# Initial characteristics and follow-up of patients with a confirmed diagnosis of angiotensin-converting enzyme inhibitors-induced angioedema

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**Abstract**

Introduction: Differential diagnosis between angiotensin converting enzyme inhibitors (ACEi) angioedema (AE) and idiopathic histaminergic AE (ihAE) is often challenging. Follow-up data may help discriminate these conditions but are scarcely reported. Our objective was to report on the follow-up of patients with suspected ACEi-AE and to describe the baseline characteristics of AE attacks in patients with a diagnosis confirmed by follow-up. Methods: Sixty-four patients with suspected ACEi-AE (i.e. with exposure to ACEi before first attack, no urticaria associated and normal C1-inhibitor levels) and at least one follow-up visit were included. Data were retrospectively collected at baseline and during follow-up. Results: After follow-up, the diagnosis of ACEi-AE was confirmed in only 30 patients. The remaining patients were reclassified as ihAE (21 patients) or undetermined-mechanism AE (13 patients). In ACEi-AE patients, attacks occurred mostly in men (61%) with a median age of 64 (interquartile range ?17) years old, with a highly variable delay from ACEi introduction (23?103 months), and preferential involvement of lips (50%), tongue (47%) and throat (30%). Patients with confirmed ACEi-AE frequently reported classical histaminergic features, such as history of allergy and atopic conditions (20%), attacks with preferential evening onset (25%) and spontaneous resolution <24h (26%). ACEi-AE attacks responded to icatibant (79%). Conclusion: A final diagnosis of ihAE is frequent in patients with an initial suspicion of ACEi-AE; and follow-up should be systematically performed to ascertain the diagnosis in this population. Baseline clinical features seem insufficient to accurately discriminate between ACEi-AE and histaminergic AE, highlighting an unmet need for diagnostic biomarkers.

## TITLE PAGE

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**ABBREVIATION LIST**

**ACEi:**angiotensin-converting enzyme (ACE) inhibitors

**AE:** angioedema

**C1-INH:** C1 inhibitor

**EENT:** Eyes, Ears, Nose and Throat

**IgE:** immunoglobulin E

**NSAIDs:** non-steroidal anti-inflammatory drugs

**TSH:** thyroid-stimulating hormone

**STATEMENTS**

Conflicts of interest

SS reports travel grants from Shire, Sanofi-Genzyme and SOBI, outside the submitted work. DSS reports research grants from Abbvie, Astrazeneca, Boehringer, Amgen/Celgène, Galderma, Eli Lilly, Leo Pharma, Novartis, Sanofi-Regeneron; board memberships from Abbvie, Astra-Zeneca, Eli Lilly, Leo Pharma, Janssen, Novartis, Sanofi, Pfizer; and speaker fees from Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi; all outside the submitted work. DL reports personal fees from Actelion, grants and personal fees from Takeda, grants and personal fees from CSL Behring, outside the submitted work.

AC, MV, SG, MMF, RP, GV, CY, SD, CP, MJ, IC and JB reports no conflict of interest.

Author contributions

All individuals listed as authors met the ICMJE guidelines for determining authorship. AC, MV, DSS, DL and SS contributed to the conception and design of the study. AC, MV, MMF, RP, GV, CY, MJ, IC, JB, DL and SS screened patients and collected clinical data. SD and CP extracted biological data. AC and MV constituted the database, performed statistical analyses and wrote the first draft of the manuscript. SS made major revisions to the manuscript. SG provided her pharmacological expertise. DSS provided her expertise on histaminergic AE. DL provided his expertise on bradykinin-mediated AE. All authors read and approved the submitted version.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request from any qualified researcher.

Ethic statement

The study complied with the recommendations of the Helsinki declaration. French legislation on noninterventional studies does not require ethics committee approval for the use of de-identified data collected during patient care. The data were de-identified and complied with the requirements of the "*Commission Nationale de l'Informatique et des Libertés* " (CNIL), the organization responsible for ensuring the ethical use of data collected for scientific purposes in France. The CNIL approved the methods used to collect and analyze data from our patient database (approval #DEC20-211).

