Douillard et al. World Allergy Organization Journal (2023) 16:100809
http://doi.org/10.1016/j.waojou.2023.100809

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Over diagnosis of bradykinin angioedema in patients treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers

Marie Douillard, MD[a,1], Zineb Deheb, MD[b,1], Agathe Bozon, MD[a], Nadia Raison-Peyron, MD[a], Olivier Dereure, MD, PhD[a], Lionel Moulis, MD[c], Angèle Soria, MD, PhD[b,d] and Aurélie Du-Thanh, MD, PhD[a]*

ABSTRACT

Background: Bradykinin angioedemas are a potentially serious side effect of angiotensin-converting enzyme inhibitors (ACEI) and more controversially of angiotensin II receptor blockers (ARB). Their challenging diagnosis is based on the absence of any recurrence after more than 6 months of drug discontinuation; otherwise mast-cell driven angioedemas as a differential diagnosis must be considered.

Objective: The aim of this study was to determine the prevalence of recurrent angioedema in patients referred for ACEI/ARB-induced bradykinin angioedema, after more than 6 months of drug discontinuation.

Methods: We included ACEI/ARB-treated patients referred for angioedema(s) without hives and unresponsive to antihistamines, after they discontinued ACEI/ARB for at least 6 months. Any C1-inhibitor deficiency was excluded. The primary endpoint was the prevalence of patients with recurrent angioedema after more than 6 months of drug discontinuation and/or developing hives during follow-up. The secondary endpoint was the identification of epidemiological factors associated with any final diagnosis.

Results: Thirty-eight of 93 patients (41%) with a suspicion of ACEI/ARB-induced bradykinin angioedema still had recurrent angioedema (n = 27) or developed hives (n = 2) or both (n = 9) after 6 months of drug discontinuation. Good response to icatibant and facial but not oral localization were predictive for the final diagnosis of ACEI/ARB-induced bradykinin angioedema and mast-cell driven angioedema, respectively.

Conclusion: In patients referred for acquired angioedema without wheals occurring during ACEI/ARB therapy, 59% finally had a diagnosis of ACEI/ARB-induced bradykinin angioedema whereas 41% were rather diagnosed with mast-cell driven angioedema. The overdiagnosis of ACEI/ARB-induced bradykinin angioedema may deteriorate the management of severe cardiovascular conditions.

[a]Department of Dermatology, St Eloi Hospital, 34000, Montpellier, France
*Corresponding author. E-mail: a-du_thanh@chu-montpellier.fr
[1] These authors participated equally to this work.
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2023.100809

Received 24 April 2023; Received in revised from 31 July 2023; Accepted 31 July 2023
Online publication date xxx

1939-4551/© 2023 Published by Elsevier Inc. on behalf of World Allergy Organization. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Angioedema, Bradykinin, Mast-cell, Angiotensin converting enzyme inhibitors, Urticaria

INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) are a major therapeutic option to reduce the risk of cardiac hypertrophy and glomerular dysfunction.[1–3] Although rather well tolerated, ACEI can induce side effects such as cough,[4,5] hypotension, or angioedema. The latter can occur in 0.7–1% of patients.[2,6–11] Angioedemas are more likely to occur in people over 65 years, African Americans, and smokers,[12–14] and whenever ACEI are prescribed for cardioprotection rather than for hypertension.[4] Angioedemas may also occur with angiotensin II receptor blockers (ARB). Thus, experts usually recommend not to switch ACEI for ARB in case of angioedema.[15] The clinical features of ACEI/ARB-induced angioedema are a localized white edema of rapid onset[16] that often affect the face (lips, tongue), but can also affect the larynx and rarely the digestive tract. To be noted, hives are never associated. They can last for several days spontaneously, not less than 48–72 h. The diagnosis criteria of these angioedemas have not yet been fully validated and there are no current validated biomarkers to confirm the diagnosis. They are considered to be bradykinin-mediated, due to the mode of action of ACEI. Thus they should resolve rapidly upon icatibant administration whereas antihistamines or epinephrine remain inefficient.[15,16] They must be considered regardless of the duration of the treatment with ACEI/ARB, but not after 6 months of discontinuation of these drugs.[15,17]

The aim of this study was to determine the prevalence of recurrent angioedema in patients referred for ACEI/ARB-induced bradykinin angioedema, after more than 6 months of ACEI/ARB discontinuation, and to determine any associated demographic or clinical factors.

