



■ Review Article

# Angiotensin–Converting Enzyme Inhibitor–Induced Non–allergic Perioral Angioedema: A Case–Based Scoping Review

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Patients with angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema (ACEIIA) may visit family physicians. The aim of this article was to describe a case of delayed-onset ACEIIA and to present a concise scoping review. Using a case report and a scoping review study design, we report a case of ACEIIA, with clinically confirmed diagnosis. The symptoms resolved after replacing the offending ACEI with another antihypertensive agent. After excluding other causes of perioral swelling and discontinuation of ACEI, the patient was symptom-free within a few days thereafter. Based on this case presentation, we performed a meta-narrative scoping review including up-to-date diagnosis and management of ACEIIA, based on published data in English, French, and German from inception to April 1, 2021. Patients with angioedema of unknown origin should be cautiously examined to rule out oral diseases, including allergy to dental materials and drug-induced angioedema. Clinicopathological aspects and current treatment guidelines for ACEI-associated angioedema are also presented.

**Keywords:** Angioedema; Angiotensin-Converting Enzyme Inhibitors; Oral Medicine; Review

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## INTRODUCTION

Perioral swelling can arise due to various diseases, and patients with unknown swelling in the orofacial region may visit family physicians for examination and proper management. In this concise article, we report a case of delayed-onset drug-induced angioedema, which was initially misdiagnosed, and provide a scoping review on diagnostic and therapeutic approaches to this disease, based on published data in English, French, and German until April 1, 2021. To the best of our knowledge, this study is the first to present evidence-based diagnostic and therapeutic protocols for drug-induced angioedema.

## CASE PRESENTATION

The patient gave written consent for publication of his clinical data and image.

### 1. Initial Presentation

A 75-year-old Caucasian man presented with a 6-month fluctuation in painless perioral swelling, which did not respond to a course of antihistamine medications prescribed by his dermatologist.

### 2. Relevant History

The patient suffered from type 2 diabetes mellitus, chronic myeloid leukemia, hypertension, and hyperlipidemia and had undergone cholecystectomy and three sets of gastroduodenoscopy and colonoscopy. There was no history of fever or other constitutional symptoms. Aller-



Figure 1. Clinical picture of the patient. The patient gave written consent for publication of his clinical data and image.

Table 1. Classification of angioedema<sup>2,8,12)</sup>

Generic	Disease	Pathogenesis	Prevalence	Features
Mast-cell mediated (allergic angioedema)	Anaphylaxis	IgE-mediated	Common	Urticaria/pruritis; exposure to allergen (food, insects, drugs, etc.); multisystem organ involvement
	Allergic reaction	IgE-mediated	Common	Preceded by exposure to allergen; rapid onset of symptoms
	Drug-induced	IgE-mediated, enhanced by prostaglandin formation	Common	Exposure to aspirin or NSAIDs (except COX-2 inhibitors); angioedema and bronchoconstriction
Bradykinin-mediated (non-allergic angioedema)	ACEIs (DINAAE)	Accumulation of bradykinin due to overproduction or impaired bradykinin degradation	Common	ACEIs (or ARB) therapy; higher incidence in African-Americans: acute or delayed onset of symptoms
	HAE type I (deficient C1-INH)	Mutations in C1-INH gene ( <i>SERPING1</i> gene) on chromosome 11q	Rare	Begin in childhood and worsen during puberty; autosomal-dominant inheritance; severe edema with respiratory distress and abdominal pain
	HAE type II (dysfunctional C1-INH)	Normal C1-INH level with dysfunction	Rare	Similar to HAE type I
	HAE type III (normal C1-INH)	Mutation in gene encoding coagulation factor XII, which cleaves prekallikrein to kallikrein	Rare	Autosomal-dominant inheritance with low penetrance; primarily affects women (estrogen use—estrogen exacerbates the gene mutation); delayed onset; face and tongue swelling
	Acquired C1-INH deficiency type I	C1-INH degraded by immune complexes	Rare	Age >40 years; angioedema without urticaria; prodrome of erythema marginatum; underlying B cell lymphoproliferative/lymphoreticular diseases
Unknown cause; bradykinin- or histamine-mediated	Acquired C1-INH deficiency type II	Anti-C1-INH-autoantibodies	Rare	Almost similar to acquired C1-INH deficiency type I
	Chronic idiopathic angioedema/chronic urticaria	Unknown cause	Rare	>3 angioedema attacks with urticaria in 1 year; indeterminate cause; diagnose after exclusion of other types
	Gleich's syndrome	Unknown cause	Rare	Elevated serum eosinophil and IgM levels; cutaneous angioedema with/without urticaria; history of treatment with calcium channel blockers, rocuronium and propofol

IgE, Immunoglobulin E; NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; ACEIs, angiotensin-converting enzyme inhibitors; DINAAE, drug-induced non-allergic angioedema; ARB, angiotensin receptor blocker; HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor; IgM, Immunoglobulin M.

gy, insect bites/stings, and familial history were also excluded.

