

Review Series: Advances in Consensus, Pathogenesis and Treatment of Urticaria and Angioedema

# Recent Advances in Drug-Induced Angioedema

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## ABSTRACT

Angioedema is the end result of deep dermal, subcutaneous and/or mucosal swelling, and is potentially a life-threatening condition in cases where the pharynx or larynx is involved. Drug-induced angioedema has been reported to occur in response to a wide range of drugs and vaccines. Drug-induced angioedema, like other cutaneous drug reactions, has been reported to be most frequently elicited by beta-lactam antibiotics and non-steroidal anti-inflammatory drugs, although reliable data from epidemiologic studies are scarce. Recent reports suggested an increasing role of angiotensin-converting enzyme inhibitors (ACEIs) in the causation of life-threatening angioedema. ACEI-related angioedema is never accompanied by urticaria and occurs via a kinin-dependent mechanism. ACEI-related angioedema not only can start years after beginning the treatment, but it can then recur irregularly while under that treatment. Furthermore, allergy tests are unreliable for the diagnosis of ACEI-related angioedema, and so the relationship between angioedema and ACEIs is often missed and consequently quite underestimated. Accordingly, better understanding of the kinin-dependent mechanism, which is particular to angioedema, is necessary for the appropriate management of drug-induced angioedema.

## KEY WORDS

angioedema, angiotensin-converting enzyme inhibitor, bradykinin, non-steroidal anti-inflammatory drugs, urticaria

## INTRODUCTION

Angioedema is defined as a deep dermal, subcutaneous and/or mucous swelling, which usually lasts for 1 to 3 days, whereas urticaria usually represents a more short-living, superficial dermal swelling due to plasma leakage and vasodilation.<sup>1,2</sup> Angioedema is associated with various causes and factors, such as foods, drugs, infection and genetic factors and can be mediated by different mechanisms.

In recent years, as more drugs become available, the number of drugs that can induce angioedema has increased. Drug-induced angioedema has been reported to result from a wide range of drugs and vaccines, including non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists, antibiotics, radiocontrast media, proton pump inhibi-

tors, statins, fibrinolytic agents, estrogens, diuretics, calcium channel blockers, beta blockers, and psychotropic drugs (serotonin reuptake inhibitors).<sup>3</sup> Drug-induced angioedema, like other cutaneous drug reactions, has been reported most frequently elicited by beta-lactam antibiotics and NSAIDs, although reliable data from epidemiologic studies are scarce.<sup>4</sup> Drug-induced angioedema is associated with urticaria in approximately 50% of cases and may be complicated by life-threatening anaphylaxis.<sup>4</sup> Although the combination of urticaria and/or angioedema with systemic symptoms like hypotension is typical for IgE-mediated allergic reactions and aspirin intolerance, some drugs like ACEIs induced isolated angioedema by a kinin-dependent mechanism, which is particular to angioedema but not urticaria. In particular, recent reports suggest an increasing role of ACEIs in the causation of angioedema resulting in life-threatening

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**Table 1** Comparison of features of angioedema and urticaria

| Features              | Urticaria                                                                                       | Angioedema                                                                                    |
|-----------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Pathology             |                                                                                                 |                                                                                               |
| Location              | Papillary dermal                                                                                | Reticular dermal, subcutaneous/submucosal                                                     |
| Vasodilation          | +++                                                                                             | +/-                                                                                           |
| Edema                 | +                                                                                               | +++                                                                                           |
| Cellular infiltration | Sparse perivascular infiltrates of mainly neutrophils, eosinophils, monocytes and T-lymphocytes | Little or no cellular infiltrate, except in allergic angioedema where eosinophils may be seen |
| Clinical features     |                                                                                                 |                                                                                               |
| Location              | Skin only                                                                                       | Skin and mucosa                                                                               |
| Duration              | Transitory (<24 h)                                                                              | Transitory (24-72 h?)                                                                         |
| Color of lesions      | Red                                                                                             | Variable<br>Skin-colored                                                                      |
| Subjective symptoms   | Itch                                                                                            | Pain and heat                                                                                 |

Modified from reference 5.

events by upper airway obstruction. Extensive clinical evaluations of commonly used inhibitors of the renin-angiotensin system have provided reliable data on the incidence and clinical manifestations of angioedema induced by these drugs. Accordingly, current data have shed new light on bradykinin playing a crucial role in the pathogenesis of most forms of non-allergic angioedema without urticaria, while histamine acts as the main biogenic mediator in allergic angioedema. Correct diagnosis is indispensable to determine the appropriate treatment, as standard, anti-allergic drugs, such as glucocorticoids and antihistamines, are most likely ineffective in treating non-allergic forms of angioedema. Unfortunately, angioedema, at present, seems to be recognized and correctly treated less than urticaria, although the management of urticaria has generally been improved since the guidelines for urticarial were proposed. Better understanding of the various forms and underlying mechanisms of angioedema, including the kinin-dependent mechanism particular to angioedema, is necessary for managing drug-induced angioedema. This review focused on recent advances in drug-induced angioedema and, especially, updated NSAID-induced angioedema and ACEI-related angioedema as representatives of drug-induced angioedema via a non-allergic mechanism.

## ANGIOEDEMA

### CLINICAL MANIFESTATIONS OF ANGIOEDEMA

Angioedema refers to abrupt and short-lived swelling of the skin, mucous membranes, or both including the upper respiratory and intestinal epithelial linings (Table 1).<sup>1,2,5</sup> Angioedema may be solitary or multiple. It is short lived and fades without visible sequelae during the course of 24 to 72 hours.

The swelling is non-pitting, erythematous or skin-colored, and shows a predilection for areas where the skin is lax rather than taut (especially the face and genitalia). In the skin, slight heat and pain are vari-

able additional symptoms, but there is rarely itching.

Edema of the respiratory can lead to life-threatening asphyxia whereas swelling of gastrointestinal tract mucosa can induce violent abdominal pain, vomiting and/or diarrhea. These symptoms occur mainly in the hereditary form with C1-esterase inhibitor (C1-INH) deficiency. Involvement of the respiratory tract may be fatal.

Angioedema refers to a group of disorders with multifactorial etiology but a similar clinical expression. Several forms of angioedema show a great variety of tissue localizations, and different underlying mechanisms such as genetic mutations, allergic reactions and non-allergic reactions exist.