METHODS

Study design and population

An ambispective, bicentric study was conducted between 2007 and 2018, including all the patients aged 18 and more, consecutively referred for acquired angioedema without wheals occurring during treatment with ACEI or ARB, and unresponsive to antihistamines.

According to the experts' recommendations for chronic spontaneous urticaria (CSU) and for bradykinin angioedema,[15,17] all the patients were prompted to discontinue the suspect treatment and were educated about the management of a further episode. Patients who continued ACEI/ARB treatment despite these recommendations and patients with hereditary or acquired C1-inhibitor (C1–INH) deficiency were excluded from the analysis by measuring serum levels of C1-inhibitor.

Demographic data, history of atopy, urticaria, autoimmunity, characteristics of the angioedema(s) such as duration, delay to onset after initiation of ACEI/ARB therapy, topography, frequency, severity, and outcome, were retrieved from the patients' medical files. The patients were further reevaluated after at least 6 months, reporting the occurrence of new episodes of angioedema or the occurrence of hives.

Outcomes

The primary endpoint was the prevalence of patients with recurrent angioedema after more than 6 months of ACEI/ARB discontinuation. According to the urticaria international recommendations[17] the diagnosis of ACEI/ARB-induced bradykinin angioedema was rejected in these patients.

Statistical analyses

Quantitative data were described by their means ($\pm$ standard deviation) and categorial data by number, frequency, and percentage. For the primary outcome, a percentage and its associated 95% confidence interval was calculated. For the analysis of factors associated with the final diagnosis, Student T or Mann-Whitney tests were

employed for continuous variables, and Chi^2 or Fisher's tests were used for categorial variables. All analyses were done with Excel, BiostatTGV. All tests were bilateral with an alpha set to 5%.

RESULTS

One hundred twenty-one patients meeting the inclusion criteria were referred for a suspicion of ACEI/ARB-induced bradykinin angioedema in the study. Ninety-three patients (*sex ratio* m/f 1.16, mean age 66.7 ± 13.2 years-old) discontinued the ACEI/ARB and completed the follow-up (Fig. 1), whose characteristics are detailed in Table 1. 37% of the patients had ACEI or ARB initiated for cardioprotection. Twelve patients (13%) were referred after their first episode of angioedema. Seventeen percent of the patients had a personal history of urticaria and 23% had a history of atopy. The mean time of ACEI/ARB treatment before angioedema occur was 55 months (± 57). After more than 6 months of ACEI/ARB discontinuation, 27 patients (29%, 95%CI [19.8%; 36.2%] had recurrent isolated angioedema(s) (mean time to recurrence: 10.5 weeks (±19.7 weeks)). Eleven patients (11.8%, 95%CI [6.1%; 20.2%]) developed hives, associated to recurrent angioedema in 9 of them. Two patients developed isolated hives, but although they did not declare further angioedema, they were considered as having CSU with isolated angioedema prior to hives.

Neither age, sex, topography, medical history, presence of cough, nor duration of ACEI/ARB treatment before the onset of angioedema was significantly associated with the development of ACEI/ARB-induced bradykinin angioedema. Angioedemas were treated almost systematically, making it impossible to assess a precise spontaneous duration of the attacks. Only a good response to icatibant was associated with ACEI/ARB-induced bradykinin angioedema ($p = 0.036$). Facial localization, other than lips/oral mucosa/oropharynx was significantly more frequent in the mast-cell driven angioedema group ($p = 0.028$).