### 3. Relevant Physical Exam Findings

Physical examination revealed firm, non-tender swelling of the lips and perioral region extending to the nasolabial folds (Figure 1), and clinically sound oral status, except for a partially edentulous area in the maxilla. There were no signs of intraoral swelling or airway obstruction.

### 4. Relevant Diagnostics

The patient's dermatologist suspected an allergy due to dental materials, that is, acrylic denture of the denture base. The blood chemical results were unremarkable. We decided to perform the allergy test in addition to suspicion of drug-induced non-allergic angioedema (DI-NAAE).

Patch testing, as described by Rai et al.,<sup>1)</sup> was performed using the Chemotechnique Dental Series of 30 materials commonly used in

dentistry, including methyl methacrylate, a component of acrylic-based denture. The readings were recorded on days 2, 3, and 4. There was no positive result, which was identified by the presence of erythema, papules, and vesicles, as recommended by the International Contact Dermatitis Research Group.<sup>1)</sup> As a result, allergy to dental materials was excluded, and the suspected diagnosis was directed to DI-NAAE.

After reviewing his comorbidities, the patient took insulin aspart, insulin human/rDNA, linagliptin, imatinib, ondansetron, betahistine, epoetin alfa, ferrous fumarate, folic acid, desloratadine, enalapril, and fenofibrate. As angiotensin-converting enzyme inhibitors (ACEIs) and non-steroidal anti-inflammatory drugs are a common cause of DI-NAAE, revision of the antihypertensive agent has been suggested.

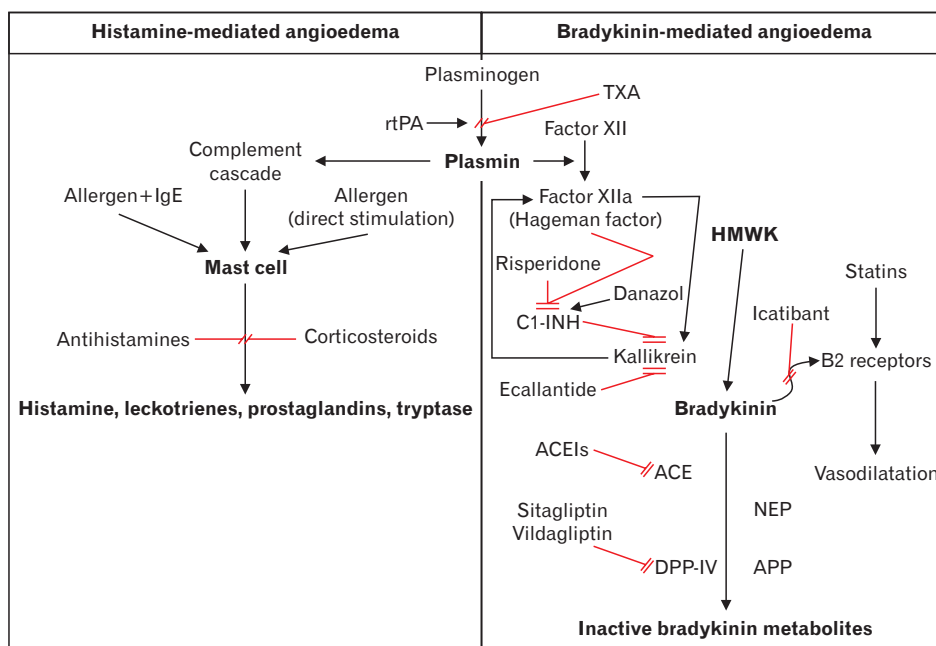
### 5. Case Progression

The patient's cardiologist replaced enalapril with candesartan, although the patient had received enalapril for over a decade. A few days

