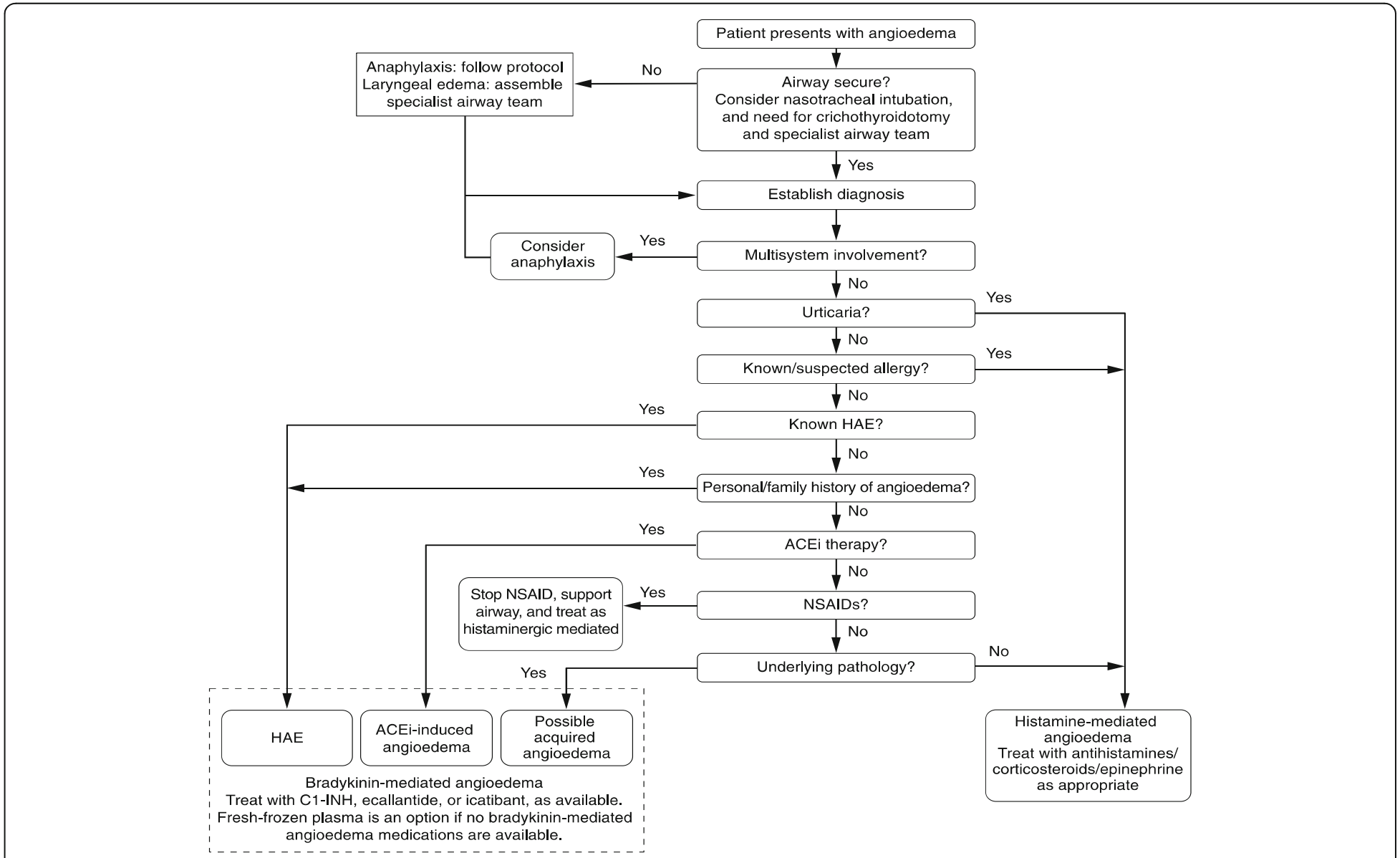
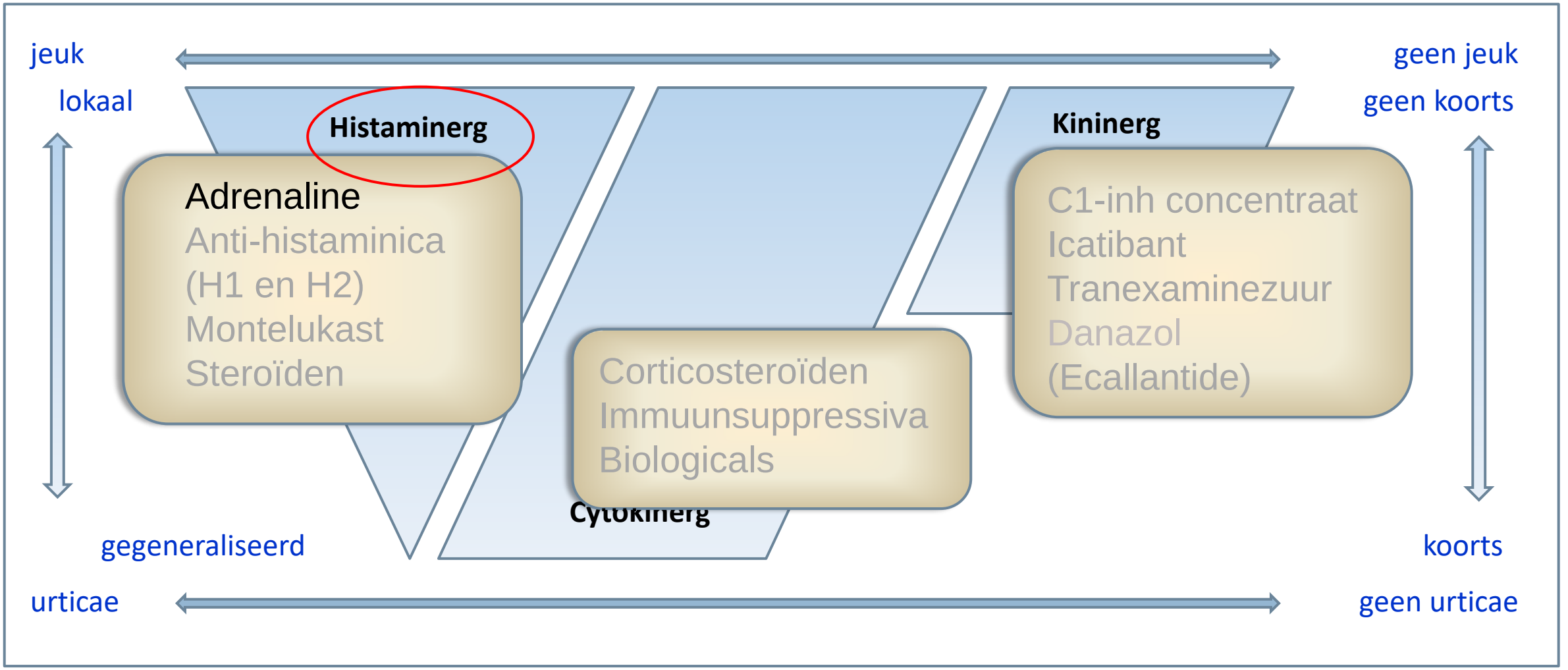


Fig. 2 Flow diagram of diagnosis of angioedema in the emergency department [21, 42]. *ACEi* angiotensin-converting enzyme inhibitor, *HAE* hereditary angioedema

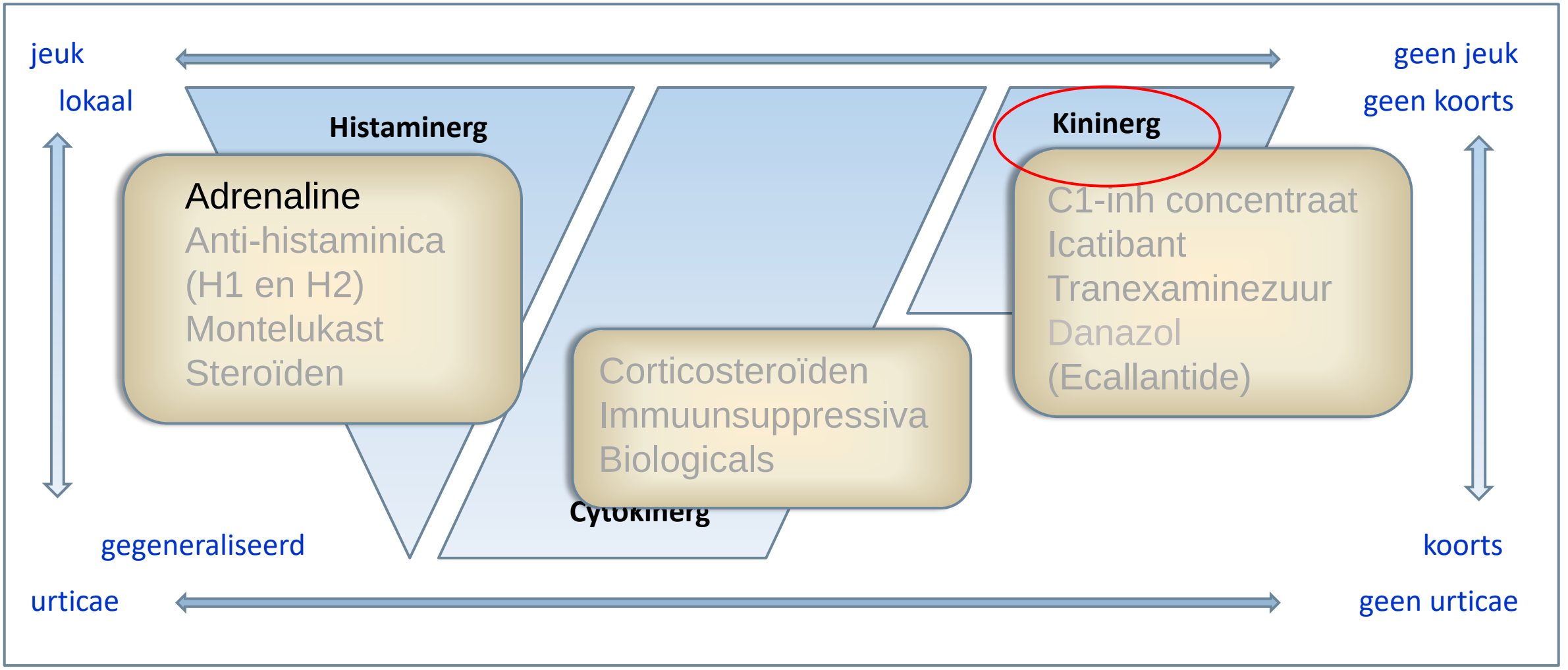
Acute treatment of angioedema

Acute treatment (in adults)				
Histamine mediated angioedema		Bradykinin mediated angioedema		
Urticaria	Allergy/anaphylaxis	HAE	Medication induced	Acquired C1-INH deficiency
Acute form: Mostly self limiting, responds well to antihistamines and glucocorticoids Physical form: Avoidance of triggers/stopping exposure, patient needs to be informed	– Adrenaline (i.m./i.v.) – Fast acting antihistamine (p.o./ i.v.) – Glucocorticoids (eg, prednisolone) [– β_2-sympathomimetic (eg, salbutamol)]	– C1-INH concentrate i. v. (human or recombinant) – Icatibant: BR2 antagonist, s.c.	To date only Off-label therapeutic options: – Antihistamine/ glucocorticoids (oral/i. v.) – C1-INH concentrate i. v. (human or recombinant) – Icatibant: BR2 antagonist, s.c.	– In general: therapy for underlying paraneoplastic/ autoimmune disorder – Acute: Icatibant s.c. (off-label)

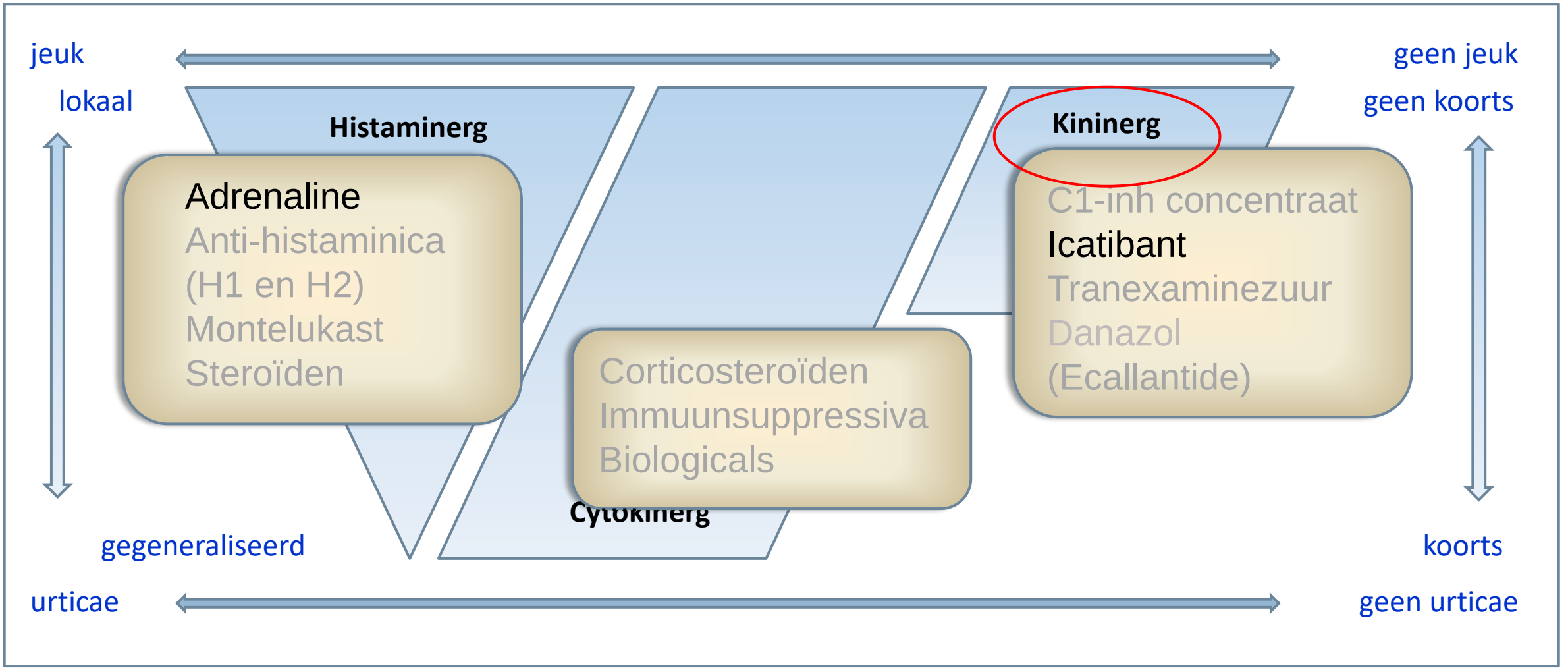
Acute treatment in AE



Acute treatment in AE



Acute treatment in AE



Icatibant effectief bij ACE-remmer geassocieerd AE

Netherlands The Journal of Medicine

LETTER TO THE EDITOR

Bradykinin-receptor antagonist icatibant: possible treatment for ACE inhibitor-related angio-oedema

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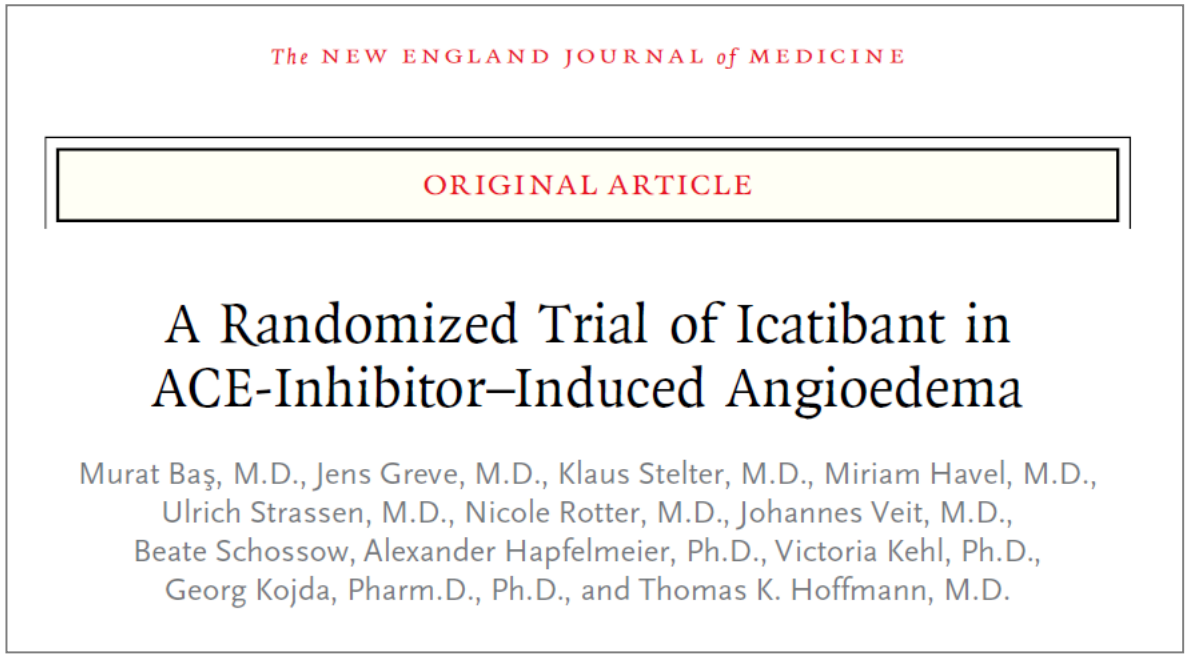
The Netherlands Journal of Medicine 2012; Oct;70(8):386-7



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Murat Baş, M.D., Jens Greve, M.D., Klaus Stelter, M.D., Miriam Havel, M.D., Ulrich Strassen, M.D., Nicole Rotter, M.D., Johannes Veit, M.D., Beate Schossow, Alexander Hapfelmeier, Ph.D., Victoria Kehl, Ph.D., Georg Kojda, Pharm.D., Ph.D., and Thomas K. Hoffmann, M.D.

The New England Journal of Medicine 2015; (Jan)372:418-25.

Icatibant bij ACE AE

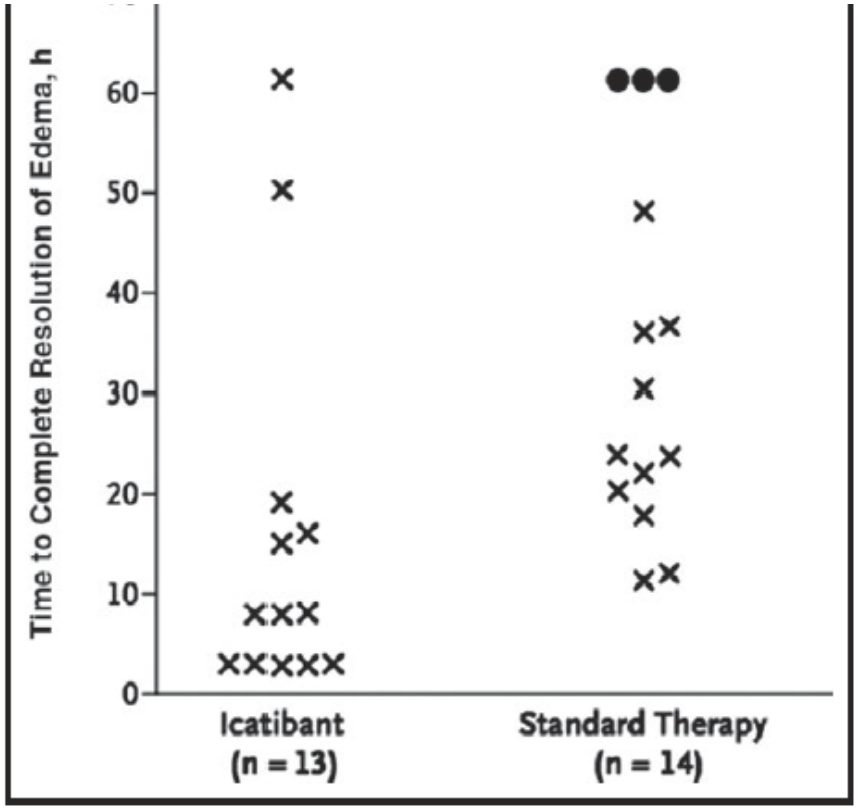


FIGURE 2 Time to complete resolution of edema according to study treatment for three patients in the standard-therapy group who required rescue intervention (circles). The time to complete resolution

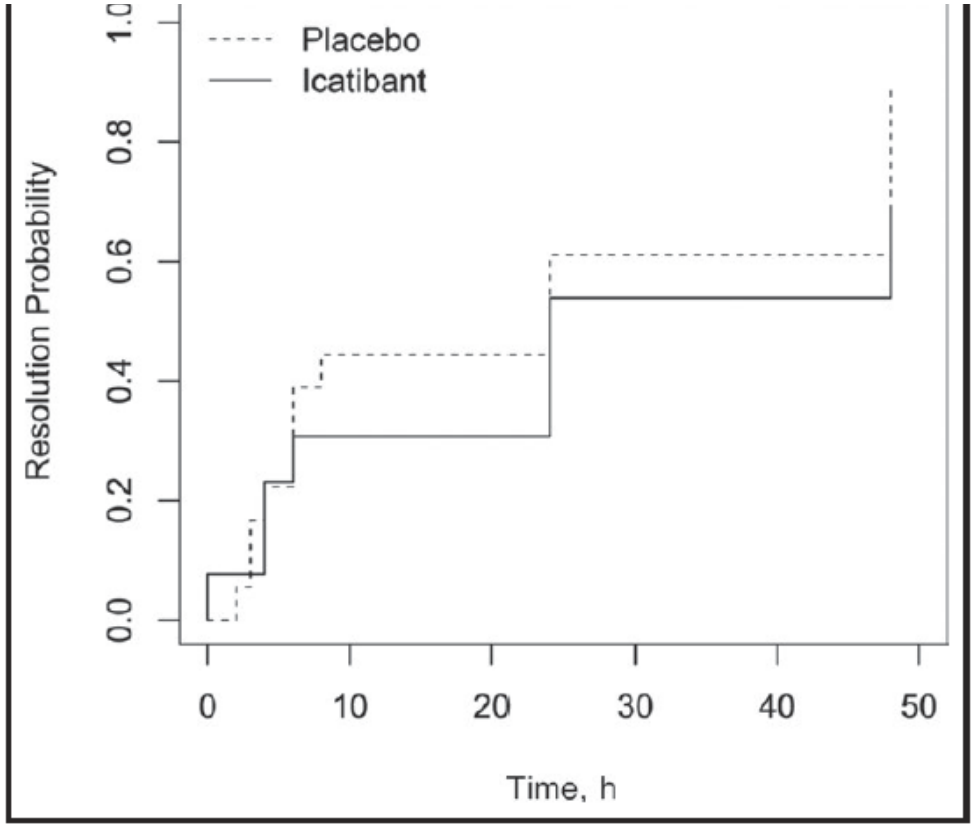


FIGURE 3 Time to resolution of primary symptoms as assessed by patients using visual analog scale in patients treated with either

Straka et al.