DISCUSSION

In this study, 41% of patients referred for a suspicion of ACEI/ARB-induced bradykinin angioedema were finally diagnosed with mast-cell driven angioedema(s), ie, idiopathic non histaminergic angioedema according to the classification by Cicardi et al[18] or deep and superficial CSU. No epidemiological or clinical factor was found discriminant for the diagnosis, among sex, age, personal history of urticaria, atopy or autoimmunity,

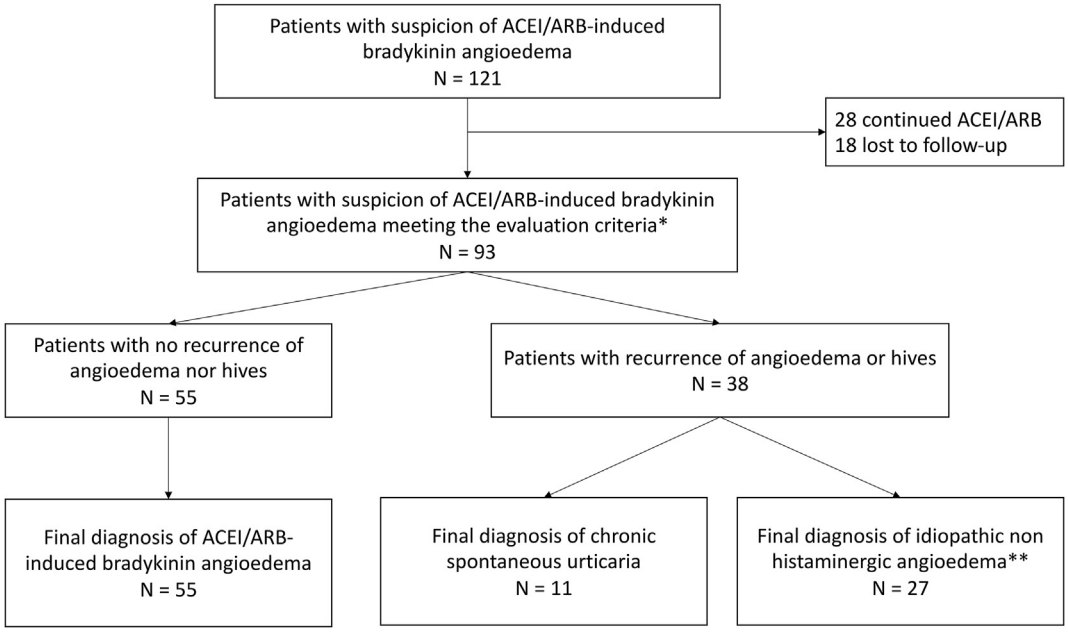

Fig. 1 Flow chart of the study. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; N, number. *discontinuation of ACEI/ARB and complete follow-up over 6 months **according to the classification by Cicardi et al. also[18] considered as mast-cell driven angioedema

	Total population N = 93	Final diagnosis		p value
		ACEI/ARB-induced bradykinin angioedema	Mast-cell driven angioedema	
Characteristics of the population				
Men, N (%)	50 (54)	27 (49)	23 (60)	0.28
Age, mean (SD)	66.7 (±13.1)	66.45 (±13.2)	67.2 (±13.33)	0.93
History of urticaria, N (%)	16 (17)	8 (14)	8 (21)	0.41
Atopy background, N (%)	21 (23)	12 (21.8)	9 (23.7)	0.83
Presence of an associated cough, N (%)	2 (2)	2 (3.9)	0	0.51
Patients taking ACEI, N (%)	55 (60)	46 (83.6)	26 (31.6)	0.08
Characteristics of the angioedema(s)				
Localization				
Digestive tract, N (%)	3 (3)	1 (1.8)	2 (5.2)	0.39
Lips/oral mucosa/ oropharynx, N (%)	44 (47)	24 (43.6)	20 (52.6)	0.39
Face (other than lips), N (%)	46 (50)	22 (40)	24 (63.2)	0.03
Complete response to icatibant, N (%)	6/8 (75)	6 (100)	0	0.04

Table 1. Characteristics of the patients and of the angioedema(s). *ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CSU, chronic spontaneous urticaria; N, number*

except the response to icatibant predicting the diagnosis of ACEI/ARB-induced bradykinin angioedema and localization of the angioedema to parts of the face other than lips/oral mucosa/oropharynx predicting the diagnosis of mast-cell driven angioedema.

