

The Angiotensin-Converting-Enzyme-Induced Angioedema



Murat Bas, MD

KEYWORDS

• ACE inhibitor • Angioedema • Bradykinin • Bradykinin receptors

KEY POINTS

- The bradykinin B2 receptor antagonist icatibant is effective in angiotensin-converting-enzyme inhibitor-induced angioedema.
- Icatibant is not approved officially for this indication and has to be administered in an emergency situation off-label.
- Corticosteroids or antihistamines do not seem to work in this condition.

ETIOLOGY AND PATHOPHYSIOLOGY OF ANGIOEDEMA

Angioedema is an edematous swelling of deeper tissue layers, which impacts both the skin and the mucosa (**Fig. 1**). When angioedema manifests in the airways, it can cause breathing difficulties and can even, in rare cases, lead to death.¹ One can divide angioedema into allergic (urticaria) and nonallergic angioedema.² Typically, nonallergic angioedema, when juxtaposed to allergic urticaria, is the lack of pruritus or erythema. Central to allergic urticaria pathophysiology is histamine, whereas the main mediator of nonallergic angioedema is bradykinin (**Fig. 2**).

This difference is important in determining the appropriate treatment for the disease. Especially problematic is chronic urticaria. Angioedema, which may appear during the course of this disease, only shows in 10% of cases an allergic cause.^{3,4} It is for this reason that this type of angioedema rarely reacts to standard antiallergy therapy, such as antihistamines and corticosteroids. Without the pruritus or erythema, the angioedema from chronic urticaria cannot easily be differentiated from nonallergic angioedema. These are differential diagnosis problems that lead to early treatment failures. Bradykinin-induced angioedema is owing to either an increased production of bradykinin or an arrested breakdown thereof. Bradykinin is a Nona-peptide, which is physiologically made in the kallikrein-kinin system. This system was discovered more than 100 years ago when Abelous and Bardier were investigating the blood dropping effect of urine.⁵ Kinins are pharmacologically active

Clinic of Otorhinolaryngology, Klinikum rechts der Isar, Technische Universität München, Ismaninger St 22, 81675 Munich, Germany
E-mail address: m.bas.hno@gmail.com

Immunol Allergy Clin N Am 37 (2017) 183–200

<http://dx.doi.org/10.1016/j.iac.2016.08.011>

0889-8561/17/© 2016 Elsevier Inc. All rights reserved.

immunology.theclinics.com



Fig. 1. Angiotensin-converting-enzyme-induced angioedema of the tongue and epiglottitis.

peptides produced by the enzymatic degradation of kininogens by kallikrein. Kinins are then released into body fluids and tissue. In comparison, the C1-esterase inhibitor (C1-INH) functions as an endogenous kallikrein inhibitor, thereby slowing kinin synthesis. The family of kinins includes bradykinin, kallidin, and methionyl-tyssyl-bradykinin, which is found in blood plasma and in urine, and can quickly be converted to bradykinin.⁶

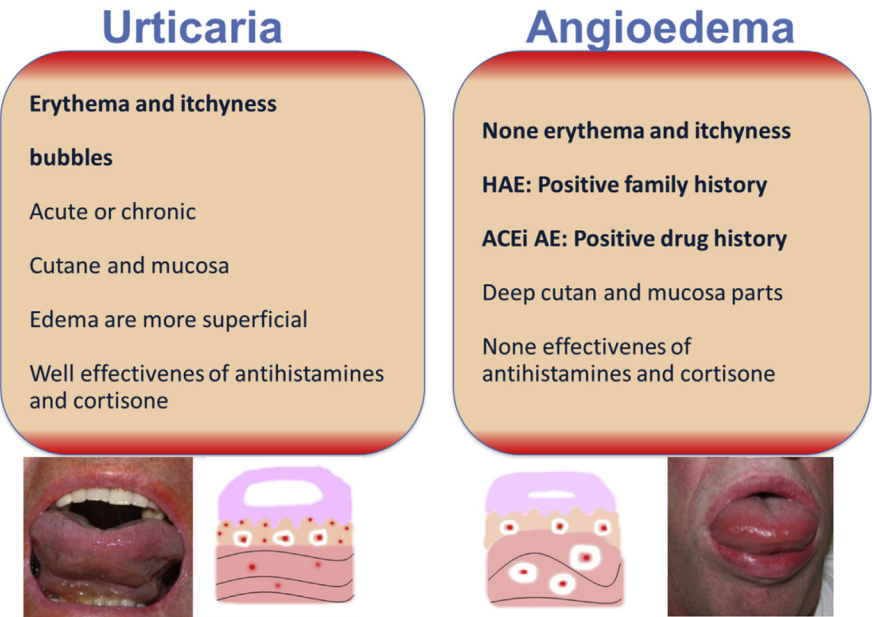


Fig. 2. Main differential criteria in angioedema (AE) and urticaria. ACEi angiotensin-converting-enzyme inhibitor; HAE, hereditary angioedema.

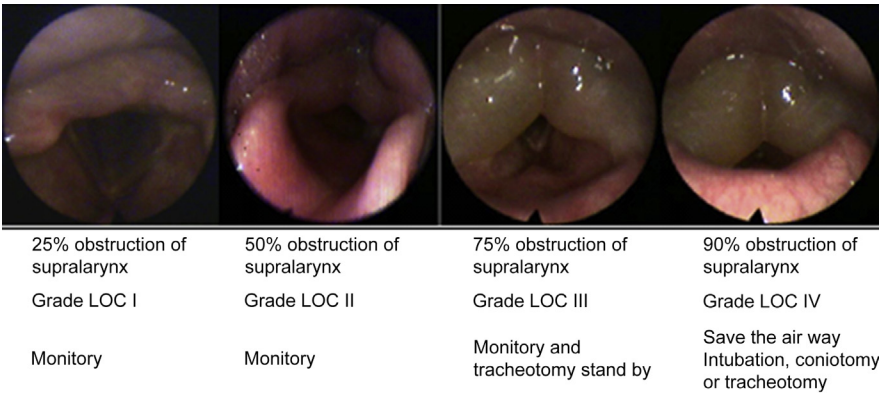


Fig. 3. Laryngeal edema classification.