- icatibant

Table 3. Case Reports and Case Series of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Icatibant Was Utilized

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Icatibant	Resolution
Schmidt, 2010 (34)	42-year-old male with edema of neck, tongue, and larynx	C4 levels WNL	i.v. methylprednisolone and diphenhydramine Nebulized epinephrine C1 esterase inhibitor (dose not specified)	s.c. 30 mg, time not discussed	Symptoms began to improve in 10–15 min
Bartal, 2015 (41)	76-year-old female with edema of tongue, lips, and face	Not reported	s.c. epinephrine ×2, i.v. methylprednisolone, ranitidine, and promethazine	s.c. 30 mg, time after initial therapy not discussed	Dyspnea relieved in min, swelling almost resolved in 30 min
Charmillon, 2014 (42)	65-year-old female with edema of the face, tongue, and macroglossia	Not reported	No other pharmacologic agents reported	s.c. 30 mg, after emergent tracheostomy, time not discussed	Almost total regression of angioedema in 1 h Decanulated 3 days later
Crooks, 2014 (43)	75-year-old female with edema of the tongue and lips	Not reported	i.v. hydrocortisone, dexamethasone, and chlorphenamine i.m. epinephrine	s.c. 30 mg, after intubation on ICU day 4, then two more doses 8 h apart	Significant decrease in tongue swelling within 30 min Resolution within the first few hours of icatibant Extubation 36 h after first icatibant dose (delayed due to development of ventilator-associated pneumonia) Mild erythema around the injection site
Gallitelli, 2012 (44)	76-year-old male with edema of left side of his face	C4 levels WNL	None	s.c. 30 mg, time not discussed	10 h after swelling had resolved almost completely and the patient was discharged
Illing, 2012 (45)	62-year-old male with edema of the tongue and epiglottis	C1 esterase levels WNL	Hydrocortisone and chlorphenamine Nebulized epinephrine	s.c. 30 mg, time not discussed	No immediate benefit with progressive upper airway edema, drooling, and inability to speak Patient intubated Slow resolution was seen over 48 h was extubated
Mahajan, 2015 (46)	40-year-old female with edema of soft palate	Not reported	No other pharmacologic agents reported	Dose not specified Patient intubated, time not	Symptoms resolved in h

- icatibant

Table 3. Continued

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Icatibant	Resolution
Manders, 2012 (47)	45-year-old female with edema of tongue	Not reported	i.m. epinephrine and clemastine i.v. Di-Adreson-F (corticosteroid)	s.c. 30 mg, after progressive swelling for several hours	Symptoms started to resolve within min.
Pucar, 2015 (48)	65-year-old female with edema of the tongue, epiglottis and left arytenoid	C4 and C1 esterase inhibitor WNL	Epinephrine, i.v. dexamethasone and glycopyrrolate i.m. promethazine	s.c. 30 mg, 5 h after progression of symptoms	Improvement after 10 min, complete resolution within 5 h No development of injection site reactions
Kaeslin, 2012 (49)	56-year-old with edema of the tongue, face, cords and larynx	C1 esterase inhibitor and C4 WNL	No other pharmacologic agents reported	Dose not specified, time not discussed	Significant decrease in symptoms by 2 h
Bas, 2010 (50)	91-year-old male with edema of larynx/pharynx	All cases had no C1 esterase inhibitor deficiency. Other complement levels not reported.	None	s.c. 30 mg, on arrival	Mean time after icatibant to first symptom improvement and complete relief: 50.6 min (SD 21 min) and 4.4 h (SD 0.8 h; range 3–5.5 h) No required intubation or tracheostomy All developed local site reactions that spontaneously resolved in ~2 h
	61-year-old male with edema of the tongue		None	s.c. 30 mg, on arrival	
	67-year-old female with edema of the tongue		None	s.c. 30 mg, on arrival	
	72-year-old male with edema of larynx/pharynx		None	s.c. 30 mg, on arrival	
	81-year-old male with edema of the tongue		None	s.c. 30 mg, on arrival	
	58-year-old male with edema of larynx/pharynx		None	s.c. 30 mg, on arrival	
	82-year-old female with edema of the tongue		None	s.c. 30 mg, on arrival	
	84-year-old female with edema of larynx/pharynx and tongue		None	s.c. 30 mg, on arrival	
Bova, 2015 (51)	82-year-old male with edema of neck, sublingual and pharyngeal mucosa	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 5 h after symptom onset	25 min to symptom relief and 8 h to complete resolution
	63-year-old male with edema of face, lips, tongue, and oropharynx	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 4 h after symptom onset	30 min to symptom relief and 4 h to complete resolution
	52-year-old male with edema of tongue	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 3 h after symptom onset	35 min to symptom relief and 4 h to complete resolution

	85-year-old male with edema of left side of face and lips	WNL	Corticosteroid	s.c. 30 mg, 3 h after symptom onset	25 min to symptom relief and 4 h to complete resolution
	69-year-old male with edema of tongue	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 3 h after symptom onset	15 min to symptom relief and 9 h to complete resolution
	81-year-old male with edema of the tongue	WNL	Corticosteroid	s.c. 30 mg, 2 h after symptom onset	30 min to symptom relief and 10 h to complete resolution
	75-year-old female with edema of lips, tongue and epiglottis	WNL	Corticosteroid, antihistamine, epinephrine	s.c. 30 mg, 8 h after symptom onset	50 min to symptom relief and 5 h to complete resolution
	86-year-old female with edema of face and tongue	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 6 h after symptom onset	30 min to symptom relief and 5 h to complete resolution
	67-year-old female with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 5 h to complete resolution
	71-year-old male with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 6 h to complete resolution
	74-year-old male with edema of tongue and pharyngeal mucosa	WNL	Corticosteroid, antihistamine	s.c. 30 mg, 2 h after symptom onset	90 min to symptom relief and 6 h to complete resolution
Jacob, 2015 (52)	4 male and 2 female with 10 episodes Mean age 69 years 4 tongue and lips, 3 tongue, lips, and face, 3 tongue only	Not reported	Epinephrine corticosteroids and antihistamines in all cases	NA, time not discussed	Resolution of symptoms within 12 h for all cases No serious adverse effects
Volans, 2013 (53)	Male in 70s with edema of submental area, tongue, lower lip, neck, and supraglottis area	Not measured	i.v. chlorpheniramine and steroids	s.c. 30 mg, 10 h after symptom onset	Symptoms began to resolve at 20 min and symptom-free by 4 h Intubation avoided
	86-year-old female with edema of the tongue and supraglottis area	Not measured	i.v. chlorpheniramine, tranexamic acid Nebulized epinephrine	s.c. 30 mg, 10 h after symptom onset	Symptoms began to resolve at 20 min and symptom-free by 4 h.
Fok, 2015 (54)	75-year-old female with edema of lip, tongue, aryepiglottic folds with mucosa prolapsing onto airway, and piriform fossa	C4 WNL	11 received epinephrine and corticosteroid. 2 patients received no other therapy	s.c. 30 mg, 70 h after intubation and 73 h after symptom onset	First symptom resolution after icatibant: 7 h
	49-year-old male with edema of the face and soft palate	C4 WNL		s.c. 30 mg, at same time as intubation and 26 h after symptom onset	First symptom resolution after icatibant: 3 h
	40-year-old female with edema of base of tongue and postnasal space	C4 WNL		s.c. 30 mg, 1 h after intubation and 8 h after symptom onset	First symptom resolution after icatibant: 3 h

(*Continued*)

Table 3. Continued

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Icatibant	Resolution
	62-year-old female with edema of submental and tongue	C4 WNL		s.c. 30 mg, at same time as intubation and 16 h after symptom onset	First symptom resolution after icatibant: 2 h
	70-year-old female with edema of tongue	C4 WNL		s.c. 30 mg, 8 h after symptom onset	First symptom resolution after icatibant: 0.5 h
	76-year-old male with edema of tongue and face	C4 WNL		s.c. 30 mg, 15 h after symptom onset	First symptom resolution after icatibant: 2 h
	87-year-old male with edema of tongue, submandibular, and lip	C4 WNL		s.c. 30 mg, 4 h after symptom onset	First symptom resolution after icatibant: 1 h
	38-year-old female with edema of tongue	C4 WNL		s.c. 30 mg, 9 h after symptom onset	First symptom resolution after icatibant: 0.5 h
	59-year-old female with edema of submandibular, tongue, and floor of mouth	C4 WNL		s.c. 30 mg, 5.5 h after symptom onset	First symptom resolution after icatibant: 3.5 h
	68-year-old male with edema of tongue, soft palate, uvula, epiglottis, and false cords	C4 WNL		s.c. 30 mg, 11 h after symptom onset; received second icatibant dose 2 h after first dose due to continued edema and symptoms consisting of loud inspiratory stridor and moist cough	First symptom resolution after second dose of icatibant: 2 h
	81-year-old male with edema of lip and tongue	C4 WNL		s.c. 30 mg, 10 h after symptom onset	First symptom resolution after icatibant: 0.25 h
	81-year-old female with edema of tongue, floor of mouth, and neck	C4 WNL		s.c. 30 mg, 83 h after symptom onset	First symptom resolution after icatibant: 3 h
	80-year-old male with edema of tongue	C4 WNL		s.c. 30 mg, 4.5 h after symptom onset	First symptom resolution after icatibant: 4 h

ICU = intensive care unit; s.c. = subcutaneous; SD = standard deviation; WNL = within normal limits; i.m. = intramuscular; i.v. = intravenous.

- C1 inH

Table 2. Cases of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Complement-1 Esterase Inhibitor Was Utilized

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of C1 Esterase Inhibitor	Resolution
Lipski, 2015 (17)	77-year-old female with edema of tongue, lips, mouth, and neck	C3 complement slightly increased and others WNL	s.c. methylprednisolone and epinephrine FFP (no dose specified)	i.v. 2000 U (20 U/kg) after no improvement 4 h after FFP given	Swelling resolved within 1 h
Nielsen, 2016 (30)	61-year-old female with edema of the tongue and arytenoids	C1-INH value WNL	i.v. hydrocortisone and dexchlorpheniramine s.c. epinephrine	i.v. 1500 U over 8 h after hospital arrival and initial treatment	Over 20 min stridor subsided, patient calmed and was able to talk
Rasmussen, 2013 (31)	63-year-old male with edema of tongue, uvula, floor of mouth, and soft palate	Not reported	Epinephrine, antihistamine, and corticosteroid	i.v. 1000 U (11 U/kg), within 20 min of arrival	Significant regression within 20 min and resolution after 2 h
Hermanrud, 2016 (32)	56-year-old male with edema of tongue, uvula, right palate-pharyngeal arch, right side of the lingual tonsil and hypopharynx, piriform sinus, right aryepiglottic fold, and right ventricular fold	Not performed in acute phase	i.v. methylprednisolone	i.v. 2000 U (18 U/kg), on arrival (did not wait for methylprednisolone to have an effect)	Patient reported rapid decrease in symptoms. Severity of swelling decreased upon fiber-optic reassessment 5 h after
Urnoski, 2015 (33)	41-year-old male with edema of the lip, tongue, and airway swelling	Not reported	i.v. diphenhydramine, methylprednisolone, and ranitidine	i.v. 1500 U (17 U/kg) after intubation and 1.5 h after arrival	Swelling decreased within 1 h and extubation occurred within 16.5 h of presentation
Schmidt, 2010 (34)	42-year-old white male with edema of neck, tongue and larynx	C4 level WNL	i.v. methylprednisolone, diphenhydramine Nebulized epinephrine	Dose not specified, time not discussed	Did not resolve symptoms, patient required icatibant injection rescue therapy

C1-INH = complement 1 esterase inhibitor; FFP = fresh frozen plasma; s.c. = subcutaneous; WNL = within normal limits; i.v. = intravenous.

Behandeling ACE induced AE - FFP

ases of Angiotensin-Converting Enzyme Inhibitor Angioedema Where Fresh Frozen Plasma Was Utilized

r, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Fresh Frozen Plasma	Resolut
13 (12)	49-year-old female with right lower lip swelling, itching, and diarrhea Started metformin the day before	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart after swelling progression	2 U 7 h after second set of conventional therapy	No further prog symptoms
	64-year-old male with upper and lower lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 4 h apart after swelling progression	3 U 7 h after second set of conventional therapy	Progression sto 4 h
	58-year-old male with upper and lower lip swelling and shortness of breath	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart	2 U 2.5 h after second set of conventional therapy	Progression sto 3 h
	62-year-old male with facial and lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2.5 h apart	2 U 5 h after second set of conventional therapy	Progression sto 2 h
	51-year-old female with lip swelling, also ate crab and lobster the previous night for the first time	Not obtained	Methylprednisolone, diphenhydramine, and famotidine	2 U 3 h after conventional therapy	Progression sto unknown
	73-year-old male with face and tongue swelling	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 3 h apart	2 U at 2 h after second set of conventional therapy	Progression sto 2 h
? (13)	75-year-old male with tongue swelling	Complement levels WNL	i.v. chlorpheniramine, hydrocortisone and i.m. epinephrine, 2nd round after intubation	4 U 24 h after intubation	Symptom impr within 2 h
	45-year-old male with lip swelling	Complement levels WNL	i.m. epinephrine, methylprednisolone, diphenhydramine and famotidine	1 U 3 h after initial therapy	Symptom impr and progress cessation wit
)4 (14)	43-year-old female with lip swelling and tongue edema	Complement levels WNL	4 days of antihistamines, corticosteroids, epinephrine, cyclosporine and i.v. immunoglobulin	2 U at hospital day 4	Full resolution a
	nale with d sublingual ogressing to x. He was earlier that day patient	Not obtained	Antihistamines and corticosteroids	2 U at time not discu	
	nale with elling	Not obtained	Hydrocortisone	2 U 3 h after convent therapy failed	
	nale with elling	Not obtained	No other therapy given	2 U 3 h after arrival	
	emale with tongue, lips, d neck	C3 complement slightly increased and others WNL	s.c. methylprednisolone and epinephrine	Not specified	
	nale with m base of the to the cricoid nd snugly otracheal tube ritubal air	Complement levels WNL	i.v. hydrocortisone and antihistamines	2 U at > 48 h after intubation	
	emale with the tongue	Not reported	i.v. diphenhydramine and methylprednisolone Nebulized racemic epinephrine	4 U after nasal intuba	
	emale with , bilateral ema, edema of , laryngeal epiglottis, left ic fold and left	Not reported	i.v. methylprednisone, diphenhydramine, subcutaneous epinephrine, and inhaled epinephrine	1 U approximately 58 after symptom ons	

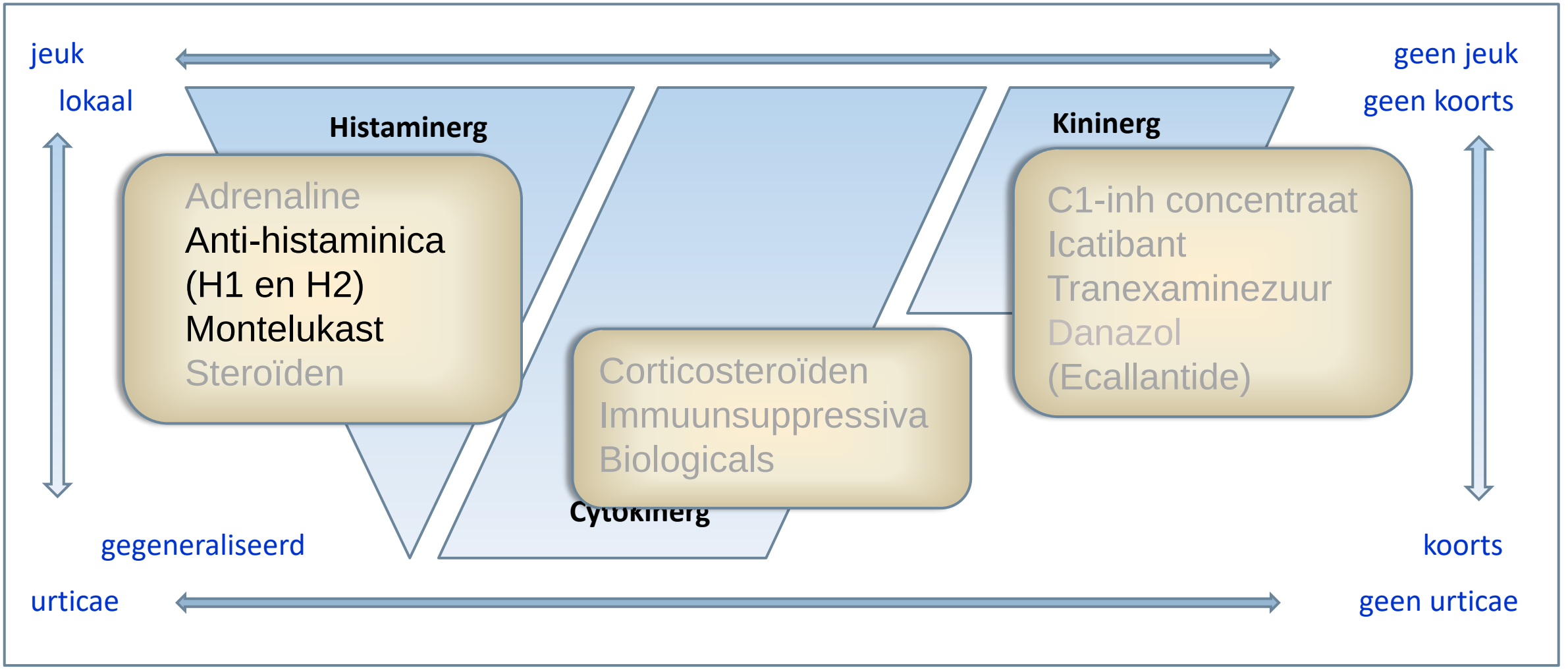
ramuscular; s.c. = subcutaneous; WNL = within normal limits; i.v. = intravenous; U = units.

First Author, Year	Case Description	Complement Proteins	Other Therapy Administered	Dose and Timing of Fresh Frozen Plasma	Resolution
Hassen, 2013 (12)	49-year-old female with right lower lip swelling, itching, and diarrhea Started metformin the day before	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart after swelling progression	2 U 7 h after second set of conventional therapy	No further progression of symptoms
	64-year-old male with upper and lower lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 4 h apart after swelling progression	3 U 7 h after second set of conventional therapy	Progression stopped within 4 h
	58-year-old male with upper and lower lip swelling and shortness of breath	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2 h apart	2 U 2.5 h after second set of conventional therapy	Progression stopped within 3 h
	62-year-old male with facial and lip swelling	Complement levels WNL	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 2.5 h apart	2 U 5 h after second set of conventional therapy	Progression stopped within 2 h
	51-year-old female with lip swelling, also ate crab and lobster the previous night for the first time	Not obtained	Methylprednisolone, diphenhydramine, and famotidine	2 U 3 h after conventional therapy	Progression stopped, time unknown
	73-year-old male with face and tongue swelling	Not obtained	Two rounds of i.m. epinephrine, methylprednisolone, diphenhydramine, and famotidine, 3 h apart	2 U at 2 h after second set of conventional therapy	Progression stopped within 2 h
Karim, 2002 (13)	75-year-old male with tongue swelling	Complement levels WNL	i.v. chlorpheniramine, hydrocortisone and i.m. epinephrine, 2nd round after intubation	4 U 24 h after intubation	Symptom improvement within 2 h
	45-year-old male with lip swelling	Complement levels WNL	i.m. epinephrine, methylprednisolone, diphenhydramine and famotidine	1 U 3 h after initial therapy	Symptom improvement and progression cessation within 2 h
Warrier, 2004 (14)	43-year-old female with lip swelling and tongue edema	Complement levels WNL	4 days of antihistamines, corticosteroids, epinephrine, cyclosporine and i.v. immunoglobulin	2 U at hospital day 4	Full resolution after 2–4 h

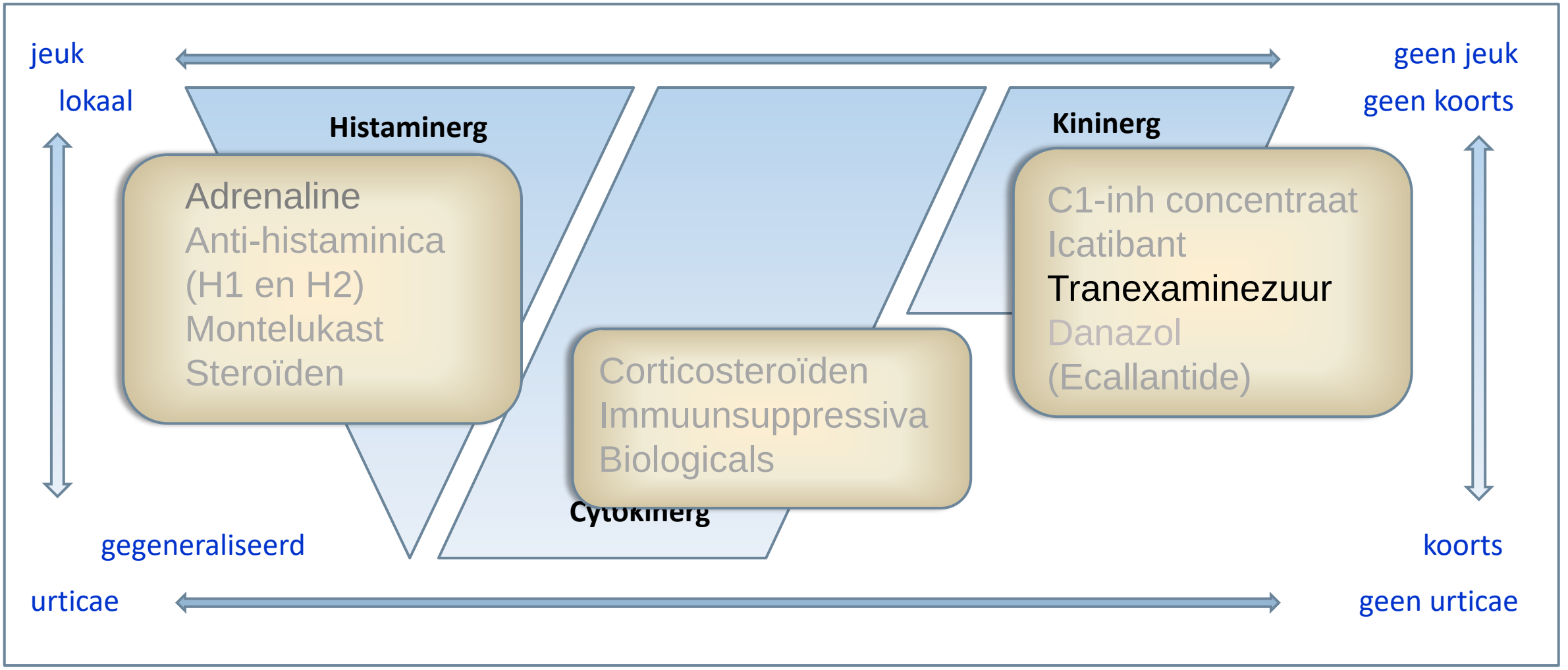
Bolton, 2012 (15)	76-year-old male with tongue and sublingual edema progressing to oropharynx. He was intubated earlier that day for an outpatient procedure	Not obtained	Antihistamines and corticosteroids	2 U at time not discussed	Full resolution after 2 h
Stewart, 2012 (16)	52-year-old male with tongue swelling	Not obtained	Hydrocortisone	2 U 3 h after conventional therapy failed	Full resolution during infusion of 2nd unit
	79-year-old male with tongue swelling	Not obtained	No other therapy given	2 U 3 h after arrival	Full resolution after 4 h
Lipski, 2015 (17)	77-year-old female with edema of tongue, lips, mouth, and neck	C3 complement slightly increased and others WNL	s.c. methylprednisolone and epinephrine	Not specified	No improvement after 4 h
Tharayil, 2014 (18)	60-year-old male with edema from base of the tongue up to the cricoid cartilage and snugly fitting endotracheal tube with no peritubal air	Complement levels WNL	i.v. hydrocortisone and antihistamines	2 U at > 48 h after intubation	Patient got tracheostomy due to persistent airway edema on day 11
Shiber, 2014 (19)	67-year-old female with edema of the tongue	Not reported	i.v. diphenhydramine and methylprednisolone Nebulized racemic epinephrine	4 U after nasal intubation	Symptoms improved over the next 6 h and was extubated the next morning
Atalay, 2015 (20)	77-year-old female with dysphagia, bilateral orbital edema, edema of the tongue, laryngeal face of the epiglottis, left aryepiglottic fold and left arytenoid	Not reported	i.v. methylprednisone, diphenhydramine, subcutaneous epinephrine, and inhaled epinephrine	1 U approximately 58 h after symptom onset	Tracheotomy and cardiac arrest before completion of FFP infusion