ACE is the major enzyme of bradykinin catabolism, thus ACEI are believed to enhance angioedema through bradykinin accumulation. Consequently, this risk increases if there is additional dysfunction in bradykinin catabolism pathways:[19] a combination with mTOR inhibitors[20,21] or gliptins[22] for instance, or an additional genetic polymorphism decreasing bradykinin catabolism,[23–26] but not the susceptibility genes of hereditary angioedema with C1–INH deficiency.[27] The diagnosis of ACEI/ARB-induced bradykinin angioedema remains difficult. Angioedemas can appear from a few days to several years after ACEI initiation: Zingale et al[28] found a mean delay of 12 months (ranging from 1 day to 13 years), with 18% of patients developing angioedema within the first month of treatment. There are no validated biomarkers yet to confirm the diagnosis. Moreover, although this is not supported in the literature, it is not known whether ACEI could induce mast-cell driven angioedemas or even angioedemas of mixed or other origins (Fig. 3).

The management of ACEI/ARB-induced bradykinin angioedema requires both rapidly efficacious on-demand treatment to treat threatening laryngeal crises and the discontinuation of the suspect drug.

On-demand treatment of ACEI/ARB-induced bradykinin angioedema is based on off-label use of icatibant 30 mg subcutaneously or plasma-derived C1-inhibitor.[15] Icatibant is a bradykinin receptor antagonist indicated in hereditary angioedema. In the literature, several studies have shown contradictory results about the efficacy of icatibant in ACEI/ARB-induced bradykinin angioedema.[29–33] In a study by Greve et al,[6] laryngeal or tongue angioedema rapidly improved in 8 patients (after a mean of 50 min) after icatibant injection, completely resolved after a few hours (mean 4.4 h) and did not require intubation or tracheostomy whereas in the control group of 47 patients, the mean time to resolution of symptoms was 33 h and

