



Angioedema: beyond histamine

Didier EBO

Immunology – Allergology - Rheumatology

Conflict of interest

- Phadia ThermoFisher Scientific
- BD Biosciences
- Shire / CAF

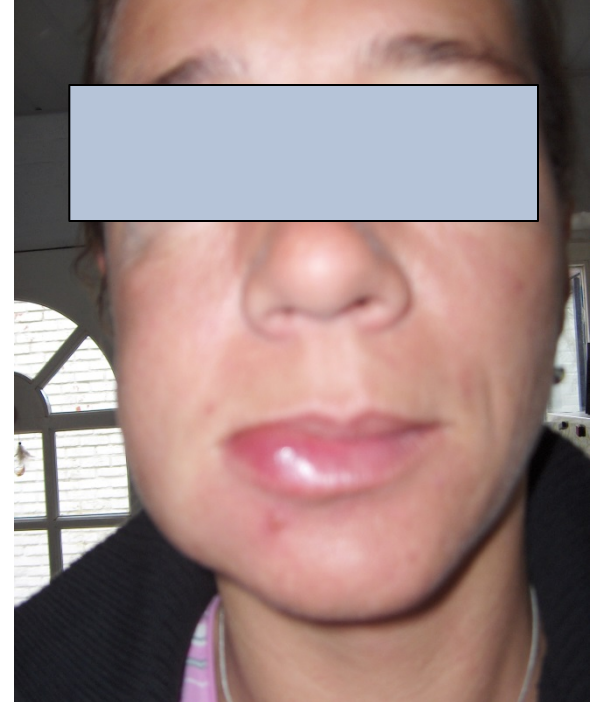


Content

- Clinics
- Causes & pathogenesis
- Drug therapy (incl. prophylaxis)
- Summary

A picture is worth a 1000 words ...





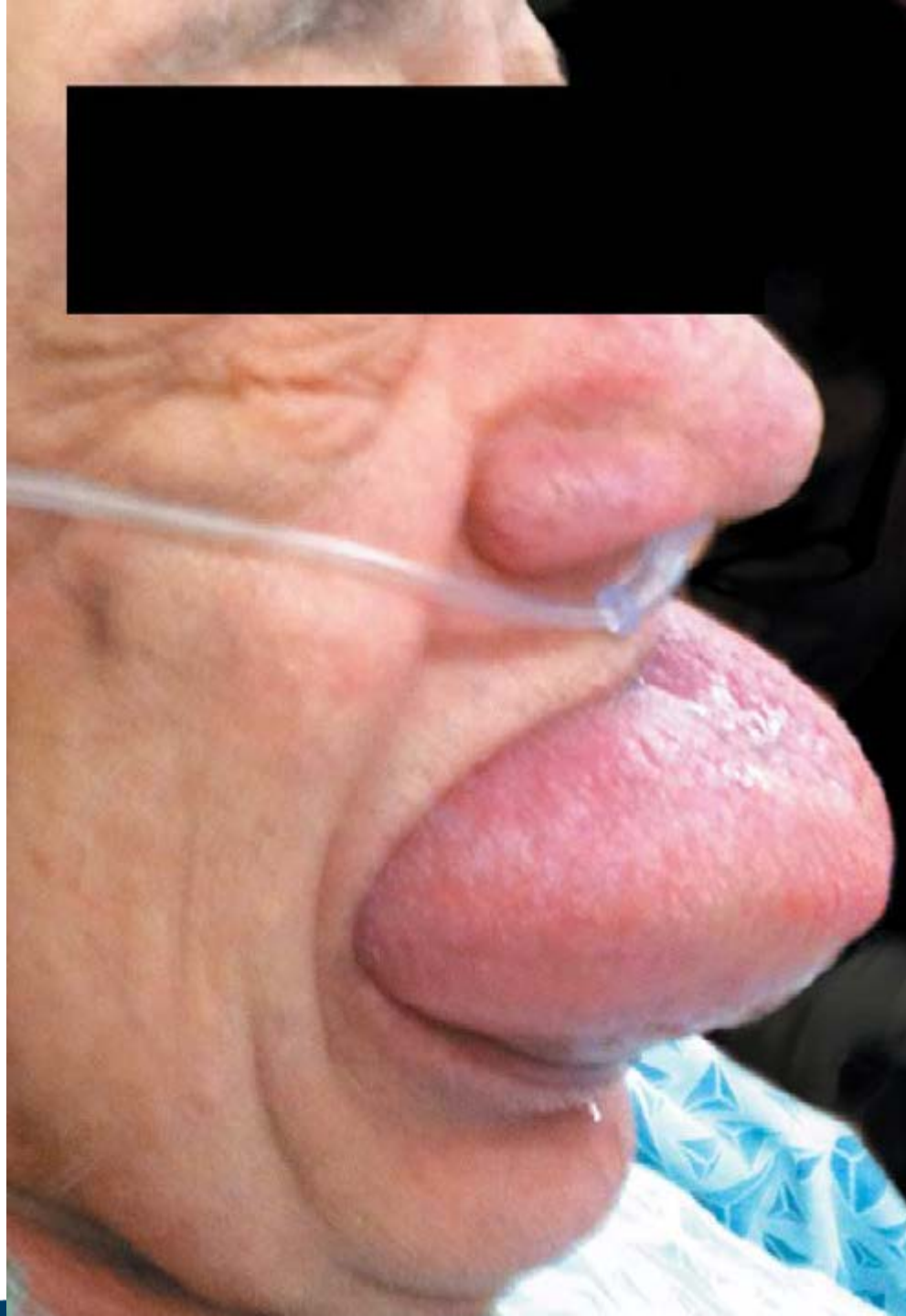
IMAGES IN CLINICAL MEDICINE

Disfiguring Angioedema



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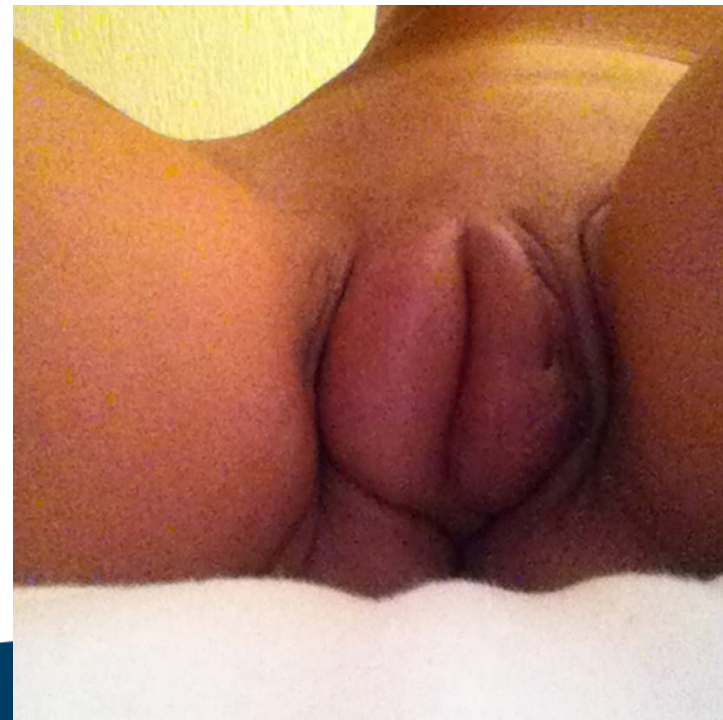
LIFE-THREATENING