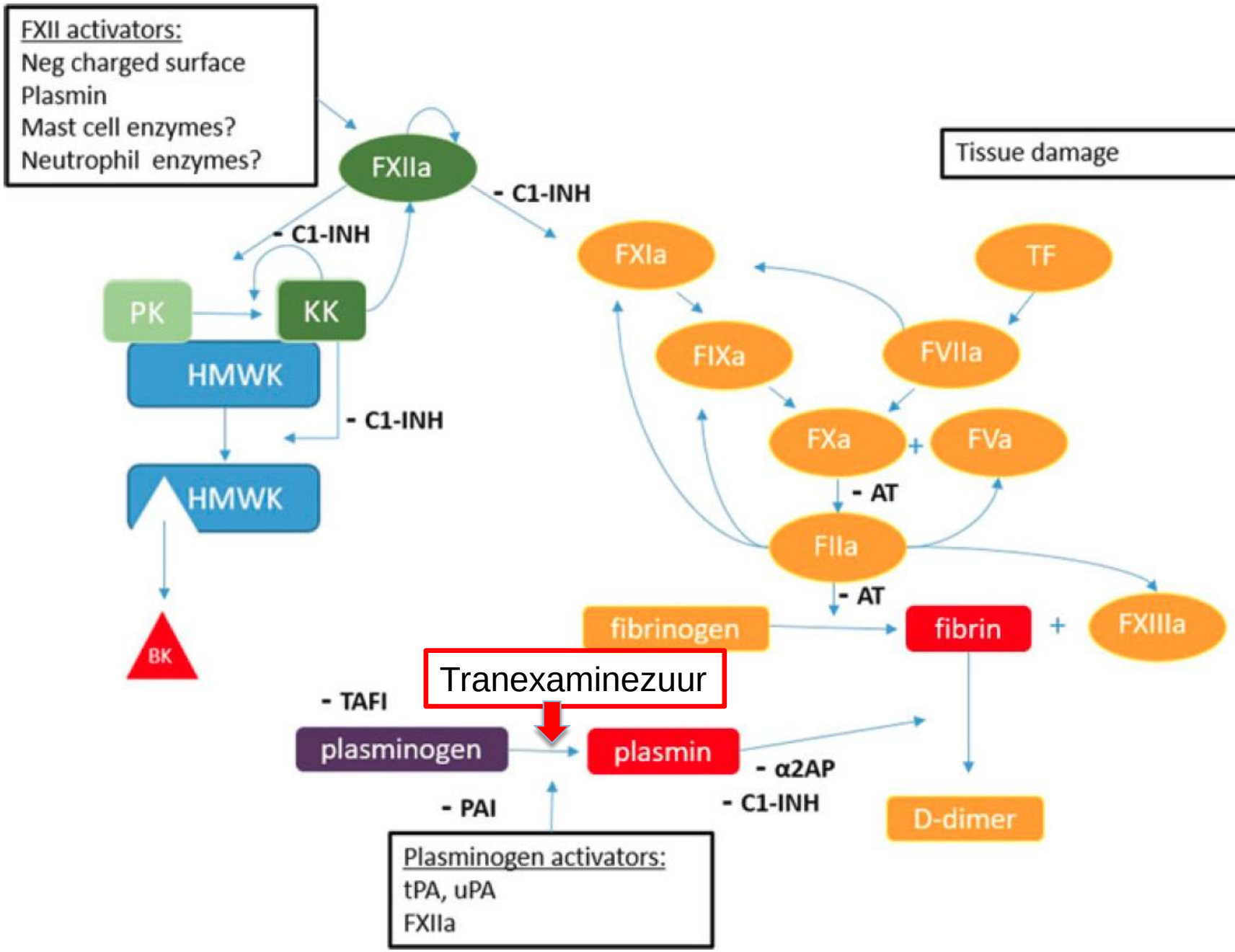
FFP = fresh frozen plasma; i.m. = intramuscular; s.c. = subcutaneous; WNL = within normal limits; i.v. = intravenous; U = units.

Preventive treatment



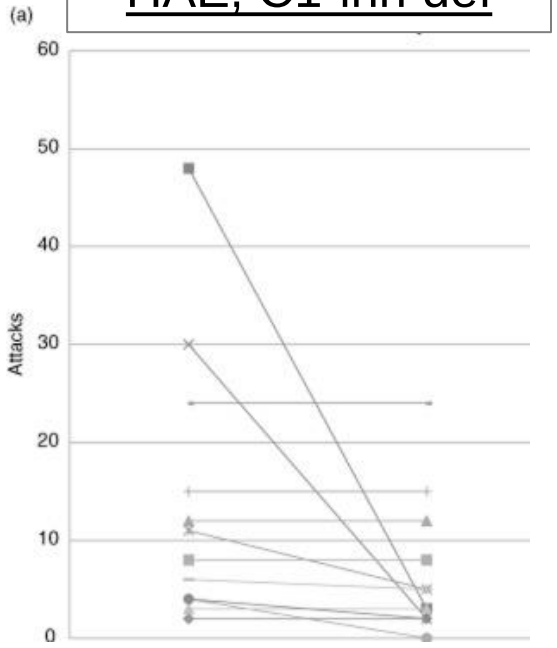
Preventive treatment in AE



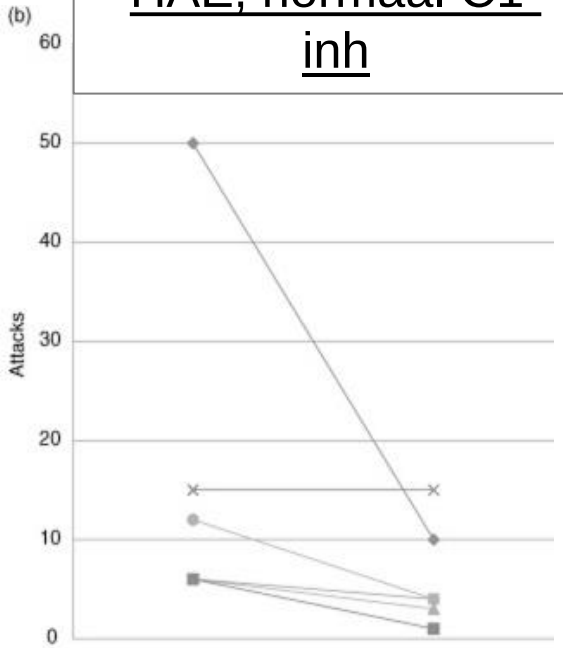

FXII activators:
Neg charged surface
Plasmin
Mast cell enzymes?
Neutrophil enzymes?
FXIIa
- C1-INH
- C1-INH
PK
KK
HMWK
- C1-INH
HMWK
BK
Tissue damage
FXIa
TF
FIXa
FVIIa
FXa
+
FVa
- AT
FIIa
- AT
fibrinogen
fibrin
+
FXIIIa
Tranexaminezuur
- TAFI
plasminogen
plasmin
- α2AP
- C1-INH
- PAI
D-dimer
Plasminogen activators:
tPA, uPA
FXIIa

TA als profylacticum vooral (?) bij idiopathisch AE

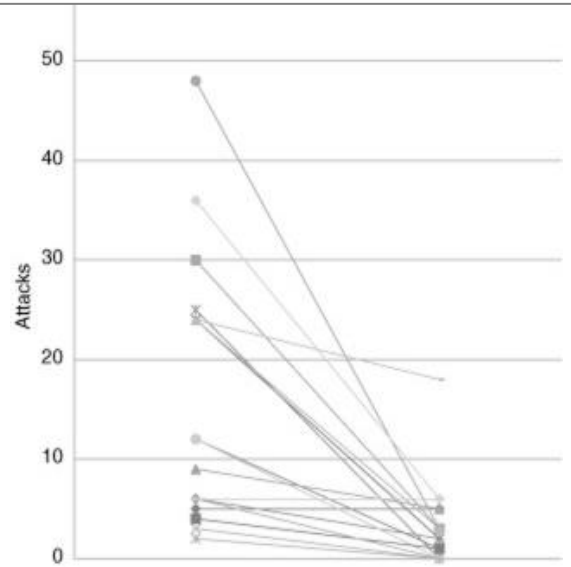
HAE, C1-inh def



HAE, normaal C1-inh



Idiopathisch non-histaminerg AE



Winteneberger G, I Boccon-Gibod, D Launay et al.
Tranexaminic acis as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. Clin Exp Immunol 2014;178:112-7

Bucher *et al. Clin Transl Allergy (2017) 7:27*
DOI 10.1186/s13601-017-0164-9

Clinical and Translational Allergy

BRIEF COMMUNICATION

Open Access

Idiopathic non-histaminergic acquired angioedema: a case series and discussion of published clinical trials

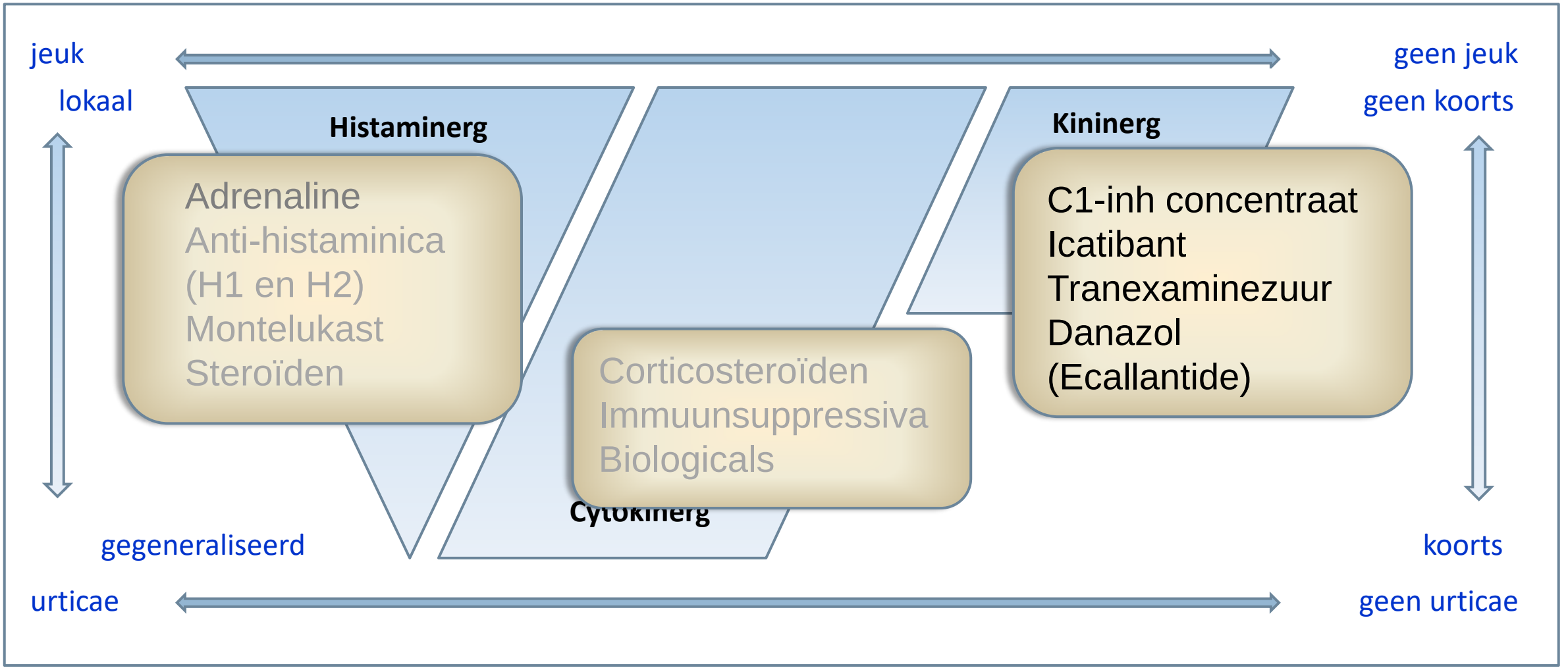
Martin Christian Bucher[1], Tatjana Petkovic[2], Arthur Helbling[3] and Urs Christian Steiner[1*]

Table 2 Comparison of the therapies most often applied in InH-AAE

	Reference	Number of patients	Drug/doses	Response: cr/pr/nr (number of patients)
Medical influence of coagulation and contact activation pathway				
Tranexamic acid	[9]	2	1–4 g per day	cr 2
	[10]	1	*NA*	cr 1
	[11]	15	0.5–3 g per day	cr 8/pr 7
	[12]	23	0.5–3 g per day	cr 12/pr 11
	[13]	19	1–3 g per day	cr 4/pr 15
	[3]	38	0.5–3 g per day	pr 37/nr 1
Ecallantide	[15]	1	30 mg (during attacks)	cr 1
	[16]	1	30 mg (during attacks)	cr 1
	[14]	1	*NA*	pr 1
Icatibant	[17]	1	30 mg (during attacks)	cr 1
	[18]	1	30 mg (during attacks)	cr 1
	[14]	1	*NA*	pr 1
	[19]	2	30 mg *(during attack)*	pr 2
C1-INH	[14]	1	1000U twice weekly	cr 1
	[19]	2	*NA*	pr 2
	[20]	1	1000U twice weekly	cr 1
Medical influence of the hormonal axis				
Progestin	[21]	20	Various dosages depending the progestin	cr 6/pr 10/nr 4
Medical influence of IgE antibodies and mast cell (Omalizumab)				
Omalizumab	[46]	3	300 mg every 3–4 weeks; 375 mg every 2 weeks	Cr 3
	[23]	1	300 mg every 4 weeks initially, then reduced to 300 mg every 8 weeks	cr 1
	[24]	1	300 mg every 4 weeks	cr 1
	[25]	8	300 mg every 4 weeks initially, then reduced to doses and intervals according to symptoms	cr 8
	[27]	2	375 mg every 2 weeks initially, then reduced to 375 mg every 4 weeks	cr 2
	[26]	5	300 mg every 2–4 weeks	cr 5
Other immunosuppressants or immunomodulatory therapies				
Dapsone	[29]	1	50 mg per day	cr 1
Ciclosporin	[28]	1	300 mg per day	nr 1
FFP	[30]	1	4 units	cr 1
Rituximab	[31]	1	560 mg (375 mg/m^2 body surface area) weekly for 4 weeks	cr 1
Cannabis	[32]	1	20 g per month, inhaled 2–3× per week	cr 1

cr complete remission, *pr* partial remission, *nr* no response, *NA* not available, *FFP* fresh frozen plasma

Preventive treatment in HAE



Hereditary Angioedema

Treatment options worldwide…

- Replacement with C1 INH : (FFP*) Cetor/Cinryze*, Berinert, Rhucin
- Stimulation of biosythesis : Danazol*
- Reduced consumption : (Tranexamic acid Cyklokapron *)
- Inhibition of mediators : Ecallantide, Icatibant*

- *available in the Netherlands

Table 2 Targeted treatment of HAE [21, 63–66]

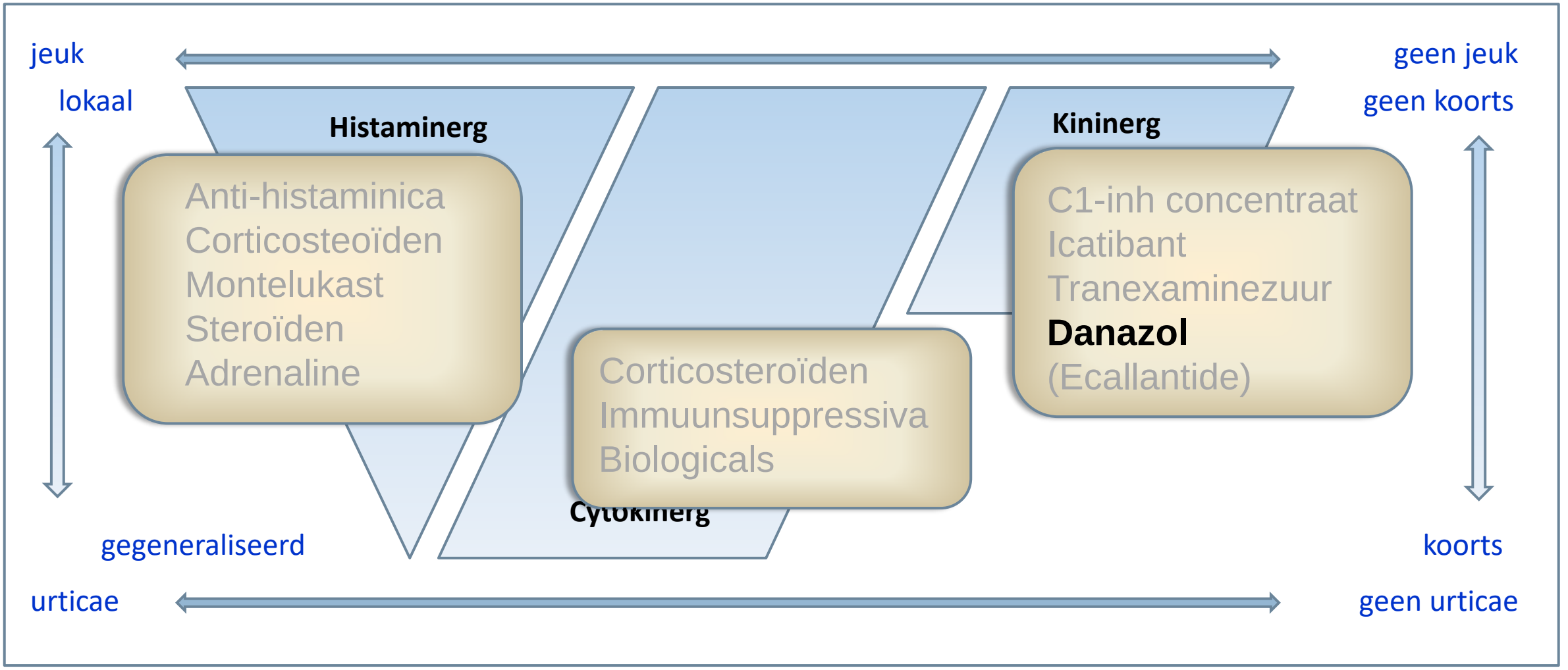
Drug	FDA-approved indication	Mechanism of action	Dose/route/ price*	Time to onset of symptom relief	Adverse effects
Plasma-derived C1-INH (Berinert)	Acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients (no lower age limit established)	C1-INH protein replacement	20 units/kg IV $8991 (1500 units)	Median: 48 min	Common: dysgeusia Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections
Plasma-derived C1-INH (Cinryze)	Prophylaxis of HAE attacks in adults and pediatric patients ≥11 years of age	C1-INH protein replacement	1000 units IV $5704 (1000 units)	Median: 30 min	Common: dysgeusia Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections
Recombinant C1-INH (Ruconest)	Acute HAE attacks in adults and pediatric patients ≥11 years of age; effectiveness not established for laryngeal attacks	C1-INH protein replacement	50 units/kg IV $12,142 (4200 IU)	Median: 90 min	Common: sinusitis, rash, pruritus Rare: anaphylaxis
Ecallantide (Kalbitor)	Acute HAE attacks in patients ≥12 years of age	Plasma-kallikrein inhibitor	30 mg SC $14,090 (30 mg)	Median: 67 min	Common: headache, nausea, pyrexia, injection site reactions Uncommon: anaphylaxis (must be administered by a health care professional)
Icatibant (Firazyr)	Acute HAE attacks in adults ≥18 years of age	Bradykinin-2 receptor antagonist	30 mg SC $10,037 (30 mg)	Median: 2 h	Common: injection site reactions, pyrexia, increased transaminases, dizziness Theoretical: worsening of an ongoing ischemic event

Behandel opties HAE

Treatment types in the Netherlands:

- Maintenance treatment : Danazol, C1-esteraseremmer
- Hospital treatment of attacks: Tranexamic acid, C1- INH, Icatibant
- “Self treatment” of attacks:, C1-INH

Preventive treatment Danazol (in HAE)



C1-inh deficientie, Danazol en APP-activiteit↑

Immune deficiencies, infection, and systemic immune disorders

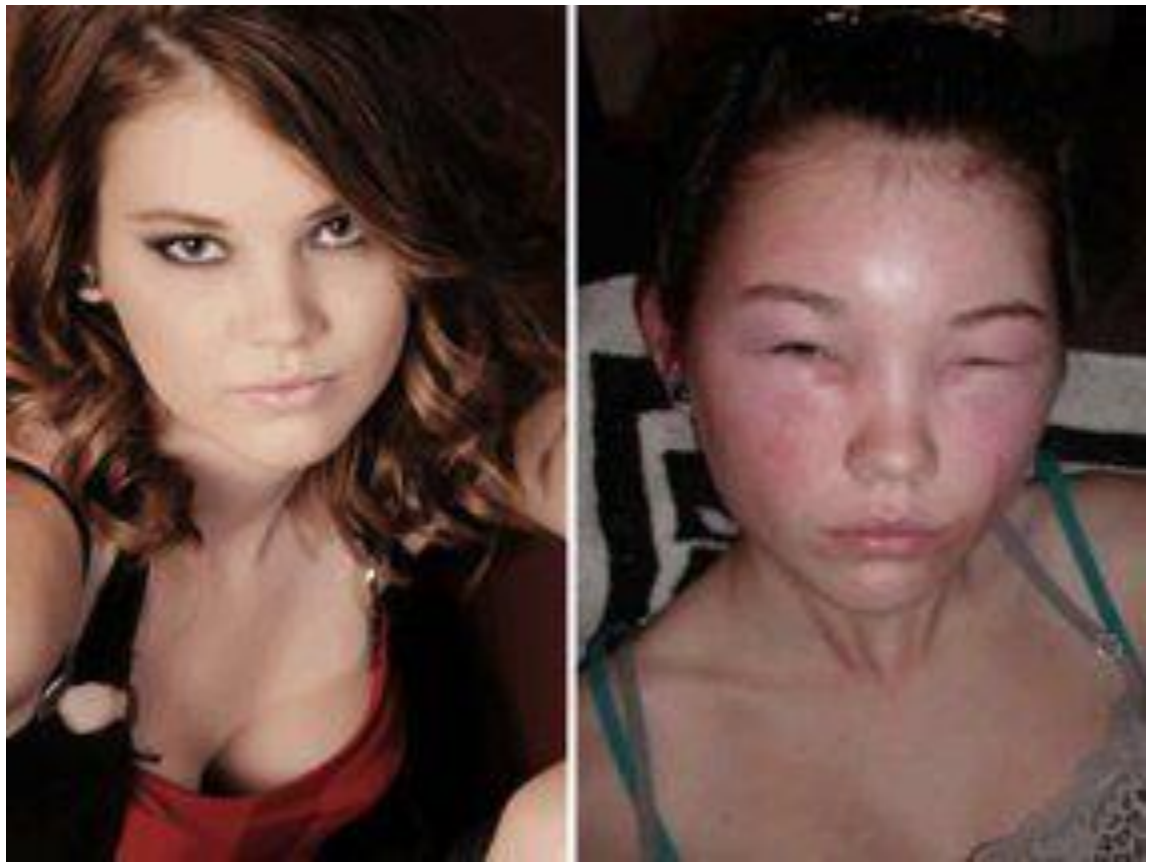
Metallopeptidase activities in hereditary angioedema: Effect of androgen prophylaxis on plasma aminopeptidase P

Christian Drouet, PhD,[a,b]* Anik Désormeaux,[c] Josée Robillard, MSc,[c] Denise Ponard,[b] Laurence Bouillet, MD, PhD,[b] Ludovic Martin, MD, PhD,[d] Gisèle Kanny, MD, PhD,[e] Denise-Anne Moneret-Vautrin, MD,[e] Jean-Luc Bosson, MD, PhD,[b] Jean-Louis Quesada, MSc,[f] Margarita López-Trascasa, PhD,[g] and Albert Adam, PhD[c]* *Grenoble, Angers, and Nancy, France, Montreal, Quebec, Canada, and Madrid, Spain*