**Table 2.** Risk factors of ACEIs-induced angioedema<sup>4,6,7,16-19)</sup>

Genetic factors	Environmental factors	Genetic/environmental factors
Black or Hispanic race C1-INH deficiency Female gender	Trauma (facial impairment, dental surgery, anesthesia, intubation, transplantation, cardiac catheterization) Smoking Aspirin and NSAIDs Immunosuppressive agents Lidocaine DPP-IV inhibitors, e.g., saxagliptin Nepriylsin inhibitors, e.g., sacubitril Estrogen mTOR inhibitors, e.g., sirolimus Fibrinolytic	Age >65 years History of cough due to ACEIs History of drug rash Seasonal allergies Food/contact allergies

ACEIs, angiotensin-converting enzyme inhibitors; C1-INH, C1 esterase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; DPP-IV, dipeptidyl peptidase IV.



**Figure 2.** Mechanism of histamine- versus bradykinin-mediated angioedema.<sup>2,8-10,22,23)</sup> TXA, tranexamic acid; HMWK, high-molecular-weight kininogen; C1-INH, C1 esterase inhibitor; ACEIs, angiotensin-converting enzyme inhibitors; ACE, angiotensin-converting enzyme; NEP, neutral endopeptidase; APP, aminopeptidase; DPP-IV, dipeptidyl peptidase IV; ↓, activation; ⊥, inhibition.

after stopping enalapril, the angioedema resolved. The diagnosis of DINAEE was clinically established with no attempt to perform further laboratory investigations, which were denied by the patient. Owing to mild-to-moderate symptoms and unclear practice guidelines in Germany at the time of diagnosis, no new targeted therapies were provided (targeted therapies are described below).

### 6. Final Case Outcome

At the time of this manuscript preparation, the patient has been off ACEI and symptom-free for 6 years since discontinuing enalapril.

## SEARCHING STRATEGY

### 1. Study Design and Samples

Using a literature review design, we searched the PubMed/Medline (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com>), Biomed Central (<https://www.biomedcentral.com/>), and Cochrane Library (<https://www.cochranelibrary.com/>) from inception until April 1, 2021, to identify literature in English, French, and German. The search terms were “angioedema” AND “angiotensin-converting enzyme inhibitors.” Only studies or reports on ACEI-related angioedema were included. No restrictions on the samples were applied. References of the selected papers were searched for relevant studies that were included in the analyses. As this was a scoping narrative review, no attempt was made to identify unpublished studies, literature in languages other than English, French, and German, to contact researchers for unpublished data, or to perform a meta-analysis.

The need for ethical approval was waived. However, the ethical guidelines of the World Medical Association’s Declaration of Helsinki version 2008 (<https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf>) and the RAMESES I (Realist and Meta-narrative Evidence Syntheses: Evolving Standards) guidelines for meta-narrative reviews (<http://www.ramesesproject.org>) were followed throughout the study.

### 2. Study Variables

The primary outcome variables were the clinical, pathological, investigative, and therapeutic aspects of ACEI-associated angioedema.

### 3. Data Collection and Analysis

We reviewed each report and abstracted the data. Appropriate statistics were computed when indicated. The highest level of evidence after the Oxford Centre for Evidence-Based Medicine (<https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>) was selected for the review.

## LITERATURE REVIEW, DISCUSSION AND TEACHING POINTS

ACEIs were first introduced in 1981 for treatment of hypertension and heart failure, and later for myocardial infarction and stroke.<sup>2-4</sup> In Germany, this drug group is the most prescribed: approximately 54.8 million prescriptions a year.<sup>2,3</sup> Classical adverse reactions due to ACEIs

**Table 3.** Pathogenesis of drug-induced non-allergic angioedema<sup>9,24</sup>

Mechanism	Drugs*	Description
Synthesis of bradykinin with C1-INH suppression	Risperidone	Increased bradykinin production by inhibiting C1-INH but increasing complement activity
Synthesis of bradykinin with increased plasmin	rtPA <sup>†</sup>	Increased bradykinin production by increasing plasmin and complement activity
Response to bradykinin at B2 receptors	Statins	Increased <i>BR2</i> gene expression on endothelial cells and their sensitivity to bradykinin
Metabolism of bradykinin and substance P with ACE and DPP-IV suppression	ACEIs on ACE; sitagliptin and vildagliptin on DPP-IV <sup>‡</sup>	Inhibit/inactivate substance P degradation. ACEI also decreases metabolism of bradykinin

C1-INH, C1 esterase inhibitor; rtPA, recombinant tissue plasminogen; ACE, angiotensin-converting enzyme; DPP-IV, dipeptidyl peptidase IV; ACEIs, angiotensin-converting enzyme inhibitors.