### CLASSIFICATIONS OF ANGIOEDEMA IN THE JAPANESE GUIDELINE

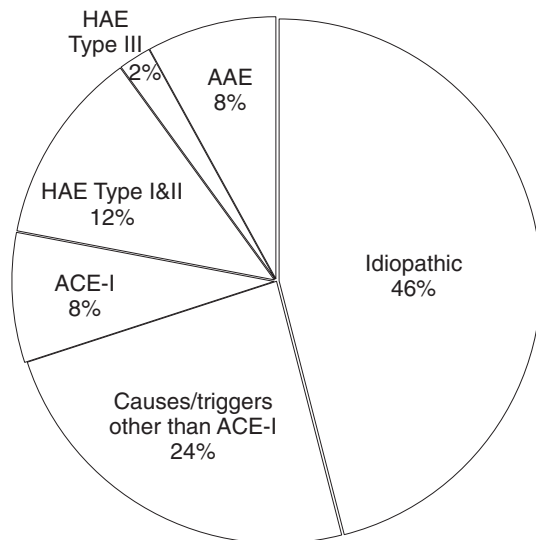
Angioedema is mainly categorized into 3 forms, namely idiopathic angioedema, extrinsic factor-induced angioedema, and angioedema with C1-INH deficiency, in the Japanese guideline (Table 2).<sup>1</sup> The first form is idiopathic angioedema, whose cause is unknown. The second form included angioedema associated with allergic and non-allergic reactions due to various antigens, such as venom, drugs, foods, pathogens, animals, latex, etc.. The third form is associated with C1-INH deficiency and, further, is divided into two subtypes, namely hereditary angioedema (HAE) and acquired angioedema (AAE).

Iwamoto *et al.* reported a nation-wide prevalence survey of HAE, which was conducted using questionnaires in Japan in 2009 (Fig. 1).<sup>1,6</sup> The questionnaires regarding the numbers, disease types, symptoms and treatments of angioedema in patients who had visited hospitals were answered by various departments of 1128 hospitals with 200 or more beds, such as Dermatology, Otolaryngology, Emergency Medical Care, Internal Medicine, Pulmonary Medicine, Allergy and Rheumatology in Japan. In 411 patients of angioe-

**Table 2** Classifications of angioedema defined in the Japanese guideline

| Classification of angioedema                             | Pathophysiology                                                  | Concurrence of urticaria |
|----------------------------------------------------------|------------------------------------------------------------------|--------------------------|
| I. Idiopathic angioedema                                 | Unknown                                                          | + or -                   |
| II. Extrinsic factor-induced angioedema                  | Allergic (IgE-mediated)                                          | + or -                   |
|                                                          | Non-allergic (Non IgE-mediated)                                  |                          |
|                                                          | interference of arachdonic acid metabolism (aspirin intolerance) | + or -                   |
|                                                          | kinin-dependent                                                  | -                        |
| III. Angioedema due to C1 esterase inhibitor dysfunction | others                                                           | + or -                   |
|                                                          | Kinin-dependent                                                  |                          |
|                                                          | hereditary<br>acquired                                           | -<br>-                   |

Modified from reference 1.

**Fig. 1** National prevalence survey of angioedema in Japan. HAE, hereditary angioedema; ACE-I, angiotensin-converting enzyme inhibitors. *n* = 411. Adapted from reference 6.

dema reported, 46% patients had idiopathic angioedema, 12% had HAE type I and II, 2% had HAE type III, 8% had AAE, 8% had ACEI-induced angioedema, and 24% had angioedema caused and triggered by causes other than ACEIs.

## DRUG-INDUCED ANGIOEDEMA

### CLASSIFICATION OF DRUG-INDUCED ANGIOEDEMA BASED ON PATHOGENESIS

Drug-induced angioedema is included in the second form of extrinsic factor-induced angioedema in the Japanese guideline.

Drug-induced angioedema can be differentiated into three main categories based on the mechanism; as these categories are shown in bold letter in Table 3.<sup>2,4</sup> Firstly, immediate hypersensitivity reactions to betalactam antibiotics constitute the most frequent allergic reactions, which are IgE-mediated.<sup>7</sup> Other

drugs that can elicit angioedema by the IgE-mediated mechanism include iodinated contrast media, neuromuscular blocking agents, pyrazolones, and quinolones. Secondly, adverse reactions to aspirin and other NSAIDs represent another important group with regard to drug-induced angioedema. NSAID-induced angioedema has been reported to be a generally non-allergic reaction in which an inhibition of cyclooxygenase results in major alternations in arachidonic acid metabolism such as cysteinyl leukotriene overproduction. Although they can also be responsible for immediate or delayed allergic reactions, e.g. to pyrazolones, in a small subset of patients, NSAIDs are common elicitors of a non-allergic reaction, so-called intolerance. Thirdly, the most important drugs eliciting angioedema apart from NSAIDs and betalactams are ACEIs. Actually, the prevalence of angioedema as an adverse reaction due to ACEIs is not high. However, ACEI-induced angioedema should receive special attention because it tends to lead to a life-threatening condition accompanied by upper airway obstruction. ACEI-induced angioedema has been reported to be due to an inhibition of the degradation of bradykinin and such a mechanism is particular to angioedema, but not to urticaria. To differentiate a kinin-dependent mechanism for angioedema, such as ACEI-related angioedema, from the IgE-mediated mechanism and NSAIDs intolerance, it is useful to determine whether angioedema is accompanied by urticaria or not.

In recent years, as various new drugs have been approved, the number of drugs that can potentially induce angioedema has increased. Newly approved drugs have been reported to induce angioedema with an incidence of more than 1%, including rituximab (a chimeric monoclonal antibody against the protein CD20), alteplase (a recombinant tissue plasminogen activator), fluoxetine (a selective serotonin reuptake inhibitor), laronidase (a drug for mucopolysaccharidosis type I), lepirudin (a recombinant hirudin, an anticoagulant that functions as a direct thrombin inhibitor) and tacrolimus, although their mechanisms have

**Table 3** Classification of drug-induced angioedema based on the pathogenesis

| Class                           | Mechanism                                                                             | Representative drugs                                                    |
|---------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Immunologic                     | <b>IgE-mediated</b><br>Immune complex formation and complement activation             | <b>Penicillins, Cephalosporins</b><br>Penicillins, Therapeutic antisera |
| Non-immunologic (Pharmacologic) | <b>NSAIDs intolerance</b><br><b>Kinin-dependent</b><br>Direct mast cell degranulation | <b>Aspirin, NSAIDs</b><br><b>ACEIs</b><br>Opiates                       |

NSAIDs, non-steroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors.