The kallikrein–kinin system is closely connected with the renin–angiotensin–aldosterone system, and to some degree even antagonizes its effects. The functional coupling between these 2 systems is owing to the unspecificity of the angiotensin-converting enzyme (ACE), which builds angiotensin II, but also degrades kinins such as bradykinin or substance P to inactive metabolites.^{7,8} Other proteases besides ACE (aminopeptidase P, dipeptidylpeptidase IV, carboxypeptidase N) also partake in bradykinin degradation. If they are inhibited in addition to ACE, then one may see an extra increase in plasma and tissue bradykinin concentrations.^{9–11}

BRADYKININ RECEPTORS

Bradykinin receptors are G-protein–coupled receptors that are present ubiquitously on cell membranes. As of yet, 2 types of receptor subtypes have been identified: the bradykinin-receptor types 1 (BKR-1) and 2 (BKR-2). Each seems to have different pharmacologic properties.^{12–18} The human gene for BKR-2 has been localized to chromosome 14q32,¹⁹ whereas BKR-1 was found to be on chromosome 14q32.1–q32.2.²⁰ The amino acid sequences from BKR-1 and BKR-2 have been shown to be 32% homologous.¹⁸ BKR-1 is created de novo by many different organs as a reaction from tissue injury, whereas BKR-2 is usually expressed constitutively.^{20–22}

BRADYKININ EFFECTS

The discovery of various selective antagonists of BKR-1 and BKR-2 in the 1980s were fundamental to the discovery of the function role of kinins.¹⁵ Recently, the development of C1-INH and BKR-2-transgene mice has produced important information concerning the role of kinins.^{23,24} This revealed the effects of bradykinin on vessel permeability through inhibition of C1-INH.²⁴ The anticonstrictive effects of bradykinin on peripheral and coronary arteries have been shown to lower blood pressure in normotensive animals. Additionally, it has antithrombotic, antiproliferative, and antifibrogenic perperties.^{22,25–29}

The cardiovascular effects of bradykinin are according to contemporary knowledge, mostly triggered through the BKR-2 activation on endothelial cells, which causes a release of nitrous monoxide, prostaglandin PGI2 and tissue plasminogen activator.^{30,31} It has also been shown that bradykinin has a cardioprotective effect, and is involved in the “preconditioning” during myocardial ischemia and by reperfusion

injury.³² Bradykinin can decrease the size of an infarct^{33,34} and can also retard the growth of cardiomyocytes.^{35,36} Additionally, kinins can cause a bronchoconstriction,³⁷ which may be associated with the ACE inhibitor-induced dry cough, which is mediated by bradykinins and substance P.^{38,39} Furthermore, the local accumulation of bradykinin can lead to an activation of locally released histamine, which may be 1 reason for the local susceptibility for the cough reflex.⁴⁰ Finally, it is shown that bradykinin stimulates insulin secretion from the B-cells of the pancreas. This effect is caused by the increase in intracellular calcium as a result of a hyperglycemia.^{41,42} Bradykinin also increases the insulin-dependent glucose transport.⁴³ Further investigations have shown that the effects of locally secreted bradykinin, namely, the intake of glucose in cells, is independent of the insulin secretion.^{44,45} These results imply that the lesser degradation of bradykinin in patients with cardiovascular disease is associated with the beneficial effects of ACE inhibitors (ACEi). This includes, for example, the lower rate of long-term injuries associated with type 2 diabetes mellitus.⁴⁶

BRADYKININ-INDUCED ANGIOEDEMA

Hereditary Angioedema

In 1882, Heinrich Irenaus Quincke described an acute and clearly circumscribed edema. Even though such an edema was described in earlier cases, it was Quincke who accurately described the illness and who clearly delineated it from urticaria.⁴⁷ Currently, the terms Quincke edema and angioedema are interchangeably used. Quincke edema is also used as an umbrella term to describe an edema without urticaria and/or pruritus.

Our contemporary understanding is that an insufficiency of the serine protease C1-INH, which is caused by a genetic defect, may play a role in the development of hereditary angioedema (HAE).⁴⁸ As a result, a series of changes within the complement system are initiated, which can be used for diagnostic purposes. Important is that the lack of C1-INH plays a physiologic role in decreased bradykinin production. This is because C1-INH are endogenous inhibitors of kallikrein. The reduced activity of C1-INH lead to a increased bradykinin production. Human C1-INH gene is located on chromosome 11 (11q12-q13.1).⁴⁹ Two variants of HAE have been described: HAE type 1 with a lowered C1-INH level and deficient function (in 85% of cases), and HAE type 2 with a normal protein concentration but a functional deficit (in 15% of cases). This is a case of a heterozygote, autosomal-dominant inheritance with an incidence of 1 in 50,000, independent of ethnicity or gender.⁴⁹ Additional causes of autosomal dominance inheritance of angioedema were discovered in 2006 as mutations in exon 9 of the F-12 gene. Amino acid position 309 of the coagulation factor XII was shown to have lysine or arginine instead of threonine.⁵⁰ A cause of the activating mutation is, as with the classical HAE types 1 and 2, an increased kinin production as a result of an increased enzymatic activity of coagulation factor XII. Activating factors XIIa change prekallikrein into kallikrein, which leads to a faster conversion of "high-molecular-weight kininogen" to bradykinin. This disease impacts mostly women, because estrogen intake is a precipitating factor. This can be explained by the fact that coagulation factor XII is synthesized in an estrogen-dependent manner. As a result, women who take medications such as oral contraceptives or who are pregnant are especially susceptible. The medication causes increased factor XII serum concentrations. Rarely are men impacted by this disease and when they are the disease is usually less pronounced. The most common symptoms of patients with HAE type 3 are swelling of the face (93%) and tongue (54%), as well as abdominal pain (50%). Larynx (25%) and uvula edema (21%) are also seen.⁵¹ The quantitative

and function of C1-INH is normal in contrast with types 1 and 2. However, only some patients have been shown to have a mutation in exon 9 of the F-12 gene. Therefore, one must assume that further unknown genetic causes for this subtype must exist. The first case of homozygote C1-INH-deficiency was discovered recently with a mutation of c.1576T>G.⁵¹ In mice, an interruption of the C1-INH impact led to increased vessel permeability, which was shown to be reversible with human plasma pool C1-INH.²⁴ Other results, which were taken from transgene mice, produced further results supporting the role of BKR-2 in the pathogenesis of angioedema. In this way was one able to dramatically reduce increased vessel permeability with the BKR-2 antagonist icatibant (see the discussion in the Icatibant section).