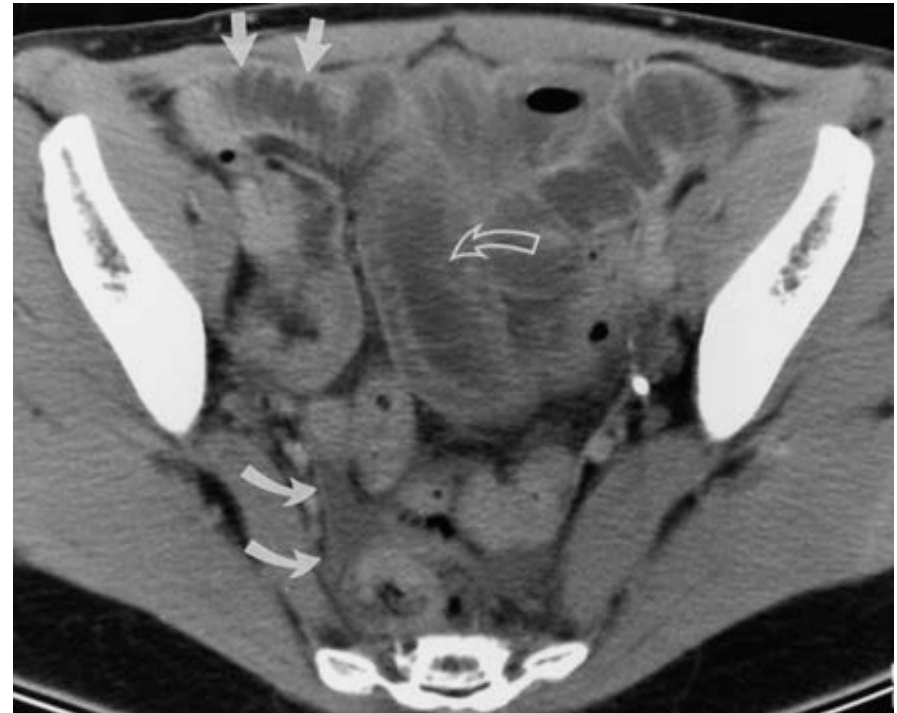
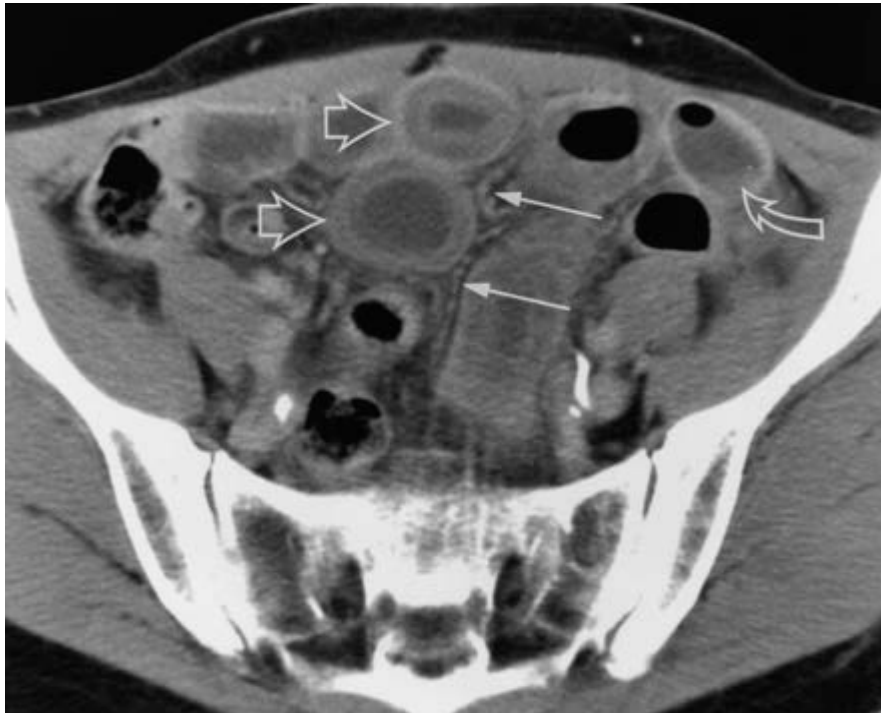






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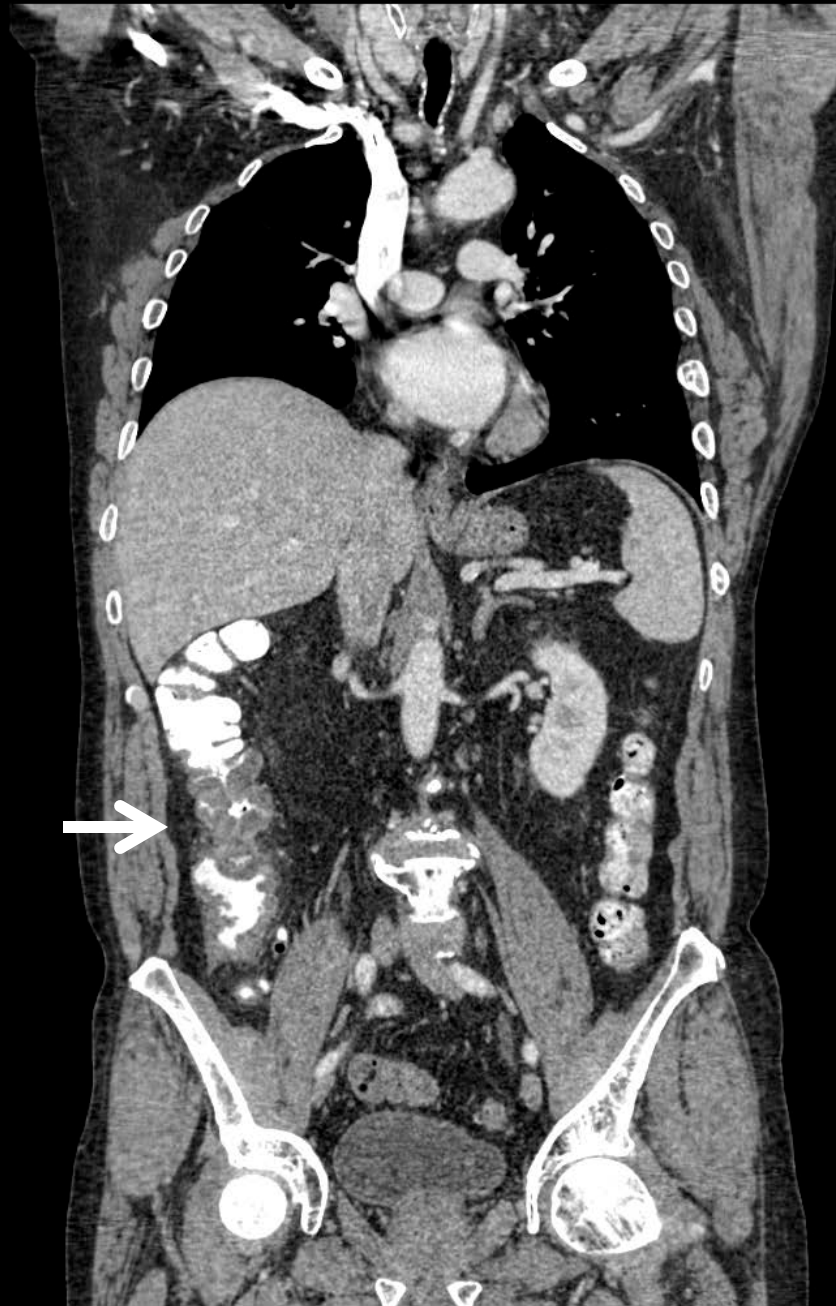


50-year-old woman with idiopathic angioedema of small bowel.

CT scans show marked bowel wall enhancement with regular thickened mucosal folds (*solid straight arrows, B*), clear delineation of different layers of small bowel wall (*open straight arrows, A*), and prominent mesenteric vessels (*long thin arrows, A*).