Modified from reference 2, 4.

**Table 4** Drugs associated with angioedema without urticaria

| Pharmacological effect                                                        | Drug                                                | Mechanism of angioedema                       |
|-------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------|
| Angiotensin-converting enzyme inhibitors                                      | Captopril, Enalapril, Lisinopril, etc.              | Inhibition of kinin degradation               |
| Angiotensin II type 1 receptor antagonists (Angiotensin II receptor blockers) | Candesartans, Varsartan, Losartan, Olmesartan, etc. | Unknown                                       |
| Nonsteroidal anti-inflammatory drugs                                          | Aspirin, Dicrofenac, Ibuprofen, etc.                | Interference with arachidonic acid metabolism |
| Fibrinolytic agents                                                           | Plasminogen activator, Streptokinase                | Increased production of bradykinin            |
| Estrogen                                                                      | Combined oral contraceptive pill                    | C1-esterase inhibitor deficiency?             |

Modified from reference 9.

never been elucidated.<sup>8</sup>

## DRUG-INDUCED ANGIOEDEMA WITHOUT URTICARIA

Drug-induced angioedema without urticaria may be caused by an immunoglobulin E-mediated allergic reaction. However, the pathogenesis remains unclear in the majority of these reactions. Therefore, since no immunological mechanism has been identified in them, skin tests and antibody determinations are typically unreliable for diagnosing them.

Such patients represent a tough diagnostic and therapeutic challenge for physicians. Therefore, before the diagnostic and therapeutic procedure, the co-existence of urticaria based on the patient history should be checked.

The causative drugs identified so far that induced angioedema refractory to antihistamines without urticaria are listed in Table 4.<sup>9</sup> ACEIs are representative of the drugs causing this type of angioedema. Zingale *et al.* investigated the patients affected by angioedema unaccompanied by urticaria who visited their hospital over the course of 11 years.<sup>10</sup> Among the 776 cases with adequate data, these types of angioedema were identified: 124 (16%) related to an external agent such as a drug, insect bite or foodstuff; 85 (11%) related to treatment with ACEIs; 55 (7%) associated with an autoimmune disease or infection; and 197 (25%) caused by C1 inhibitor deficiency. In the other 315 cases (41%), the etiology was undiscovered.

Scattered reports describe angioedema without urticarial as caused by a number of other drugs, such as

metoprolol, calcium channel antagonists, and amiodarone for cardiovascular diseases and risperidone and paroxetine as psychotropic drugs.<sup>11-16</sup>

## NSAID-INDUCED ANGIOEDEMA

### ANGIOEDEMA AS A RESULT OF NSAID INTAKE

Stevenson *et al.* proposed a classification of allergic and non-allergic reactions induced by NSAIDs that includes six distinct categories of patients (Table 5).<sup>17</sup>

Angioedema as a result of NSAID intake is generally a non-allergic reaction, i.e. so-called “intolerance”, rather than the IgE-mediated, allergic reactions in otherwise healthy patients. However, non-allergic reactions to NSAIDs resemble superficially allergic angioedema and are, also, often termed “pseudoallergic”. The non-allergic reactions have been considered to develop due to pharmacologic properties of the drugs.

Other than NSAID-induced angioedema in an otherwise healthy individual, aspirin and other NSAIDs can also induce or aggregate clinical symptoms in 20-40% of patients with chronic idiopathic urticaria/angioedema.<sup>18,19</sup> The exacerbation of wheals by aspirin in chronic urticaria was more obvious when larger doses of aspirin were used and at times when wheals were most active.<sup>20</sup>

Meanwhile, aspirin asthma is a counterpart of NSAID-induced urticaria/angioedema, but both rarely co-exist. NSAID intolerance occurs in 2-23% of patients with asthma.<sup>21-23</sup> In our study, 20% of 20 patients with NSAID-urticaria and/or angioedema, which were diagnosed based on single-blind, placebo-

**Table 5** Classification of allergic and non-allergic reactions induced by non-steroidal anti-inflammatory drugs

| Type of allergic/non-allergic reactions                          | Suspected mechanism            | Underlying disorder                         | Cross-reaction/ reaction on first exposure |
|------------------------------------------------------------------|--------------------------------|---------------------------------------------|--------------------------------------------|
| 1 Asthma and rhinitis exacerbated by NSAID                       | Non-allergic                   | Asthma/sinitis/<br>polyposis                | Yes                                        |
| 2 Urticaria/angioedema exacerbated by NSAID                      | Non-allergic                   | Chronic urticaria                           | Yes                                        |
| 3 Urticaria/angioedema from single NSAID                         | Allergic <sup>†</sup>          | None                                        | No                                         |
| 4 Acute urticaria/angioedema from multiple NSAIDs                | Non-allergic                   | None                                        | Yes                                        |
| 5 Anaphylaxis from single NSAID                                  | Allergic <sup>†</sup>          | None                                        | No                                         |
| 6 Blended respiratory/cutaneous reaction from one or more NSAIDs | Non-allergic<br>or<br>Allergic | Asthma/rhinitis/<br>polyposis<br>or<br>None | Yes<br>or<br>No                            |

<sup>†</sup> IgE-mediated. NSAID, non-steroidal anti-inflammatory drug.

Modified from reference 17.

controlled challenge tests, has history of aspirin asthma.<sup>24</sup> Furthermore, NSAIDs can act as a cofactor with food allergies to enhance allergic reactions.<sup>25</sup>

### EPIDEMIOLOGY

The prevalence of aspirin and other NSAID intolerance in the average population is 0.3 to 0.9%.<sup>26</sup> However, precise figures for the incidence of aspirin or other NSAID reactivity in patients presenting with angioedema are not available.