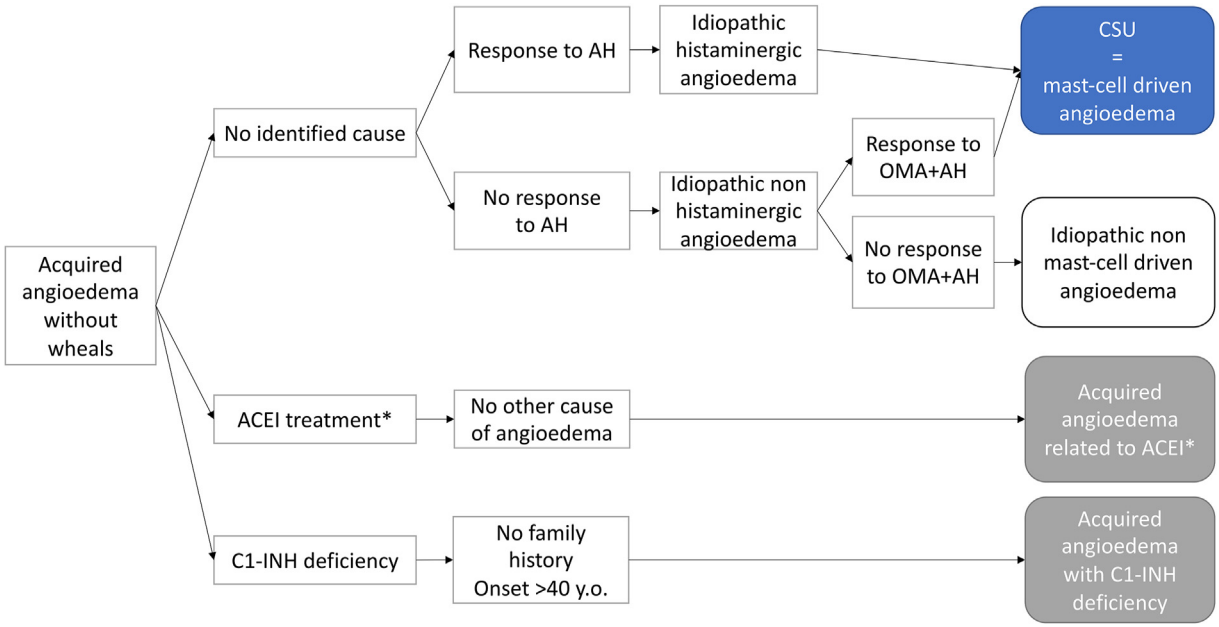

Fig. 2 Classification of acquired angioedema without wheals, adapted from Cicardi et al.[18]. ACEI, angiotensin-converting inhibitors; C1-INH, C1-inhibitor; CSU, chronic spontaneous urticaria; y.o, years-old. *others drugs such as angiotensin II receptor blockers, gliptins, etc. are also believed to be involved. Blue blocks represent mast-cell driven entities, gray blocks represent bradykinin mediated entities

5 patients required tracheostomy or intubation ($p < 0.001$). Consistently, two multicenter double-blind studies (icatibant vs placebo and icatibant vs tranexamic acid, respectively) showed the efficacy of icatibant in ACEI/ARB-induced bradykinin angioedema.[30] On the contrary, 2 further randomized double-blind trials did not find any difference between icatibant and placebo[31,32] in the management of ACEI/ARB-induced bradykinin angioedema. It is important, however, to consider that all those results might have been altered by an initial misdiagnosis of ACEI/ARB-induced bradykinin angioedema. A single dose of icatibant costs approximatively 950 euros and can be administered 3 times in a 24 h period of time. Thus, overdiagnosis of ACEI/ARB-induced bradykinin angioedema could lead to overuse of icatibant and consequently high medico-economic costs. Indeed, acquired

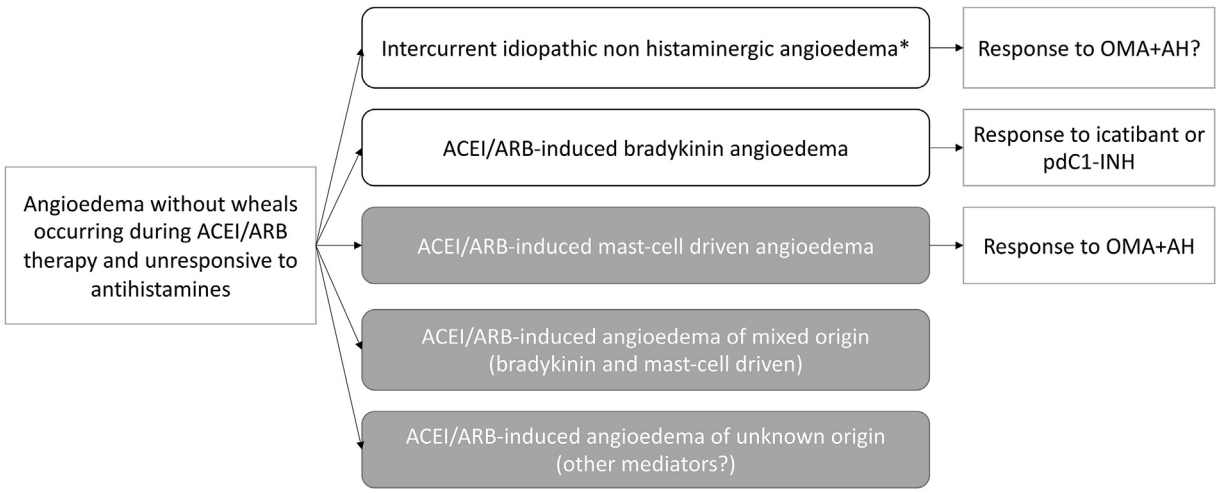

Fig. 3 Differential diagnoses of angioedema without wheals occurring during ACEI/ARB therapy. ACEI, angiotensin-converting inhibitors; ARB, angiotensin II receptor blockers; OMA, omalizumab; AH, antihistamines; pdC1-INH, plasma derived C1-inhibitor. *according to the classification of acquired angioedema by Cicardi et al.[18] those angioedema are believed to be mast-cell driven. Grey blocks represent entities that are not currently supported by the literature