French legislation on noninterventional studies requires collecting the non-opposition of patients but does not require written consent. As such, non-opposition was confirmed from each patient included in the study for the use of their de-identified medical record data.

## ABSTRACT

*Introduction:* Differential diagnosis between angiotensin converting enzyme inhibitors (ACEi) angioedema (AE) and idiopathic histaminergic AE (ihAE) is often challenging. Follow-up data may help discriminate these conditions but are scarcely reported. Our objective was to report on the follow-up of patients with suspected ACEi-AE and to describe the baseline characteristics of AE attacks in patients with a diagnosis confirmed by follow-up.

*Methods***:** Sixty-four patients with suspected ACEi-AE (*i.e.* with exposure to ACEi before first attack, no urticaria associated and normal C1-inhibitor levels) and at least one follow-up visit were included. Data were retrospectively collected at baseline and during follow-up.

Results: After follow-up, the diagnosis of ACEi-AE was confirmed in only 30 patients. The remaining patients were reclassified as ihAE (21 patients) or undetermined-mechanism AE (13 patients). In ACEi-AE patients, attacks occurred mostly in men (61%) with a median age of 64 (interquartile range ±17) years old, with a highly variable delay from ACEi introduction (23±103 months), and preferential involvement of lips (50%), tongue (47%) and throat (30%). Patients with confirmed ACEi-AE frequently reported classical histaminergic features, such as history of allergy and atopic conditions (20%), attacks with preferential evening onset (25%) and spontaneous resolution <24h (26%). ACEi-AE attacks responded to icatibant (79%).

*Conclusion:* A final diagnosis of ihAE is frequent in patients with an initial suspicion of ACEi-AE; and follow-up should be systematically performed to ascertain the diagnosis in this population. Baseline clinical features seem insufficient to accurately discriminate between ACEi-AE and histaminergic AE, highlighting an unmet need for diagnostic biomarkers.

## INTRODUCTION

Angioedema (AE) is characterized by swelling of the deep dermis, subcutaneous tissue, or mucous membranes. A distinction is made between histamine-mediated AE, due to histaminoliberation (anaphylactoid reaction, drug-induced, chronic idiopathic histaminic AE), and bradykinin-mediated AE (1,2). Bradykinin, similarly to histamine, is a vasodepressor that relaxes vascular smooth muscle cells, lowers blood pressure and increases vascular permeability (3). Bradykinin-mediated AE can be caused by C1 inhibitor (C1-INH) deficiency (either genetic or acquired), by genetic mutations with a normal C1-INH (like factor XII or plasminogen mutations), or by bradykinin-releasing drugs, such as angiotensin-converting enzyme inhibitors (ACEi) (4,5).

It is estimated that 0.1 to 0.7% of patients treated with ACEi develop ACEi-induced angioedema (ACEi-AE) (2,5–7). Attacks usually appear within the first 3 months of treatment, but can develop at any time during the treatment course, even several years after its initiation (6,8). As they are bradykinin-mediated, urticaria is deemed to never occur during ACEi-AE attacks. So far, there is no validated set of diagnostic criteria and no specific biomarker for ACEi-AE; and the diagnosis can only be made with certainty on a retrospective basis, in the absence of urticaria and relapse after at least 6 months of treatment discontinuation (9,10).

Thus, the initial management of a patient presenting with a first AE attack, no urticaria and ACEi treatment can be difficult, as it is not always easy to discriminate between a first attack of an undiagnosed idiopathic histaminergic AE and ACEi-AE. Few studies have tried to determine the attack characteristics that are specific to ACEi-AE; and since most of them did not follow up patients after treatment cessation, they may have mistakenly included idiopathic histaminergic AE (8,11–13).

The objective of this study was thus to report on the follow-up of patients with suspected ACEi-AE and to describe the baseline characteristics of patients and AE attacks in a population with a definitive diagnosis of ACEi-AE, confirmed by a long-term follow-up.