A variety of NSAIDs can cause angioedema. Aspirin and ibuprofen are the most common causes of such NSAID-induced angioedema.<sup>5,27</sup>

### PATHOPHYSIOLOGY

The proposed mechanism of non-allergic, NSAID-induced angioedema is one that involves cyclooxygenase (COX) as a common pathway. Non-selective NSAIDs interfere with arachidonic acid metabolism through the inhibition of the constitutive COX-1 and inducible COX-2 pathways with lipoxygenase pathways diversion, resulting in overproduction of cysteinyl leukotrienes (LT), including LTC<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> (Fig. 2).<sup>5</sup> There is also a reduction of the prostaglandin (PG) E<sub>2</sub>, which inhibits immunologically activated rat peritoneal mast cell degranulation and may have a direct inhibitory effect on cysteinyl LT production. Thus, the mast cell is presumably the main cellular target in these reactions.

As this mechanism occurs via a pharmacological pathway but not via an immunological pathway, many individuals with NSAID-induced angioedema react to multiple NSAIDs that are structurally and chemically unrelated and often on first exposure.

Recent studies suggested that HLA-DRB1\*1302 and DQB1\*0609, and ALOX5 (encoding 5-lipoxygenase) and FcεRIα promoter polymorphisms may contribute to the pathogenesis of aspirin-related urticaria/angioedema.<sup>28</sup>

### CLINICAL FEATURES

The clinical features of NSAID-induced angioedema do not differ significantly from those of acute allergic angioedema, and like allergic angioedema, cutaneous and/or mucosal angioedema generally occurs within minutes to a few hours of ingestion, injection or topical application of the offending NSAIDs.

### DIAGNOSTIC PRINCIPLES

As most patients are aware of their sensitivity to the relevant drugs, the offending drugs are easily identified based on the patient's history. The only reliable test for NSAID sensitivity is oral challenge, as IgE detections, such as measurements of specific IgE antibody and skin tests, cannot identify NSAID intolerance via a non-allergic mechanism. A high proportion (92%) of patients suspected of aspirin-sensitive urticaria and/or angioedema, based on history, will be positive on aspirin challenge.<sup>29</sup> The patients with NSAID-induced angioedema often react to multiple NSAIDs, whereas in IgE-mediated allergy due to NSAIDs, the causative drug is usually single (Table 5).<sup>19</sup> Although there has been a single report of aspirin-specific IgE in one asthmatic patient with aspirin-induced angioedema, IgE anti-salicyloyl antibodies appear to be very rare and there is currently no *in vitro* test for them.<sup>30</sup> In a provocation test, reactivity to aspirin and other non-selective COX inhibitors can predict multi-responders or single responders.<sup>31</sup>

Tests for histamine and LT release after provocation with NSAIDs are cumbersome, costly, and are not used routinely. LTC<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> releases have been demonstrated from basophils and eosinophils of patients with NSAID intolerance using the cellular antigen stimulation test in specialized centers.<sup>32,33</sup>

### TREATMENT

In case of NSAID-induced angioedema, the emergency measures are basically the same as those for

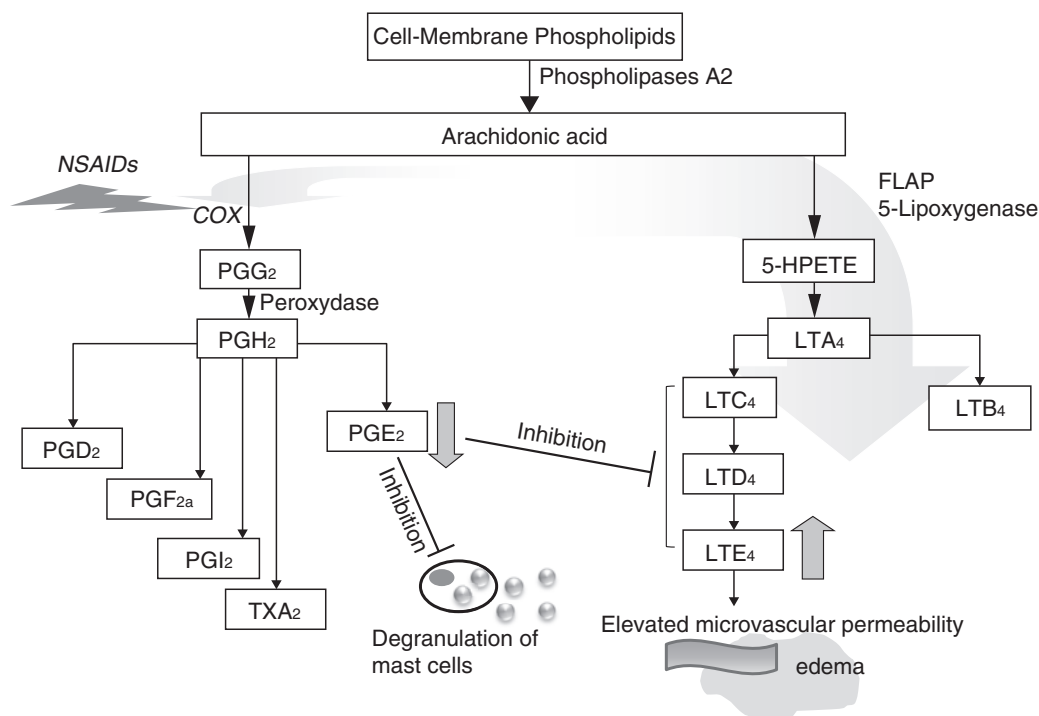


**Fig. 2** Effect of NSAIDs on arachidonic acid metabolism. 'Lightening' symbol indicates inhibition. NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; PG, prostaglandin; TX, thromboxane; LT, leukotriene; 5HPETE, 5 hydroperoxyeicosatetraenoic acid; FLAP, five lipoxygenase activating factor. Modified from reference 5.

acute allergic angioedema. Patients should be warned to avoid NSAIDs as a class until safe alternatives can be confirmed through examinations.