angioedema without wheals can be mast-cell driven (Fig. 2): up to 10% of CSU have such a clinical expression and isolated angioedema can precede hives for several weeks or months in the course of CSU.[17] Moreover, the non-response to antihistamines may not always distinguish mast-cell driven from bradykinin mediated conditions,[17] since genuine CSU/mast-cell driven angioedema refractory to antihistamines are not rare and may respond to omalizumab (Fig. 2). Also, the spontaneous duration of episodes of angioedema does not always distinguish mast-cell from bradykinin mediated angioedema: the first can last from only a few hours to 48–72 h whereas the latter never last fewer than 48–72 h. In real-life practice, the spontaneous duration and the response to treatment of a threatening angioedema of the larynx or the tongue cannot always be accurately assessed: in tertiary referral hospitals, antihistamines, epinephrin and icatibant or plasma-derived C1–INH can be administered subsequently in a short period of time.

The discontinuation of the culprit drug is mandatory, although patients must be aware that angioedema can still occur up to 6 months after ACEI discontinuation. Continuation of the suspect drug exposed up to a 10-fold higher relapse rate of angioedema whenever ACEI was not interrupted (18.7/100 vs 1.8/100; $p = 0.001$).[34] The discontinuation of ACEI implies the choice of alternative therapy according to their former indication. Previous studies[35] showed the equivalence of ARB vs ACEI in high risk vascular disease, with a lower rate of side effects. However, the safety of ARB to replace ACEI is still debated in case of ACEI-induced bradykinin angioedema. In a meta-analysis by Makani H et al,[36] the risk of angioedema was 2.2 times lower with ARB versus ACEI. When ACEI are replaced with ARB, the risk of angioedema recurrence was considered less than 10% in another meta-analysis.[9] In a study by Cicardi et al,[11] ARB replaced ACEI in 26 patients diagnosed with ACEI-induced bradykinin angioedema: only 2 patients had persisting recurrent angioedemas with ARB, which resolved upon their discontinuation. A retrospective study was conducted on Danish population between 1994 and 2016:[37] 5507 (0.5%) patients had a diagnosis of ACEI-induced bradykinin angioedema among 1 106 024 ACEI users. The risk of angioedema recurrence if ACEI were continued was 1.45, but if ARB replaced ACEI, the risk decreased to 0.39. In the 2022 guideline for the management of heart failure, ARB can be proposed with precautions in case of any contraindication to ACEI, including angioedema.[38] To our knowledge, no study has yet characterized the putative loss of chance in terms of cardioprotection or nephroprotection in case of discontinuation of ACEI/ARB because of ACEI/ARB-induced bradykinin angioedema. Overall, recent data in the literature encourage an individual assessment of the benefit/risk ratio to prescribe ARB in a patient with a history of ACEI-induced angioedema, when ACEI was considered as essential to cardioprotection or nephroprotection or difficult-to-treat hypertension. However, for isolated hypertension, the precautionary principle should prevail: beta-blockers, calcium channel blockers or diuretics should rather be considered.

The major limitation of this retrospective study was an inclusion bias: when data collection started, both ACEI and ARB were considered to be high-risk drugs for drug-induced bradykinin angioedema and we followed the experts' recommendations to not switch ACEI for ARB if possible. To be noted, 9 of the 55 patients finally diagnosed with ACEI/ARB-induced bradykinin angioedema were taking ARB. None of the patients analyzed had ARB in replacement of ACEI because it was an exclusion criterion. Effectives of the ACEI and the ARB groups were too small to compare their characteristics. Regarding the recent literature, further studies about drug-induced bradykinin angioedema should focus on ACEI instead of ARB.