\*Also see Figure 2. <sup>†</sup>rtPA-induced angioedema is both histamine- and bradykinin-mediated (see Figure 2). <sup>‡</sup>Vildagliptin causes angioedema only in patients who also take ACEI concomitantly.

**Table 4.** Laboratory investigations of different types of bradykinin-mediated angioedema<sup>12,22</sup>

Variable	Decreased C1-INH			Normal C1-INH	
	HAE type I	HAE type II	Acquired C1-INH deficiency	HAE type III	ACEIs (DINAEE)
C1-INH concentration	<50%	Normal (or increased)	<50%	Normal	Normal
C1-INH function	<50%	<50%	<30%	Normal	Normal
C4 concentration	Normal (or decreased)	Normal (or decreased)	<50% (70% of cases)	Normal	Normal
C4 function	<50%	<50%	<50%	Normal	Normal
Anti-C1-INH antibodies	Absent	Absent	Present (70% of cases)	Absent	Absent
Mutation	<i>SERPING1</i> (95% of cases)	<i>SERPING1</i> (95% of cases)	Absent	<i>F12</i> and <i>PLG</i>	Absent

C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; ACEIs, angiotensin-converting enzyme inhibitors; DINAEE, drug-induced non-allergic angioedema.

include dry/nonproductive cough (5.3%), angioedema (“Quincke’s edema,” 0.1%–0.7%), hyperkalemia (0.4%), and bronchospasm/wheezing (0.3%).<sup>2,4-7</sup>

Angioedema manifests as sudden localized, non-pitting swelling of certain body parts including skin and mucosa.<sup>7-10</sup> It is important to segregate allergic, histamine-mediated angioedema from its non-allergic, often bradykinin-mediated counterparts.<sup>2</sup> The latter form of angioedema lacks pruritus, urticaria, hypotension, tachycardia, or increased airway pressure because of no mast-cell involvement.<sup>5,8,10-12</sup>

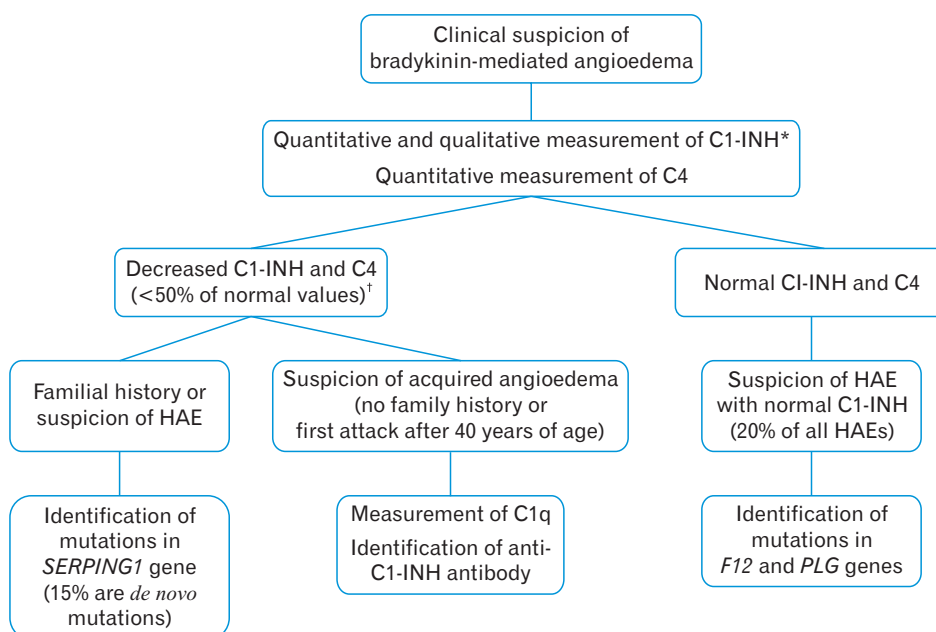
Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency is a rare autosomal dominant disease (ORPHA:91378), with a prevalence of 1:50,000. It arises from a mutation in the *SERPING1* gene, which encodes C1-INH.<sup>13,14</sup> Recurrent DINAEE is another form of non-histaminergic angioedema. African-Americans are at higher risk of DINAEE, probably due to the C-2399A genetic polymorphism of the bradykinin-degrading enzyme aminopeptidase (encoded by the X-linked *XPNPEP2* gene).<sup>7,8,10,15,16</sup> Stress, anxiety, menstruation, anesthetic agents (e.g., disoprivan, remifentanyl), immunosuppressants, *Helicobacter pylori* infection, and smoking can precipitate an exacerbation of DINAEE,<sup>2,4,12</sup> while diabetes and obesity seem to be protective factors against the disease severity.<sup>6,7</sup> A recent study unveiled the histomorphological differences between angioedema from C1-INH deficiency and DINAEE due to ACEIs; only the former had structural capillary alterations, that is increased intercapillary distance, apical, internal and external diameters, irregular capillary distribution, and tortuous morphology, as well as decreased microvascular density. These morphological changes confirm endothelial dysfunction in angioedema from C1-INH deficiency, but not ACEIs-induced angioedema.<sup>14</sup> Table 1 summarizes the classification of angioedemas,<sup>2,8,12</sup> and Table 2 concludes risk factors of DINAEE due to ACEIs.<sup>4,6,7,16-19</sup>