Evidence of the effectiveness of LT receptor antagonist for preventing the exacerbations of angioedema as a result of NSAIDs is not sufficient, although LT receptor antagonists are theoretically expected to have an effect on NSAID-induced angioedema.<sup>34</sup> Pacor *et al.* reported that the results of a double-blind, placebo-controlled study demonstrated that montelukast orally administered once a day is very effective for the treatment of cutaneous symptoms in patients with chronic urticaria due to food additives and/or aspirin.<sup>35</sup> However, in some anecdotal cases, the administration of LT antagonists concurrently with aspirin or the use of LT antagonist itself provoked anaphylactic episodes with urticaria and angioedema.<sup>5,36</sup>

## ALTERNATIVES IN NSAID-INDUCED ANGIOEDEMA

Subjects with cross-intolerance are often intolerant to acetylsalicylic acid and other strong COX-1 inhibitors and, in some cases, to weak inhibitors such as meloxicam and paracetamol.<sup>24,37,38</sup> Paracetamol (acetaminophen) is generally tolerated, even by patients sensitive to aspirin, most likely because of very weak COX-1 inhibition. A classification of the most important NSAIDs according to their inhibitory effect on

COX isoenzymes is shown in Table 6.<sup>31</sup>

The newly introduced selective inhibitors of COX-2 (coxibs) appear to represent safer alternatives in the patients with NSAID-related urticaria and/or angioedema.<sup>39</sup> However, the safety of selective COX-2 inhibitors is controversial. Some reports have indicated that 0.2-3% of patients with cutaneous symptoms with cross-intolerance to NSAIDs are intolerant to COX-2-selective inhibitors.<sup>40-42</sup> In contrast, Dona *et al.* recently indicated a higher incidence of intolerance to etoricoxib, as assessed by provocation tests in 252 patients with urticaria and/or angioedema, caused hypersensitivity owing to cross-intolerance to NSAIDs. Twenty-five percent of 47 patients intolerant to paracetamol and 6% of 205 patients tolerant to paracetamol were intolerant to etoricoxib. The results indicated that selective COX-2 inhibitors may be unsafe in subjects with urticaria and/or angioedema caused by hypersensitivity reactions to NSAIDs with cross-intolerance if they are intolerant to paracetamol. In addition, intolerance to paracetamol seems to be a strong predictor for response to COX-2 inhibitors as has been previously suggested by other authors.<sup>43,44</sup>

More data from controlled studies are required to determine the safety of COX2 inhibitors in NSAID-induced angioedema.

**Table 6** Classification of the most commonly employed NSAIDs according to the inhibitory effect on COX isoenzymes

| Selectivity of inhibitory effect on COX isoenzymes | NSAIDs                       |                                                                                                    |
|----------------------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------|
|                                                    | Class                        | Example                                                                                            |
| COX-1/COX-2 inhibitors                             | Salicylates                  | Aspirin, diflunisal, salsalate                                                                     |
|                                                    | Oxicams                      | Piroxicam                                                                                          |
|                                                    | Propionic acid derivatives   | Ibuprofen, naproxen, loxoprofen <sup>†</sup> , ketoprofen <sup>†</sup> , flurbiprofen <sup>†</sup> |
|                                                    | Arylacetic acids             | Indomethacin, diclofenac, etodolac, sulindac, tolmetin                                             |
|                                                    | Fenamates                    | Mefenamic acid, meclofenamate                                                                      |
|                                                    | Pyrropyrrole                 | Ketorolac                                                                                          |
|                                                    | Pyrazolones                  | Phenylbutazone, oxyphenbutazone, feprazone, noramidopyrine                                         |
|                                                    | Paracetamol (acetoaminophen) |                                                                                                    |
| Weak COX-1/COX-2 inhibitors                        | Meloxicam, nimeslide         |                                                                                                    |
| Preferential COX-2 inhibitors                      | Coxibs                       | Celecoxib, etoricoxib, rofecoxib                                                                   |

<sup>†</sup> NSAIDs, which are contained in poultice and application in Japan.

COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs.

Modified from reference 31.

### ACE-INHIBITORS-RELATED ANGIOEDEMA

ACEIs are now widely prescribed for the treatment of hypertension as well as to provide cardiovascular and renal protection in patients with heart failure and chronic kidney disease and those at high risk of cardiovascular events.<sup>45</sup> The issue of adverse effects of ACEIs is clinically relevant due to the large number of subjects exposed to these drugs, which is increasing.

Unlike allergic angioedema or NSAIDs-induced angioedema, angioedema as a result of ACEIs is not associated with urticaria. Moreover, although angioedema may occur during the first week of therapy, some patients may take the ACEI without any problem for months or years before angioedema develops.<sup>46,47</sup> Therefore, ACEIs are often overlooked as a cause of angioedema and this leads to unfortunate consequences, because continuing administration tends to lead to more severe attacks.<sup>48</sup>

However, Grabb *et al.* found that in more than 50% of the cases of ACE-related angioedema, ACEI therapy has been continued.<sup>49</sup> Accordingly, Agostoni *et al.* indicated that in ACEI-associated angioedema, ACEIs may facilitate angioedema in predisposed individuals rather than cause angioedema independently.<sup>31</sup>

### EPIDEMIOLOGY

Angioedema occurs in 0.1 to 0.7% of patients taking ACEIs, and it can affect approximately 1 of 2500 patients during the first week of exposure.<sup>48,50</sup> Although the reported incidence of ACEI-associated angioedema is not very high, it represents the most frequent causes of recurrent drug-induced angioedema.<sup>9</sup>

The mortality worldwide is 0.1% in these cases. Considering that, at present, 40 million patients

worldwide are treated with ACE inhibitor, this drug class could account for several hundred deaths per year due to laryngeal edema according to the report by Messerli *et al.* in 2000.<sup>51</sup>

Various risk factors for ACEI-related angioedema have been indicated, including black race, female gender, past history of angioedema such as HAE, previous drug rash, smoking habit, age older than 65 years, seasonal allergies, recent initiation of ACEIs (first week of therapy), obesity, upper airway surgery or trauma, sleep apnea and immunosuppression in cardiac and renal transplant recipients.<sup>52-54</sup>

### CLINICAL FEATURES

The manifestations of ACEI-related angioedema are similar to those observed in patients with C1INH deficiency. In ACEI-related angioedema, however, edema is more frequently localized to the head and neck, such as the face, mouth mucosa, tongue, lips, pharynx and larynx, while the occurrence of painful intestinal and/or genital edema is a more rare manifestation than HAE.<sup>55</sup> Reports indicating the existence of a partial defect of C1INH have been confirmed.<sup>56</sup> Therefore, the co-existence of C1INH deficiency should be differentiated in the diagnostic work-up.