## METHODS

Study population

This was a retrospective study conducted in our national reference center for bradykinin-mediated AE in Lille University Hospital (CREAK, France). Eligible patients were identified by screening our consultation database using the diagnostic code for AE. They were included if they met all the following criteria: (1) confirmed diagnosis of AE; (2) treatment by ACEi concomitant to at least one AE attack; (3) normal C1-INH levels and activity; (4) baseline visit between January 1$^{sts}$ 2014 and December 31$^{st}$, 2019; (5) at least one follow-up visit at least 6 months after ACEi cessation.

Patients whose diagnosis of ACEi-AE could readily be refuted based on baseline visit data (*i.e.,* patients with urticaria before or during AE attacks, or with AE attacks before ACEi introduction) were excluded from the study, as there is usually no diagnostic challenge regarding the AE mechanism and no therapeutic hesitation in this situation.

The remaining patients were classified in 3 different groups based on follow-up data. Patients were classified as "*undetermined AE* " if follow-up data did not allow to properly discriminate between ACEi-AE and histaminergic AE (*i.e.,* no recurrence of AE attacks after ACEi cessation but with concomitant introduction of prophylactic treatment by antihistamine and/or corticosteroids). They were classified as "*probable histaminergic AE* " if they met at least one of the following criteria: (1) recurrence of AE after the 6$^{\text{th}}$month of ACEi withdrawal; (2) no recurrence of AE despite re-exposure to ACEi; (3) occurrence of urticaria during follow-up. They were classified as "*probable ACEi-AE* " in any other cases.

Data collection

Relevant data were retrospectively retrieved from medical records at baseline visit (defined as the first consultation in our centre) and up until the last follow-up visit. At baseline, we collected patient characteristics (age, gender, previous medical history of relevant conditions), treatment data (date of introduction and withdrawal of bradykinin-releasing drugs, antihistamines, corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs)), AE attack characteristics (total number, triggering factors, prodromes, localization, associated signs, duration, attack treatments) and biological results (serum complement, eosinophils, immunoglobulin E (IgE), tryptase, thyroid-stimulating hormone (TSH), anti-thyroglobulin and anti-thyroperoxydase levels). During follow-up, we assessed ACEi discontinuation and/or re-exposure, recurrence of AE attacks (and their characteristics), occurrence of atopic manifestations and/or typical lesions of urticaria and therapeutic data (treatment by bradykinin-releasing drugs, antihistamines, corticosteroids and/or NSAIDs).

Statistical analyses

Characteristics of the population were described using median (± interquartile range) for quantitative variables, and number (percentage) for qualitative variables. Comparison between "probable histaminergic AE" and "probable ACEi-AE" groups was performed using Fisher's exact test for qualitative variables and Mann-Whitney's test for quantitative variables. Statistical analyses were carried out using Graph Pad Prism v8 software. Significance was set at $p < 0.05$.

## RESULTS

Classification of patients

Among the 507 patients screened (*Figure 1* ), 92 were referred for a suspected ACEi-AE, with a first visit between 2014 and 2019 and at least one follow-up visit. Among them, 28 patients were excluded because the diagnosis of ACEi-AE was immediately refuted (due to occurrence of urticaria or AE attacks before ACEi introduction). This left 64 patients with a possible ACEi-AE based on the data available at baseline visit.

These 64 patients were classified in 3 groups based on data collected during a median follow-up of 26.5 (±35.5) months. A first group of 13 patients (20%) was considered to have "undetermined AE" because follow-up did not allow to accurately discriminate between ACEi-AE and histaminergic AE. A second group of 21 patients (33%) was classified as having "probable histaminergic AE": 6 due to occurrence of AE attacks after the 6$^{\text{th}}$ month of ACEi cessation; 14 due to re-exposure to ACEi with no recurrence of AE; and 16 due to episodes of urticaria. A third group comprising the 30 remaining patients (47%) was thus considered to have "probable ACEi-AE".

Characteristics of the "probable ACEi-AE" cohort at baseline

Using this reliable population, we next studied the baseline characteristics of patients, ACEi exposure, AE attacks and laboratory tests.

*Patient characteristics*

Patients with "probable ACEi-AE" were mostly male (61%) with a median age of 64 (±17) years old at baseline (*Table 1* ). Among them, 6/30 (20%) patients had previous history of allergy or atopic conditions: atopic dermatitis in 2 cases, atopic rhinitis and conjunctivitis in 1 case, food allergy in 2 cases, and asthma

in 2 cases. None of them had previous history of autoimmune diseases. Familial history of AE (4 patients, 13%), of allergy or atopic conditions (5 patients, 17%) were also frequently reported.