Although angioedema has many subtypes, the core pathogenesis is

a temporary increase in endothelial permeability of postcapillary veins, which in turn leads to plasma extravasation in the deeper layers of the dermis and submucosa. While facial and genital skin is mostly affected, the extremities, airways, and intestinal tract may also be involved. Laryngeal symptoms vary from mild edema to severe respiratory distress and asphyxiation. Intestinal tract angioedema may present as abdominal pain with/without nausea, vomiting, diarrhea, and ascites, which may be confused with a surgical abdomen, and may even result in psychiatric referrals.<sup>4,7,8,12,16-18,20</sup>

Bradykinin is a local inflammatory mediator that activates bradykinin beta-2 adrenergic (B2) receptors, resulting in the release of nitric oxide and prostacyclin. Both mediators elicit vasodilation and increased vascular permeability and cause smooth muscle cells to contract via pathways involving vascular endothelial cadherin, endothelial nitric oxide synthase, and vascular endothelial growth factor-A. Angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), aminopeptidase P, DPP-IV (dipeptidyl peptidase IV), and kininase I degrade bradykinin and substance P, and synthesize angiotensin II from angiotensin I in the renin-angiotensin-aldosterone system. Inhibition of bradykinin degradation by ACEIs enhances the half-life of bradykinin and results in plasma extravasation into submucosal/subcutaneous tissue. Substance P also increases vascular permeability through its action on NK1 receptors. Moreover, DINAEE due to ACEIs is also linked to an impairment of cytokine degradation with an increase in the level of C-reactive protein (Figure 2).<sup>2,6,8-10,12-14,16,21-23</sup> This adverse reaction is medication-specific, but not dependent upon dosage.<sup>2,5</sup> The different pathogenesis of DINAEE are presented in Table 3.<sup>9,24</sup> DINAEE due to drugs other than ACEIs may occur in patients with and without ACEI therapy.<sup>10</sup>

Until now, no useful diagnostic test for DINAEE from ACEIs is available. The diagnostic criteria can therefore be established using history



**Figure 3.** The 2019 French guideline on laboratory investigation of bradykinin-mediated angioedema according to the French National Centre of Reference for Angioedema (“Centre de Référence National des Angioédèmes”; CREAK).<sup>22</sup> HAE, hereditary angioedema. \*C1 esterase inhibitor (C1-INH) measurement in patients on C1-INH or danazol therapy requires “drug-pause” interval 1 and 4 weeks before the test, respectively. †The test should be repeated, if the result shows 50%–60% of normal values.

taking concerning ACEI therapy, regardless of dose/duration of use, non-specific angioedema, resolution of symptoms after stopping the ACEI and lack of another diagnosis.<sup>4,17,18)</sup> Most DINAAEs are mild and resolve within 48–72 hours after discontinuing the offending ACEIs.<sup>6,7)</sup> Clinically, approximately 1/3 of the cases present with swelling of lips, tongue, and face, and probably, tongue, pharynx and larynx, which may cause life-threatening upper airway obstruction.<sup>2,7,11,21)</sup> It is therefore recommended to admit DINAAE patients with airway involvement in an intensive care unit for at least 12–24 hours, and artificial airway (intubation, cricothyrotomy, tracheostomy) may be necessary.<sup>2,11)</sup> Chiu et al.<sup>25)</sup> classified angioedema into three classes to predict airway risks: class 1 involves the face and oral cavity only, class 2 extends to the oral floor and oropharynx, and class 3 invades glottis and supraglottis. Class 2 and 3 angioedema require endotracheal intubation and hospitalization for a minimum of 12–24 hours of observation. Rapid progression of symptoms within the first 6 hours of angioedema onset, anterior tongue swelling, vocal changes, drooling, and dyspnea