Background: Aminopeptidase P (APP) plays an important role in the catabolism of kinins in human plasma, mostly for des-Arg^9-bradykinin. Impaired degradation of this active bradykinin metabolite was found to be associated with a decreased APP activity in hypertensive patients who experienced angioedema while being treated with angiotensin

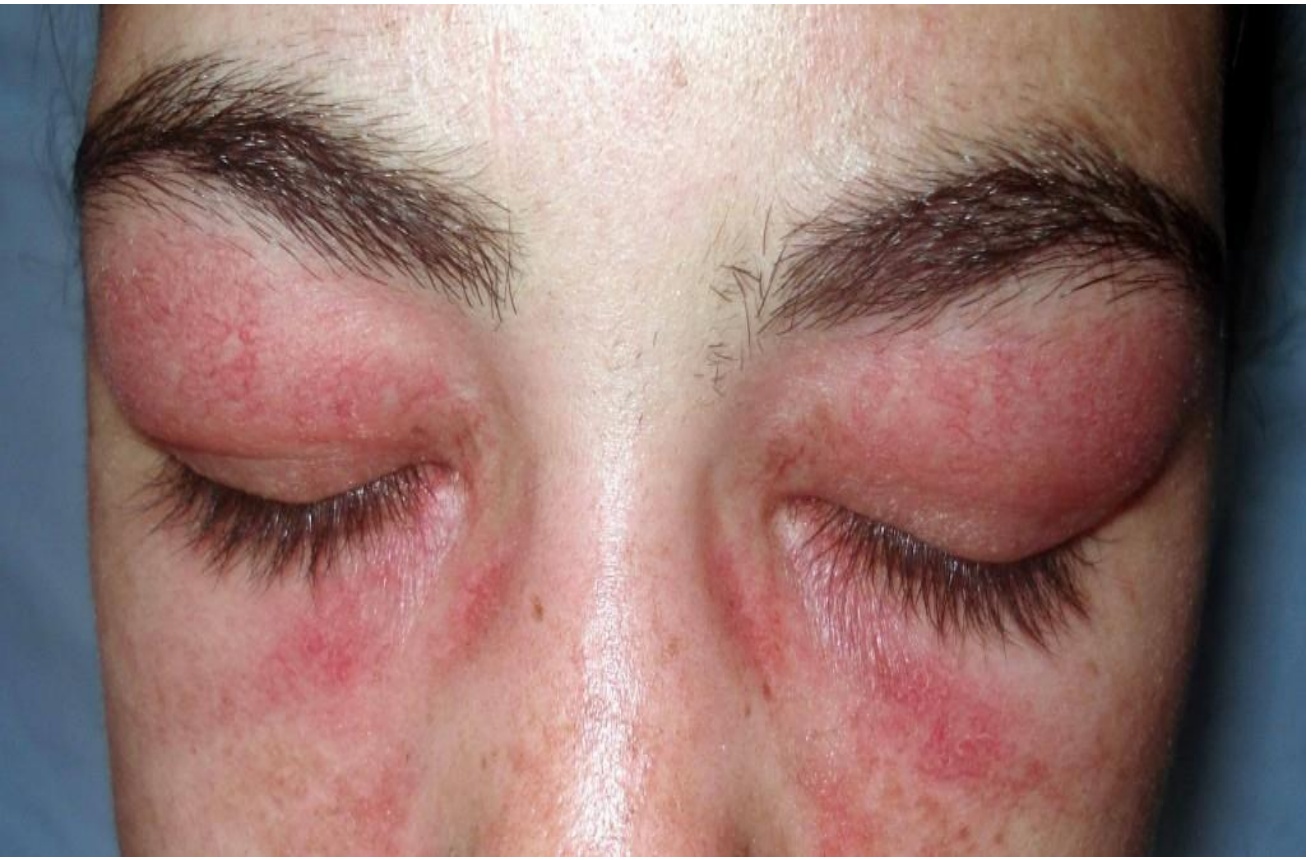
Conclusion: In addition to the effect on circulating CI-INH levels, the increase in APP levels brought on by androgens could contribute to a more effective control of the kinin accumulation considered to be responsible for the symptoms of angioedema.
(J Allergy Clin Immunol 2008;121:429-33.)

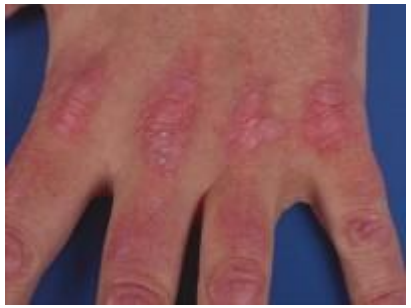
Differentiaaldiagnose



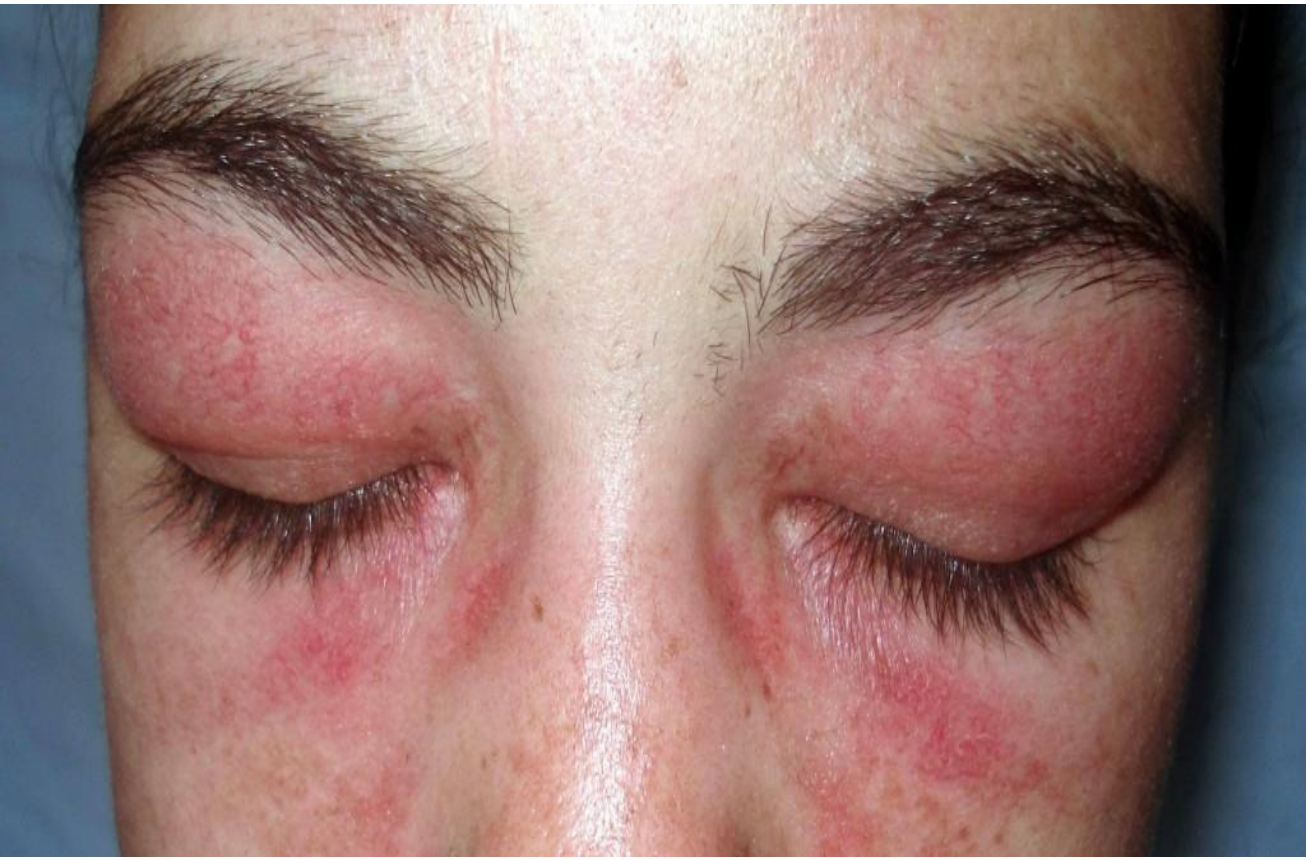
Contact dermatitis: PPD - paraphenyldiamine

- haarverven
- tijdelijke henna tatoeages
- halffabrikaat bij de productie van azo-verf, bontverf, lederverf
- in sinasappelschil
- in sommige fotokopieer systemen
- in druk-kleurstoffen

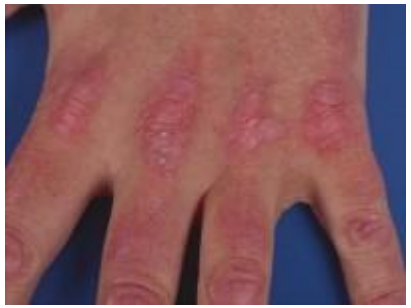




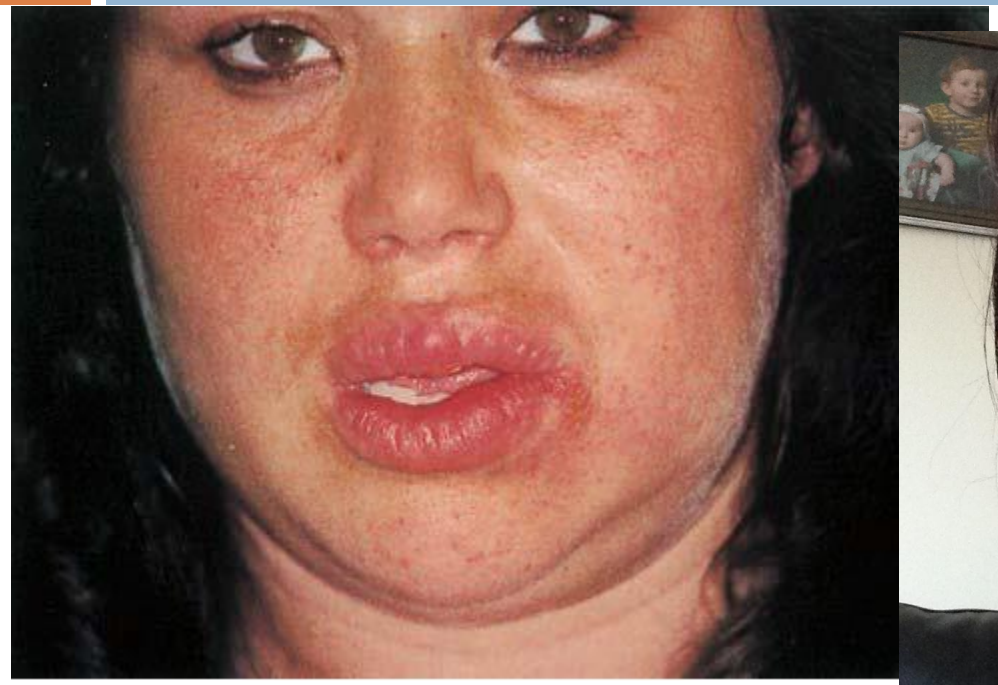
Dermatomyositis

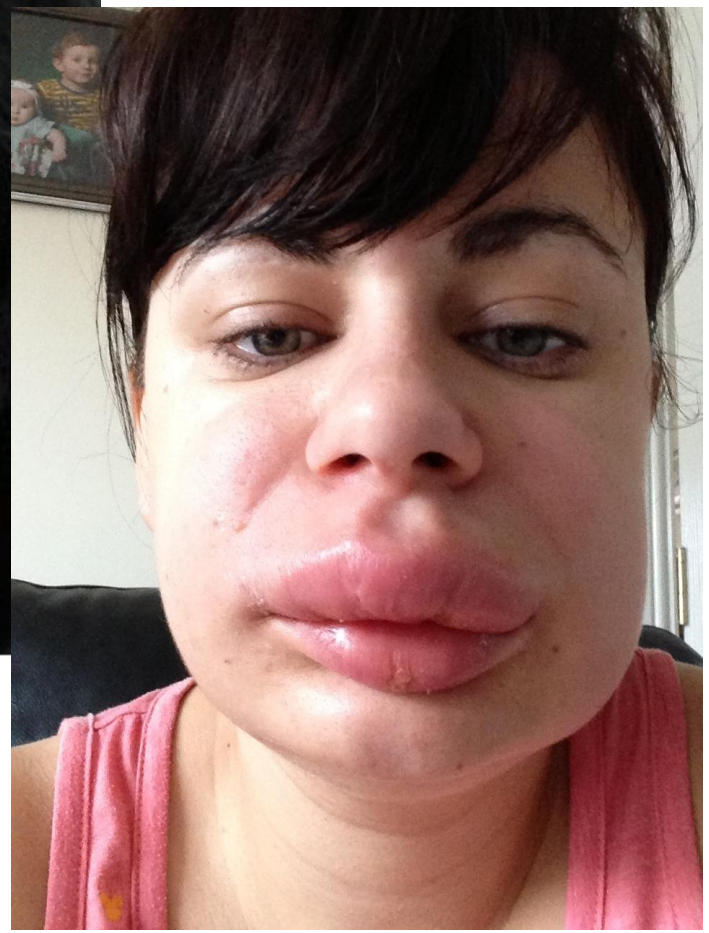


- Proximale spierzwakte
- Heliotrope rash
- Gottron's sign



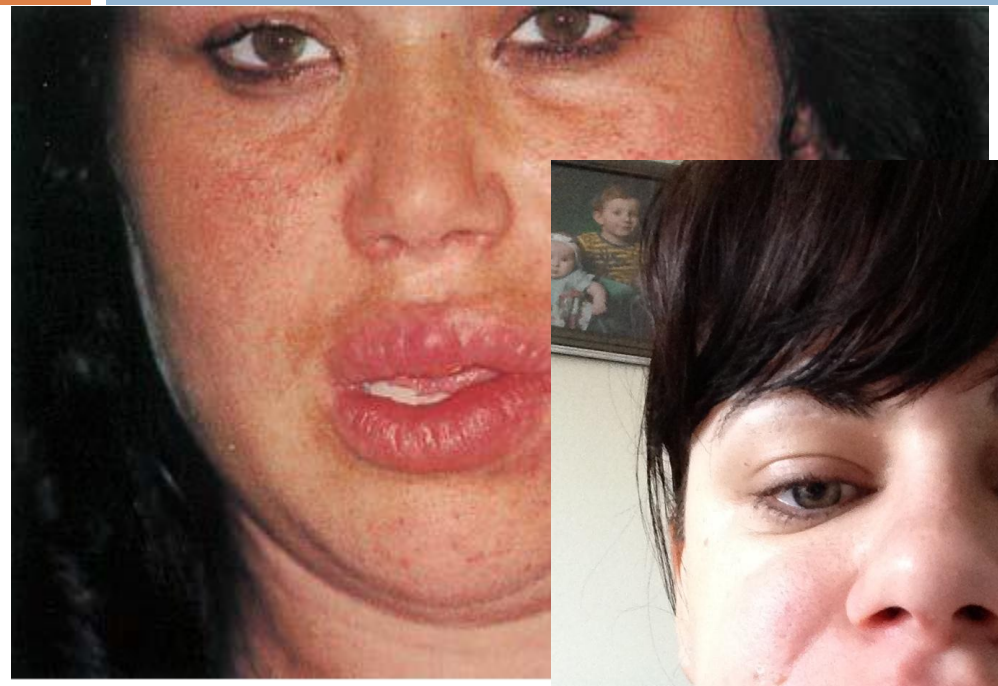
- Vermoeidheid, gewichtsverlies, koorts

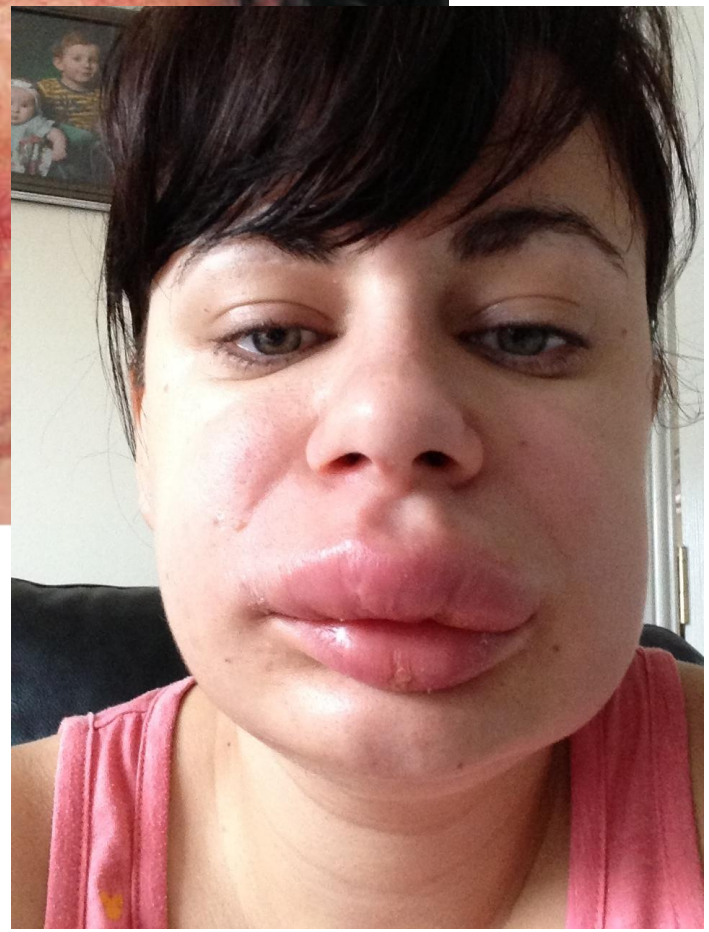





Globalskinatlas.com

Melkerson Rosenthal syndroom

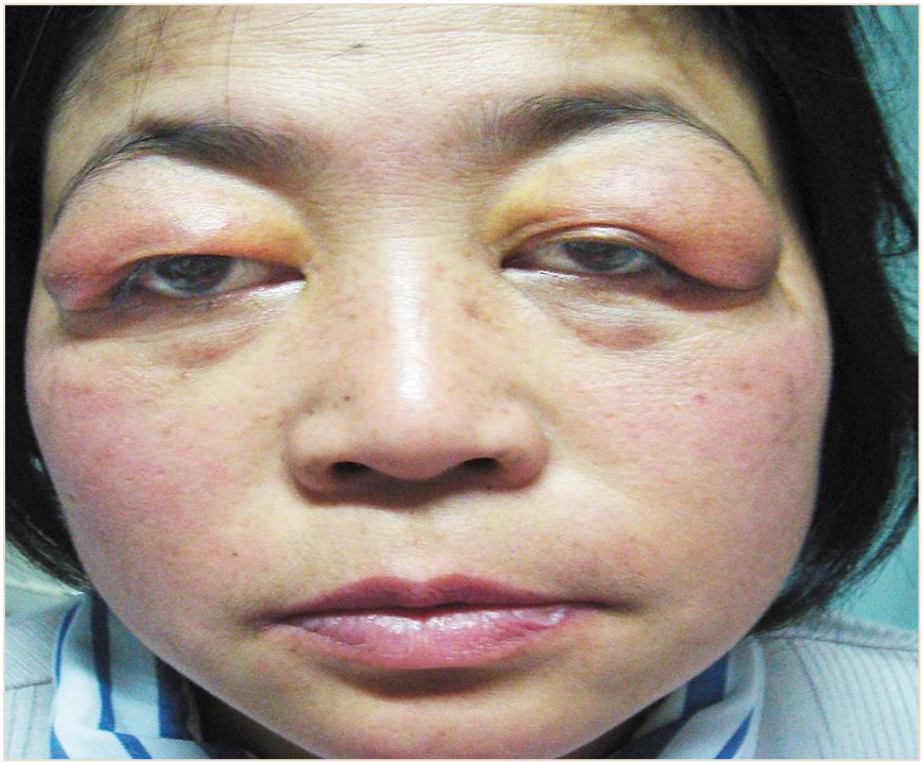




- Cheilitis granulomatosa
- Orofaciaal oedeem
- (voorheen) n. facialis paralyse
- Fissuur tong (Lingua plicata)

This patient presented with xerostomia and xerophthalmia.

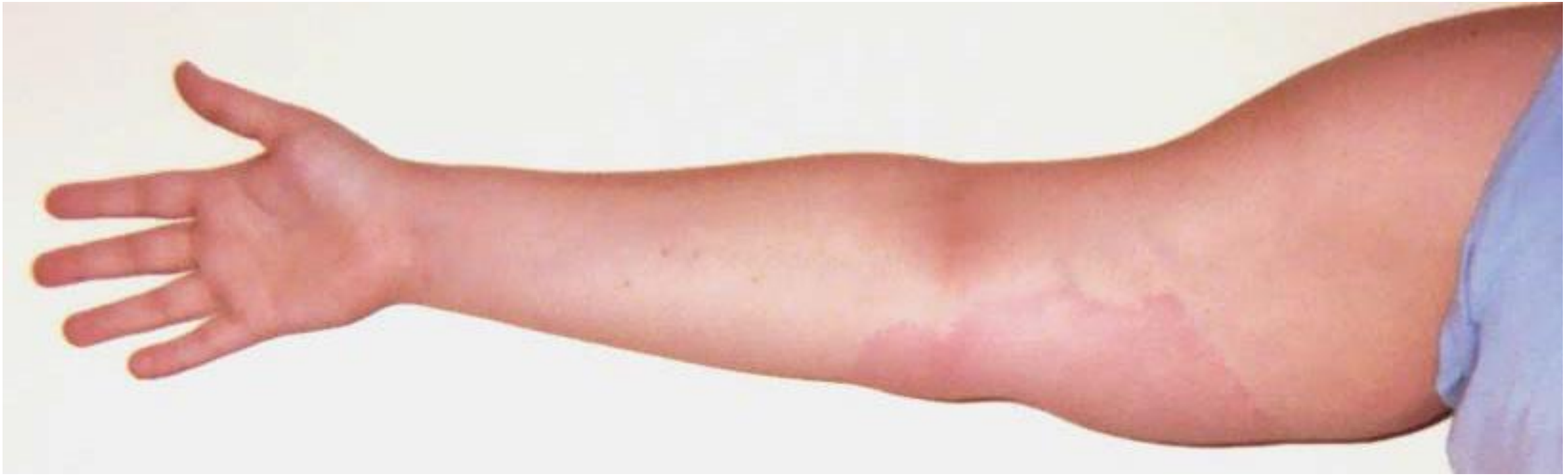
1. Angioedema
2. Contact dermatitis
3. Follicular lymphoma
4. Hypothyroidism
5. Sjögren's syndrome