Trigger Factors

Patients with HAE describe a large number of factors that induce angioedema, including cold exposure, mechanical trauma (eg, cold compresses, sitting or standing for long periods of time), food (eg, eggs or alcohol), infection, pesticide contact or other chemicals, stress or anxiety, and certain pharmaceuticals such as ACE inhibitors and estrogen.⁴⁸ These mostly anecdotal accounts are rarely investigated and often seem to be associated with individual patient characteristics. One exception is the intake of estrogen as seen in hormone replacement therapy. It has been shown in multiple HAE patients that women with higher estrogen levels, as seen during the menstrual cycle as well as during pregnancy or with hormone replacement therapy, all have an higher incidence rate.^{51,52} Other researchers have found similar cases in men and women who used antiandrogenous medication in the form of Cyproteron.⁵³ Indeed, also pharmaceuticals that inhibit bradykinin *degradation* can lead to increased incidence, this is why ACE inhibitors are contraindicated in HAE patients.^{54,55}

IATROGENIC INDUCED BRADYKININ ANGIOEDEMA

The most common reason for bradykinin-induced angioedema is the intake of pharmaceuticals that lead to an inhibition of the breakdown of bradykinin. This includes ACE inhibitors like enalapril as well as angiotensin-1 blockers like losartan and the renin inhibitor aliskiren. The arrested breakdown of bradykinin by this group of medications, which are often used to treat cardiovascular disease, is not a desired effect. However, it is believed that the ACE inhibitors have a stronger inhibiting effect on bradykinin breakdown than the other agents in this category.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA

A characteristic of ACE inhibitor-induced angioedema is its constant manifestation in the airways. Swelling in the head and neck areas, especially in the pharynx and larynx, make multiple-day ward stays for patients necessary.

The incidence of ACE inhibitor-induced angioedema varies in different investigations, which is most likely owing to ethnic differences. In Caucasians, an incidence of ACE inhibitor-induced angioedema of 0.1% to 0.7%^{1,48,49,56,57} was found, whereas the incidence in African Americans was much higher.⁵⁸ A recent metaanalysis of the side effects of pharmaceuticals for treating cardiovascular disease found a 3 times greater relative risk for the manifestation of an ACE inhibitor-induced angioedema in African Americans as compared with Caucasians.⁵ With the approximately 7 million patients taking ACE inhibitors in Germany and an assumed angioedema incidence of 0.3% to 0.5%, one can extrapolate that to about 20,000 to 35,000 cases present every year. The incidence itself is calculated to be 1 in 4000. This means that ACE

inhibitor-induced angioedema is more common than HAE.⁵⁹ If additional enzymes, besides ACE, that arrest bradykinin breakdown, are inhibited, then the one can assume an even higher plasma bradykinin concentration.^{9–11} This effect is seen especially well with omapatrilat, which inhibits both ACE and the neutral endopeptidase. During clinical examinations a 3 times greater rate of angioedema was found in comparison with the ACE inhibitor enalapril (2.17% vs 0.68%), which is why this particular drug was not approved.

ANGIOTENSIN-1 BLOCKER-INDUCED ANGIOEDEMA

Angiotensin-1 blockers rarely cause angioedema in comparison with ACE inhibitors.^{57,59} In the VALIANT Study (Valsartan in Acute Myocardial Infarction Trial), 4900 patients were treated with valsartan, captopril, or the combination of both. In the valsartan group, 0.2% of patients incurred an angioedema; in the other groups, 0.5% of the patients had this side effect. It seems surprising that angioedema can occur, when looking at the drugs method of action, through the effects of bradykinin. The fact that the combined intake of valsartan and captopril did not cause more angioedema than captopril alone suggests that it may not be associated. However, a recent clinical study showed that angiotensin-1 blockers increase bradykinin levels in hypertensive patients.^{60,61} Blood levels of angiotensin II increase when patients are treated with angiotensin-1 blockers, possibly because these interrupt the physiologic negative feedback mechanism, which regulates angiotensin-II production through the secretion of renin.⁶² Concurrently, all the angiotensin type 1 receptors are blocked, which allows angiotensin type 2 receptors to be activated by angiotensin II. In this context it is important to note that the activation of angiotensin type 2 receptors is regulated through an as-of-yet unknown mechanism, which also leads to an inhibition of ACE activity.^{63–65} As a result, the angiotensin-1 inhibition, as seen in Campbell and colleagues' study,⁶¹ and increased bradykinin concentration in plasma, could be owing to the inhibition of bradykinin breakdown. However, this theory needs to still be shown valid through animal experiments. Hypothetically, patients who experience an angiotensin-1 blocker-induced angioedema should not continue to receive angiotensin-1 blockers. Potential alternatives are calcium blockers. In cases with severe heart failure and renal dysfunction, the use of angiotensin-1 blockers is possible. The patients must be informed regarding side effects like angioedema. The risk to develop an angioedema with angiotensin-1 blockers are limited.

RENIN INHIBITOR-INDUCED ANGIOEDEMA

A further pharmacologic alternative to influence the renin–angiotensin–aldosterone system is through the relatively new renin inhibitor, aliskiren, which is also approved for the treatment of hypertension by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA). The inhibition of renin leads neither to a direct inhibition of ACE nor to an increased activity of angiotensin type 2 receptors, and therefore probably not to an increased plasma bradykinin concentration. However, aliskiren has not been shown to be any better than ACE inhibitor or sartans.^{66–69} In the initial approval studies, all patients with mild or moderate hypertension were excluded. In contrast with other antihypertensive medications, no reduced cardiovascular morbidity or mortality has been shown with aliskiren.^{66–69} Additionally, aliskiren is not indicated for patients who suffered an angioedema with ACE inhibitor or with a sartan, because this has been judged a therapeutic contraindication (Decision of the Federal Committee of initiation of an opinion process to amending the official drug guideline).