are common signs of severe airway obstruction.<sup>26)</sup>

After an acute angioedema attack, C4 levels should be investigated for the diagnosis of HAE, and testing tryptase levels aids in the diagnosis of allergic angioedema. Low C4 is associated with HAE and is therefore a good screening test for C1-INH deficiency. Tryptase is normal in HAE but may be elevated in mast-cell disorders or other causes of anaphylaxis manifesting as angioedema.<sup>8)</sup> Recently, the French National Centre of Reference for Angioedema (“Centre de Référence Nationale des Angioedèmes”; *CREAK*) issued the guideline on laboratory investigation of bradykinin-mediated angioedema (Table 4, Figure 3).<sup>12,22)</sup> C1-INH and C4 testing should be performed thrice within an appropriate interval, that is, 2–4 weeks.<sup>22)</sup>

Family physicians, emergency physicians, otolaryngologists, dermatologists, and dentists should be familiar with DINAAE. In Germany, all cases with DINAAE must be reported to the German’s Federal Institute for Drugs and Medical Devices (“Bundesinstitut für Arzneimittel und Medizinprodukte”: *BfArM*).<sup>2)</sup> With the average rate of ACEIs-in-

**Table 5.** US Food and Drug Administration-approved targeted therapies/prophylaxis for acute attacks of bradykinin-mediated, non-allergic angioedema<sup>2,8,11,12)</sup>

Generic name	Brand name (manufacturer)	Description	Dose	Side effects	Remarks
Icatibant	Firazyr (Shire, Lexington, MA, USA; approved in 2011)	Synthetic bradykinin B2 receptor antagonist, which displaces bradykinin from B2 receptors	30 mg s.c., repeat after 6–8 hours if symptoms persist (maximum 3 times/d)	Rash, headache, nausea, local irritation at the injection site, fever, fatigue, asthenia, dizziness	Only for HAE patients ≥18 years of age; off-labelled use for DINAAE; administration by healthcare professionals only; no accumulation following multiple doses
Ecallantide	Kalbitor (Shire, Lexington, MA, USA; approved in 2009)	Potent and selective human plasma kallikrein inhibitor	10 mg s.c. 3 times/d	Similar to icatibant; anaphylactoid-type reactions (3%); prolonged aPTT (precaution when used together with aspirin, heparin or other anticoagulants)	Only for HAE patients ≥12 years of age; off-labelled use for DINAAE; administration by healthcare professionals only
C1-INH	Berinert (CSL Behring, King of Prussia PA, USA; approved in 2011)	Human plasma-derived C1-INH, which inhibits several targets (activated C1s, kallikrein, factor XIIa, factor Xia, thrombin, tPA and plasmin)	20 IU/kg i.v.	Dysgeusia (>4%), headache, nausea, rash, vomiting, risk of blood-borne infections, risk of thromboembolism in patients with risk factors (indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of estrogen/androgen, morbid obesity and immobility)	For treatment of acute HAE attacks involving facial, abdominal, or laryngeal regions in adults and adolescents; use as prophylaxis within 6 post-procedure hours (at a dose of 1,000 IU); administration by healthcare professionals only
	Cinryze (Shire, Lexington, MA, USA; approved in 2008)	Similar to Berinert	1,000 IU i.v. every 3–4 days	Similar to Berinert, risk of thromboembolism in case of long-term HAE prophylaxis	Self-administration as prophylaxis of HAE attacks in adolescence and adults
	Haegarda (CSL Behring, King of Prussia PA, USA; approved in 2017)	Similar to Berinert	20 IU/kg s.c. every 3–4 days	Injection site reaction, hypersensitivity, nasopharyngitis, dizziness	Self-administration as prophylaxis of HAE attacks in adolescence and adults
	Ruconest (Salix, Raleigh, NC, USA; approved in 2014)	Recombinant C1-INH, purified from raw milk of transgenic rabbits	<84 kg: 50 IU/kg i.v. >84 kg: 4,200 IU (2 vials) i.v.	Headache, vertigo, diarrhea, risk of thromboembolism similar to Berinert	For treatment of acute HAE attacks; administration by healthcare professionals only
Danazol	Danol (Sanofi, Berkshire, UK; approved for laryngeal angioedema in 2012)	Synthetic steroid with antigonadotropic and anti-estrogenic activities	200 mg p.o. 2–3 times/d (increased dose up to 200 mg/d)*	Androgen-like effects (weight gain, acne, seborrhea, hirsutism, hoarseness; in females, menstrual disturbances, flushing, sweating, vaginal dryness, decreased estrogen), hepatic toxicity	For treatment of endometriosis and fibrocystic breast disease and for prophylaxis of HAE attacks in females and males