5. Sjögren's syndrome

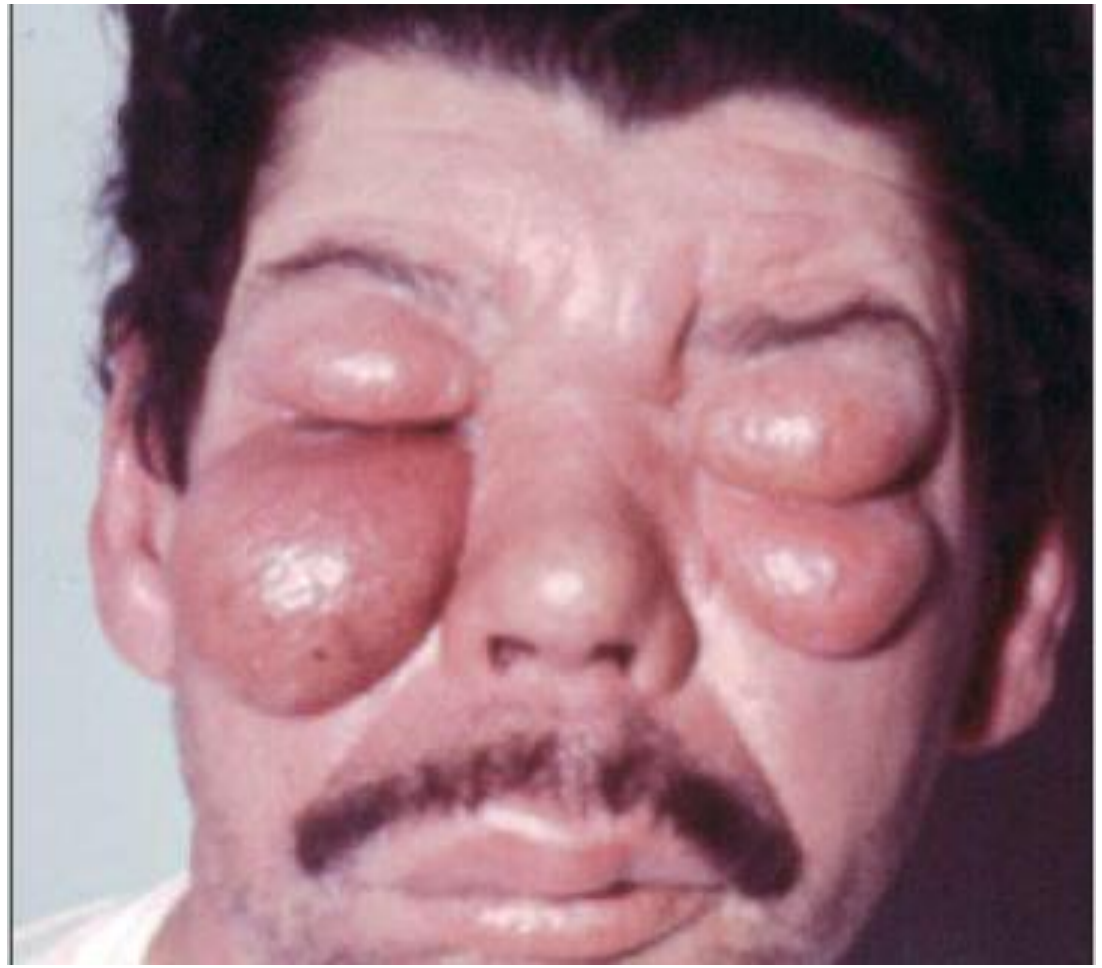
Xerostomia and xerophthalmia are typical presenting features of Sjögren's syndrome. Patients with Sjögren's syndrome can also present with enlarged salivary and lacrimal glands. The patient improved following treatment with glucocorticoids

The NEW ENGLAND JOURNAL of MEDICINE



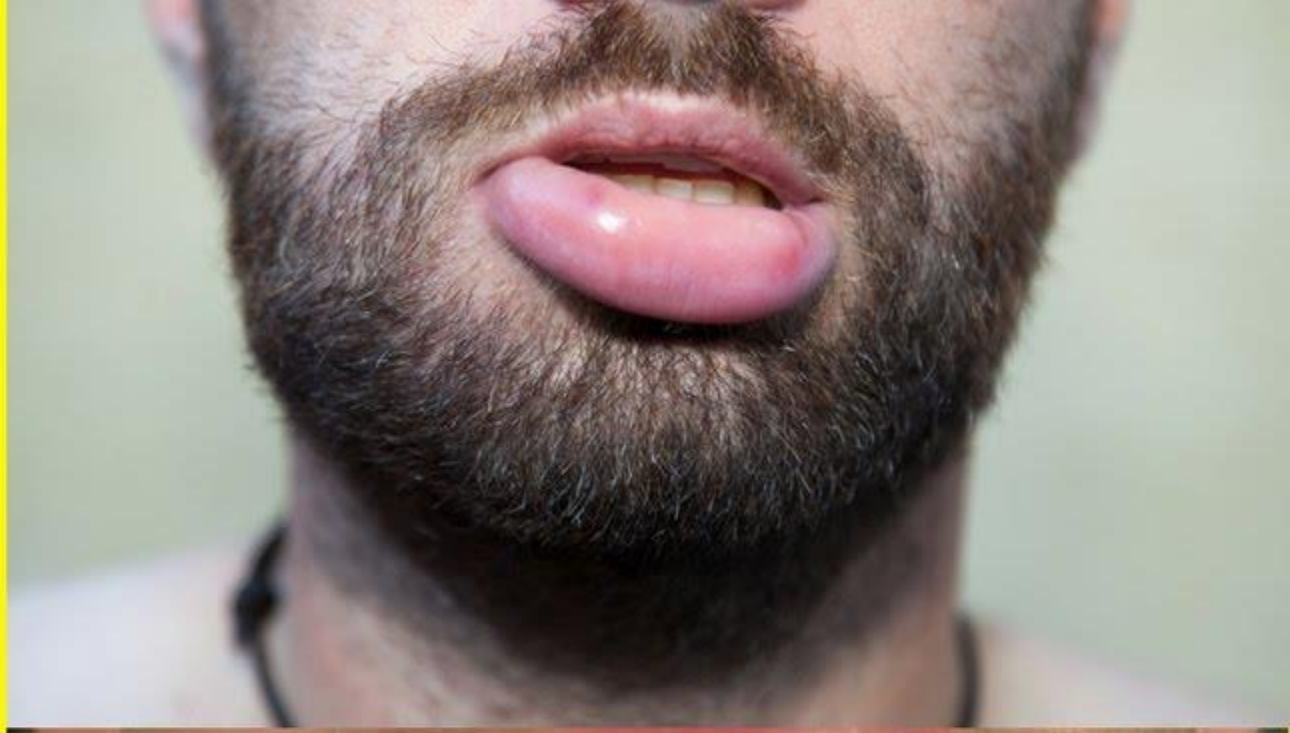
Onderliggend maagcarcinoom

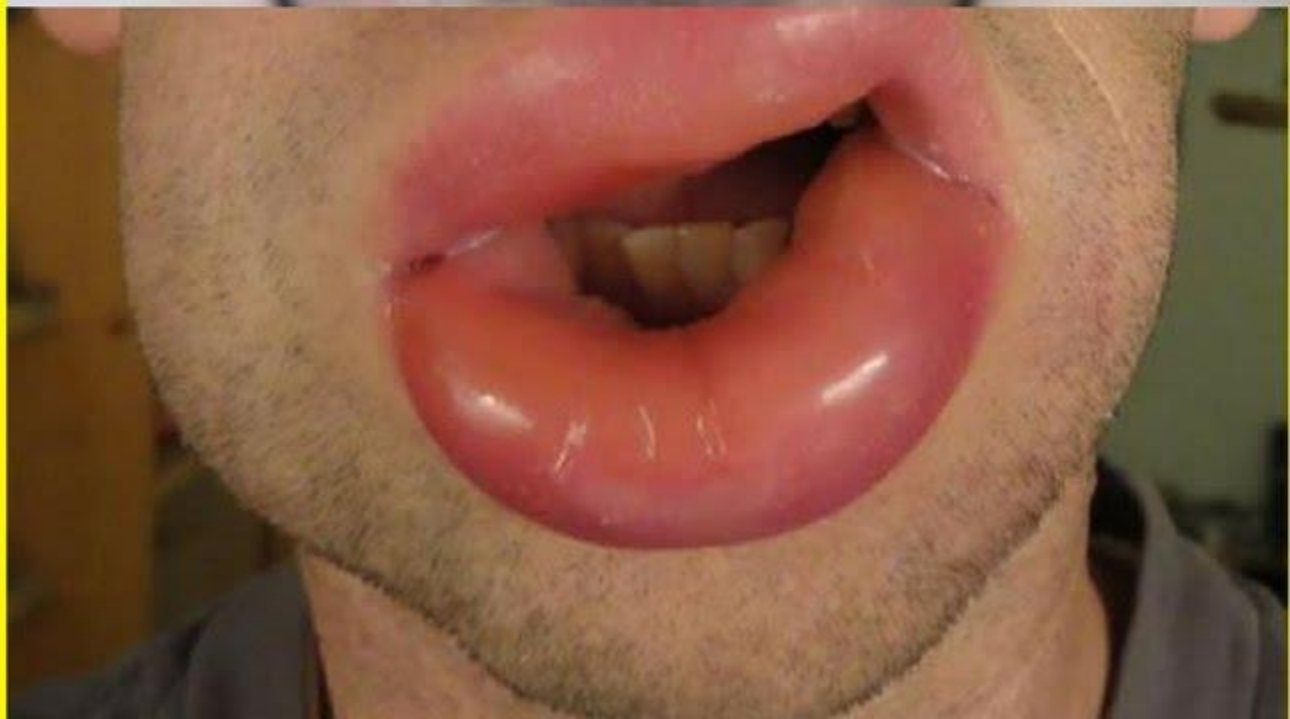
- Na resectie zijn klachten over.



ANGIOEDEMA TREATMENT

100 % SAFE & NATURAL





Milk Baths For An

Oatmeal Paste For Angioedema

http://www.searchherbalremedy.com/top-natural-cures-for-angioedema/

Goldenseal For Angioedema

Hydrotherapy For Angioedema

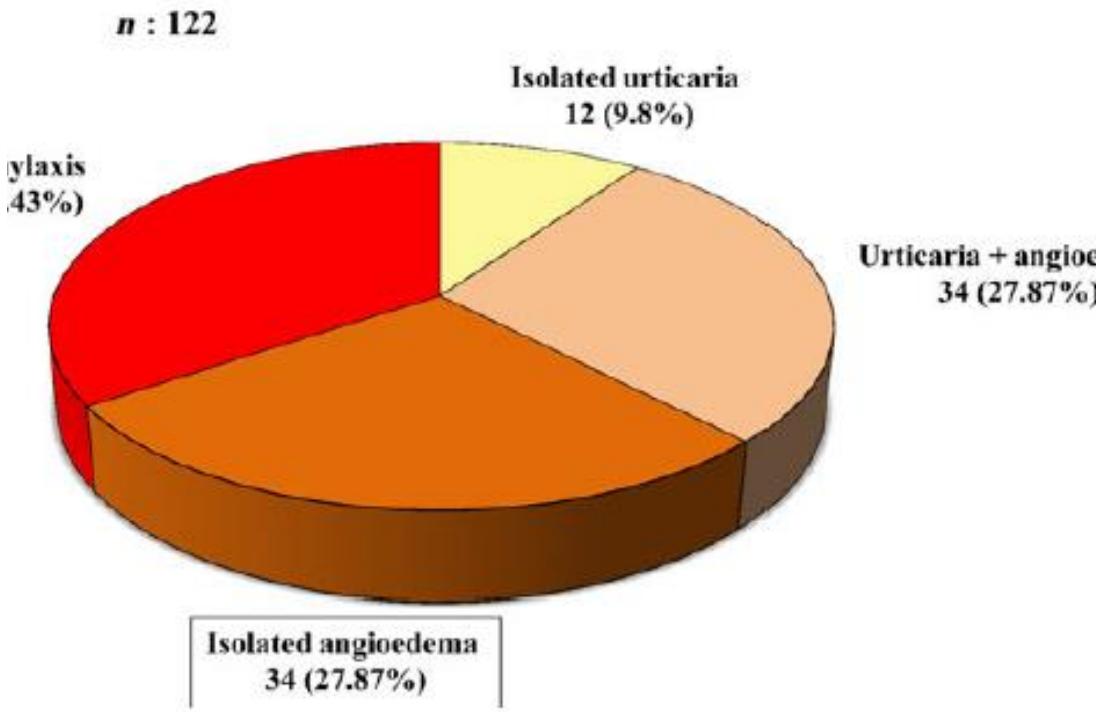
Chamomile For Angioedema

Licorice For Angioedema


Home Remedies For
Swollen Lips


5
Diet To Treat
Angioedema

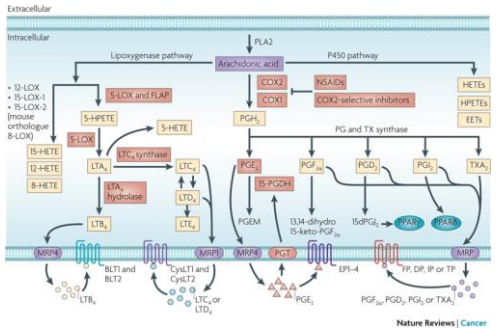
3. Non-histaminerg non-bradykinin



l. Clinical manifestations of hypersensitivity reactions to
dal anti-inflammatory drugs with cutaneous involvement.