Unlike in other cases of drug-induced angioedema, adverse reactions to ACEIs are frequently missed because of the irregular clinical course. Actually, physicians expect angioedema, generally allergic or non-allergic in nature, to occur in close temporal relationship to the time that the causative drug is taken. However, ACE-related angioedema can not only start years after the treatment is begun, but it recurs irregularly while the patient is under that treatment. Additionally, some cases of late onset of angioedema have also been observed weeks after the discontinuation of the ACEIs.<sup>9</sup> In ACEI-related angioedema, the

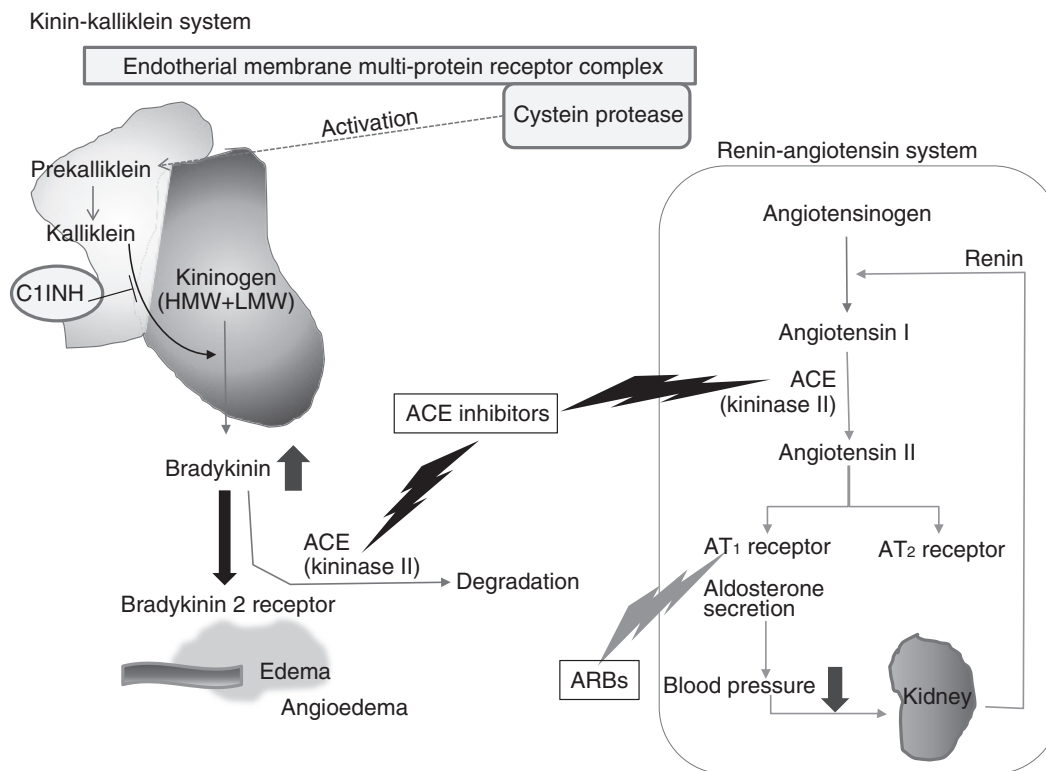


**Fig. 3** Mechanism of bradykinin-mediated angioedema as a result of therapy with inhibitors of the renin-angiotensin-aldosterone system. 'Lightening' symbol indicates inhibition. ACE, angiotensin converting enzyme; AT<sub>1</sub>, angiotensin II type-1; AT<sub>2</sub>, angiotensin II type-2; ARBs, angiotensin receptor blockers; HMW, high molecular weight; LMW, low molecular weight. Modified from reference 59.

interval between the first intake of ACEIs and the onset of angioedema varies from a few hours to 8 years. Sixty percent of the Japanese cases experienced the first angioedema in a week after starting the administration of ACEIs.<sup>47</sup> A Japanese case with severe angioedema after the first intake of ACEIs has been reported.<sup>57</sup> When angioedema involved the face and viscera, it developed within the first week in 60% and 59% of cases, respectively.<sup>46</sup> Furthermore, life-threatening edema of the upper airway is present in up to approximately 40% of cases and can be resistant to treatment or even fatal.<sup>46,58</sup>

### **PATHOPHYSIOLOGY**

The pathogenetic mechanism appears to be mainly linked to the decreased degradation of bradykinin, which potentially dilates blood vessels, mediates inflammation, increases vascular permeability and activate nociceptors.

ACE, also known as kininase II, does not just act on angiotensin I, but it is also a major inactivator of bradykinin (Fig. 3).<sup>59</sup> Pharmacological inhibition of ACE leads to increased levels of bradykinin. Actually, high levels of bradykinin have been demonstrated in plasma during an acute episode of angioedema.<sup>60</sup>

Bradykinin degradation is blocked in all patients

treated with ACEIs. Nevertheless, angioedema appears inconstantly and in just a small percentage of such patients. Therefore, it is likely that factors other than impaired bradykinin degradation by ACE are involved in the development of angioedema.

In contrast with what happens in HAE, no cleaved high molecular weight kininogen, a precursor of bradykinin, was detectable in plasma.<sup>56</sup> This finding supports the hypothesis that the pathogenetic mechanism of ACEI-related angioedema lies in the catabolic site of bradykinin metabolism. Therefore, studies which aimed to identify the factors predisposing patients to ACEI-induced angioedema focused their attention on the discovery of abnormalities in enzymes involved in bradykinin catabolism.

Bradykinin is degraded primarily by ACE (Fig. 4).<sup>61</sup> However, during ACE inhibition, other enzymes, including neutral endopeptidase (NEP-24.11), aminopeptidase P (APP), and kininase I (carboxypeptidase N), are presumed to play greater role in the metabolism of bradykinin.

In a large cohort of patients with ACEI-related angioedema, the mean plasma levels of kininase I were slightly reduced compared with those in patients who did not develop adverse effects.<sup>62</sup> However, the large overlap of kininase I levels between the 2 groups lim-

