

## ACE Inhibitor-Induced Angioedema

### Introduction

1. The overall prevalence of ACE inhibitor angioedema is low (~0.2-0.7%), however it makes up the majority of visits to the ED for angioedema
2. ACE inhibitor angioedema is caused by the buildup of bradykinin which leads to increased vascular permeability and the release of substance P resulting in vasodilation and fluid extravasation into tissues
3. ACE inhibitor angioedema can occur at any time, with the majority of cases occurring within the first month of therapy.
4. Risk factors for ACE inhibitor angioedema includes female sex, African American race, chronic heart failure, coronary artery disease, history of smoking, and concomitant use of dipeptidyl peptidase 4 (DPP4) inhibitors

### Pharmacology

	Fresh Frozen Plasma (FFP)	Icatibant	Tranexamic Acid (TXA)
<b>Dose</b>	2-4 units	30 mg	1000 mg
<b>Administration</b>	Intravenous	Subcutaneous	Intravenous
<b>PK/PD</b>	Onset: ~ 2 hours	Onset: 2 hours Duration: 6 hours	Onset: ~ 2 hours
<b>Adverse Effects</b>	Hypervolemia, TRALI, thrombosis, hyperfibrinolysis, infection	Injection site reactions, LFT elevations, dizziness	Abdominal pain, headache, musculoskeletal pain/spasms
<b>Drug Interactions and warnings</b>	Calcium administration within the same line (may produce precipitants)	None	Contraindicated in patients with SAH or active intravascular clotting
<b>Compatibility</b>	N/A	N/A	Compatible with NS, D5W, or LR
<b>Comments</b>	Takes ~ 30-45 minutes to thaw & process once ordered	Costs ~ \$4,500 per 30 mg syringe (AWP)	Available in most emergency departments. Inject 1000 mg TXA in 100 mL of diluent

## Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Baş, 2015	RCT (n = 27)	SubQ Icatibant 30 mg vs. prednisolone + clemastine	Time to complete symptom resolution: 8 hours vs. 27.1 hours (P=0.002).  Time to onset of symptom relief: 2 hours vs. 11.7 hours (P=0.03).  All patients experienced complete resolution of edema.
Straka, 2017	RCT (n = 33)	SubQ Icatibant 30 mg vs placebo	Time-to-resolution (12.7 hrs vs 10.3 hrs) and amount of swelling over time were similar in placebo and icatibant treatment groups.
Sinert, 2017	RCT (n = 121)	SubQ Icatibant 30 mg vs placebo	There were no difference time to meeting discharge criteria between groups (4 hrs vs 4 hrs).
Karim, 2002	Case Report (n = 1)	4 units FFP following chlorpheniramine, hydrocortisone, and epinephrine	Dramatic improvement within 2 hours following FFP administration allowing for extubation.
Warrier, 2004	Case Report (n = 1)	2 units FFP following antihistamine, corticosteroid, epinephrine, antileukotrienes, cyclosporine, and IVIG (all without improvement)	Complete resolution of symptoms within 2-4 hours following FFP administration.
Bolton, 2012	Case Report (n = 1)	2 units FFP following antihistamine and corticosteroid administration	Near complete resolution of symptoms within 2 hours following FFP administration.
Hassen, 2013	Case series (n = 7)	2 units FFP following antihistamine and corticosteroid administration	Temporal association between the administration of FFP and <b>improvement in angioedema in 7 cases of presumed ACEI-induced angioedema</b> that were refractory to histamine-related anaphylaxis.
Stewart, 2013	Case Report (n= 2)	2 units FFP administered	Administration of FFP resulted in rapid resolution of symptoms in both patients.
Beauchêne, 2018	Case Series (n = 33)	Tranexamic Acid IV: 24 patients (73%) PO: 8 patients (24%) Unknown: 1 patient (3%)  Dosage: 500 mg – 4 grams (55% received 1 g)	81.8% patients achieved significant improvement following TXA administration alone.  39.3% patients experienced symptom improvement within 1 hr of TXA administration.
Wang, 2020	Case Report (n = 1)	TXA 1000 mg IVPB over 10 minutes administered following diphenhydramine, famotidine, methylprednisolone, and epinephrine	Improvement in speech observed within 30 minutes of TXA administration with complete resolution of symptoms at 2 hrs.  Patient discharged 2.5 hours following presentation to ED.
Manzano, 2021	Case series (n = 11)	TXA 1000 mg IV	The median length of stay in the hospital was 1.2 days (0.4-18.2 days).  No noted adverse effects related to medication administration of TXA.