*Characteristics of ACEi exposure*

Patients were exposed to ACEi for a median of 23 (±103) months at referral. ACEi were associated to another bradykinin-releasing drug in 5 patients (17%): 4 with dipeptidyl peptidase-4 inhibitors and 1 with angiotensin-receptor blockers.

*Characteristics of AE attacks*

Patients had a median of 2 (±2) attacks at referral. The first attack occurred a median of 2 (±20) months before referral. In at least 6/24 (25%) patients, attacks usually happened in the evening, at night or were noticed when waking up. Prodromes and triggering factors were scarcely reported.

Attacks were mostly localized on the lips (15/30; 50%), tongue (14/30; 47%), throat (9/30; 30%), uvula (3/30; 10%), oral cavity (7/30; 23%), and face (3/10; 10%). Limbs, digestive tract and genitalia attacks were not reported. No patient reported skin lesions of urticaria; and only one mentioned mild pruritus during an attack. ENT symptoms such as dyspnea (4/30; 13%), dysphonia (7/30; 23%) and dysphagia (5/30; 17%) were frequently noted.

Nine patients (30%) reported occurrence of AE attacks that resolved without treatment; and 8 (27%) noted spontaneous resolutions within 24h of AE onset. Classical treatments of histaminergic AE attacks were nearly never reported as effective: antihistamines (1/19; 5%), corticosteroids (1/18; 6%), adrenalin (0/3; 0%). When used, patients seemed to respond to treatments of bradykinin-mediated attacks more consistently: tranexamic acid (7/10; 70%), icatibant (15/19; 79%) and C1-INH concentrate (3/4; 75%). No patient required airway control.

*Biological characteristics*

Elevated IgE, tryptase and eosinophil levels were documented in 4, 1 and 2 cases, respectively. None had abnormal TSH levels, anti-thyroperoxydase or anti-thyroglobulin antibodies.

### Discriminating features between "probable ACEi-AE" and"probable histaminergic AE" patients at baseline

As to better identify clinical features that could help discriminating between the 2 AE mechanisms at referral, baseline characteristics of probable ACEi-AE patients were compared to those of probable histaminergic AE patients.

There was no statistically significant difference between the 2 groups. Notably, classical histaminergic features such as evening onset and duration $< 24$h were not significantly different between probable ACEi-AE patients and probable histaminergic AE patients.

## DISCUSSION

To our knowledge, few studies have focused on describing clinical features of ACEi-AE attacks in a cohort of patients with a diagnosis defined and confirmed by follow-up. Our results can be summarized as follows: (1) overdiagnosis of ACEi-AE is frequent at baseline, with at least a third of patients later reclassified as having histaminergic AE; (2) in our probable ACEi-AE population, attacks occurred mostly in elderly men, with a highly variable delay from ACEi introduction, and preferential involvement of oral cavity and throat; (3) classical histaminergic features (such as history of allergy and atopic conditions, attacks with preferential evening onset and spontaneous resolution $< 24$h) seemed non-rarely reported in ACEi-AE patients; (4) ACEi-AE attacks appear refractory to histamine-mediated AE treatments (antihistamine, corticosteroids and adrenalin) and sensitive to bradykinin-mediated AE treatments (tranexamic acid, icatibant and C1-INH).

Diagnosis of ACEi-AE is usually suspected in patients presenting with an AE attack, no urticaria and exposure to ACEi. However, idiopathic histaminergic AE, a frequent condition, can also occur in patients treated by ACEi; and there is no definitive way to discriminate between these 2 mechanisms at referral. This is a major issue, as it yields important therapeutic consequences (treatment modalities of AE attacks, unnecessary eviction of ACEi in case of misdiagnosed histaminergic AE...). Follow-up can help better differentiate these 2 mechanisms, as occurrence of urticaria and/or AE attacks after 6 months of ACEi discontinuation pleads for histaminergic AE. Using follow-up data, our study suggested that at least a third of patients referred for a suspected ACEi-AE were actually misdiagnosed idiopathic histaminergic AE. This highlights the relevance of performing systematic follow-up in these patients.