s.c., subcutaneously; HAE, hereditary angioedema; DINAAE, drug-induced non-allergic angioedema; aPTT, activated partial thromboplastin time; C1-INH, C1 esterase inhibitor; IU, international units; i.v., intravenously; p.o., oral doses.

\*Dose for prophylaxis of HAE attacks.

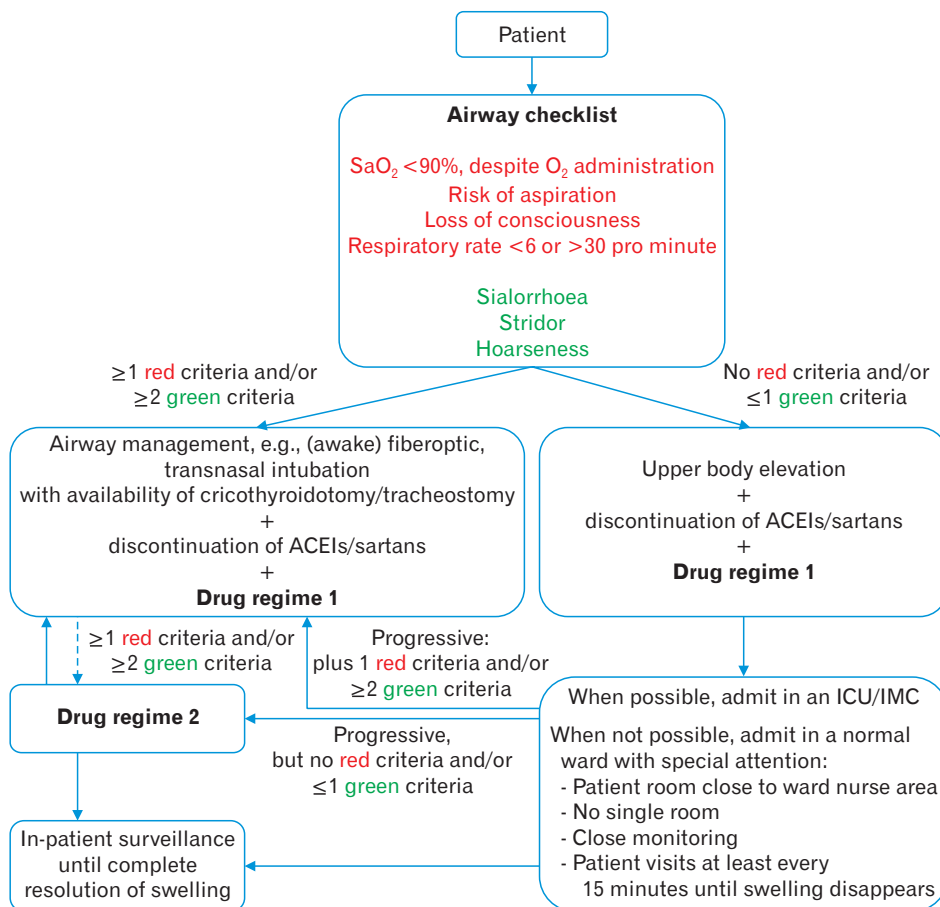
duced angioedema of 0.4% and approximately 7-million ACEIs users, it can be expected that nearly 30,000 ACEIs-induced angioedema cases per year in this country should be diagnosed.<sup>2,10</sup> Enalapril prescription in Germany is approximately 5.5 million per year and causes angioedema in more than 10% of the patients,<sup>27</sup> compared to the international incidence rate of 0.7%.<sup>16</sup> It is estimated that 10%–30% of angioedema patients attending emergency departments are DINAAE due to ACEIs.<sup>26</sup>