CONCLUSION

In patients referred for a suspected diagnosis of ACEI/ARB-induced bradykinin angioedema, 59% were actually considered as correctly diagnosed. For them, ACEI remain contra-indicated but ARB might be individually discussed as an alternative option for difficult-to-treat conditions, in tertiary specialized centers. On the contrary, 41% rather had mast-cell driven angioedema or another cause of angioedema (mixed mast-cell and bradykinin origin, other mediators). For them, the imputability of ACEI/ARB remains questionable. Further studies are needed: first to establish the long-term safety

of replacing ACEI with ARB in case of ACEI-induced bradykinin angioedema and to discuss the systematic prescription of on-demand icatibant; second, to establish the long-term safety of continuing ACEI/ARB in case of mast-cell driven angioedema; finally, validating biomarkers to distinguish bradykinin from mast-cell mediated angioedema would facilitate the management of these patients.

Abbreviations
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; C1–INH, C1-inhibitor; CSU, chronic spontaneous urticaria; pdC1-INH, plasma derived C1-inhibitor.

Funding
None.

Authors contributions
MD, ZD and AB collected data and participate in writing the manuscript.
NRP and OD supervised the work and reviewed the manuscript.
LM performed the statistic analysis.
AS and ADT collected data, participated in writing the manuscript, supervised the work and reviewed the manuscript.

Authors' consent
All authors consent to publication.

Ethics approval
The study was conducted in accordance with the Data Protection Committee. Institutional Review Board and local ethics committee approval for long-term follow-up of AE in patients undertaking ACEI/ARB was obtained in March 2018 (CHU Montpellier, IRB number: 2018_IRB-MTP_05-01).
Data and materials are available on demand.

Declaration of competing interest
None.

Acknowledgement
Acknowledgement to Claire Duflos, Clinical and epidemiological research unit, CHU Montpellier, 34000, France for her reviewing of the manuscript.

Author details
[a]Department of Dermatology, St Eloi Hospital, 34000, Montpellier, France. [b]Médecine Sorbonne Université, Service de Dermatologie et Allergologie, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [c]Clinical and Epidemiological Research Unit, CHU, Montpellier, 34000, France. [d]Cimi-Paris, INSERM 1135, Paris, France.

REFERENCES

1. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. *Clin Exp Allergy*. 2010;40(1):50–61.
2. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology and incidence of ACE inhibitor angioedema utilizing a large electronic health record. *J Allergy Clin Immunol Pract*. 2017;5(3):744–749.
3. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med*. 2019 Mar;33(2):363–382.
4. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006 Jan 1;129(1, Supplement):169S–173S.
5. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors. *Am J Cardiovasc Drugs*. 2012 Aug 1;12(4):263–277.
6. Therapeutic Efficacy of Icatibant in Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: A Case Series - ScienceDirect [Internet]. [cited 2022 Mar 6]. Available from: % https://www-sciencedirect-com.ezpum.scdi-montpellier.fr/science/article/pii/S0196064410002799?via%3Dihub.
7. Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis*. 2018 May 4;13:73.
8. Pfaue A, Schuler PJ, Mayer B, Hoffmann TK, Greve J, Hahn J. Clinical features of angioedema induced by renin-angiotensin-aldosterone system inhibition: a retrospective analysis of 84 patients. *J Community Hosp Intern Med Perspect*. 2019 Dec 14;9(6):453–459.
9. Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol*. 2008 Nov;101(5):495–499.
10. Floccard B, Javaud N, Deroux A, et al. Diagnosis and treatment of upper airway oedema caused by acute angio-oedema in the emergency department: a French consensus statement. *Eur J Emerg Med*. 2017 Oct;24(5):318–325.
11. Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med*. 2004 Apr 26;164(8):910–913.
12. Kostis J. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004 Feb;17(2):103–111.
13. Angioedema Incidence in US Veterans Initiating Angiotensin-Converting Enzyme Inhibitors [Internet]. [cited 2022 Apr 1]. Available from: https://www.ahajournals.org/doi/epub/10.1161/HYPERTENSIONAHA.108.110270.