In order to avoid mistakenly-included histaminergic AE, we used a strict definition of ACEi-AE, using long-term follow-up. In this population, most of our results supported previous data from other studies with different designs (*Table 2* ) (4,8,11–23): male predominance (although this is not consistently reported), elderly population, highly variable delay between ACEi introduction and first attack, preferential involvement of oral cavity (especially lips and tongue) and throat.

Interestingly, our data suggest that patients with probable ACEi-AE can present with classical histaminergic features. History of allergy and atopic conditions were reported in at least 20% of patients, although this stays within range of the prevalence of atopy in the general population (24). AE attacks with preferential evening onset and spontaneous resolution <24h occurred in about 25% of our patients. Previous studies have yielded heterogeneous results regarding the duration of untreated ACEi-AE attacks, which can be explained by the difficulty to accurately delineate the beginning and end of an attack (notably onset of symptom relief *vs* complete resolution) and the possible inclusion of idiopathic histaminergic AE(4,17,19–21). Nonetheless, spontaneous resolution <24h have previously been reported (4,23). Only one work has previously studied the time of day of ACEi-AE onset, suggesting that attacks frequently occurred outside regular work hours (11). ACEi-AE consists in bradykinin-mediated attacks, which are traditionally described as occurring at any time of day and lasting at least 24h. However, this classical semiology description mainly stems from hereditary AE patients; and these characteristics may not all apply to other types of bradykinin-mediated attacks (25). Overall, these data suggest that clinical features alone seem insufficient to discriminate between ACEi-AE and histaminergic AE at referral; and highlight an unmet need for diagnostic biomarkers.

Interestingly, our study confirmed that icatibant, a bradykinin receptor antagonist, seems effective in ACEi-AE attacks. Data regarding the efficiency of icatibant in this indication are conflicting, with one randomized clinical trial favoring treatment (20) and two others observing no difference from placebo (18) In line with other real-life data (15–17), our results plead for using icatibant in ACEi-AE patients, as now recommended in some expert guidelines (9).

Our study draws strength from its originality, as it uses an innovative and strict definition of ACEi-AE and focused heavily on the follow-up of a suspected ACEi-AE population to ascertain the diagnosis. It also has some limitations that mainly stem from its retrospective design, missing data and small sample size. Excluding patients with no follow-up data may have biased the study population; however, since it is a common practice in our department to perform at least one systematic follow-up visit to patients referred for ACEi-AE, we believe this had only a limited effect.

## CONCLUSION

By examining follow-up data in patients with suspected ACEi-AE, our study revealed that misdiagnosis is frequent in this population. Patients with a diagnosis of ACEi-AE confirmed by follow-up had attacks that could display characteristics classically associated with histamine-mediated AE and were responsive to icatibant. These results need to be confirmed on prospective studies performed on larger cohorts.

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**FIGURE 1**

**Hosted file**

`image1.emf` available at https://authorea.com/users/727550/articles/709296-initial-characteristics-and-follow-up-of-patients-with-a-confirmed-diagnosis-of-angiotensin-converting-enzyme-inhibitors-induced-angioedema

**Figure 1 title: Flow chart of study**

**Figure 1 legend:** AE: angioedema; ACEi: angiotensin-converting enzyme inhibitor; C1-INH: C1-inhibitor.

**TABLE 1**

| | N | Value |
|---|---|---|
| **Male**, n (%) | 30 | 19 (63%) |
| **Age at baseline visit** (years old), median (IQR) | 30 | 64 (17) |
| **Duration of follow-up** (months), median (IQR) | 30 | 21 (37) |
| Past medical history | | |
| **Personal history of allergy or atopic conditions**, n (%) | 30 | 6 (20%) |
| - Urticaria, n (%) | | 0 (0%) |
| - Atopic dermatitis, n (%) | | 1 (3%) |
| - Asthma, n (%) | | 2 (7%) |
| - EENT atopy, n (%) | | 1 (3%) |
| - Food allergy, n (%) | | 2 (7%) |
| - Drug allergy, n (%) | | 0 (0%) |
| **Personal history of autoimmune diseases**, n (%) | 30 | 0 (0%) |
| **Familial history of AE**, n (%) | 30 | 4 (13%) |
| **Familial history of allergy or atopic conditions**, n (%) | 30 | 5 (17%) |
| - Urticaria, n (%) | | 0 (0%) |
| - Atopic dermatitis, n (%) | | 0 (0%) |
| - Asthma, n (%) | | 3 (10%) |
| - EENT atopy, n (%) | | 2 (7%) |