ACQUIRED ANGIOEDEMA

Acquired angioedema develops owing to a nongenetic deficiency of C1-INH, and usually impacts adults.⁶⁸ It can develop as a result of a severe disease, for example, a malignant lymphoma. Patients with lymphoproliferative diseases can develop an angioedema, which is associated with low C1-INH plasma concentrations.^{70–72} In comparison with HAE with lowered C1-INH synthesis and/or activity, acquired angioedema is characterized by a greater number of idiotype anti-idiotype immune complexes (autoantibodies), which breakdown C1-INH and C1q-molecules. Other diseases, for example, liver cell carcinoma and liver cirrhosis, are also characterized by lower C1-INH concentration, although in these cases angioedema is not a known problem. To note is that some lymphoma-associated angioedema cases are known to have normal C1-INH plasma levels.⁷³ A recent study found that a newly discovered C1-INH mutation was associated with monocyte-inhibited C1-INH secretion.⁷³

THERAPY OF THE ACUTE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA

Angioedema in the head and neck region is especially dangerous owing to the danger of airway closure, and thereby asphyxiation. As a result, it is always important to inform patients about where the angioedema is found and its severity. Patients need to be informed about the possibility of asphyxiation and any need for intervention. One can differentiate different general therapeutic options of angioedema of the head and neck region; these include:

- Mechanical protection of the airways,
- Supportive therapeutic measures,
- Symptomatic (nonspecific) pharmacologic measures, and
- Causal (specific) pharmacotherapy.

Mechanical Protection of the Airways

Mechanical protection of the airways must be considered if asphyxiation is threatening if there is:

- Inability to swallow,
- Inspiratory stridor, and/or
- Cyanosis.

If these symptoms are present, one should immediately begin mechanical safeguarding of the airways.

Forms of Mechanical Safeguarding

The methods can depend on the localization of the angioedema (**Table 1**). Besides these symptoms, the severity and degree of angioedema are important in the decision. The degree of laryngeal (**Fig 3**) and tongue angioedema (**Fig. 4**) should be ascertained. Additionally, the mechanical intervention can lead to further tissue damage and inflammation, which can last for days.

Supportive Procedures in the Therapy

The use of ice cubes in cases with angioedema in the mouth cavity and oropharynx is potentially helpful. Patients with hypotension should be treated with a sodium chloride infusion. An upright position of the upper part of the body is favored.

Table 1 Forms of mechanical safeguarding of the airways	
Location	Method
Lip, Face (Cheeks, Periorbital)	None Necessary
Tongue, mouth	• Nasal fiberoptic intubation ◦ Wendl-Tubue
Oropharynx (soft palate, uvula, oropharyngeal back-wall, tonsillar region)	• Wendl-Tubus • Nasal fiberoptic intubation • Tracheotomy
Tongue base, hypopharynx, larynx (supralarynx)	• Nasal fiberoptic intubation • Oral intubation • Tracheotomy

Symptomatic Pharmacotherapy

Vasoconstricting agents can be helpful in the therapy of renin–angiotensin–aldosterone system blocker-induced angioedema (RAE). Epinephrine (inhalation or spray) can be (off-label) used (dosage up to 8 mg/application). Unfortunately, there are no studies demonstrating treatment efficacy of epinephrine. Treatment with epinephrine is therefore not evidence based. Treatment with all classes of analgesics is possible if required.

Nonspecific Pharmacotherapy

Corticosteroids

At the time of this writing, here is no EMA or FDA approved treatment for RAE. Despite a lack of approval, RAE has been treated in the past with glucocorticosteroids (methylprednisolone 250–500 mg) and H2 antihistamines (clemastine 2 mg). There are no studies supporting this therapeutic scheme. A retrospective case series could not show a faster remission of symptoms with glucocorticosteroids versus placebo.⁷⁴ Three of 47 patients treated with cortisone had to be tracheotomized, 2 had to be intubated, and 12 received a second dose of cortisone. The time of complete symptom remission was 33 hours and did not differ statistically from placebo. A recent

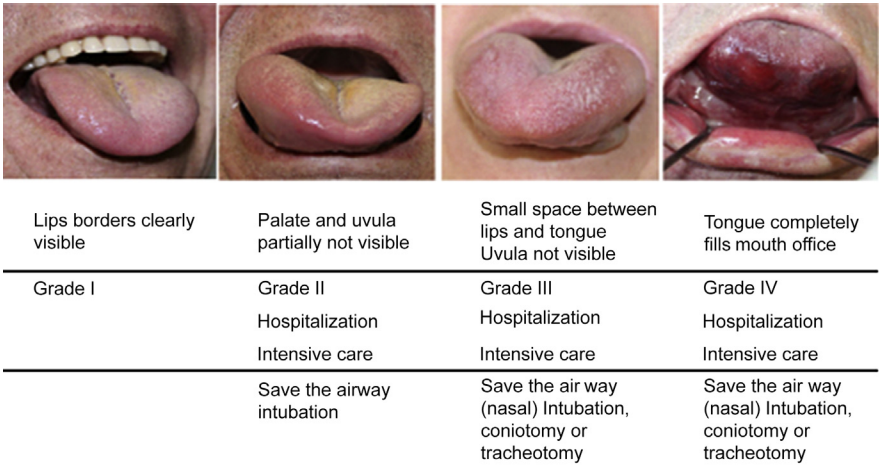


Fig. 4. Emergency managements of tongue angioedema.

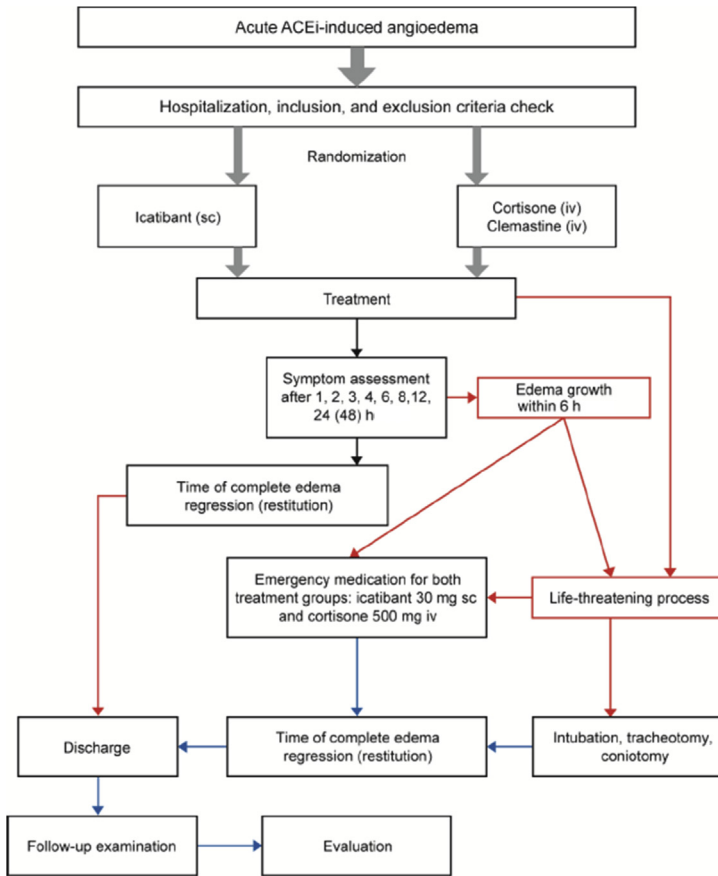


Fig. 5. Study design of AMACE (AMelioration of Angiotensin Converting Enzyme Inhibitor Induced Angioedema Study). ACEi, angiotensin-converting enzyme inhibitor; IV, intravenous; SC, subcutaneous.