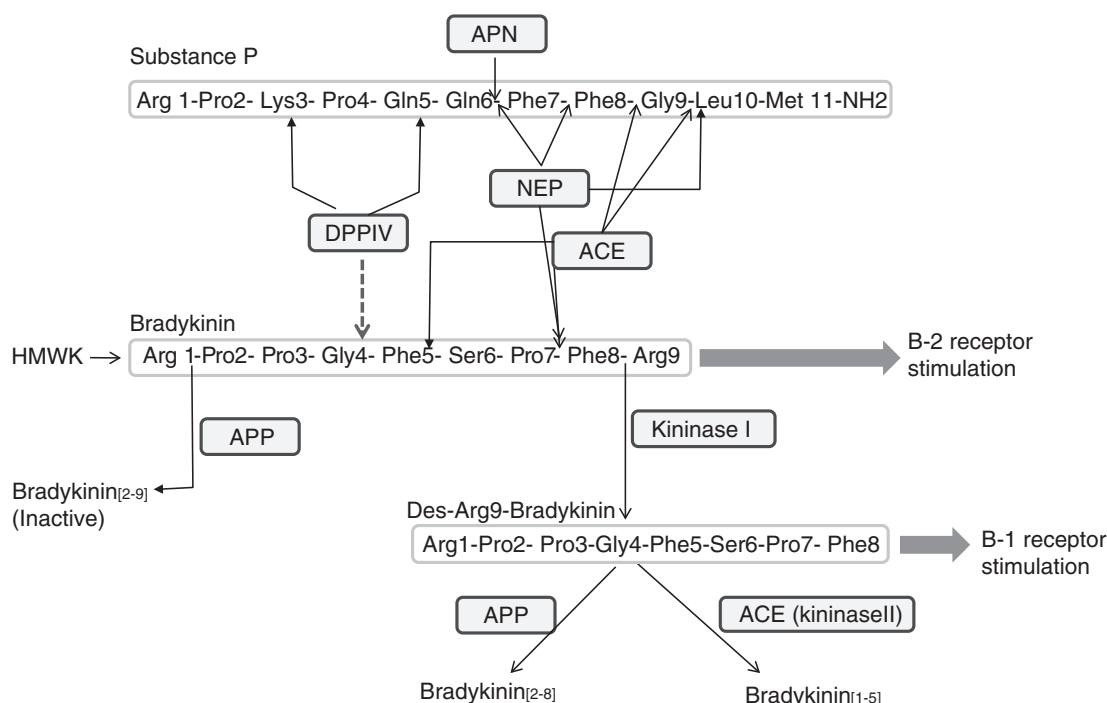


**Fig. 4** The schema of the degradation of bradykinin and substance P. HMWK, high molecular weight kininogen; APN, aminopeptidase N; NEP, neutral endopeptidase; DPPIV, dipeptidyl peptidase IV; APP, aminopeptidase P; ACE, angiotensin-converting enzyme. Dashed line shows cleavage of an inactive bradykinin fragment. Modified from reference 61.

its the value of kininase I measurement to predict the risk of ACEI-related angioedema.

Cleavage of bradykinin by kininase I yields the active metabolite des-Arg9-bradykinin, which is inactivated primarily by APP. According to a report by Blais *et al.*, nearly half of the patients with ACEI-related angioedema have a defect in a serum enzyme which involves the des-Arg bradykinin metabolism, leading to its accumulation.<sup>63</sup>

Byrd JB *et al.* indicated that decreased APP activity and dipeptidyl peptidase IV (DPPIV or CD26) in the substance P degradation pathways may also play a role in ACEI-associated angioedema.<sup>61</sup> ACE also degrades substance P, which produce tracheal edema in animals, as well as bradykinin. Bradykinin stimulates the release from sensory nerves of substance P, which causes increased vascular permeability by acting at the NK1 receptor, in addition to increasing vascular permeability directly via its B2 receptor.<sup>64</sup> In the setting of ACE inhibition, DPPIV, however, sequentially degrades substance P to substance P 5-11, which is susceptible to further degradation by aminopeptidase N (APN or CD13).<sup>65</sup>

Recently, a polymorphism of XPNPEP2 (the -2399 A variant), a candidate gene encoding membrane-bound APP, is associated with reduced APP activity and a higher incidence of ACEI-related angioedema.<sup>66</sup> Whereas the gene encoding for membrane-

bound APP, the source of circulating APP activity, is X linked, ACEI-related angioedema is thought to be more common in women than in men.<sup>66,67</sup>

Taken together, these findings suggest that increased plasma bradykinin levels play a key role in the course of ACEI-related angioedema, but additional factors are probably involved in the underlying pathophysiological pathways.

## DIAGNOSTIC PRINCIPLES

The diagnosis of ACEI-related angioedema should be preceded by the exclusion of other pathologies such as allergic and non-allergic reactions due to antigens, such as foods and venoms, C1INH deficiency, and infection. Furthermore, it is important to keep in mind that patients taking ACEIs can develop angioedema even after many years of uneventful ACEI treatment, as no reliable tests can differentiate ACEI-related angioedema from angioedema due to other causes.

## TREATMENT

Following basic emergency treatment, it is important to discontinue any drugs suspected to induce angioedema. Furthermore, anti-allergic drugs and anti-inflammatory drugs, such as glucocorticoids, are often used, although current evidence suggests that such therapy is rather ineffective in ACEI-related angioedema.<sup>68,69</sup> Thus, symptom-related medical care

should be provided until the swellings are dissolved. The swellings will normally subside in approximately 72 hours with or without treatment. In 1993, Thompson T, an otolaryngologist, reported that in 36 patients with angioedema due to ACEIs who visited his hospital in the U.S., 2 patients were intubated, 1 had the placement of a nasal trumpet, which is a nasopharyngeal airway designed to be inserted into the nasal passageway to secure an open airway, and 3 required tracheostomies, although 30 patients were successfully managed with medical therapy.<sup>70</sup> The author emphasized that the recognition that angioedema resulting from ACEIs is probably not IgE mediated and that antihistamines and steroids may not alleviate the airway obstruction is highly necessary for the treatment of ACEI-related angioedema.

Weber *et al.* recently proposed the introduction of a bradykinin inhibitor, icatibant, as a new treatment for ACEI-associated angioedema. They indicated that since bradykinin is a major mediator of angioedema from ACEIs, icatibant, presently used in patients with HAE, could be effective for these patients.<sup>45</sup> New approaches targeting the kallikrein-kinin system, such as kallikrein inhibitors and bradykinin type-2 receptor antagonists, might improve treatment for ACEI-induced angioedema in the near future.

## ALTERNATIVES IN ACEI-RELATED ANGIOEDEMA

Safe alternatives should be recommended for patients with ACE-related angioedema to manage hypertension.

Various ACEIs, including enalapril, lisinopril, captopril, ramipril, imidapril, benazepril, trandolapril and perindopril, are in use in many countries. Since angioedema is, however, a drug class effect, it is very important that physicians consider these drugs in the differential diagnosis of angioedema and give proper advice to these patients on avoiding all ACEIs.