| | N | Value |
|---|---|---|
| - Food allergy, n (%) | | 0 (0%) |
| - Drug allergy, n (%) | | 0 (0%) |
| Incriminated treatment | | |
| **Therapeutic class(es)** | 30 | |
| - ACEi alone, n (%) | | 25 (83%) |
| - ACEi + ARBs, n (%) | | 1 (3%) |
| - ACEi + DPP-4i, n (%) | | 4 (13%) |
| **Duration of exposure** (total in case of multiple exposures) (months), median (IQR) | 26 | 23 (103) |
| Characteristics of AE attack - onset | | |
| **Number of attacks**, median (IQR) | 29 | 2 (2) |
| **Time span between first and last attacks** (or first attack and consultation) (months), median (IQR) | 30 | 2 (20) |
| **Time of day of attack onset** | 24 | |
| - Attacks preferentially occur in the evening or at night (or are noticed when waking up), n (%) | | 6 (25%) |
| - Attacks preferentially occur in the morning or the afternoon, n (%) | | 8 (33%) |
| - No preferential time of day identified, n (%) | | 10 (42%) |
| **Presence of prodromes**, n (%) | 29 | 1 (3%) |
| **Triggering factor**, n (%) | 30 | 3 (10%) |
| Characteristics of AE attack - plateau | | |
| **Affected sites** | 30 | |
| - Lips, n (%) | | 15 (50%) |
| - Tongue, n (%) | | 14 (47%) |
| - Uvula, n (%) | | 3 (10%) |
| - Oral cavity (excluding lips, tongue and uvula), n (%) | | 7 (23%) |
| - Throat (pharynx, larynx), n (%) | | 9 (30%) |
| - Face (excluding lips), n (%) | | 3 (10%) |
| - Digestive tract, n (%) | | 0 (0%) |
| - Genitalia, n (%) | | 0 (0%) |
| - Upper limbs, n (%) | | 0 (0%) |
| - Lower limbs, n (%) | | 0 (0%) |
| **Cutaneous symptoms**, n (%) | 30 | 1 (3%) |
| - Urticaria, n (%) | | 0 (0%) |
| - Pruritus, n (%) | | 1 (3%) |
| **ENT symptoms**, n (%) | 30 | 10 (33%) |
| - Dyspnea, n (%) | | 4 (13%) |
| - Dysphonia, n (%) | | 7 (23%) |
| - Dysphagia, n (%) | | 5 (17%) |
| **Digestive symptoms**, n (%) | 30 | 0 (0%) |
| Characteristics of AE attack - resolution | | |
| **Occurrence of attacks resolving without treatment**, n (%) | 30 | 9 (30%) |
| Occurrence of attacks resolving <24h without treatment, n (%) | 30 | 8 (27%) |
| Duration of attacks without treatment (hours), median (IQR) | 9 | 24 (42) |
| **Treatments of attacks** | | |
| Antihistamines, n (%) | 30 | 19 (63%) |
| - effective treatment, n (%) | 19 | 1 (5%) |
| Corticosteroids, n (%) | 30 | 18 (60%) |
| - effective treatment, n (%) | 18 | 1 (6%) |
| Adrenalin, n (%) | 30 | 3 (10%) |
| - effective treatment, n (%) | 3 | 0 (0%) |
| Tranexamic acid, n (%) | 30 | 10 (30%) |
| - effective treatment, n (%) | 10 | 7 (70%) |