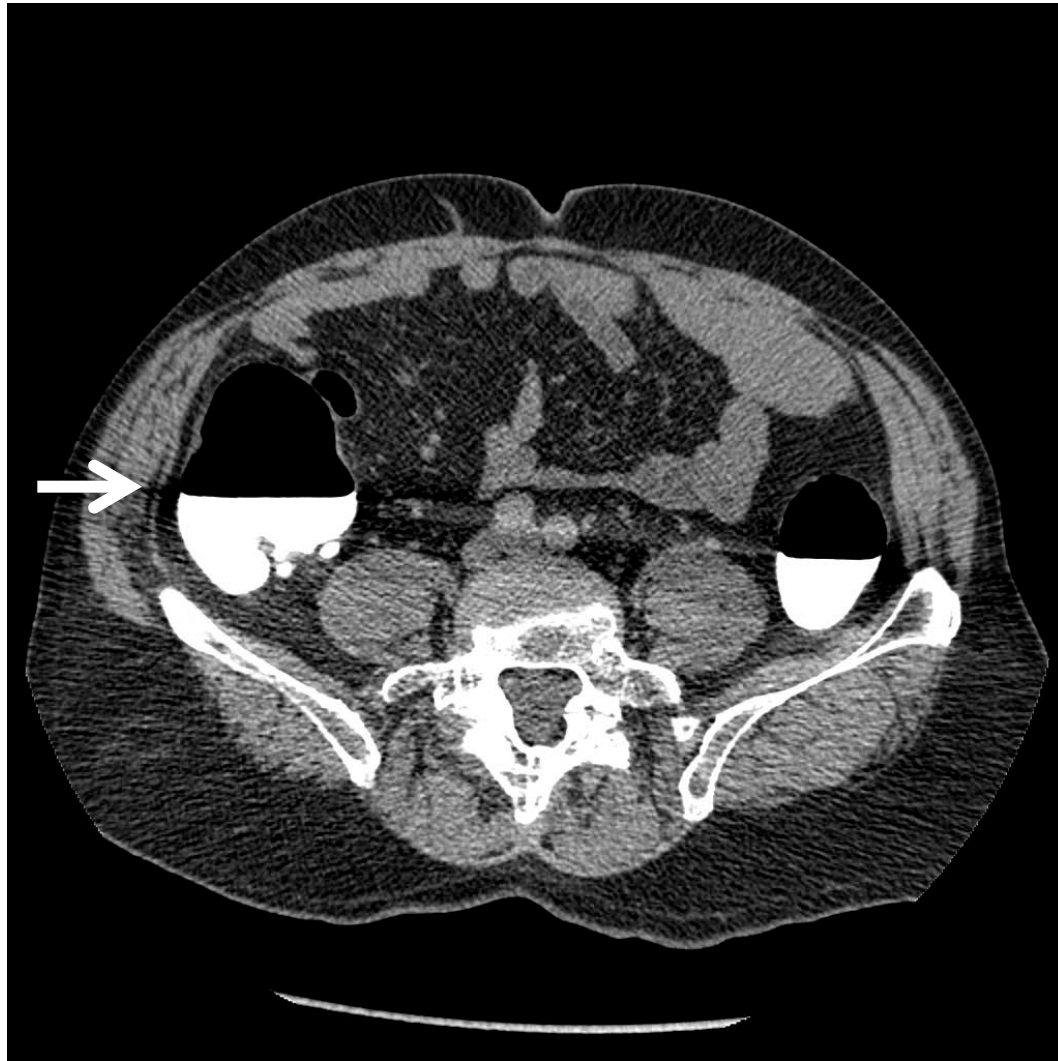
Fluid accumulation within dilated small-bowel loops (*open curved arrows A, B*) and ascites (*solid curved arrows, B*) are also present.