Angiotensin-II type-1 receptor antagonists, also known as angiotensin receptor blockers (ARBs) or AT1-blockers, have been thought to be relatively safe alternatives for patients with previous history of ACEI-associated angioedema, because ARBs block the angiotensin II at the receptor levels and, theoretically, have no direct effect on the inhibition of bradykinin breakdown. In the literature, although the incidence of angioedema in patients receiving ARBs has rarely reported, it is estimated to be lower than in patients receiving ACEIs. An overall incidence of 0.3% ( $n = 25$  of 8576) angioedema was reported for ACEIs, whereas the use of ARBs was associated with a much lower risk of angioedema (0.1%;  $n = 10$  of 8542 patients) during the ONTARGET study.<sup>71</sup>

According to Malde *et al.*, only 8% of patients who experienced angioedema due to ACEIs previously developed angioedema with ARBs.<sup>72</sup> Actually, various ARBs have recently been shown to increase serum

bradykinin levels, probably via the angiotensin-II activation of angiotensin-II type-2 (AT2) receptors and the subsequent inhibition of bradykinin breakdown (Fig. 4).<sup>73,74</sup> Thus, for practical purposes, ARBs should not be considered an ideal alternative for ACEI treatment.<sup>75</sup> Although the incidence of angioedema induced by AT1-blockers is lower than that for angioedema related by ACEIs, patients who developed ACEI-related angioedema are more likely to be susceptible to angioedema due to AT1 blockers than individuals of general populations.<sup>76,77</sup> However, rare entities like calcium channel blocker-associated small bowel angioedema may have an impact on therapeutic decision-making in hypertensive patients as well.

The first oral direct renin inhibitor, aliskiren, received Food and Drug Administration approval for the treatment of hypertension in 2007 and, in Japan, was also approved in 2009. A more complete renin-angiotensin system inhibition than that obtained with existing agents is produced by the novel mechanism of action of aliskiren, namely the inhibition of renin's catalytic activity. As direct renin inhibition should not alter local or circulating bradykinin, aliskiren may be an alternative in patients with ACEI and ARB-related angioedema.<sup>78</sup> However, a recent pharmacovigilance analysis showed angioedema and renal dysfunction to be potential adverse reactions associated with aliskiren.<sup>79</sup>

Accordingly, ARBs and renin inhibitors should be used with caution in patients who previously reacted with angioedema to ACEIs, and only if there are no other alternative satisfactory treatments, until more information from larger studies becomes available.

## DIAGNOSTICS OF DRUG-INDUCED ANGIOEDEMA

Firstly, a thorough patient history is indispensable, particularly in determining the frequency of occurrence, previous angioedema with or without the same family history, known allergies and other diseases, medications and possible triggering cofactors such as physical exercise, alcohol, NSAID intake and infections.

Secondly, a general predisposition to recurrent anaphylaxis due to mastocytosis and a congenital predisposition to angioedema due to complement deficiency have to be excluded.

Finally, previous unknown food hypersensitivity should be ruled out. Recently, patients with wheat-dependent, exercise-induced anaphylaxis after sensitization to hydrolyzed wheat proteins (HWPs) through the skin and mucosa when using a soap containing HWPs, have increased dramatically in Japan.<sup>80,81</sup> The major clinical manifestation of wheat allergy via cutaneous and/or mucosal sensitization to HWPs is swelling of the face, especially the eyelids. As food allergy in adulthood is often enhanced by cofactors, such as exercise and NSAIDs intake, in the

case of sporadic recurrent angioedema, the relevant cause should be identified among foods, drugs, and exercise by means of examinations.<sup>82</sup>

After physical examination, to exclude possible eliciting factors and predisposition factors, tests, such as C1-INH, C4, and C1q for HAE, should be considered according to the patient history. In cases of suspected drug-induced angioedema, specific allergy tests must be performed, including skin tests, such as skin prick tests and intradermal tests, as well as *in vitro* determination of specific IgEs, basophil activation test, and lymphocyte transformation tests, if necessary. These tests are often necessary to differentiate allergic and non-allergic mechanisms of relevant drugs, even though in angioedema due to NSAID intolerance and kinin-dependent angioedema these tests tend to show negative results. Finally, provocation tests may be performed in cases with non-life-threatening reactions to determine tolerated alternative drugs.

## PREVENTING DRUG-INDUCED ANGIOEDEMA

The first criterion for prevention relies on taking the patient's history. As a general rule, patients with a previous history call for particular attention. Thus, estrogen and ACE inhibitors should be avoided in patients with hereditary and acquired C1-INH deficiency. In addition, ACEIs should be avoided in patients who have experienced idiopathic angioedema, if possible. In these patients, caution should also be used when fibrinolytic agents or ARBs are needed. As not enough data to draw conclusions about particular means of prevention in patients with some angioedema has been collected, further surveillance is needed.

In the case of ACEI-related angioedema, it should be emphasized that angioedema has to be considered a class effect and that no attempt to switch to another compound of the same class should be made in patients developing angioedema. As the predictive factors for developing ACEI-related angioedema have not been identified yet, all patients who are prescribed ACEIs, should be made aware of the possibility of this adverse reaction.

## CONCLUSIONS

Drug-induced angioedema can be elicited by several main pathophysiological mechanisms, namely IgE-mediated allergic reactions, aspirin and other NSAID intolerance, e.g. due to pharmacological inhibition of cyclooxygenase, and bradykinin-related reactions. The main point emerging from the recent reports is that ACEI-related angioedema prominently differs from the allergic reactions and NSAID intolerance with regard to the clinical manifestations. Unlike in other cases of drug-induced angioedema, ACEI-related angioedema is frequently missed as it may de-

velop several hours or long after the drug is started and may disappear without discontinuation of the causative ACEIs.

Currently, not enough data on drug-induced angioedema have been accumulated to prevent and manage the condition. No treatment effective for kinin-dependent angioedema due to drugs has been established, in contrast to allergic angioedema due to drugs. In tandem with the introduction of various new drugs to the market, trends in drug-induced angioedema can change. Accordingly, it is necessary to monitor instances of angioedema occurring with any drug in order to obtain significant data and identify the predisposition factors for drug-induced angioedema. Furthermore, it is important to share the collected data regarding drug-induced angioedema with physicians in a timely way in order to diagnose and manage drug-induced angioedema appropriately.

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