Intolerance for

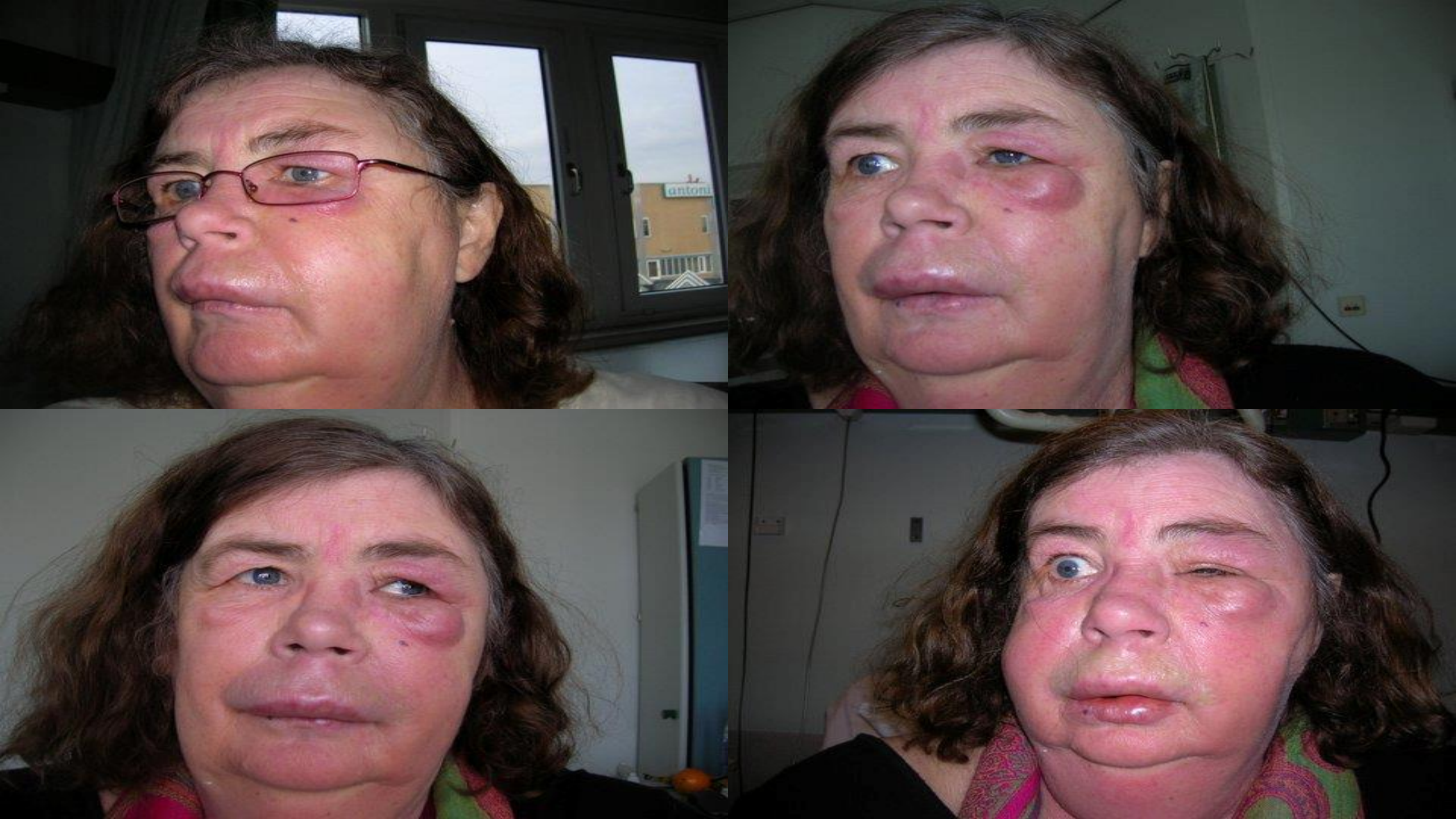
- ASA
- NSAID's

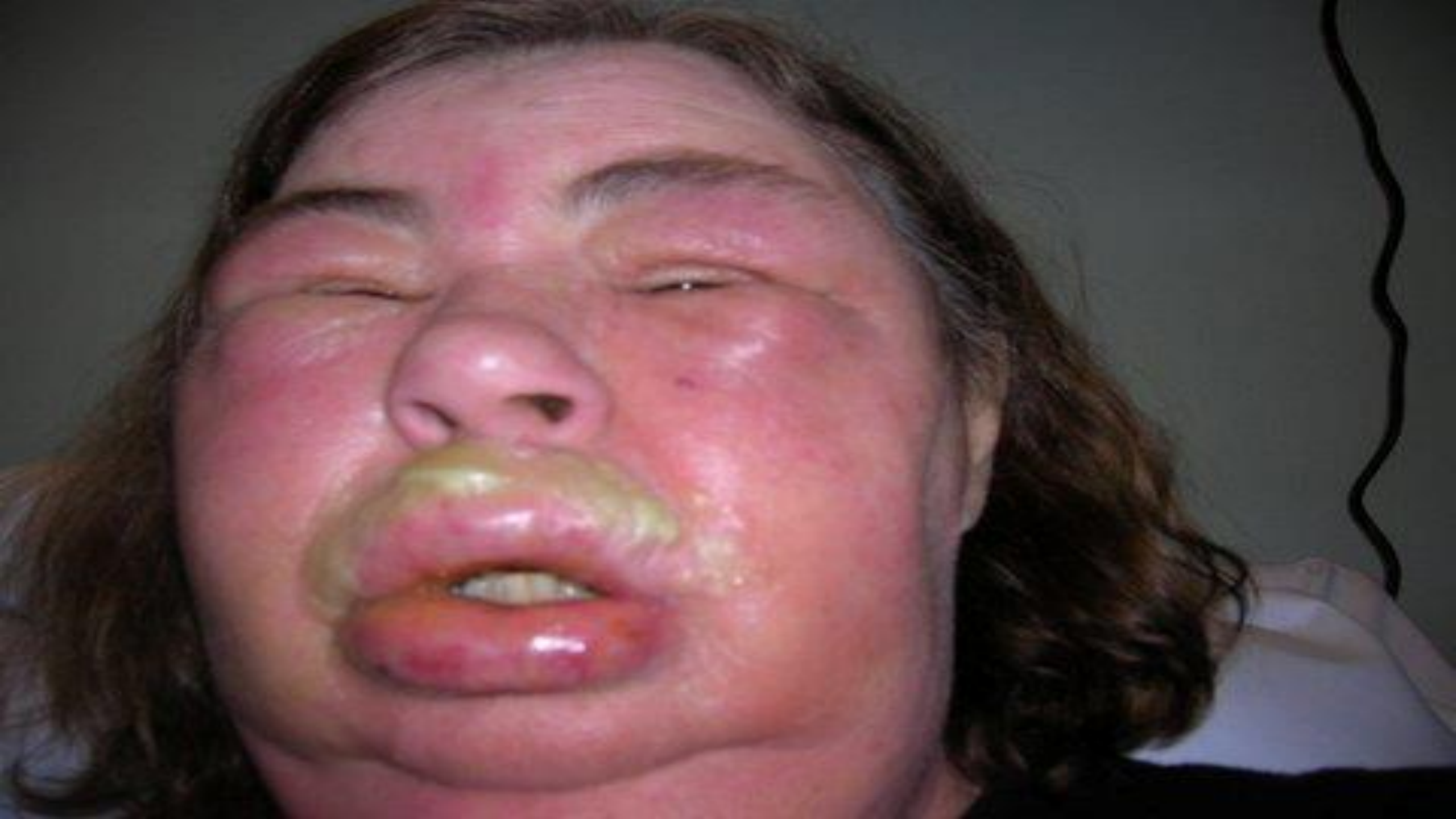


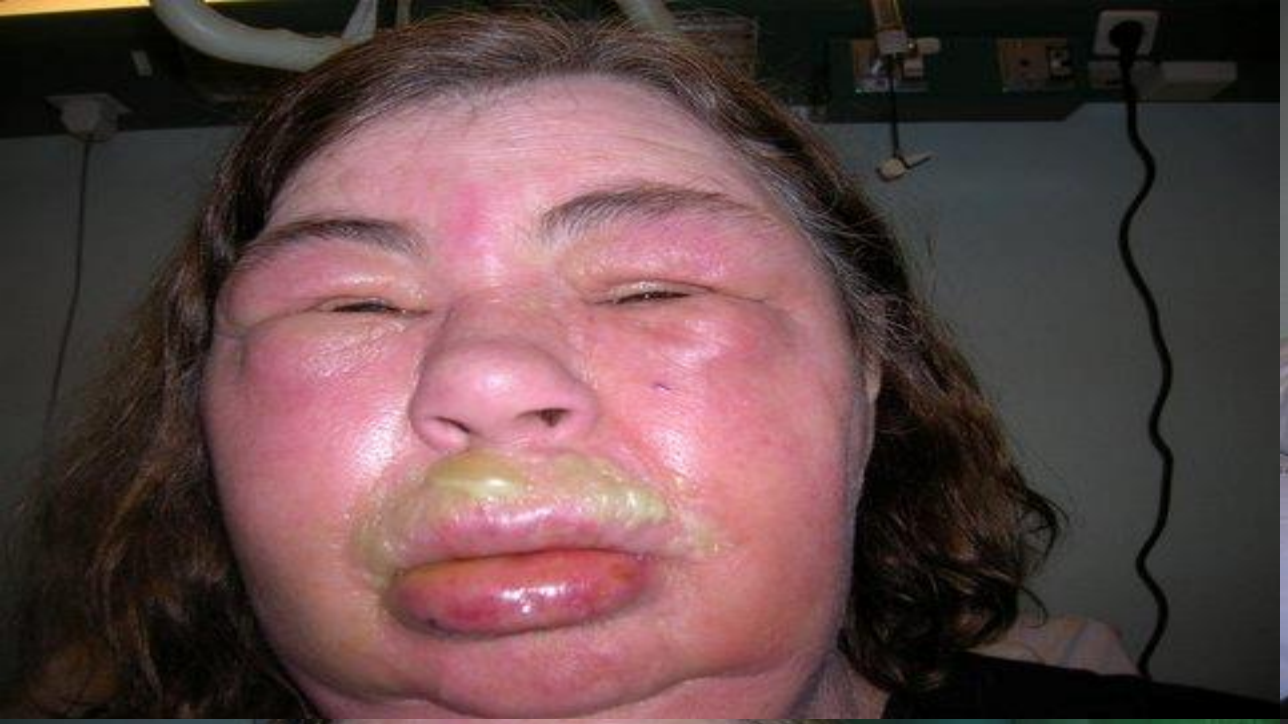
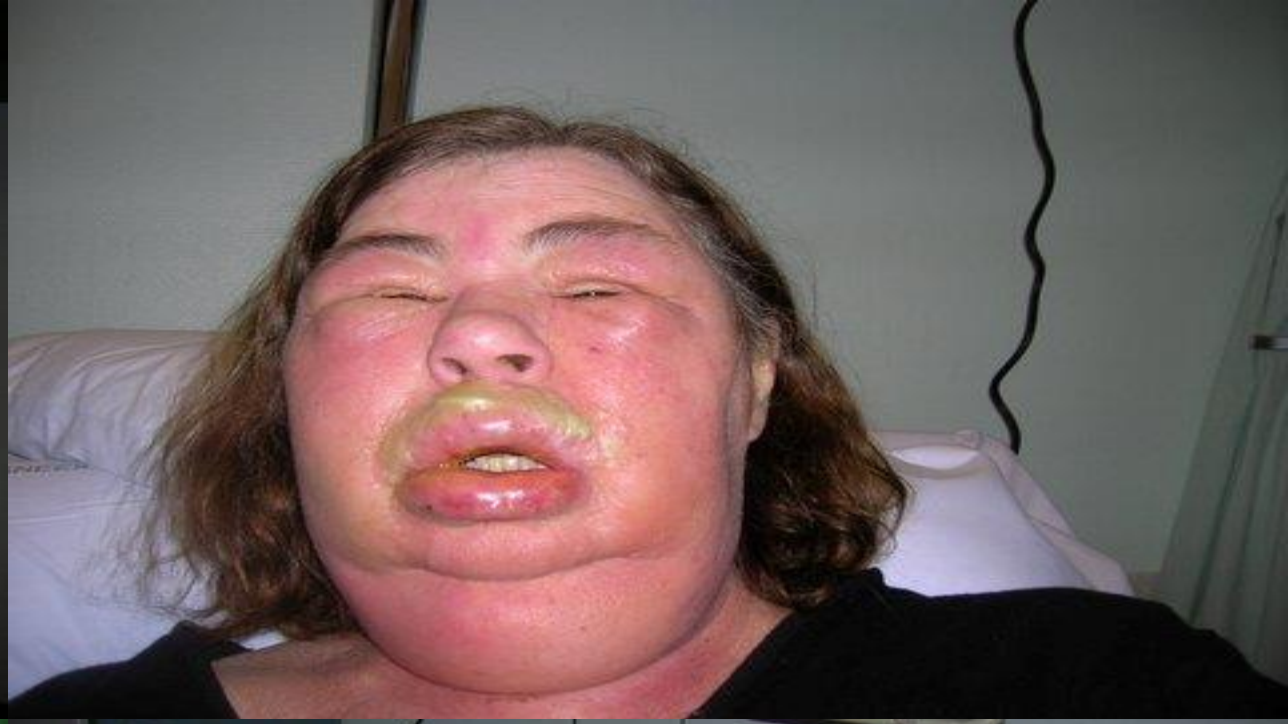
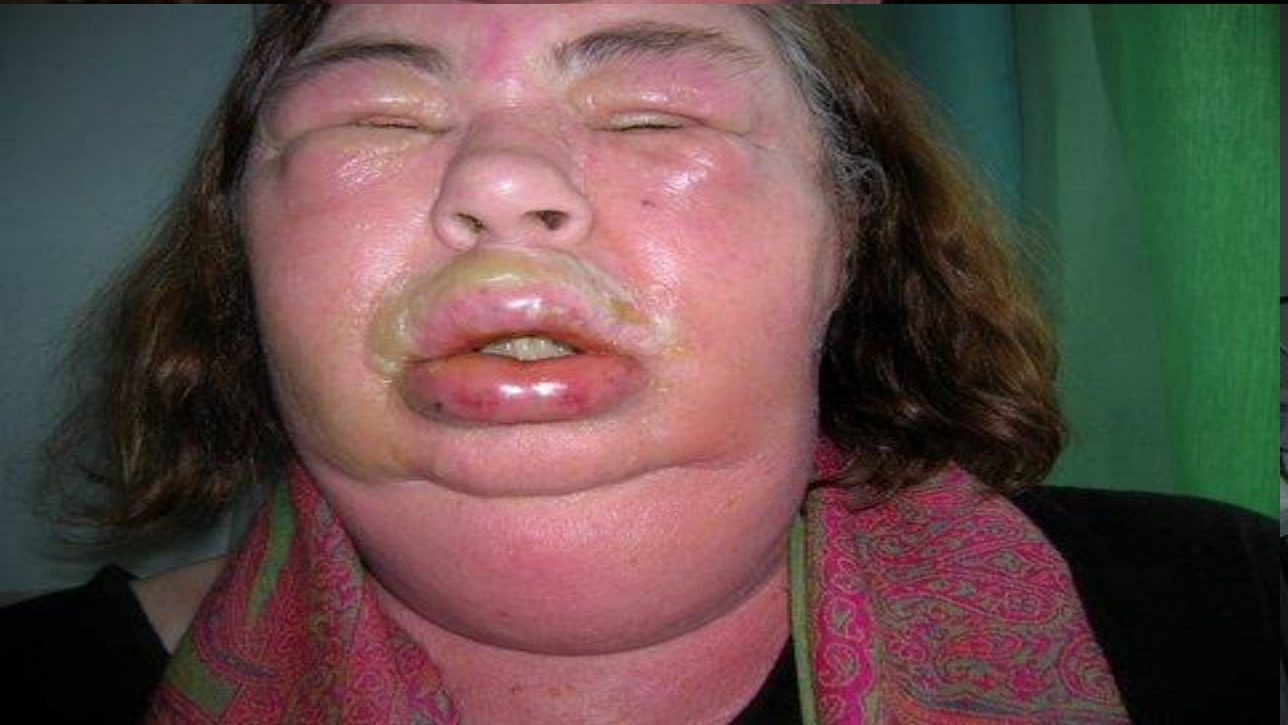
- Prostaglandins
- leukotriens

4. Non-histaminerg non-bradykinin

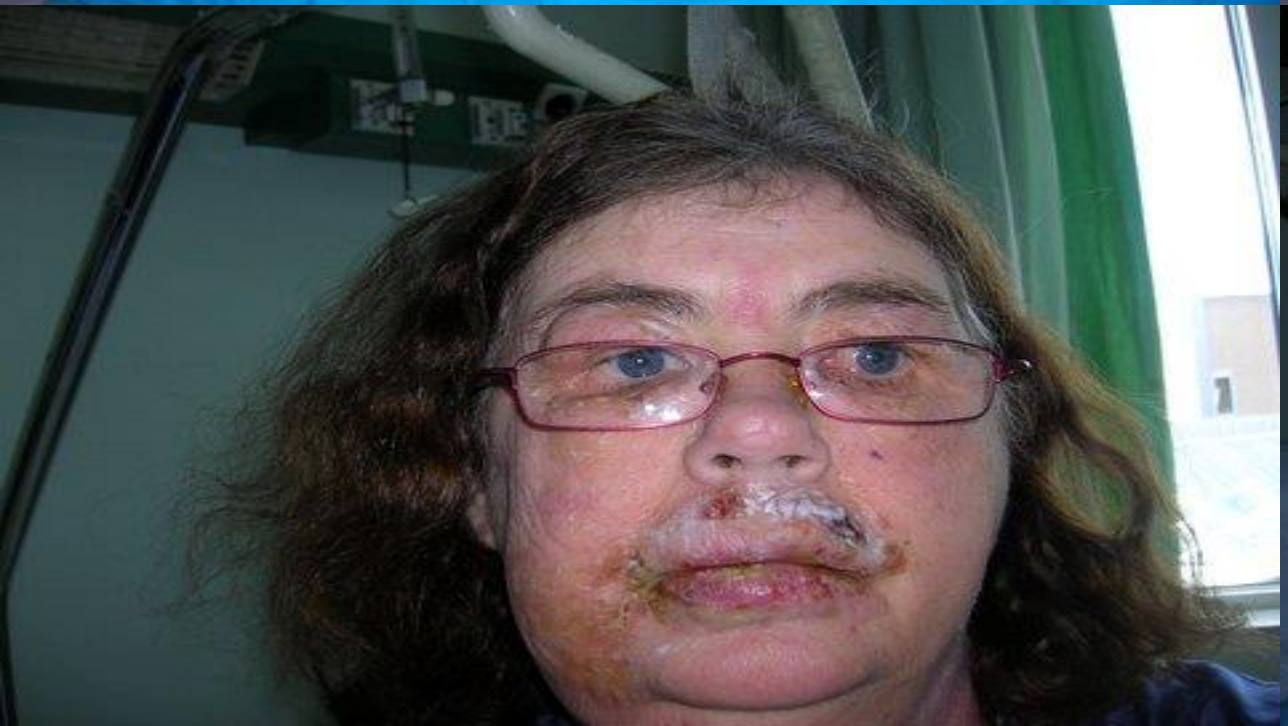
- Cytokine?








Diagnosis

- No (?) available diagnostic tests
- to distinguish histaminerg from bradykinergic angioedema
- Nor to establish activation in eg C1INH def patients

- Search for biomarker

- Histaminerg: tryptase, MH, MIMA
- Prostaglandin: PGD2
- Bradykin: ? D-dimer(?)

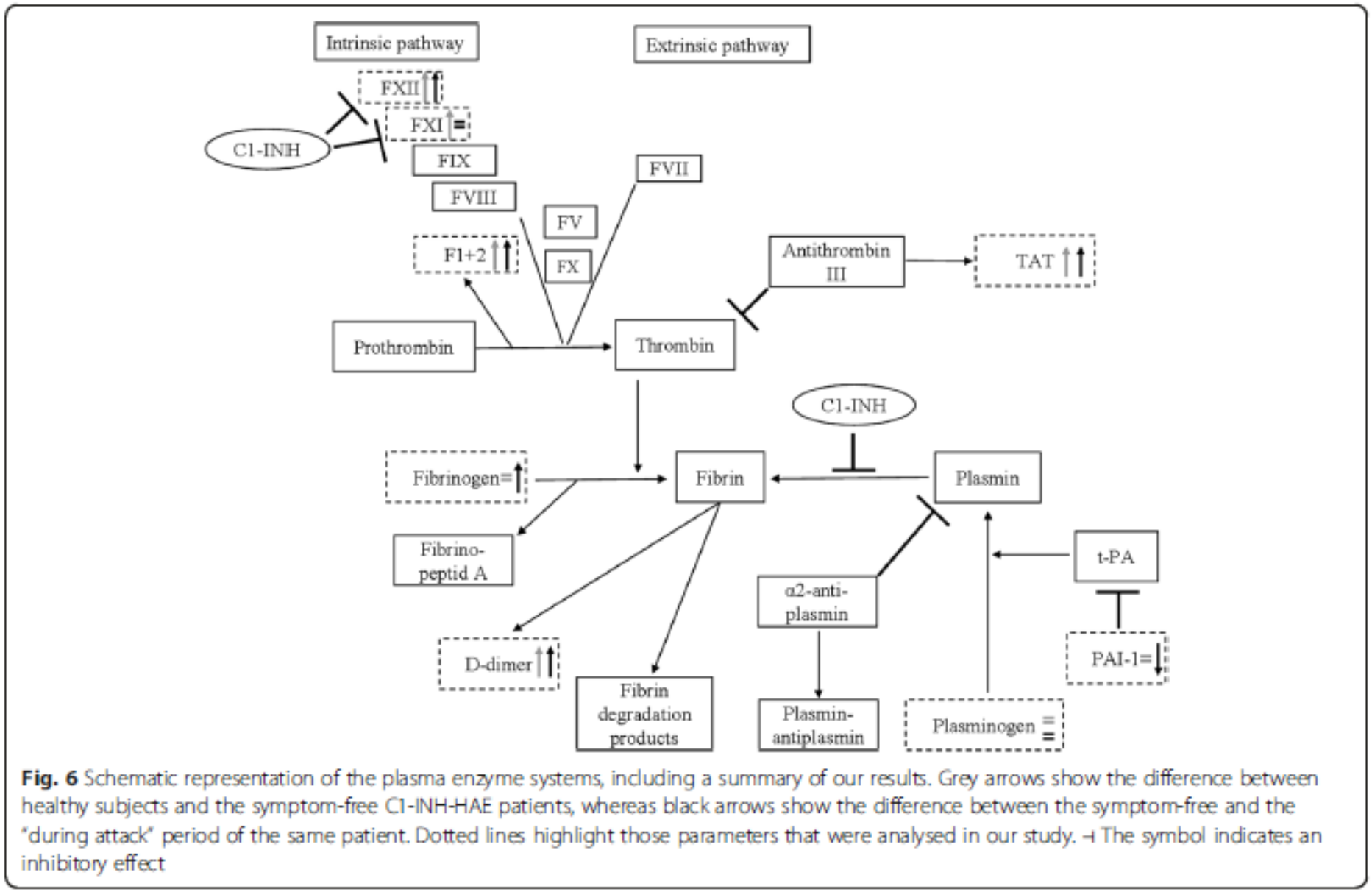
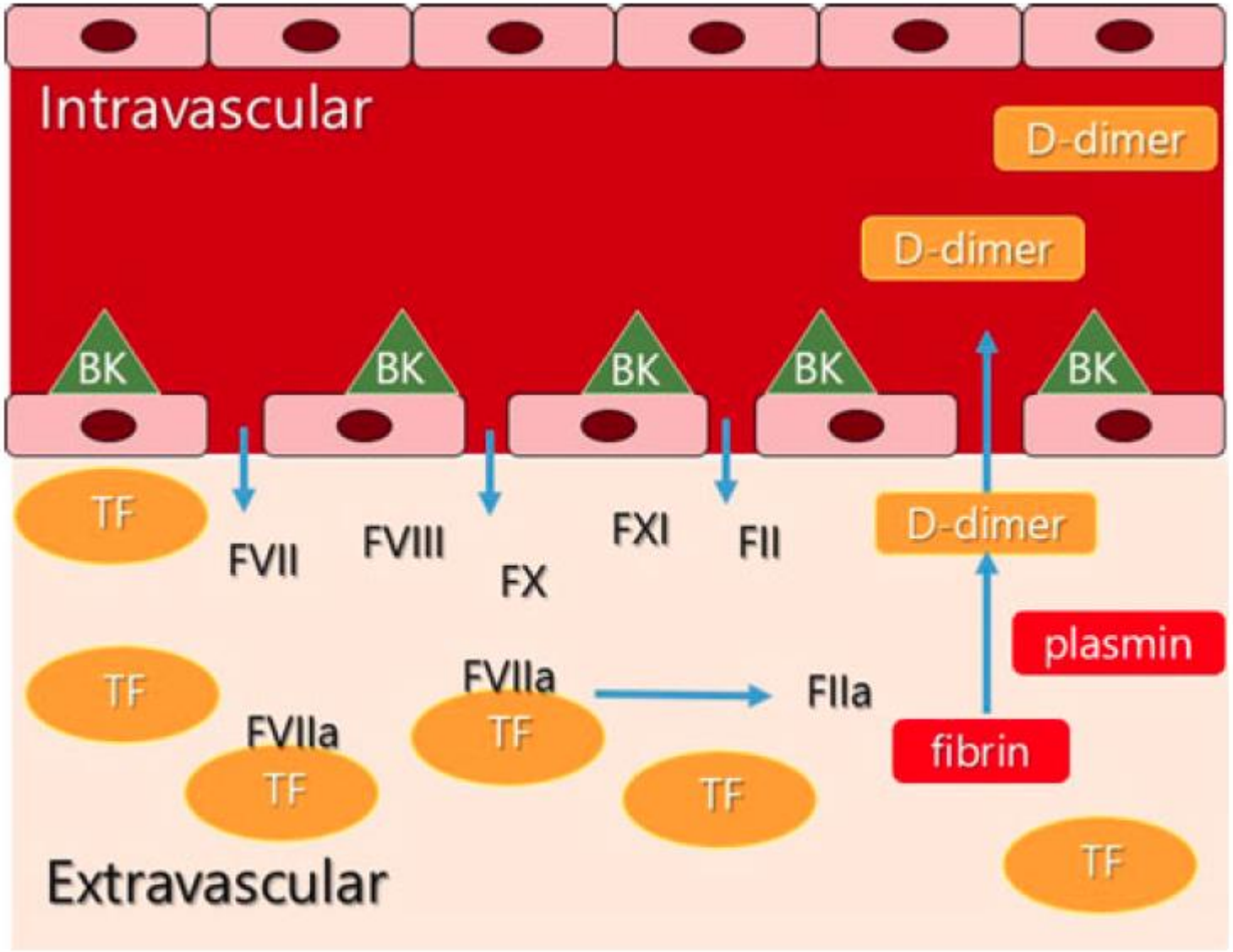


Fig. 6 Schematic representation of the plasma enzyme systems, including a summary of our results. Grey arrows show the difference between healthy subjects and the symptom-free C1-INH-HAE patients, whereas black arrows show the difference between the symptom-free and the "during attack" period of the same patient. Dotted lines highlight those parameters that were analysed in our study. ⊣ The symbol indicates an inhibitory effect

Csuka et al Orphanet J of Rare diseases 2015


Intravascular
D-dimer
D-dimer
BK
BK
BK
BK
BK
TF
FVII
FVIII
FX
FXI
FII
D-dimer
plasmin
TF
FVIIa
FVIIa
TF
FIIa
fibrin
TF
TF
TF
Extravascular

Maas C 2015

Diagnosis based on clinical data

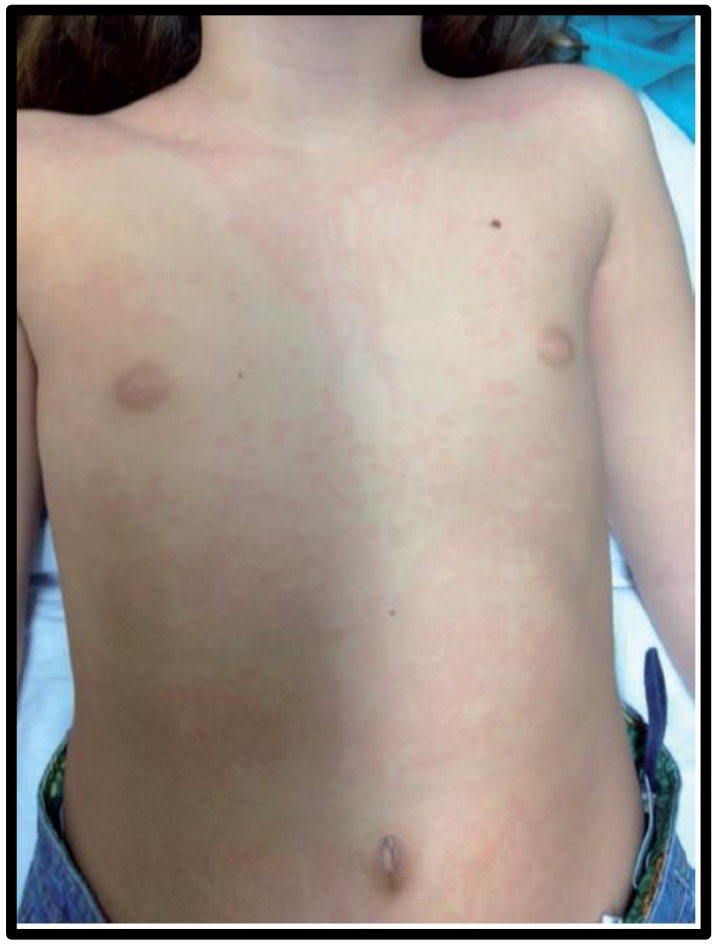
Table II. Differential features of bradykinin and histamine-mediated angioedema.

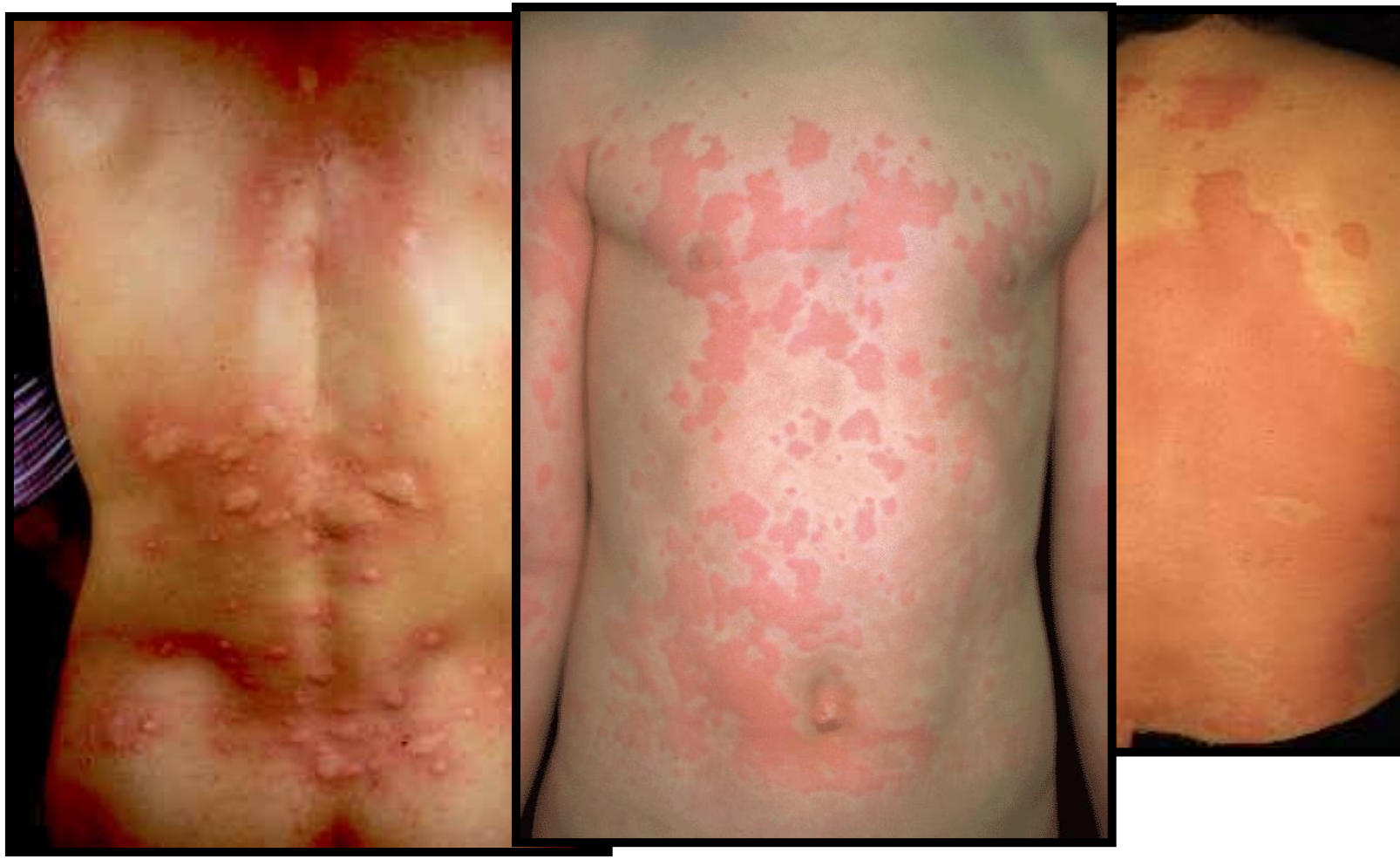
Angioedema features	Bradykinin-mediated angioedema	Histamine-mediated angioedema
Clinical features	Non-erythematous, non-pruritic	Erythemathous, pruritic
Time of onset/Duration	Slower onset/48–96 hours (up to 5 days)	Rapid onset/24–48 hours
Cutaneous rash	Without urticaria, sometimes erythema marginatum	Commonly associates urticaria
Response to treatment	Unresponsive to antihistamines, corticoids, and epinephrine Response to pdhC1-inhibitor/icatibant/ecallantide	Responsive to antihistamines, corticoids, and epinephrine –
Personal or family history	Personal or familiar history of HAE (25% *de novo* mutations)	Frequent personal or familiar history of atopy (but not always)

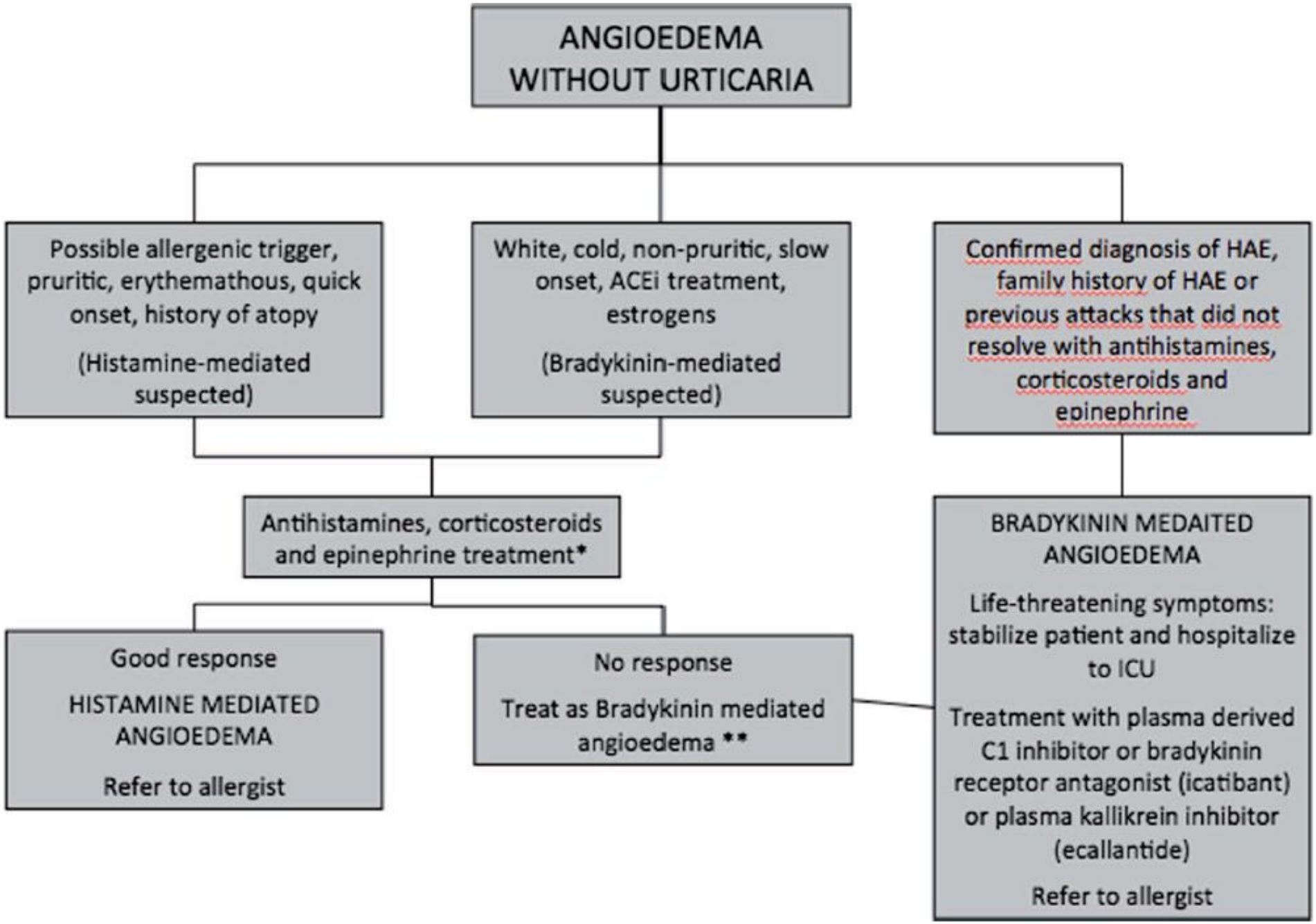
HAE = hereditary angioedema.