PSEUDOTUMOUR











Kindly provided by V. Berckmans



Kindly provided by V. Berckmans





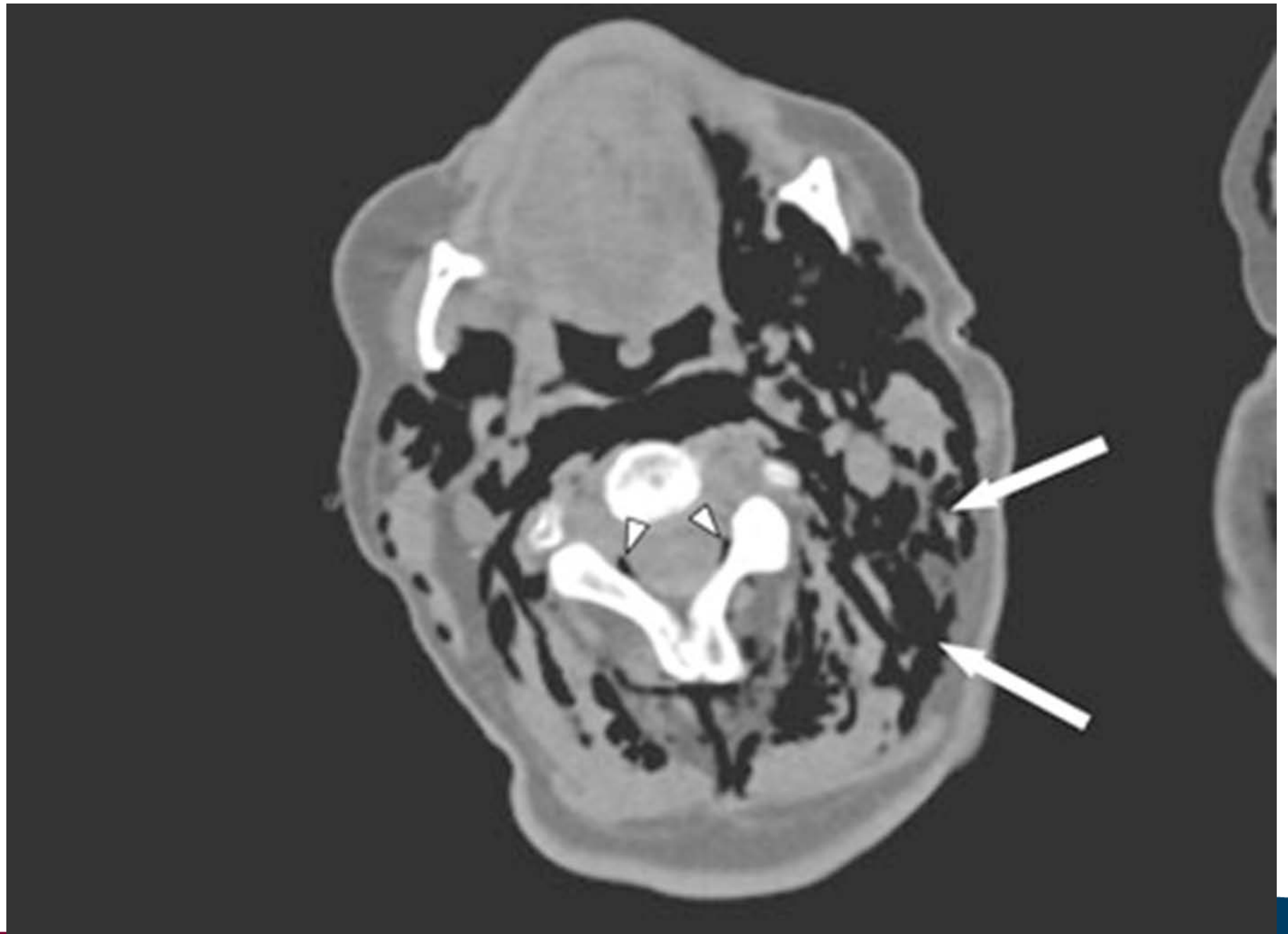


Se:4
Im:1



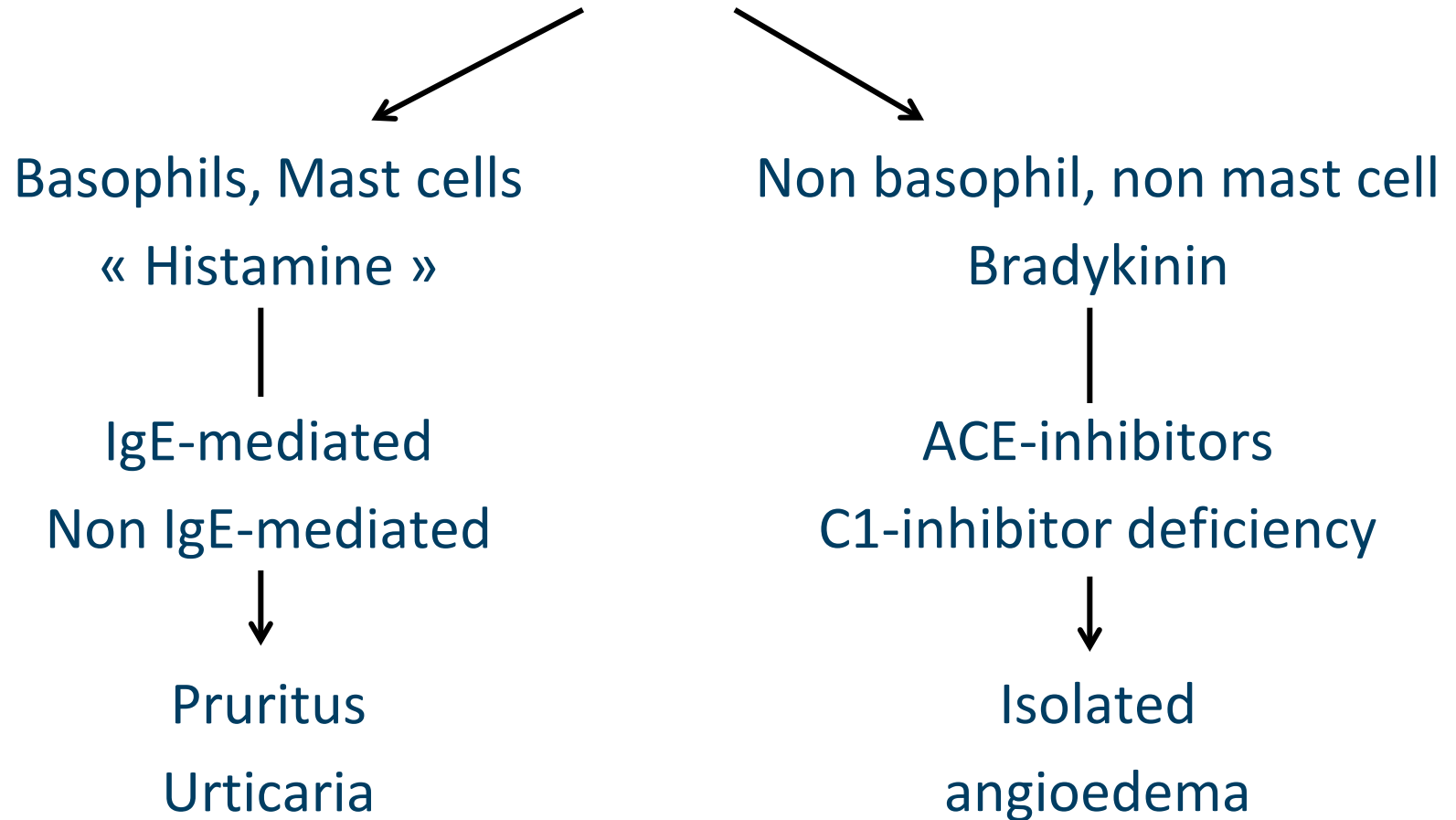
RAD_Thorax Prof

C1093
W2187



Causes & pathogenesis

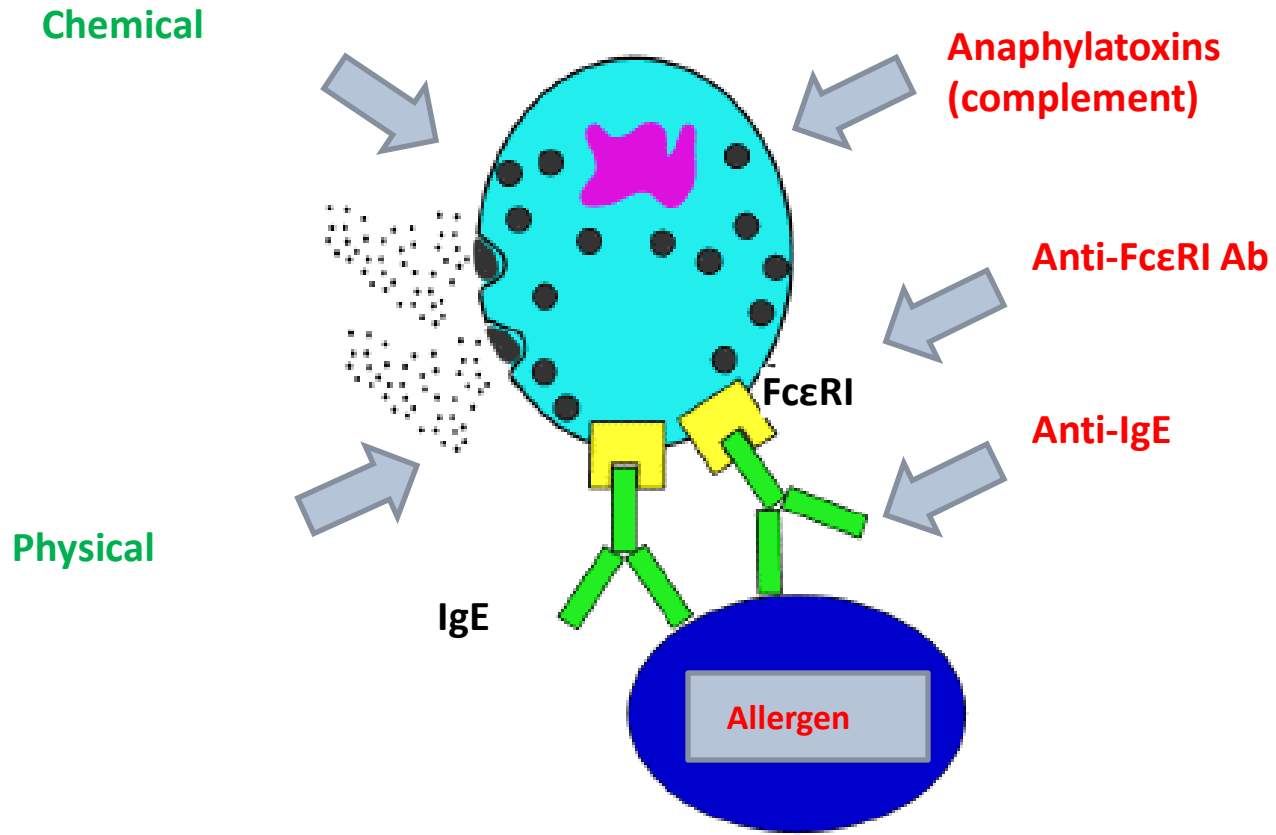
Angioedema



Non-immunologic

Immunologic

Mast cell / basophil



Basophil/mast cell-induced: etiology

Etiology	Mechanism	Ex.	Investigations
Idiopathic	Unknown		Negative
Auto-immune	IgG autoantibodies >< IgER or IgE		ANA, TPO, ASST, AIBAT
Physical	Direct mast cell release		Challenge: exercise, ice, ...
Drugs	Leukotrienes MRGPRX2	NSAID Quinolones	Response to avoidance
Infection	Complement activation	EBV, HBV, HCV, parasites	Serology
Allergic	IgE	Food, venom, NRL	sIgE, skin test
Non-specific mast cell degranulation	Non-receptor mediated	Opiates, contrast	Response to avoidance
Vasculitis	Deposition IC, complement	Urticarial vasculitis	ESR, CIC, serology, C3, biopsy, ...
...			



Austria

Belgium

Czech Republic

Denmark

France

Germany

Greece

Hungary

Italy

The Netherlands

Poland

Portugal

Spain

Sweden

Switzerland

Turkey

United Kingdom

Other Countries

Belgium



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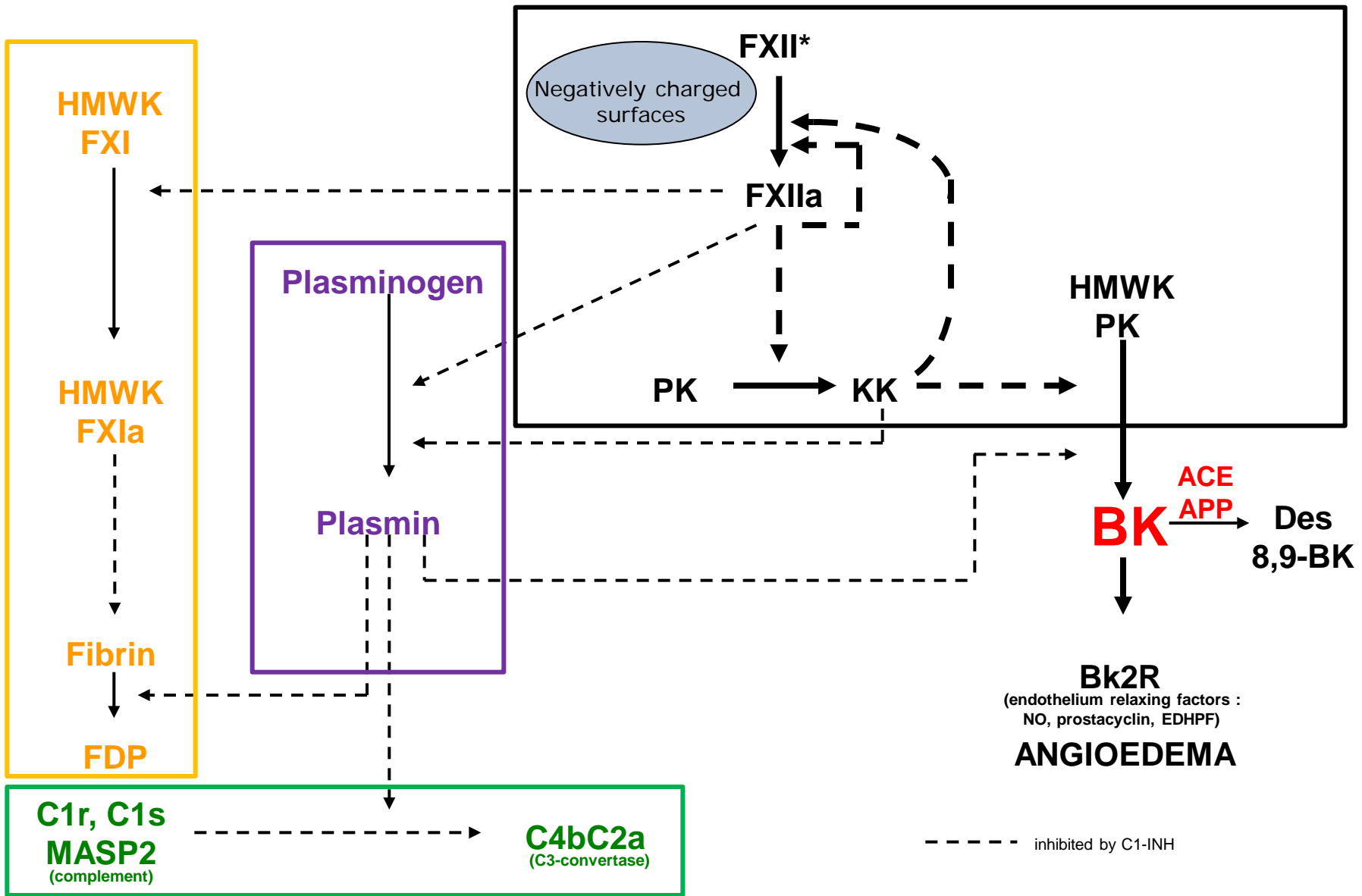
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Bradykinin (BK)-induced angioedema