14. Weisman DS, Arnouk N, Asghar MB, et al. ACE inhibitor angioedema: characterization and treatment versus non-ACE angioedema in acute hospitalized patients. *J Community Hosp Intern Med Perspect*. 2020 Jan 2;10(1):16–18.

15. Nosbaum A, Bouillet L, Floccard B, et al. Prise en charge des angiœdèmes induits par les inhibiteurs de l'enzyme de conversion de l'angiotensine : recommandations du Centre de référence national des angiœdèmes. *Rev Médecine Interne*. 2013 Apr;34(4):209–213.

16. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004 Sep 1;114(3, Supplement):S51–S131.

17. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69(7):868–887.

18. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69(5):602–616.

19. Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension*. 2009 Sep;54(3):516–523.

20. Cassano N, Nettis E, Di Leo E, Ambrogio F, Vena GA, Foti C. Angioedema associated with dipeptidyl peptidase-IV inhibitors. *Clin Mol Allergy CMA*. 2021 Dec 6;19(1):24.

21. Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor–associated angioedema. *Hypertension*. 2008 Jan;51(1):141–147.

22. Arcani R, Martinez S, Gayet S. Sitagliptin and angioedema. *Ann Intern Med*. 2017 Jul 18;167(2):142–143.

23. Couture R, Blaes N, Girolami JP. Kinin receptors in vascular biology and pathology. *Curr Vasc Pharmacol*. 2014 Mar;12(2):223–248.

24. Javaud N, Achamlal J, Reuter PG, et al. Angioedema related to angiotensin-converting enzyme inhibitors. *Medicine (Baltim)*. 2015 Nov 13;94(45), e1939.

25. Interactive Effect of Ethnicity and ACE Insertion/Deletion Polymorphism on Vascular Reactivity [Internet]. [cited 2022 Mar 30]. Available from: https://www.ahajournals.org/doi/epub/10.1161/01.HYP.37.1.46.

26. Genetic susceptibility to angiotensin-converting enzyme-inhibitor induced angioedema: A systematic review and evaluation of methodological approaches - PubMed [Internet]. [cited 2022 Apr 8]. Available from: https://pubmed-ncbi-nlm-nih-gov.ezpum.biu-montpellier.fr/31710633/.

27. Mathey CM, Maj C, Scheer AB, et al. Molecular genetic screening in patients with ACE inhibitor/angiotensin receptor blocker-induced angioedema to explore the role of hereditary angioedema genes. *Front Genet*. 2022;13, 914376.

28. Zingale LC, Beltrami L, Zanichelli A, et al. Angioedema without urticaria: a large clinical survey. *CMAJ Can Med Assoc J*. 2006 Oct 24;175(9):1065–1070.

29. Baş M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor–induced angioedema. *N Engl J Med*. 2015 Jan 29;372(5):418–425.

30. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010 Aug 5;363(6):532–541.

31. Sinert R, Levy P, Bernstein JA, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor–induced upper airway angioedema. *J Allergy Clin Immunol Pract*. 2017 Sep 1;5(5):1402–1409.e3.

32. Straka BT, Ramirez CE, Byrd JB, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2017 Jul;140(1):242–248.e2.

33. Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema: icatibant in ACE-I associated angioedema. *Intern Med J*. 2015 Aug;45(8):821–827.

34. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor–associated angioedema. *JAMA*. 1997 Jul 16;278(3):232–233.

35. Yusuf S, Teo KK, Pogue J, et al, ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008 Apr 10;358(15):1547–1559.

36. Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin–angiotensin system inhibitors. *Am J Cardiol*. 2012 Aug;110(3):383–391.

37. Rasmussen ER, Pottegård A, Bygum A, von Buchwald C, Homøe P, Hallas J. Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors - a nationwide registry-based cohort study. *J Intern Med*. 2019 May;285(5):553–561.

38. Writing Committee Members. ACC/AHA joint committee members. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Card Fail*. 2022 May;28(5):e1–e167.