randomized controlled study could show a mean time to complete symptom remission of 27 hours after treatment with cortisone and H₂ antihistamines and therefore confirmed a lack of efficacy of this therapeutic concept.⁷⁴ It can be concluded that there is no evidence for the effectiveness of glucocorticosteroid or H₂ antihistamines in the therapy of RAE.

SPECIFIC PHARMACOTHERAPY

Because it can be safely assumed that RAE belong to the group of ACE inhibitor-induced angioedema in which a potential effectiveness of pharmacotherapeutic agents reducing the production of bradykinin or blocking the bradykinin 2 receptor can be expected. The aim of this therapy is to prevent the angioedema from spreading to the upper airways and to reduce an existing edema.

Icatibant

Because most of the nonallergic angioedema are related to a pathologic increase in bradykinin concentration an effectiveness of the synthetic B₂ receptor antagonist

icatibant (Firazyr) can be assumed. Icatibant is a competitive receptor antagonist. Icatibant is approved by the FDA and EMA for the treatment of acute type 1 and 2 HAE attacks. Standard therapy is applied subcutaneously in the belly region. Standard dosage is 30 mg. A first symptom improvement can be expected in average after 45 minutes. Systemic side effects have not been reported up until now. A local erythema at the injection site appears regularly.

Since market approval, dozens of ACE inhibitor patients have been successfully off-label treated with icatibant. There are 4 original papers on the subject. Three of these are case series showing successful treatment in a total of 33 patients. Parts of the patients had previously received glucocorticosteroids or had been intubated. Complete remission of symptoms had been approximately reached after 4 to 5 hours.

The fourth publication is a randomized, double blind controlled 2-armed multicenter trial. Thirty-two patients were screened and 30 patients were included in the study. The patients received icatibant plus placebo versus prednisolone plus clemastine plus placebo in a randomized fashion.⁷⁴

Eligible patients were randomly assigned, in a 1:1 ratio, to receive, within 10 hours after symptom onset, subcutaneous icatibant at a dose of 30 mg injected into the abdominal wall or standard therapy consisting of intravenous prednisolone (Solu-Decortin H, Merck, Kenilworth, NJ) at a dose of 500 mg plus clemastine (Tavegil, Novartis, Basel, Switzerland) at a dose of 2 mg. Randomization was performed online with the use of variable block sizes to ensure that the number of study participants in the treatment groups was balanced. Normal saline (0.9%, B. Braun, Melsungen, Germany) was administered as an intravenous placebo in patients who were receiving icatibant and as a subcutaneous placebo in those who were receiving standard therapy. The patients and the investigators who were responsible for the assessment of efficacy outcomes were unaware of the study assignments; the investigators who were responsible for randomization, study drug administration, and assessment of injection site reactions were aware of the study assignments.

Patients assessed the intensity of 6 symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) before treatment and at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment with the use of a visual analog scale that ranged from 0 to 10, with higher scores indicating more severe symptoms. A composite score on the visual analog scale was calculated as the average of the measurements for the 6 symptoms. Investigators who were unaware of the treatment assignments also assessed the severity of the same 6 symptoms at the same time points, using a scale from 0 (no symptoms) to 3 (severe symptoms); a composite symptom score was calculated from the average of the 6 symptom scores. In addition, investigators assessed the severity of angioedema at 4 locations (lips and cheeks, tongue, oropharynx, and hypopharynx or larynx), using a scale from 0 (no angioedema) to 4 (very severe angioedema). Angioedema of the oropharynx and hypopharynx was assessed by an ear, nose, and throat specialist, who performed endoscopy when necessary. A composite angioedema score was calculated as the average of the 4 symptom scores (Fig. 5).

If no reduction in symptoms had occurred by 6 hours after treatment, the investigator could administer rescue medication (30 mg of icatibant with 500 mg of prednisolone), regardless of the group to which the patient had been randomly assigned. In life-threatening situations, appropriate rescue procedures (including intubation or tracheotomy) could be implemented. A final follow-up visit was scheduled 14 days after hospital admission.

The primary endpoint was the time to the complete resolution of edema after administration of the study treatment, as evaluated on the basis of investigator-assessed

and patient-assessed symptom scores, as well as the investigator's assessment of the severity of angioedema on the basis of the physical examination. Secondary end-points included the proportion of patients who did not have a response to treatment (ie, patients who required rescue therapy); the proportion of patients with complete resolution of edema at 4 hours after treatment; the time to the onset of symptom relief, which was defined as the time to the first improvement (ie, decrease) of at least 1 point in the composite score of the investigator-assessed symptom score, the angioedema score, or the score on the patient-assessed visual analog scale; and the composite and individual investigator-assessed symptom scores, angioedema scores, and scores on the patient-assessed visual analog scale, as well as the change in the composite scores from the pretreatment scores, at each protocol-specified time point. Safety was evaluated by assessment of the incidence of and time to rescue intervention, adverse event reporting, documentation of local (injection site) reactions, measurement of vital signs, and clinical laboratory testing.

All patients in the per protocol population had complete resolution of edema; however, 3 patients in the standard therapy group required rescue therapy (icatibant and prednisolone) and were classified as having had treatment failure. One of these patients also required a tracheotomy for dyspnea that was classified as a serious adverse event (see below; [Fig. 6](#)). The maximum recorded time to the complete resolution of edema (61.2 hours) was used to replace the data for these 3 patients in the primary efficacy analysis.