- Pathomechanism
- Causes
 - ACE-inhibitors
 - Hereditary & acquired angio-edema



Bold arrows indicate the major pathogenic pathway of angioedema in hereditary angioedema

* The FXII gene has oestrogen-responsive elements in its promoter region

BK: bradykinin

HMWK: high-molecular-weight kininogen, PK; prekallikrein, KK: kallikrein, C1-INH: C1 inhibitor, FDP: fibrin degradation products,

MAASP: mannan-binding lectin (MBL)-associated serine protease, 2 Bk2R: bradykinin 2B receptor

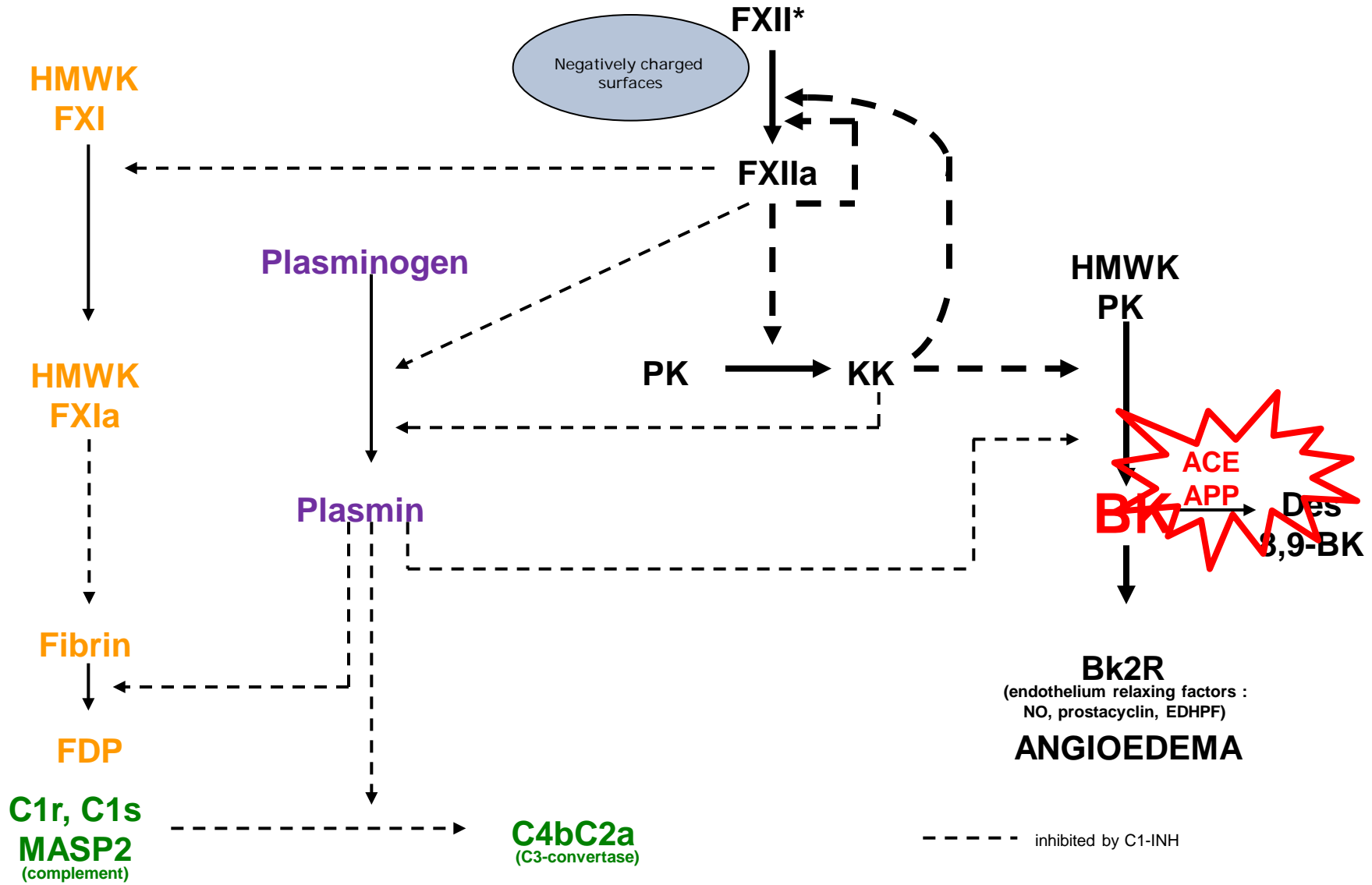
EDHPF: endothelium-derived hyperpolarizing factor

Immunologie

Reumatologie

ACE-I : case

- A 74-year-old woman
- Life-threatening angioedema oropharynx/tongue
 - Progressive deterioration: emergency tracheotomy (asystoly → reanimation)
 - Postanoxic coma (4 days) → cortical blindness and epilepsy.
- History & medical record:
 - “allergy towards an unknown cause”.
 - Severe angioedema of tongue and oropharynx
 - Without prodrome
 - Refractory to antihistamines, corticosteroids and epinephrine
 - Lisinopril/hydrochlorthiazide (Zestoretic® 1 co/day) + bisoprolol (Bisoprolol EG® 5 mg 1 co/day) for arterial hypertension.
 - Laboratory investigations (3-4 weeks after the acute event): normal



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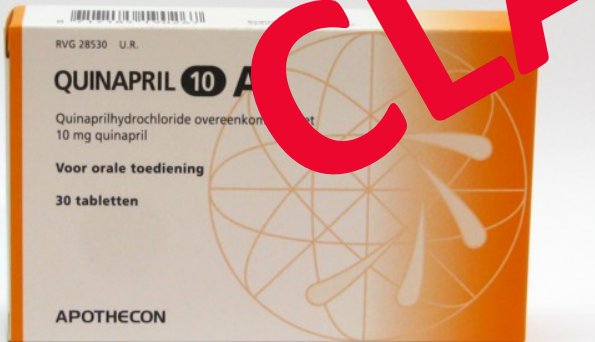
Immunologie

Reumatologie

Angioedema & ACE-inhibitors

- 0.1-0.7% (1/6 all angioedema's)
- Cave late onset (years)
- Oropharynx, viscera
- Fatalities
- Up to months after withdrawal of drug
- Clinical diagnosis
- Sartans: generally safe (<10%)

Hoover T et al. Angiotensin converting enzyme induced angioedema:
a review of pathophysiology and risk factors. Clin Exp All 2010