| | N | Value |
|---|---|---|
| Bradykinin B2-receptor antagonist (icatibant), n (%) | 30 | 19 (63%) |
| - effective treatment, n (%) | 19 | 15 (79%) |
| Human or recombinant C1-INH concentrate, n (%) | 30 | 4 (13%) |
| - effective treatment, n (%) | 4 | 3 (75%) |
| Upper airway control procedures, n (%) | 30 | 0 (0%) |
| Biological characteristics | | |
| Low CH50 levels, n (%) | 30 | 0 (0%) |
| Low C4 levels, n (%) | 30 | 0 (0%) |
| Low C1-INH levels, n (%) | 30 | 0 (0%) |
| Low C1-INH activity, n (%) | 30 | 0 (0%) |
| High IgE levels, n (%) | 8 | 4 (50%) |
| High tryptase levels, n (%) | 13 | 1 (7%) |
| Hyper-eosinophilia, n (%) | 27 | 2 (7%) |
| Abnormal TSH, n (%) | 20 | 0 (0%) |
| Positive anti-thyroperoxydase and/or anti-thyroglobulin antibodies, n (%) | 15 | 0 (0%) |

**Table 1 title:** Characteristics of the probable ACEi-AE group

**Table 1 legend:** ACEi: angiotensin-converting enzyme inhibitors; AE: angioedema; ARBs: angiotensin-receptor blockers; C1-INH: C1-inhibitor; C4: complement fraction 4; CH50: total hemolytic complement; DPP-4i: dipeptidyl peptidase-4 inhibitors; EENT: eyes, ears, nose and throat; IgE: immunoglobulin E; NSAIDs: non-steroidal anti-inflammatory drugs; TPO: anti-thyroperoxydase antibodies**;**TSH: thyroid-stimulating hormone.

| | Present work |
|---|---|
| **Sample size** | 30 |
| **Study design** | retrospective |
| | case control |
| | monocenter |
| **Study period** | 6 years |
| | 2014-2019 |
| **ACEi-AE definition** | no urticaria no C1-INH deficiency no attacks before introduction |
| **Inclusion criteria** | ACEi-AE referred to AE consult |
| Patient characteristics | |
| **Male** | 63% |
| **Age at baseline visit** | median 64 yo (IQR 17) |
| **Follow-up** | median 21 mo (IQR 37) |
| **Personal history of allergy or atopic conditions** | 20% |
| ACEi exposure | |
| **Therapeutic class(es)** | |
| - ACEi alone | 83% |
| - ACEi + ARBs | 3% |
| - ACEi + DPP-4i | 13% |
| **Duration of exposure** | median 23 mo (IQR 103) |
| Characteristics of AE attack - onset | |
| **Previous attacks** | median 2 (IQR 2) |
| **Preferential attack onsent in evenings and night** | 25% |
| Characteristics of AE attack - plateau | |
| **Affected sites** | |

| | **Present work** |
|---|---|
| - Lips | 50% |
| - Tongue | 47% |
| - Uvula | 10% |
| - Oral cavity (excluding lips, tongue and uvula) | 23% |
| - Throat (pharynx, larynx) | 30% |
| - Face (excluding lips) | 10% |
| **Urticaria** | 0% |
| **Dyspnea and/or dyspnhonia** | 33% |
| Characteristics of AE attack - resolution | |
| **Duration of attacks without treatment** | median 24 (IQR 42) hr |
| **Treatments of attacks** | |
| Antihistamines | 60% |
| Corticosteroids | 60% |
| Adrenalin | 10% |
| Tranexamic acid | 30% |
| Icatibant | 63% |
| C1-INH concentrate | 13% |
| Upper airway control procedures | 0% |

**Table 2 title:** Review of the available literature regarding the characteristics of ACEi-AE patients

**Table 2 legend:**

ACEi: angiotensin-converting enzyme inhibitors; AE: angioedema; ARBs: angiotensin-receptor blockers; C1-INH: C1-inhibitor; d: day; DPP-4i: dipeptidyl peptidase-4 inhibitors; ED: emergency department**;**hr: hours; min: minutes; mo: months; IQR: interquartile range; y: years; yo: years old**;** ORL: oto-rhino-laryngology**;** RAA: renin-angiotensin-aldosterone**;** SD: standard deviation.