Bradykinine **vs** **Histamine**

Erythema marginatum *vs* *Urticaria*






ANGIOEDEMA WITHOUT URTICARIA
Possible allergenic trigger, pruritic, erythemathous, quick onset, history of atopy
(Histamine-mediated suspected)
White, cold, non-pruritic, slow onset, ACEi treatment, estrogens
(Bradykinin-mediated suspected)
Confirmed diagnosis of HAE, family history of HAE or previous attacks that did not resolve with antihistamines, corticosteroids and epinephrine
Antihistamines, corticosteroids and epinephrine treatment*
Good response
HISTAMINE MEDIATED ANGIOEDEMA
Refer to allergist
No response
Treat as Bradykinin mediated angioedema **
BRADYKININ MEDAITED ANGIOEDEMA
Life-threatening symptoms: stabilize patient and hospitalize to ICU
Treatment with plasma derived C1 inhibitor or bradykinin receptor antagonist (icatibant) or plasma kallikrein inhibitor (ecallantide)
Refer to allergist

Lab evaluatie angio-oedeem

	C1-INH	C1-INH Activiteit	C3	C4	C1q
HAE type I	laag	laag	nl	laag	nl
HAE type II	nl of hoog	laag	nl	laag	nl
HAE type III	nl	nl	nl	nl	nl
AAE type I	laag	laag	nl	laag	laag
AAE type II	nl of laag	laag	nl	laag	laag
Allergisch AE	nl	nl	nl	nl	nl
Idiopathisch	nl	nl	nl	nl	nl

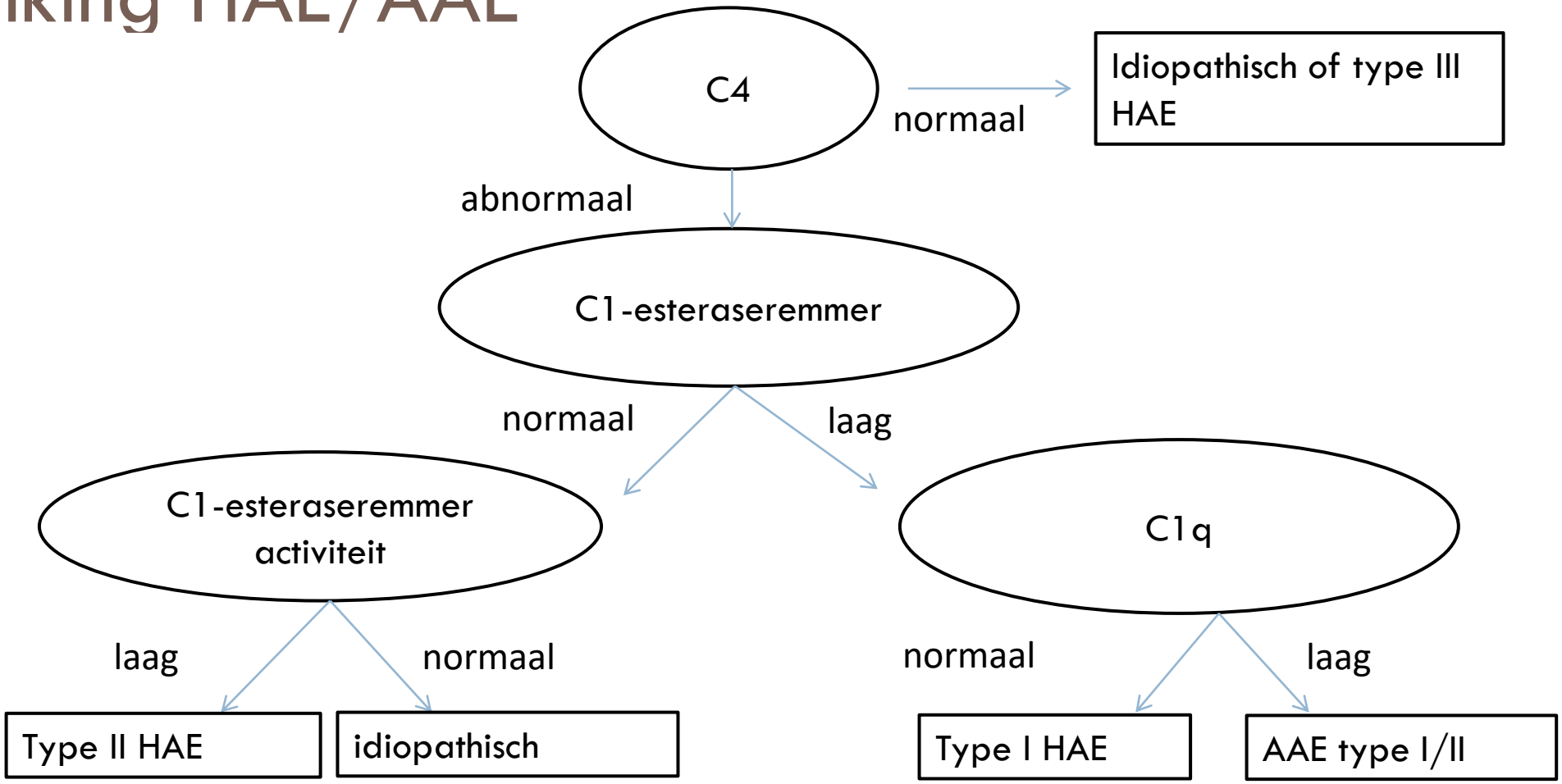
HAE = Hereditair angio-oedeem
AAE = Verworven angio-oedeem
AE = angio-oedeem
C1-INH = C1-esteraseremmer

Evaluatie angio-oedeem bij verdenking HAE/AAE

Stap 1.

Stap 2.

Stap 3.



HAE = Hereditair angio-oedeem
AAE = Verworven angio-oedeem

Behandel mogelijkheden

Key messages

- Angioedema develops mainly as a result of the release of two different vasoactive peptides, histamine or bradykinin.
- Nevertheless clinical presentation may be similar.
- Thus, angioedema evaluation in the emergency department (ED) should aim to distinguish between histamine- and bradykinin-induced angioedema, in order to provide patients with appropriate treatment, which is substantially different in each case.

Biomarkers

- Histamine metabolieten (MH en MIMA)
- Tryptase
- D-dimeer

Implicaties voor chronische behandeling

Histaminerg

- Histamine receptor blokkers
  - H1
  - H2
- Leukotrienen antagonisten
- Corticosteroiden

Bradykinine

- tranexaminezuur

Future

- Search for biomarker
- Better and more specified treatment options

Hereditary Angioedema

Treatment options worldwide…

- Replacement with C1 INH : (FFP*) Cetor*/Cynryze, Berinert, Rhucin
- Stimulation of biosythesis : Danazol*
- Reduced consumption : (Tranexamic acid Cyklokapron *)
- Inhibition of mediators : Ecallantide, Icatibant*
  - *available in the Netherlands

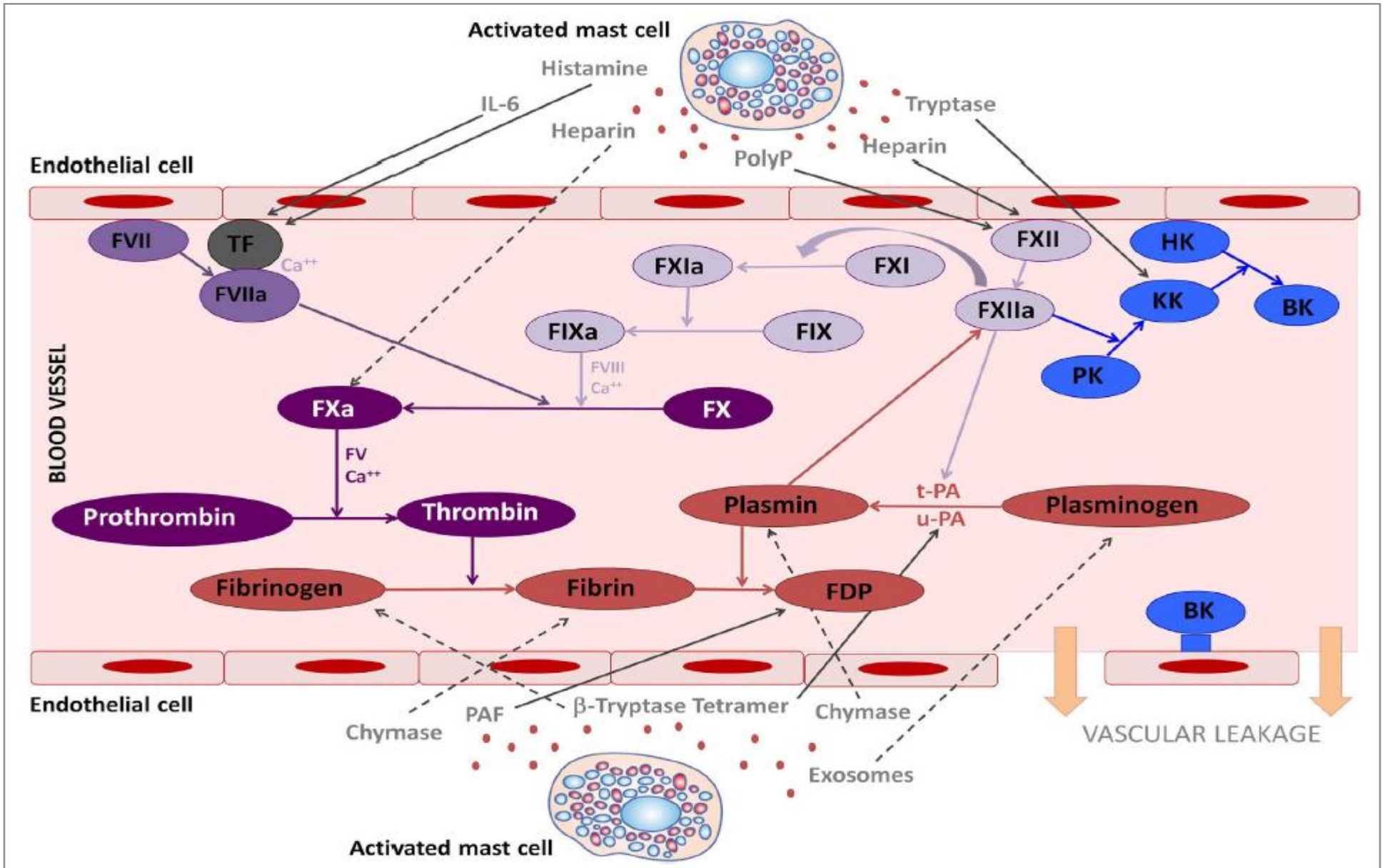
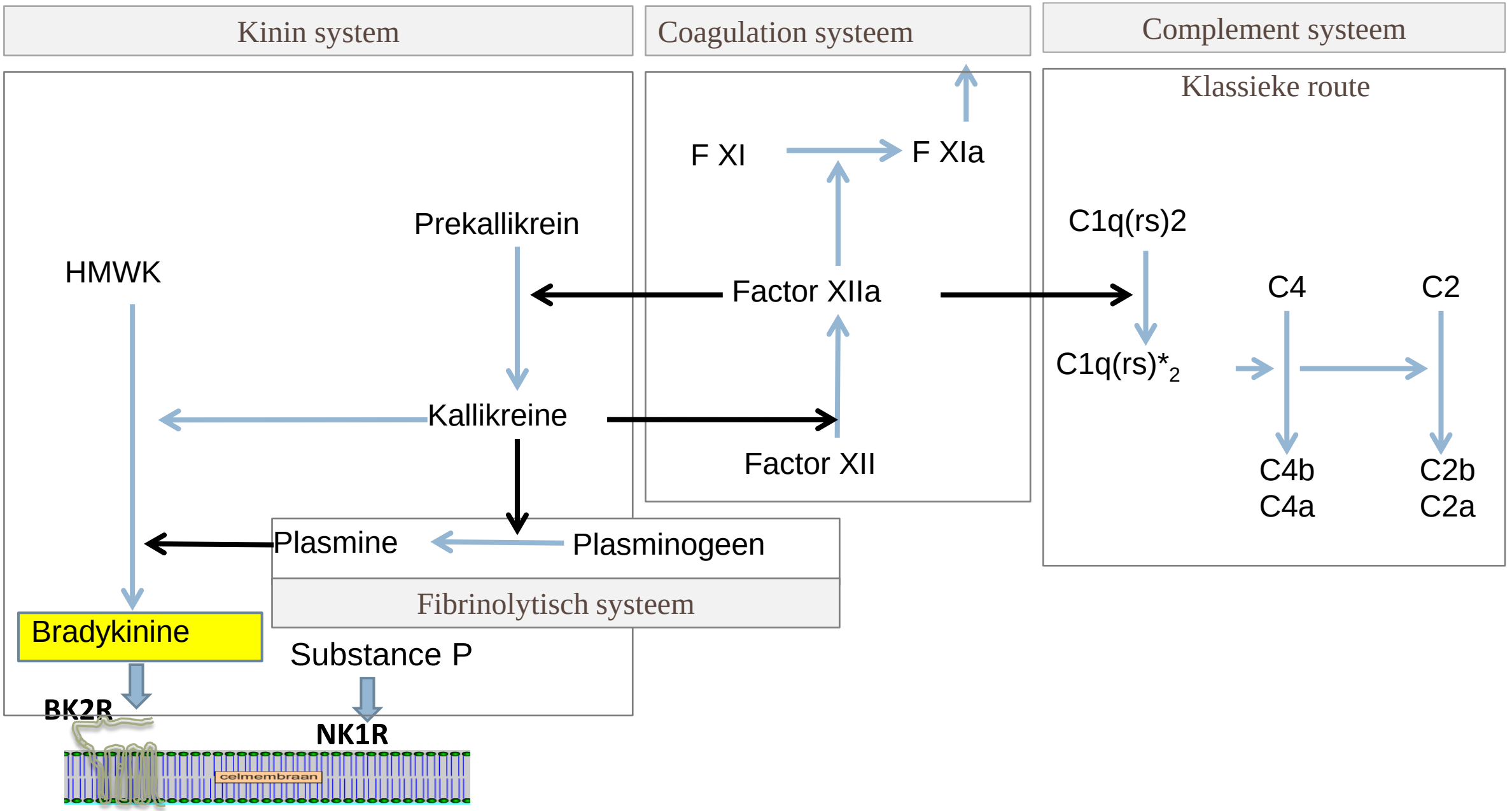
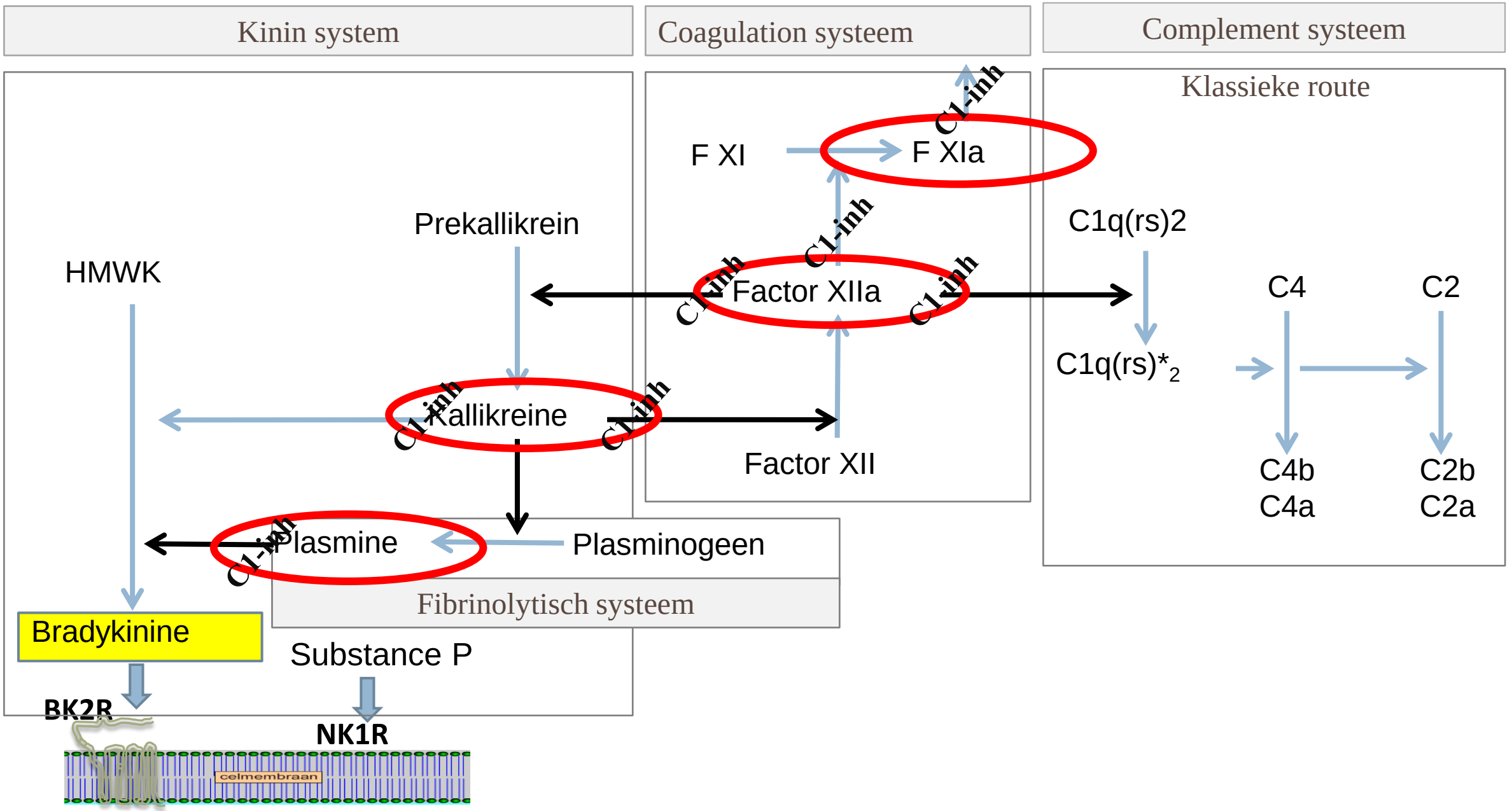


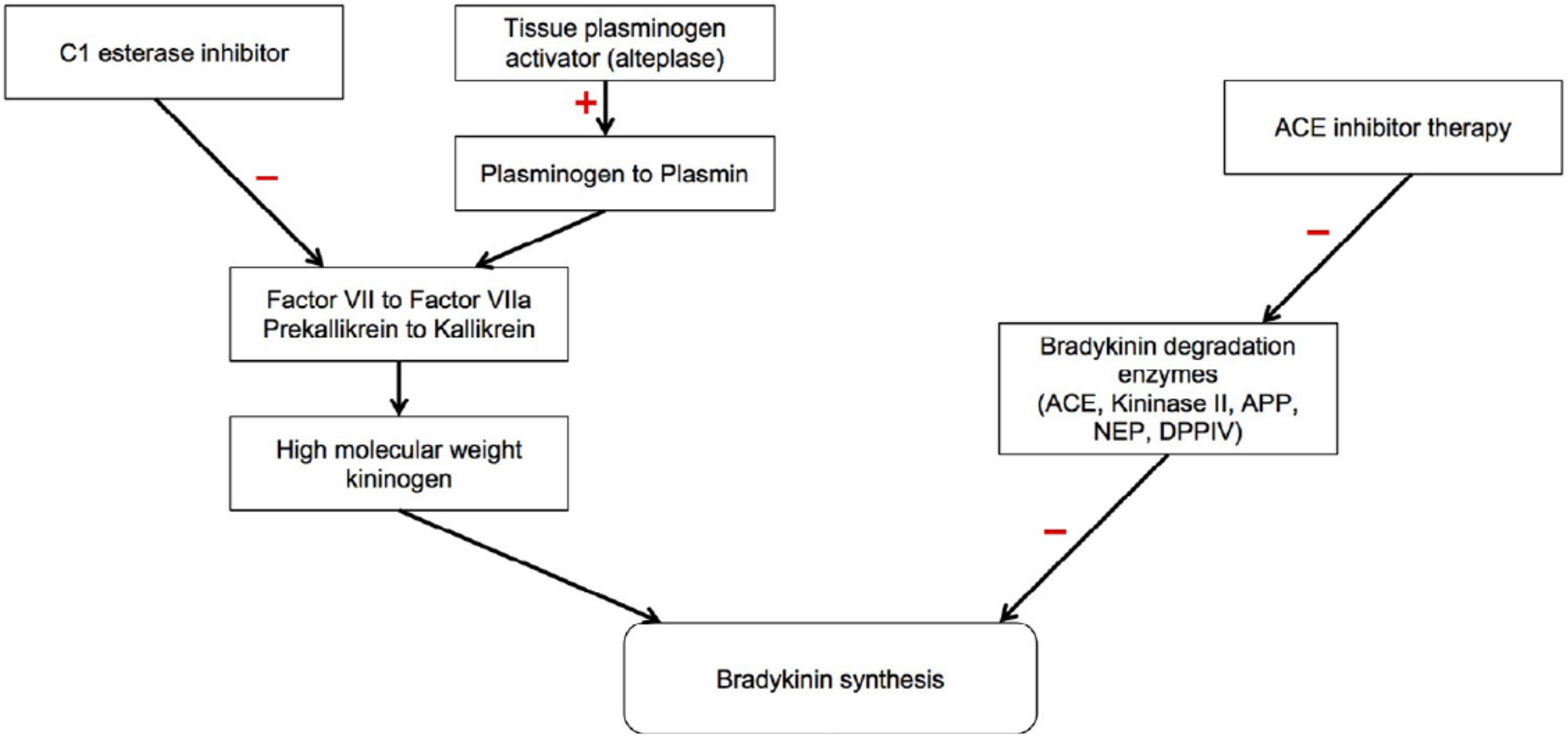
FIGURE 1 | The involvement of mast cell mediators in the coagulation and kallikrein–kinin system. The figure illustrates the effects that mast cells mediators released upon activation during anaphylaxis exert in the kallikrein–kinin, coagulation, and fibrinolytic systems. Solid lines represent activated pathways. Dashed lines are inhibitory pathways. Kinin-forming system factors are represented in blue; the fibrinolytic system is represented in red; the common coagulation pathway in dark purple; the extrinsic coagulation pathway in medium purple; the intrinsic coagulation pathway in light purple. PolyP, polyphosphates; TF, tissue factor; PK, prekallikrein; KK, Kallikrein; BK, bradykinin; HK, high molecular-weight kininogen; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator;