CLASS EFFECT

Hereditary & acquired angioedema

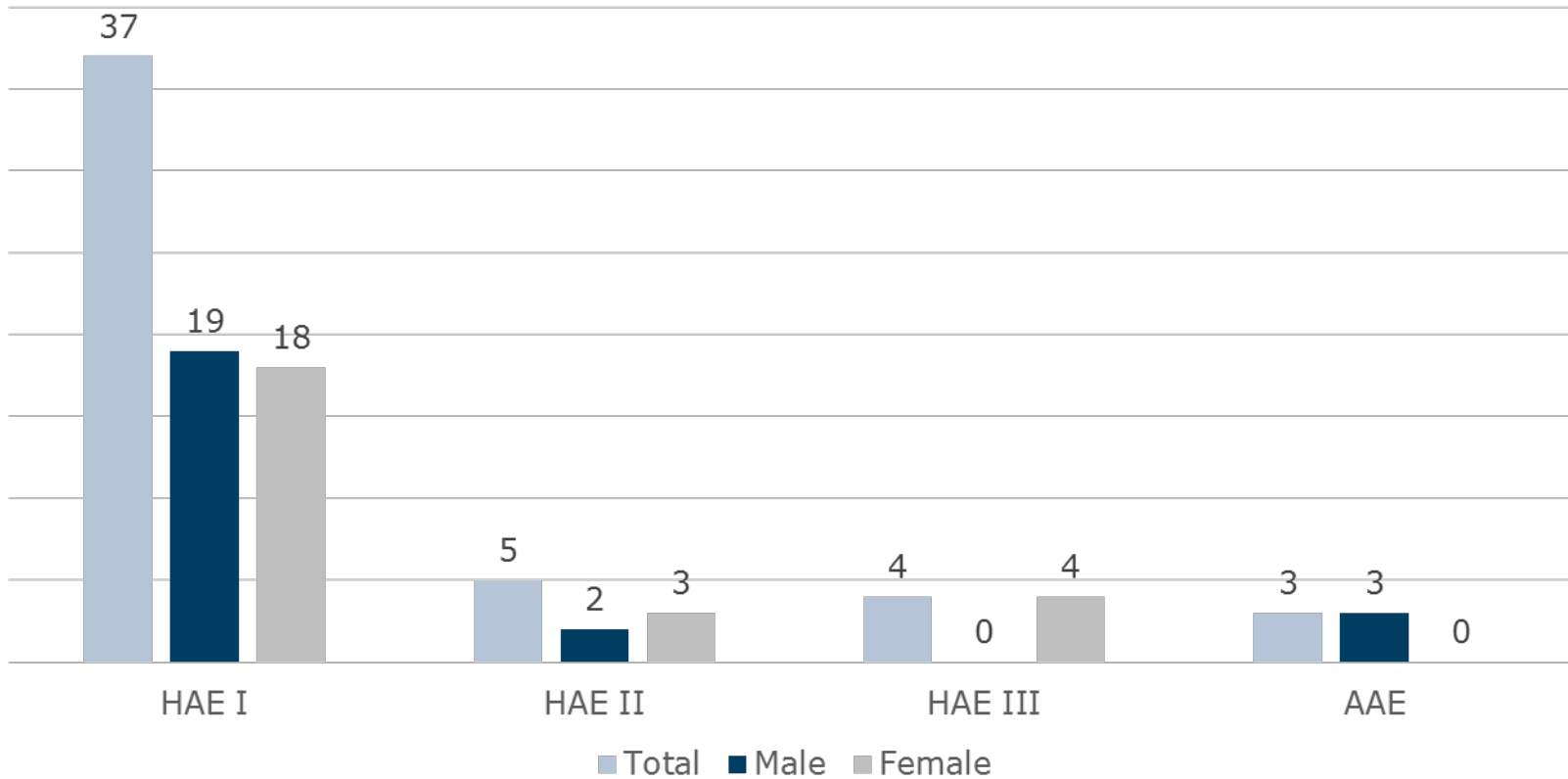
RARE
(HAE 1/50,000-1/100,000)



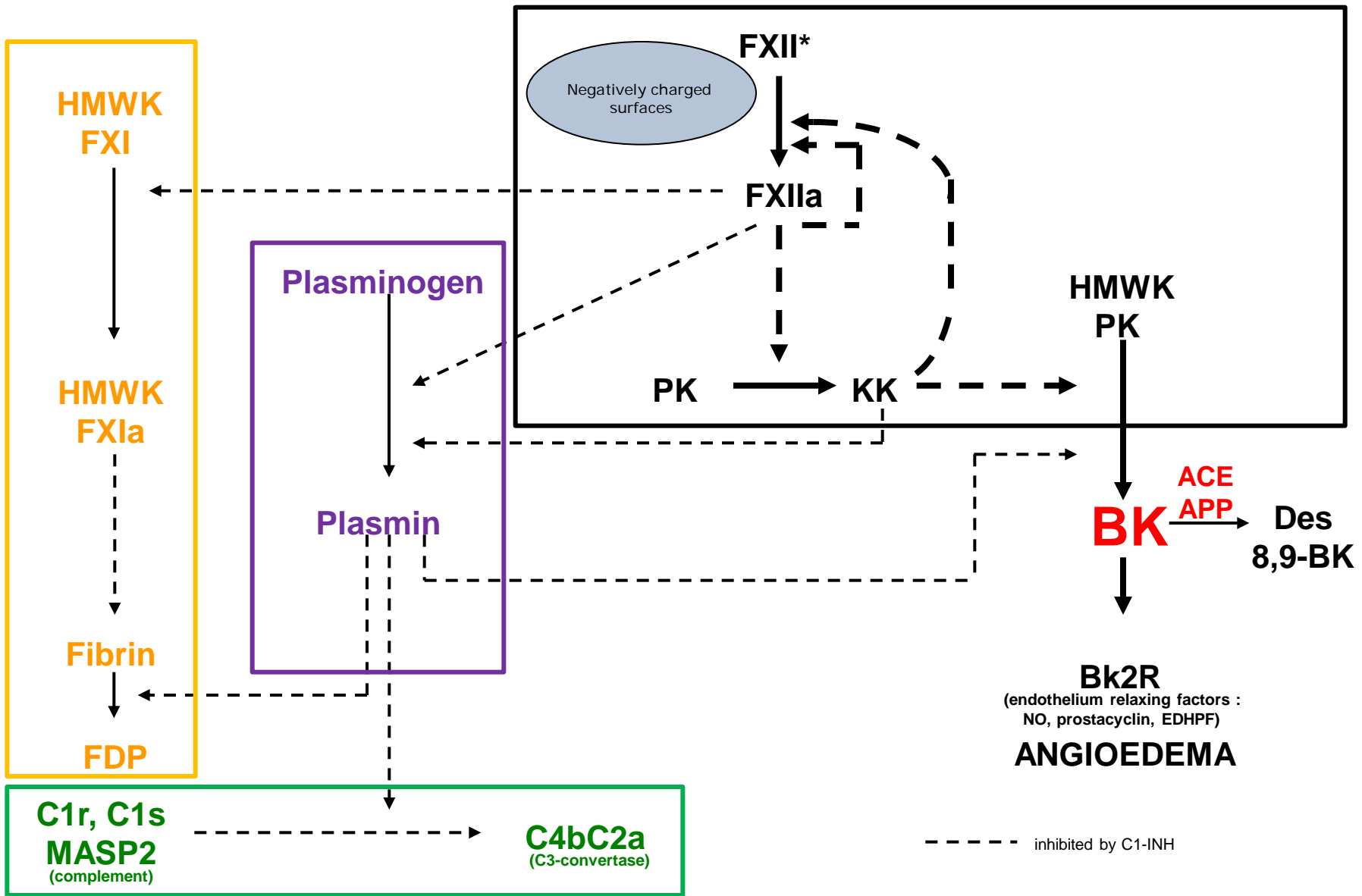
60-120

Angioedema: HAE & AAE

Type	Defect
Hereditary angioedema (HAE)	
Type I	quantitative (antigenic) deficiency C1 INH*
Type II	qualitative (functional) deficiency C1 INH*
Type III (EDIA)	~ gain-of-function mutations factor XII gene (oestrogen-dependent promotor) + mutations in ACE and APP
Acquired angioedema (AAE)	
Type I	increased catabolism (quantitative defect) ~ CIC that activate C1
Type II	C1-INH specific Ab
* autosomal dominant C1 INH gene (SERPINGEN1 > 200 mutations)	



HAE I, II:
aged 2-64 year
7 routine therapy



Bold arrows indicate the major pathogenic pathway of angioedema in hereditary angioedema

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MAASP: mannose-binding lectin (MBL)-associated serine protease, 2 Bk2R: bradykinin 2B receptor

EDHF: endothelium-derived hyperpolarizing factor

Immunologie

Reumatologie

HAE & AAE: alarm signs

- Recurrent isolated angioedema*
- Laryngeal edema
- Recurrent abdominal pain, vomiting
- Positive familial history (HAE)
 - 25% *de novo* mutation !!!
 - HAE-C1 INH gene 11q12-q13.1
 - Mosaicism

* = absence of pruritus & urticaria
(prodromal serpiginous rash)



Prodrome: tingling

Triggers

- Physical and emotional stress
- Traumata
- Stings
- Infection
- ACE-inhibitors
- Oestrogens (contraceptives, pregnancy):
 - ↓C1-INH, ↓ACE, (↓)APP
 - ↑ factor XII