The median time to the complete resolution of edema was 8.0 hours (interquartile range, 3.0–16.0) with icatibant as compared with 27.1 hours (interquartile range, 20.3–48.0) with standard therapy ($P = .002$; [Table 2](#)). The respective mean $\pm$ standard deviation times to complete resolution of edema were 15.4 ± 18.8 hours and 33.2 ± 18.0 hours. Kaplan–Meier sensitivity analyses in which the data for the 3 patients

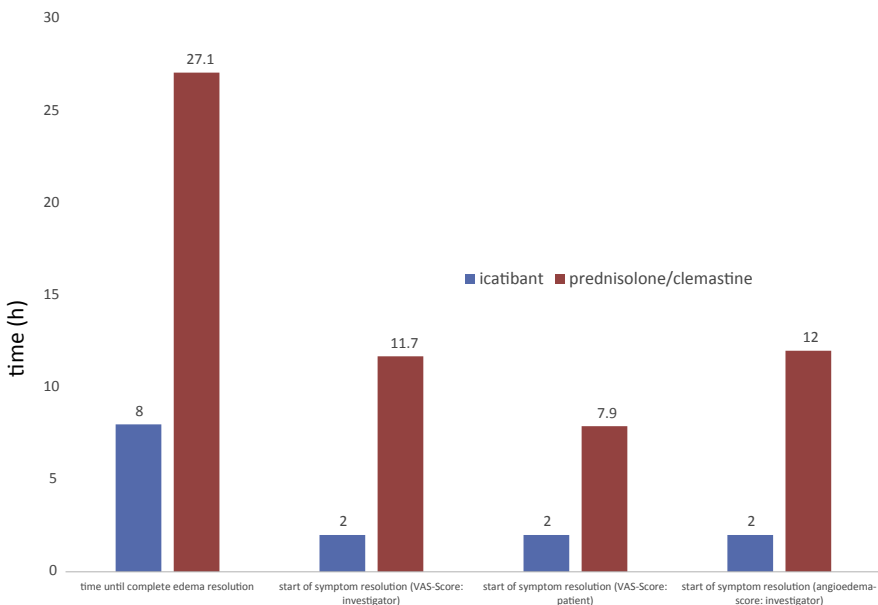


Fig. 6. Main results of AMACE (AMelioration of Angiotensin Converting Enzyme Inhibitor Induced Angioedema Study) icatibant (blue) and prednisolone/clemastin (red). VAS, visual analog scale.

Table 2 Results of AMACE			
Outcome	Icatibant (n = 13)	Standard Therapy (n = 14)	P Value
Median (IQR) time to complete edema resolution (primary end point), h	8.0 (3.0–16.0)	27.1 (20.3–48.0)	.002
Proportion of patients with complete edema resolution at 4 h after treatment, n (%)	5 (39)	0 (0)	.02
Median (95% CI) time to onset of symptom relief (composite investigator-assessed symptom score), h	2.0 (1.0–8.1)	11.7 (8.0–18.0)	.03
Median (95% CI) time to onset of symptom relief (composite patient VAS score), h	2.0 (2.0–6.3)	7.9 (1.2–11.8)	.36
Median (95% CI) time to onset of symptom relief (composite investigator-assessed angioedema score), h	2.0 (2.0–12.0)	12.0 (11.3 to NE)	.003

Abbreviations: AMACE, AMelioration of Angiotensin Converting Enzyme Inhibitor Induced Angioedema Study; CI, confidence interval; IQR, interquartile range; VAS, visual analog scale.

who received rescue intervention were censored at the time of the first rescue event resulted in similar estimates of the median time to complete resolution of edema—8.0 hours (95% confidence interval [CI], 3.0–16.0) with icatibant versus 23.7 hours (95% CI, 17.8–35.9) with standard therapy ($P = .008$). Five patients (38%) who received icatibant, as compared with none who received standard therapy, had complete resolution of edema within 4 hours after treatment ($P = .02$). On the basis of Kaplan–Meier analyses, the median time to the onset of symptom relief was shorter with icatibant than with standard therapy—2.0 hours (95% CI, 1.0–8.1) versus 11.7 hours (95% CI, 8.0–18.0; $P = .03$). In conclusion, the AMACE (AMelioration of Angiotensin Converting Enzyme Inhibitor Induced Angioedema Study) study demonstrated the effectiveness of icatibant, a bradykinin B2 receptor blocker in ACE inhibitor induced angioedema.

C1 INHIBITOR

Two human C1-INH concentrates (Berinert and Cinryze) are available for the treatment of HAE attacks. A third C1-INH concentrate, obtained from transgenic rabbits milk, is approved for the treatment of acute HAE. It has been hypothesized that C1-INH concentrates, which inhibits the synthesis of bradykinin, would also be an effective therapy for ACE inhibitor-induced angioedema.^{75–77} However, data on clinical effectiveness are lacking. In **Table 3**, published cases are listed. Recently, a case series was published with first data about C1-INH in ACE inhibitor-induced angioedema. A small group of patients suffering from ACE inhibitor-induced angioedema was treated with C1-INH, and we compared the outcomes to those of a historical control group that had been treated conventionally with corticosteroids and antihistamines.^{75,78}

The mean time $\pm$ standard deviation interval to first improvement of symptoms after pasteurized C1-INH administration (1000 IE) was 88 ± 39 minutes, and the mean $\pm$ standard deviation time to complete resolution of symptoms after drug administration was 10.1 ± 3.0 hours. Further interventions such as intubation, tracheotomy,

Table 3

Published data about the effectiveness of C1-esterase-inhibitor in angiotensin-converting-enzyme-induced angioedema

Author	Journal	Type	First Onset of Symptom Relief	Time to Complete Symptom Resolution	Conclusion	Notes
Gelée et al, ⁸¹ 2008	Rev Med Interne	1 Case	20 min	—	Successful treatment	1000 IE
Nielsen et al, ⁷⁹ 2006	Acta Anaesthesiol Stand	1 Case	20 min	—	Successful treatment	1500 IE treatment after 8 h AE onset
Steinbach et al, ⁸⁰ 2001	Anaesthesiol Reanim	1 Case	—	—	Successful treatment	—
Greve et al, ⁷⁵ 2015	Laryngoscope	Case series	—	10 h	Successful	—

retreatment with pasteurized C1-INH, or additional medication such as corticosteroids were not necessary. No local side effects or systemic serious adverse events were reported directly after the injection or over a follow-up period of 3 months to 2 years. Furthermore, there were no recurrent angioedema within 6 months to 2 years after the cessation of ACE inhibitor treatment.

SUMMARY

The bradykinin B2 receptor antagonist icatibant is effective in ACE inhibitor-induced angioedema. The drug is not officially approved for this indication and has to be administered in emergency situation off-label. Corticosteroids or antihistamines do not seem to work in this condition. The effectiveness of C1 INH in ACE inhibitor-induced angioedema must be verified in a double-blind study.