The highest incidence of ACEI-induced DINAAE occurred during the first month after initiation of therapy (3.6 events per 1,000 patients), and before a sharp decline until weeks 9–12. After week 12, the incidence is usually low and constant (0.3–0.6 events per 1,000 patients).<sup>16</sup> This may be a clear explanation why many patients tolerate the ACEIs well, so that angioedema may attack many months or years after the beginning of uneventful treatment,<sup>2,6,16,17</sup> as seen in our patient. Bas et al.<sup>28</sup> found that DINAAE developed on average after taking ACEIs for 3 years. Latent DINAAE may attack even after discontinuation of ACEI.<sup>6,8,17</sup>

Based on the recent European ADR database EudraVigilance of the European Medicine Agency, Dubrall et al.<sup>19</sup> found that ACEI-associated DINAAE tended to be life-threatening without urticaria and required prolonged hospitalization in comparison with DINAAE from angiotensin receptor blocker (ARB) sartans and aliskiren (renin inhibi-

tor). Sartans are often used instead of ACEIs in patients developing ACEI-associated side effects.<sup>20</sup> However, a large series (n=14,703) reported by Pfeffer et al.<sup>29</sup> demonstrated no significant difference in the incidence of DINAAE between ACEIs and sartans. A recent pharmacogenomic study revealed an association between intronic-1 variants in the calcium-activated potassium channel subunit alpha-1 (*KCNMA1*) gene on chromosome 10 and both DINAAE from ACEIs and ARBs. Calcium-activated potassium channel genes are expressed in vascular smooth muscle and endothelium, and encode effector proteins essential for the control of vascular tone and blood pressure. *KCNMA1* encodes the pore-forming alpha subunit of the large-conductance calcium-dependent potassium big K (BK) channel, which is important for repolarization of the cell membrane. Thus, it is reasonable to believe that the deficient transport of calcium and/or potassium across the cell membrane plays a role in the development of angioedema.<sup>15</sup> As this genetic alteration was found in both DINAAE from ACEIs and ARBs, close follow-up is also important even for patients with sartan therapy after quitting ACEIs.

There is no international standard treatment for DINAAE. Early evidence recommended infusion of fresh-frozen plasma in an acute setting because it provides C1-INH. However, the risks of transmission of blood-borne pathogens, fluid overload, and hypersensitivity reactions should be kept in mind.<sup>2,8,11,16</sup> Wang et al.<sup>23</sup> advised the addition of



**Figure 4.** The 2019 emergency care algorithm for treatment of adult drug-induced non-allergic angioedema patients with acute airway compromise proposed by the University Hospital of Ulm, Germany.<sup>20</sup> Drug regime 1: Prednisolon 250–1,000 mg i.v. + dimetindene 4–8 mg i.v. + ranitidine 50 mg i.v. + adrenaline 0.2–0.5 mg i.m.; Drug regime 2: C1 esterase inhibitor (C1-INH) concentrate Berinert 20 IU/kg i.v. or Icatibant 30 mg s.c. SaO<sub>2</sub>, oxygen saturation; ACEIs, angiotensin-converting enzyme inhibitors; ICU, intensive care unit; IMC, intermediate medical care ward; i.v., intravenous; i.m., intramuscular; s.c., subcutaneous.

tranexamic acid to epinephrine, corticosteroids, and H1- and H2-blockers (Figure 2). Nevertheless, DINAAE often resists common therapies for histaminergic or anaphylactic etiologies, such as adrenaline, H-1 antagonists, and corticosteroids. Recently, the US Food and Drug Administration approved new, targeted therapies/prophylaxis for acute attacks of non-histaminergic angioedema (Table 5).<sup>2,8-12,16)</sup> In 2019, an emergency care protocol for the treatment of DINAAE was developed at the University Hospital of Ulm, Germany (Figure 4).<sup>20)</sup> Notwithstanding the positive treatment outcomes reported in the literature, it is noteworthy that all drugs used in this algorithm are still off-label.

## CONCLUSION

Although most patients with recurrent orofacial swelling suffer from odontogenic infections, DINAAE should be considered in the differential diagnosis. When this angioedema type is suspected, the causal drug should be discontinued and substituted with other agents as soon as possible. Our patient was a typical case of delayed-onset DINAAE due to enalapril (reported incidence 0.7%).<sup>16)</sup> Emergency measures in a timely manner are required for patients with acute airway compromise, such as asphyxiation, stridor, retractions, and paradoxical chest movement. Targeted therapy for DINAAE remains off-label.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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