HAE & AAE: diagnosis

C4 ↓ *
&
Funct C-1 INH ↓
(C1q) ↓ **

* 2% normal between attacks, cave testing < 1 year
No indication CH50, C3, C3d

** AAE: 75%

HAE & AAE: diagnosis

Disease	C1-INH level		Complement		Paraprotein	Anti-C1-INH Ab
	Antigenic	Functional	C4	C1q		
HAE						
Type I	↓	↓	↓	No	-	-
Type II	No (↑)	↓	↓	No	-	-
Type III	No	No	No	No	-	-
AAE						
Type I	↓	↓	↓	↓	+	-
Type II	No (↓)	↓	↓	↓	-	+

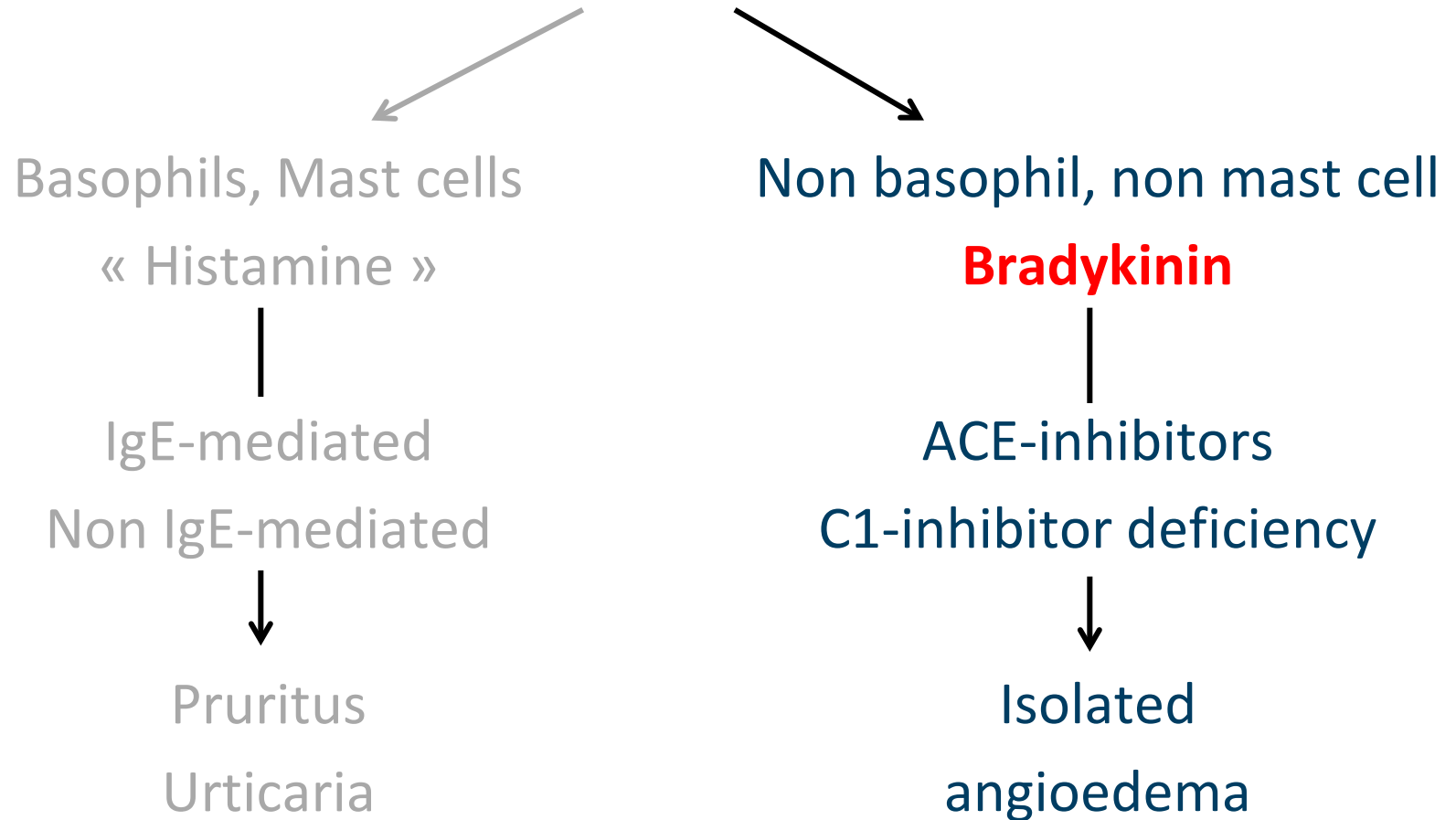
HAE: hereditary angioedema, AAE: acquired angioedema

HAE type III: FXII 5q33-qter

Laboratory	Entire coding region	Selected codons	Targeted mutations	Prenatal diagnosis
AMC, Amsterdam, NL DNA Diagnostics Laboratory Kg_dna@amc.uva.nl		+		
Centogene GmbH, D Institute Molecular Diagnostics samplerequest@centogene.com	+			
Diagenom GmbH, D Medical Genetics Laboratory mail@diagenom.de			+	
GeneDX, USA chrisgc@genedx.com			+	+
Sisternas Genomicos SL, ES David.garcia@sisternasgenomicos.com			+	+

Drug therapy

Angioedema



ACE-inhibitor angioedema: therapy

Drug	Efficacy
Antihistamines (H1, H2)	Undetermined
Glucocorticosteroids	Undetermined
Epinephrine	Undetermined
Tranexamic acid	Anecdotal
pdC1-INH concentrate	Not beneficial
Fresh Frozen Plasma	Anecdotal
Icatibant (Bk2R-inhib)	Yes

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.

CONCLUSIONS

Among patients with ACE-inhibitor–induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine. (Funded by Shire and the Federal Ministry of Education and Research of Germany; ClinicalTrials.gov number, NCT01154361.)

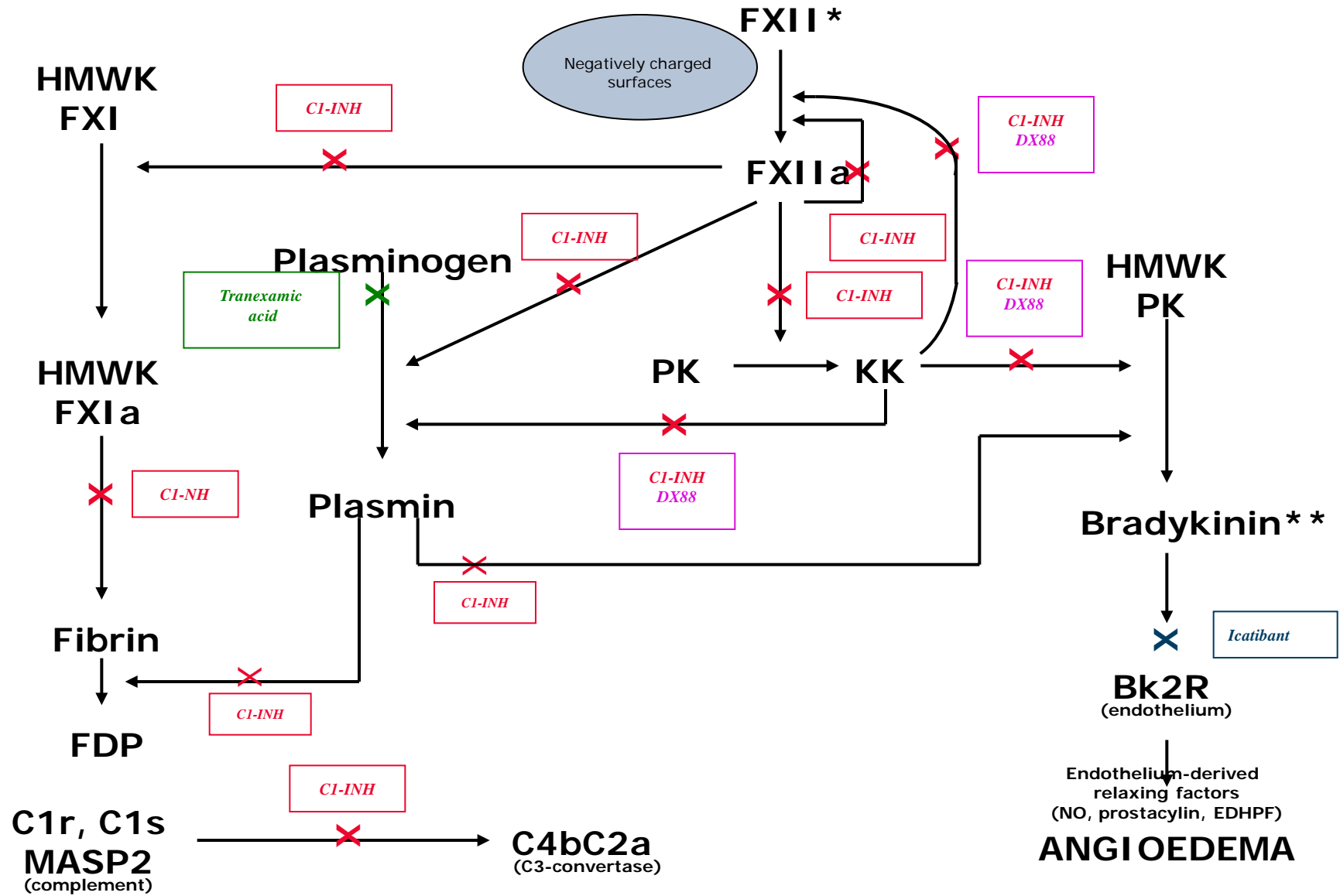
8h (IQR 3-16) vs 27.1h (IQR 20.3-48)