REFERENCES

1. Bas M, Hoffmann TK, Kojda G. Evaluation and management of angioedema of the head and neck. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:170–5.
2. Bas M, Adams V, Suvorava T, et al. Non-allergic angioedema. Role of bradykinin. *Allergy* 2007;62(8):842–56.
3. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009; 39:777–87.
4. Maurer M, Grabbe J. Urticaria: its history-based diagnosis and etiologically oriented treatment. *Dtsch Arztebl Int* 2008;105:458–66.
5. McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ* 2006;332:1177–81.
6. Sharma JN. Does kinin mediate the hypotensive action of angiotensin converting enzyme (ACE) inhibitors? *Gen Pharmacol* 1990;21:451–7.
7. Yang HY, Erdos EG, Levin Y. Characterization of a dipeptide hydrolase (kininase II: angiotensin I converting enzyme). *J Pharmacol Exp Ther* 1971;177:291–300.
8. Yang HY, Erdos EG, Levin Y. A dipeptidyl carboxypeptidase that converts angiotensin I and inactivates bradykinin. *Biochim Biophys Acta* 1970;214:374–6.
9. Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angio-oedema. *Lancet* 1998;351:1693–7.
10. Adam A, Cugno M, Molinaro G, et al. Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. *Lancet* 2002;359:2088–9.
11. Lefebvre J, Murphey LJ, Hartert TV, et al. Dipeptidyl peptidase IV activity in patients with ACE-inhibitor-associated angioedema. *Hypertension* 2002;39:460–4.
12. Vavrek RJ, Stewart JM. Competitive antagonists of bradykinin. *Peptides* 1985;6: 161–4.
13. Roberts RA. Bradykinin receptors: characterization, distribution and mechanisms of signal transduction. *Prog Growth Factor Res* 1989;1:237–52.
14. Regoli D, Rhaleb NE, Drapeau G, et al. Kinin receptor subtypes. *J Cardiovasc Pharmacol* 1990;6(15 Suppl):S30–8.
15. Regoli D, Barabe J. Pharmacology of bradykinin and related kinins. *Pharmacol Rev* 1980;32:1–46.
16. Hess JF, Borkowski JA, Young GS, et al. Cloning and pharmacological characterization of a human bradykinin (BK-2) receptor. *Biochem Biophys Res Commun* 1992;184:260–8.
17. McEachern AE, Shelton ER, Bhakta S, et al. Expression cloning of a rat B2 bradykinin receptor. *Proc Natl Acad Sci U S A* 1991;88:7724–8.

18. Menke JG, Borkowski JA, Bierilo KK, et al. Expression cloning of a human B1 bradykinin receptor. *J Biol Chem* 1994;269:21583–6.
19. Ma JX, Wang DZ, Ward DC, et al. Structure and chromosomal localization of the gene (BDKRB2) encoding human bradykinin B2 receptor. *Genomics* 1994;23:362–9.
20. Chai KX, Ni A, Wang D, et al. Genomic DNA sequence, expression, and chromosomal localization of the human B1 bradykinin receptor gene BDKRB1. *Genomics* 1996;31:51–7.
21. Regoli DC, Marceau F, Lavigne J. Induction of beta 1- receptors for kinins in the rabbit by a bacterial lipopolysaccharide. *Eur J Pharmacol* 1981;71:105–15.
22. Bhoola KD, Figueroa CD, Worthy K. Bioregulation of kinins: kallikreins, kininogens, and kininases. *Pharmacol Rev* 1992;44:1–80.
23. Madeddu P, Emanuelli C, Gaspa L, et al. Role of the bradykinin B2 receptor in the maturation of blood pressure phenotype: lesson from transgenic and knockout mice. *Immunopharmacology* 1999;44:9–13.
24. Han ED, MacFarlane RC, Mulligan AN, et al. Increased vascular permeability in C1 inhibitor- deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 2002;109:1057–63.
25. Groves P, Kurz S, Just H, et al. Role of endogenous bradykinin in human coronary vasomotor control. *Circulation* 1995;92:3424–30.
26. Hall JM. Bradykinin receptors: pharmacological properties and biological roles. *Pharmacol Ther* 1992;56:131–90.
27. Ellis EF, Heizer ML, Hambrecht GS, et al. Inhibition of bradykinin- and kallikrein induced cerebral arteriolar dilation by a specific bradykinin antagonist. *Stroke* 1987;18:792–5.
28. Marceau F, Regoli D. Bradykinin receptor ligands: therapeutic perspectives. *Nat Rev Drug Discov* 2004;3:845–52.
29. Duchene J, Schanstra JP, Pecher C, et al. A novel protein- protein interaction between a G protein-coupled receptor and the phosphatase SHP-2 is involved in bradykinin-induced inhibition of cell proliferation. *J Biol Chem* 2002;277:40375–83.
30. Busse R, Fleming I. Regulation of endothelium-derived vasoactive autacoid production by hemodynamic forces. *Trends Pharmacol Sci* 2003;24:24–9.
31. Smith D, Gilbert M, Owen WG. Tissue plasminogen activator release in vivo in response to vasoactive agents. *Blood* 1985;66:835–9.
32. Giannella E, Mochmann HC, Levi R. Ischemic preconditioning prevents the impairment of hypoxic coronary vasodilatation caused by ischemia/reperfusion: role of adenosine A1/A3 and bradykinin B2 receptor activation. *Circ Res* 1997; 81:415–22.
33. Zhu P, Zaugg CE, Simper D, et al. Bradykinin improves postischaemic recovery in the rat heart: role of high energy phosphates, nitric oxide, and prostacyclin. *Cardiovasc Res* 1995;29:658–63.
34. Leeser MA, Stoddard MF, Manchikalapudi S, et al. Bradykinin-induced preconditioning in patients undergoing coronary angioplasty. *J Am Coll Cardiol* 1999; 34(3):639–50.
35. Ritchie RH, Marsh JD, Lancaster WD, et al. Bradykinin blocks angiotensin II-induced hypertrophy in the presence of endothelial cells. *Hypertension* 1998; 31:39–44.
36. Maestri R, Milia AF, Salis MB, et al. Cardiac hypertrophy and microvascular deficit in kinin B2 receptor knockout mice. *Hypertension* 2003;41:1151–5.
37. Fuller RW, Dixon CM, Cuss FM, et al. Bradykinin-induced bronchoconstriction in humans. Mode of action. *Am Rev Respir Dis* 1987;135:176–80.