C1-inh remt (ook) FXII/kallikreine activiteit



C1-inh remt (ook) FXII/kallikreine activiteit




C1 esterase inhibitor
Tissue plasminogen activator (alteplase)
+
Plasminogen to Plasmin
ACE inhibitor therapy
–
Factor VII to Factor VIIa
Prekallikrein to Kallikrein
Bradykinin degradation enzymes (ACE, Kininase II, APP, NEP, DPPIV)
High molecular weight kininogen
–
Bradykinin synthesis

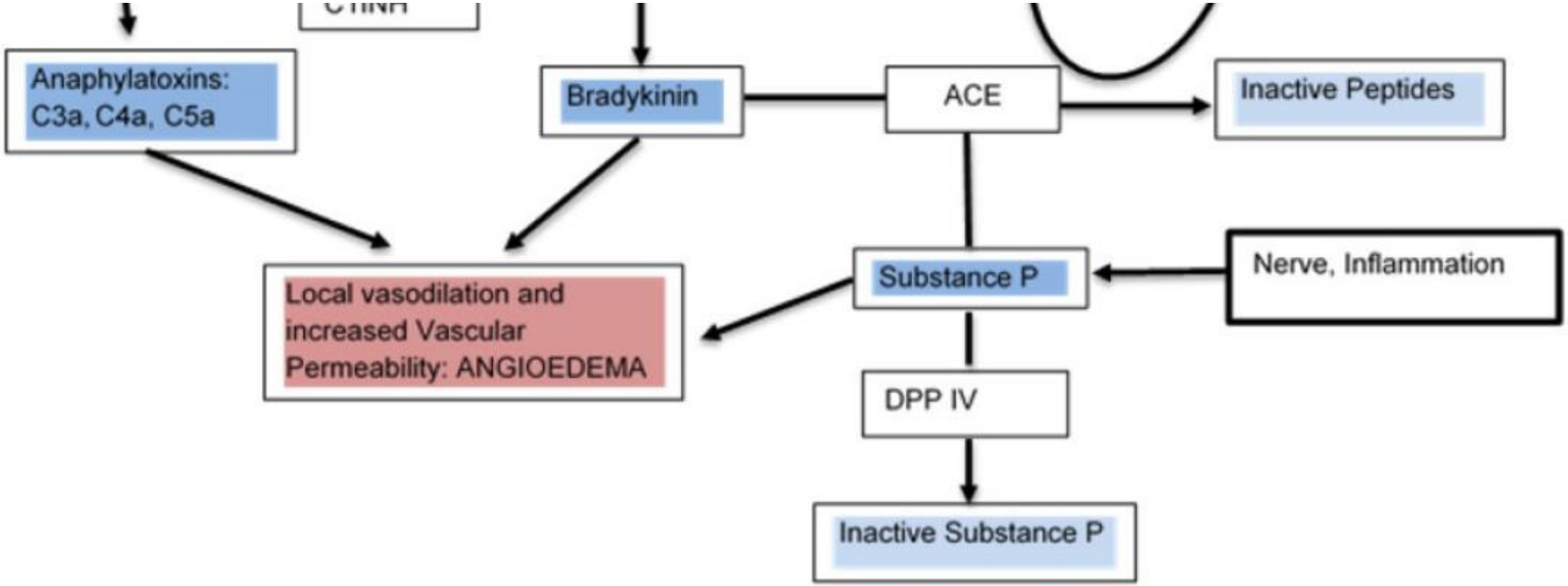
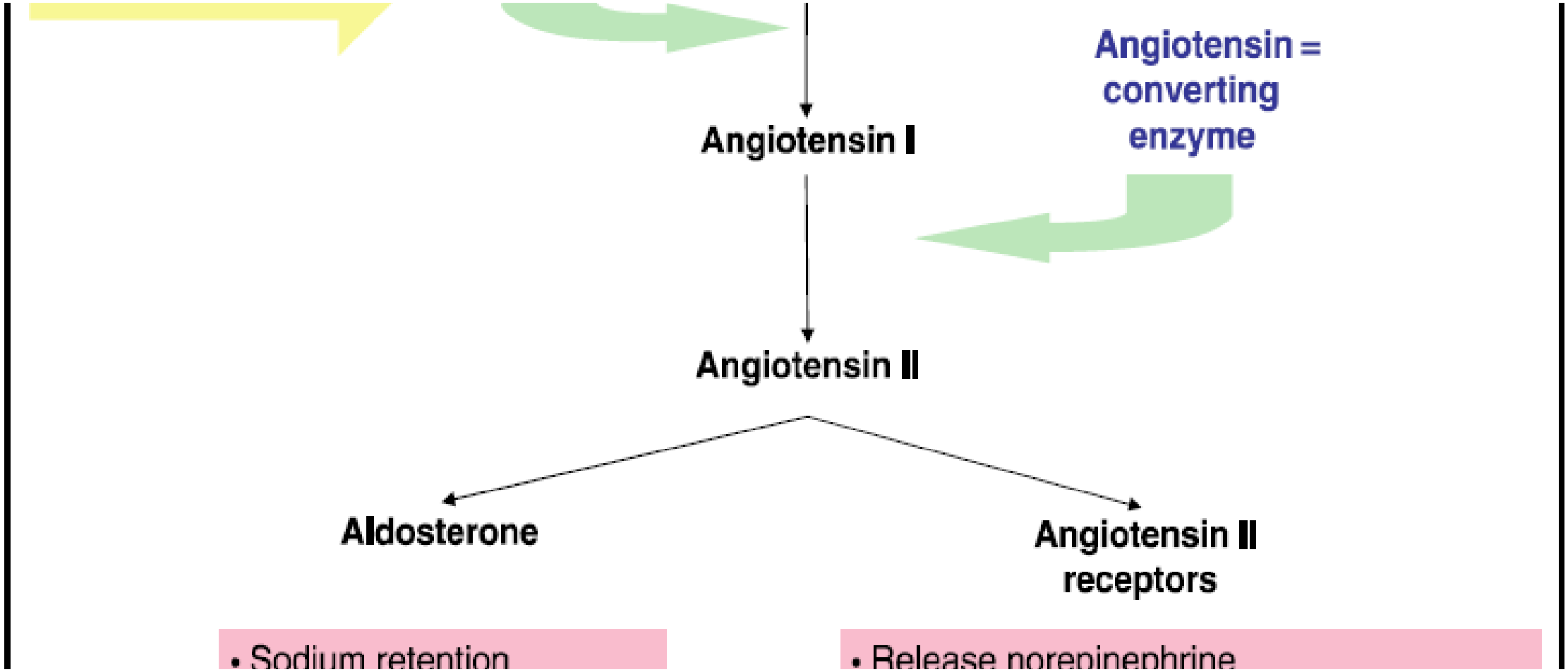
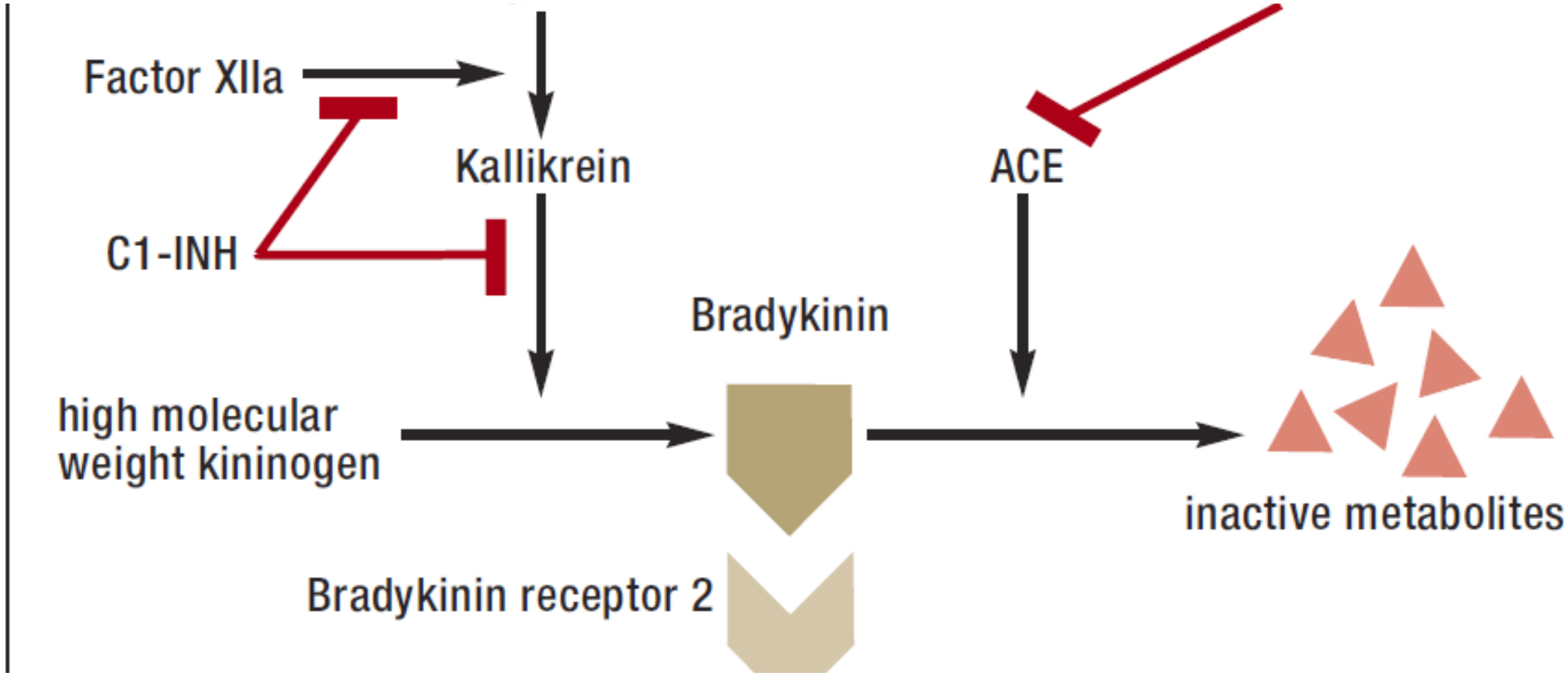


FIGURE 1: Interaction of kallikrein-kiting system (KKS), renin


Angiotensin I
Angiotensin = converting enzyme
Angiotensin II
Aldosterone
Angiotensin II receptors
• Sodium retention
• Release norepinephrine


Factor XIIa
Kallikrein
C1-INH
ACE
Bradykinin
high molecular
weight kininogen
inactive metabolites
Bradykinin receptor 2

E volgende 2 dias

frontiers in Immunology

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Check for updates

Factor XII-Driven Inflammatory Reactions with Implications for Anaphylaxis

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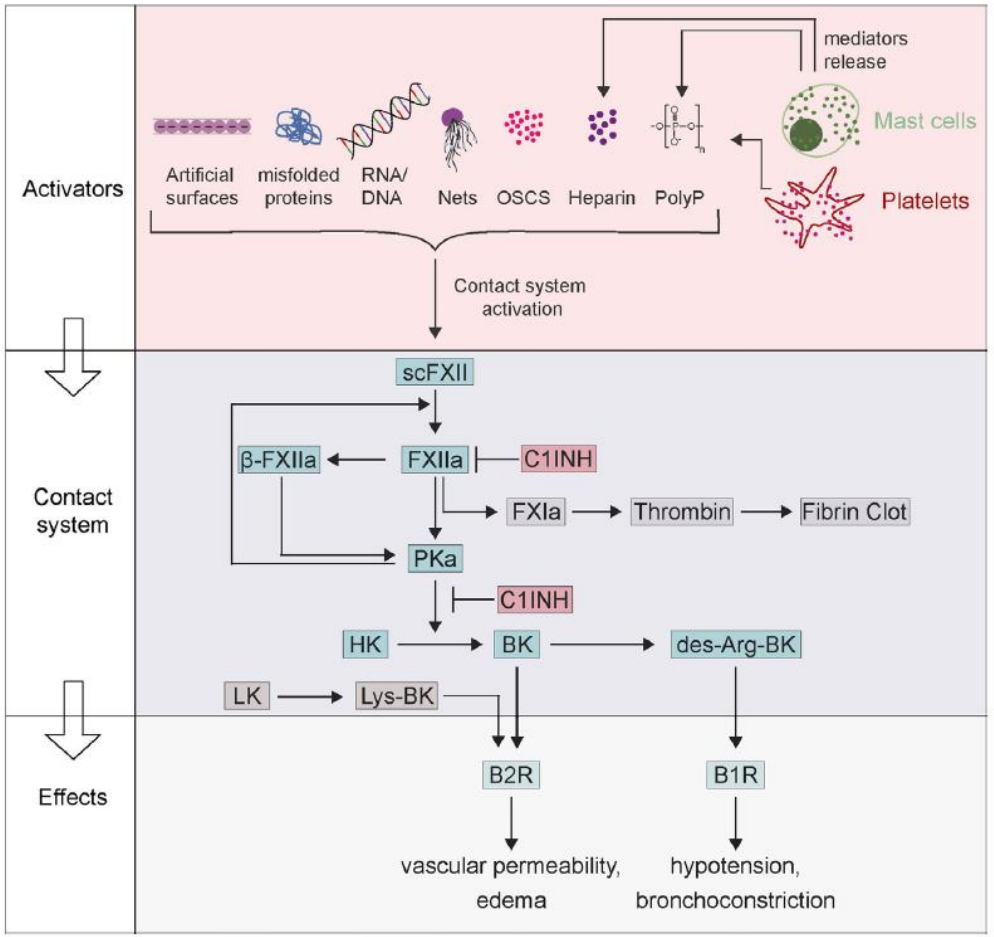

FIGURE 1 | Factor XII (FXII)-driven contact system in activation of anaphylaxis. Zymogen scFXII becomes activated to FXIIa either by endogenous activators [misfolded proteins, RNA/DNA, neutrophil extracellular traps (NETs), polyP, oversulfated chondroitin sulfate-contaminated heparin (OSCS-heparin) and heparin] or by artificial surfaces. Anaphylaxis can activate mast cells with the release of their mediators (polyP and heparin), which also leads to FXIIa. FXIIa proceeds to activate prekallikrein, which reciprocally cleaves both FXIIa into β-FXIIa and high-molecular-weight kininogen (HK) to bradykinin (BK). BK binds receptor B2 (B2R) and triggers inflammation, edema, and symptoms of anaphylaxis. BK can be further proceeding to des-Arg-BK and mediates B1 receptor (B1R) activation resulting in hypotension and bronchoconstriction. The contact system can be inhibited by the C1INH that inhibits both FXIIa and plasma kallikrein.

Emerging Therapies in Hereditary Angioedema

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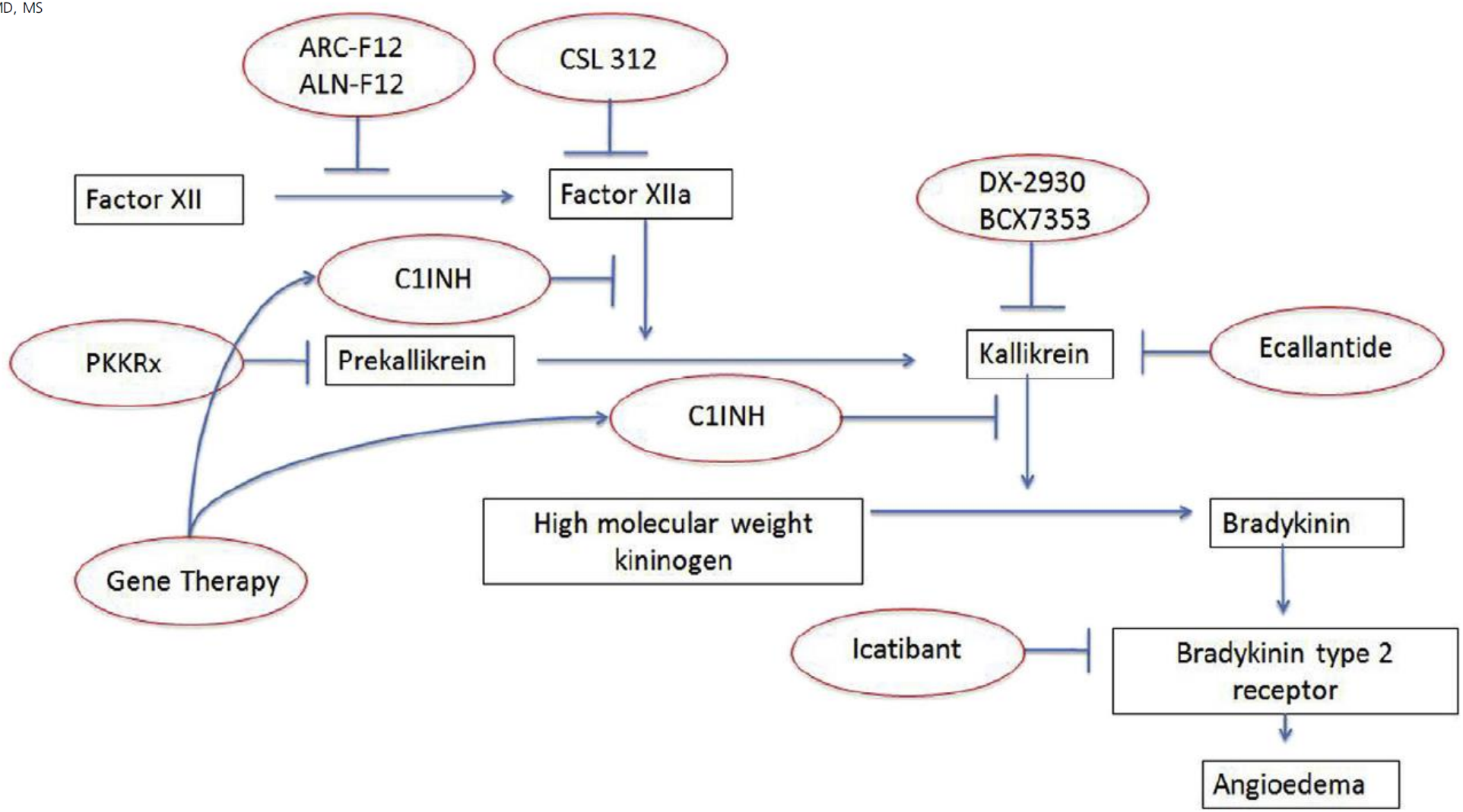
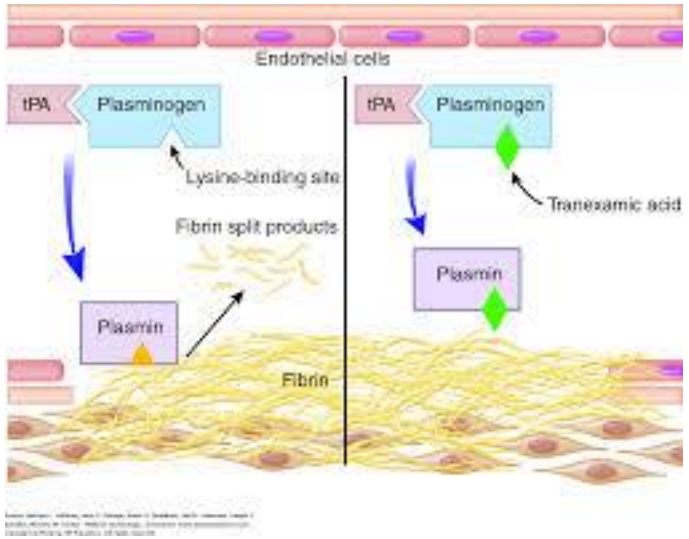
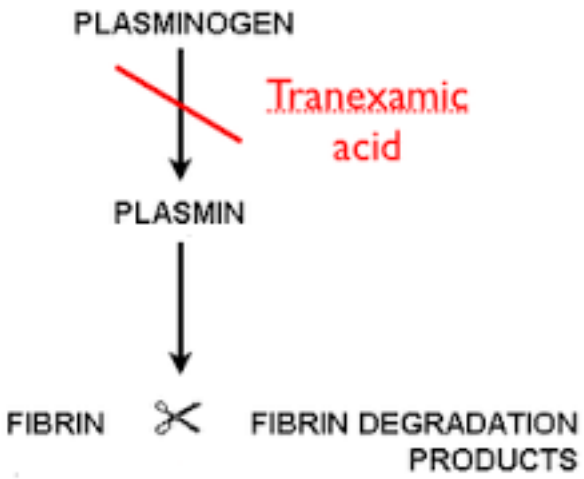
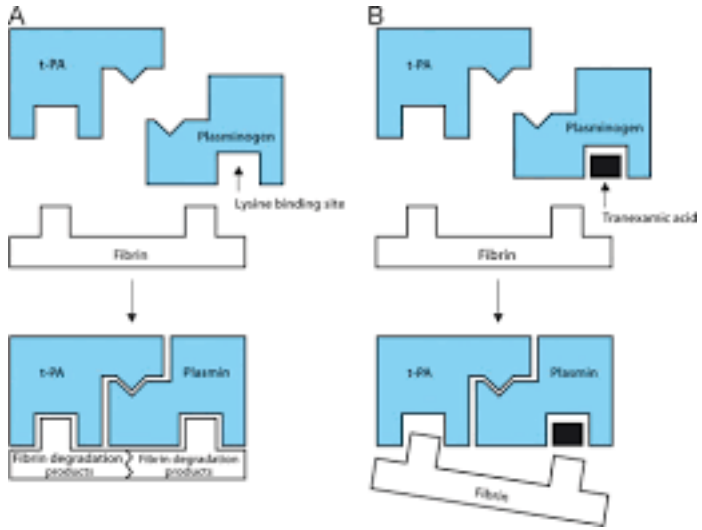


Fig. 1. Pathogenesis of bradykinin-mediated angioedema with targets for existing and developing therapies. C1INH, complement component 1 inhibitor.


Endothelial cells
tPA
Plasminogen
Lysine-binding site
Fibrin split products
Plasmin
Fibrin
tPA
Plasminogen
Tranexamic acid
Plasmin


PLASMINOGEN
Tranexamic acid
PLASMIN
FIBRIN
FIBRIN DEGRADATION PRODUCTS


A
t-PA
Plasminogen
Lysine binding site
Fibrin
t-PA
Plasmin
Fibrin degradation products
Fibrin degradation products
B
t-PA
Plasminogen
Tranexamic acid
Fibrin
t-PA
Plasmin
Fibrin