N Engl J Med 2015;372:418-25.

DOI: 10.1056/NEJMoa1312524

HAE & AAE: therapy / prophylaxis

- Mode of action
- Acute bouts / prophylaxis (short/long term)



* The FXII gene has oestrogen-responsive elements in its promoter region

** is degraded by angiotensin converting enzyme into inactive peptides

HMWK: high-molecular-weight kininogen, PK: prekallikrein, KK: kallikrein, C1 INH: C1 inhibitor, FDP: fibrin degradation products,

MA: mannose-binding lectin (MBL)-associated serine protease, 2 Bk2R: bradykinin 2B receptor, DX88: ecallantide

Immunologie

Reumatologie

HAE & AAE: acute bouts

- pdC1-INH concentrate*
- Icatibant*
- ~~Tranexamic acid~~
- DX88 (US)
- rhC1 INH (EMA)

* registered/reimbursed HAE type I and II

Short term prophylaxis

Minor
Manipulations



No prophylaxis
(as pdC1-INH is available)

Major
Manipulations (intubation)



pdC1-INH

1-6h

1000 U Cinryze®

2nd dose: to be available

Long term prophylaxis

Repetitive bouts of (severe)
angioedema



pdC1-INH
1000 U Cinryze®
2-3x/ week

pdC1 esterase INH concentrate

- Berinert[®]: HAE I, II: acute angioedema
- Cinryze[®]: HAE I, II: acute, short term, maintenance
 - Acute: 20 U/kg (Berinert[®]) vs. 1000 U (Cinryze[®])
 - < 50kg: 500 U, 50-100 kg: 1000 U, >100 kg: 1500 U
 - can be repeated
 - Short term: Cinryze[®] 1000 U
 - Maintenance: Cinryze[®] 1000 U 2-3/wk
- IV; 10 min (do not shake)
- Safe (no viral transmission 15 nm), pregnancy & lactation



Berinert® P

Active ingredient: C1 esterase inhibitor, human
ingrediente activo: inhibidor de la esterasa humana C1
Powder for intravenous administration after reconstitution with
sterilized diluent

The reconstituted preparation should be used immediately!
Para su administración intravenosa después de la
reconstitución con diluyente estérilizado
El preparado reconstituido se debe usar inmediatamente
Keep out of the reach of children
Manténgase alejado del alcance de los niños

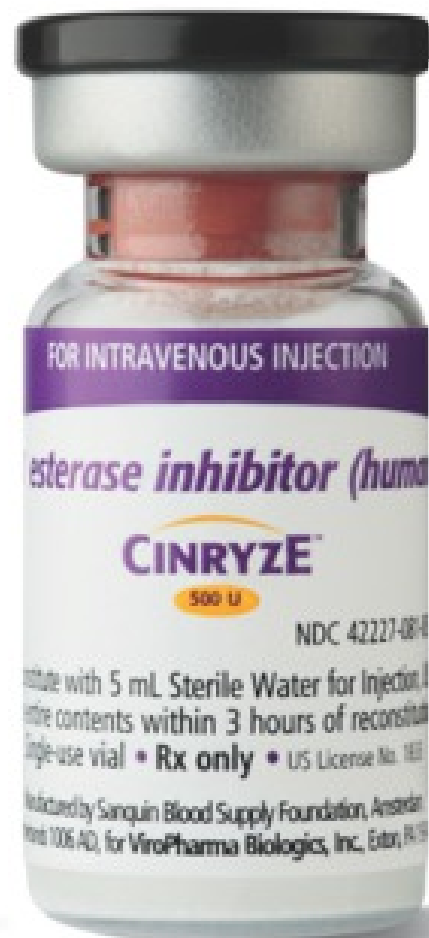
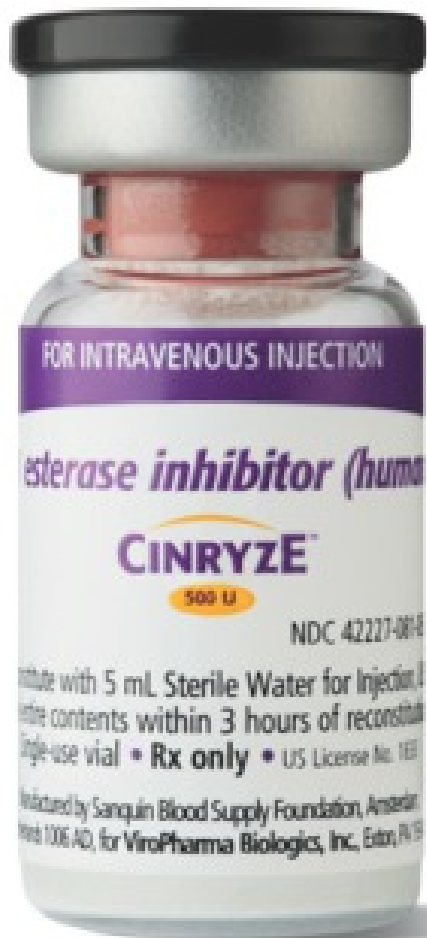
Keep package insert carefully!
Averde cuidadosamente las
instrucciones de empleo

Amicus Biotech GmbH,
D-75002 Marburg, Germany

10g (500mg) vial
1mg (50mg) vial
100 mg (5000 mg) vial

Berinert® P

Active ingredient: C1 esterase inhibitor, human
ingrediente activo: inhibidor de la esterasa humana C1
Powder for intravenous administration after reconstitution
Store at +2 to +8 °C
Keep out of the reach of children
Amicus Biotech GmbH
D-75002 Marburg, Germany



Icatibant

- Firazyr[®]
- Registered HAE I, II: acute angioedema
- Bradykinin 2 receptor inhibitor
- 30 mg SC (up to 3x)
- No data on prophylaxis, pregnancy, lactation
- Local discomfort



Reimbursement: from IVbis to ...

- Hereditary angioedema type I & II
 - Clinical presentation: repetitive attacks
 - ↓ functional C1-inhibitor activity
 - ↓ C4
 - Family history
- Hospital pharmacist
- C1-INH: 20U/kg (Berinert) – 1000 U Cinryze; Firazyr: 3x30 mg / 24h
- Paper work

What about

- 25% no family history
- 2% normal C4
- Prevention (short term); maintenance: only Cinryze®
- Other conditions
 - Type III HAE
 - AAE
 - ACEI-induced angioedema

Tranexamic acid

- Exacyl®
- Not registered, no controlled studies (off-label !!!)
- inhibits generation of plasmin > less conversion HMWK to bradykinin
- PO / IV
- CI: pregnancy, anti-clotting and anti-coagulation

DX 88: ecallantide

- US: Kalbitor[®], not EU
- Kallikrein inhibitor
- Recombinant bovine protein (*P. pastoris*)
- Acute bouts HAE
- 30 mg SC

rhC1 INH

- Positive opinion EMA (Rhuconest[®])
- Recombinant human protein (milk transgenic rabbits)
 - Cave milk & rabbit allergy
- Acute bouts HAE
- 50 – 100 U IV

Summary

- Different pathogenesis & mediators (correct diagnosis!)
- « Histamine »
 - Anti-H1 / Epinephrine
- Bradykinin
 - ACE-I, HAE/AAE (C4, fC1-INH)
 - pdC1-INH / icatibant

Thank you