38. Tsukagoshi H, Sun J, Kwon O, et al. Role of neutral endopeptidase in bronchial hyperresponsiveness to bradykinin induced by IL-1 beta. *J Appl Physiol* (1985) 1995;78:921–7.
39. Mukae S, Aoki S, Itoh S, et al. Bradykinin B(2) receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. *Hypertension* 2000;36:127–31.
40. Hulsmann AR, Raatgeep HR, Saxena PR, et al. Bradykinin-induced contraction of human peripheral airways mediated by both bradykinin beta 2 and thromboxane prostanoid receptors. *Am J Respir Crit Care Med* 1994;150:1012–8.
41. Yang C, Hsu WH. Glucose-dependency of bradykinin-induced insulin secretion from the perfused rat pancreas. *Regul Pept* 1997;71:23–8.
42. Damas J, Bourdon V, Lefebvre PJ. Insulin sensitivity, clearance and release in kininogen-deficient rats. *Exp Physiol* 1999;84:549–57.
43. Duka I, Shenouda S, Johns C, et al. Role of the B(2) receptor of bradykinin in insulin sensitivity. *Hypertension* 2001;38:1355–60.
44. Rett K, Wicklmayr M, Dietze GJ. Metabolic effects of kinins: historical and recent developments. *J Cardiovasc Pharmacol* 1990;15(Suppl 6):S57–9.
45. Kishi K, Muromoto N, Nakaya Y, et al. Bradykinin directly triggers GLUT4 translocation via an insulin-independent pathway. *Diabetes* 1998;47:550–8.
46. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53.
47. Goring HD, Bork K, Spath PJ, et al. Hereditary angioedema in the German-speaking region. *Hautarzt* 1998;49:114–22 [in German].
48. Agostoni A, Ygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 2004;114:S51–131.
49. Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005;53:373–88.
50. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med* 2003;114:294–8.
51. Blanch A, Roche O, Urrutia I, et al. First case of homozygous C1 inhibitor deficiency. *J Allergy Clin Immunol* 2006;118:1330–5.
52. Bouillet L, Ponard D, Drouet C, et al. Angioedema and oral contraception. *Dermatology* 2003;206:106–9.
53. Pichler WJ, Lehner R, Spath PJ. Recurrent angioedema associated with hypogonadism or anti-androgen therapy. *Ann Allergy* 1989;63:301–5.
54. Agostoni A, Cicardi M, Cugno M, et al. Angioedema due to angiotensin-converting enzyme inhibitors. *Immunopharmacology* 1999;44:21–5.
55. Berkun Y, Shalit M. Hereditary angioedema first apparent in the ninth decade during treatment with ACE inhibitor. *Ann Allergy Asthma Immunol* 2001;87:138–9.
56. Messerli FH, Nussberger J. Vasoepitidase inhibition and angio-oedema. *Lancet* 2000;356:608–9.
57. Agostoni A, Cicardi M. Drug-induced angioedema without urticaria. *Drug Saf* 2001;24:599–606.
58. Gainer JV, Nadeau JH, Ryder D, et al. Increased sensitivity to bradykinin among African Americans. *J Allergy Clin Immunol* 1996;98:283–7.
59. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893–906.

60. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004;17:103–11.
61. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005;111:315–20.
62. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;334:1649–54.
63. Hiyoshi H, Yayama K, Takano M, et al. Stimulation of cyclic GMP production via AT₂ and B₂ receptors in the pressure-overloaded aorta after banding. *Hypertension* 2004;43:1258–63.
64. Gohlke P, Pees C, Unger T. AT₂ receptor stimulation increases aortic cyclic GMP in SHRSP by a kinin-dependent mechanism. *Hypertension* 1998;31:349–55.
65. Hellebrand MC, Kojda G, Hoffmann TK, et al. Angioedema due to ACE inhibitors and AT₁ receptor antagonists. *Hautarzt* 2006;57(9):808–10 [in German].
66. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007;370:221–9.
67. Oparil S, Yarows SA, Patel S, et al. Dual inhibition of the renin system by aliskiren and valsartan. *Lancet* 2007;370:1126–7.
68. Yarows SA, Oparil S, Patel S, et al. Aliskiren and valsartan in stage 2 hypertension: subgroup analysis of a randomized, double-blind study. *Adv Ther* 2008;25:1288–302.
69. Solomon SD, Appelbaum E, Manning WJ, et al. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009;119:530–7.
70. Agostoni A, Cicardi M. Hereditary and acquired C1- inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206–15.
71. Cicardi M, Zingale LC, Pappalardo E, et al. Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine (Baltimore)* 2003;82:274–81.
72. Markovic SN, Inwards DJ, Frigas EA, et al. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med* 2000;132:144–50.
73. Gaur S, Cooley J, Aish L, et al. Lymphoma associated paraneoplastic angioedema with normal C1- inhibitor activity: does danazol work? *Am J Hematol* 2004;77:296–8.
74. Baş M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med* 2015;372(5):418–25.
75. Greve J, Bas M, Hoffmann TK, et al. Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema. *Laryngoscope* 2015;125(6):E198–202.
76. Rasmussen ER, Bygum A. ACE-inhibitor induced angio-oedema treated with complement C1-inhibitor concentrate. *BMJ Case Rep* 2013.
77. Lipski SM, Casimir G, Vanlommel M, et al. Angiotensin-converting enzyme inhibitors-induced angioedema treated by C1 esterase inhibitor concentrate (Berinert®): about one case and review of the therapeutic arsenal. *Clin Case Rep* 2015;3(2):126–30.
78. Bas M, Greve J, Stelter K, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. *Ann Emerg Med* 2010;56(3):278–82.

79. Nielsen EW, Gramstad S. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. *Acta Anaesthesiol Scand* 2006;50(1):120–2.
80. Steinbach O, Schweder R, Freitag B. C1-esterase inhibitor in ACE inhibitor-induced severe angioedema of the tongue. *Anaesthesiol Reanim* 2001;26(5): 133–7 [in German].
81. Gelée B, Michel P, Haas R, et al. Angiotensin-converting enzyme inhibitor-related angioedema: emergency treatment with complement C1 inhibitor concentrate. *Rev Med Interne* 2008;29(6):516–9 [in French].