### Conclusions

1. Many cases of ACE inhibitor angioedema will resolve on their own with the cessation of the offending agent.
2. More studies are needed to evaluate the use of investigational therapies including tranexamic acid and FFP.
3. In severe cases of ACE inhibitor angioedema, it is reasonable to consider using tranexamic acid or FFP if icatibant is unavailable after weighing the risks versus benefits.

## References

1. Lexicomp Online, Hudson, Ohio: UpToDate, Inc.; 2021; April 22, 2021. Available from: <http://online.lexi.com/lco/action/home>
2. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: a review of the literature. *J Clin Hypertens*. 2017;19:1377-1382.
3. Campo P, Fernandez TD, Canto G, et al. Angioedema induced by angiotensin-converting enzyme inhibitors. *Curr Opin Allergy Clin Immunol*. 2013;13:337-344.
4. Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor-associated angioedema. *Hypertension*. 2008;51:141-147.
5. Straka BT, Ramirez CE, Byrd JB, Stone E, Woodard-Grice A, Nian H, Yu C, Banerji A, Brown NJ. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2017 Jul;140(1):242-248.e2. doi: 10.1016/j.jaci.2016.09.051. Epub 2016 Nov 29. PMID: 27913306; PMCID: PMC5705179.
6. Sinert R, Levy P, Bernstein JA, Body R, Sivilotti MLA, Moellman J, Schranz J, Baptista J, Kimura A, Nothaft W; CAMEO study group. Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor-Induced Upper Airway Angioedema. *J Allergy Clin Immunol Pract*. 2017 Sep-Oct;5(5):1402-1409.e3. doi: 10.1016/j.jaip.2017.03.003. Epub 2017 May 25. PMID: 28552382.
7. Baş M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med*. 2015;372:418-425.
8. Karim MY, Masood A. Fresh-frozen plasma as a treatment for life-threatening ACE-inhibitor angioedema. *J Allergy Clin Immunol*. 2002;109(2):370-1.
9. Warriar MR, Copilevitz CA, Dykewicz MS, et al. Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. *Ann Allergy Asthma Immunol*. 2004;92:573-575
10. Hassen GW, Kalantari H, Parraga M, Chirurugi R, Meletiche C, Chan C, Ciarlo J, Gazi F, Lobaito C, Tadayon S, Yemane S, Velez C. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. *J Emerg Med*. 2013 Apr;44(4):764-72. doi: 10.1016/j.jemermed.2012.07.055. Epub 2012 Oct 28. PMID: 23114109.
11. Bolton MR, Dooley-Hash SL. Angiotensin-converting enzyme inhibitor angioedema. *J Emerg Med*. 2012;43(4):e261-262.
12. Stewart M, McGlone R. Fresh frozen plasma in the treatment of ACE inhibitor-induced angioedema. *BMJ Case Rep*. 2012;2012:bcr2012006849.
13. Wang K, Geiger H, McMahan A. Tranexamic acid for ACE inhibitor induced angioedema – A case report. *Am J Emerg Med*. 2020;S0735-6757(20)30923-2.
14. Beauchêne C, Martins-Héricher J, Denis D, et al. Tranexamic acid as first-line emergency treatment for episodes of bradykinin-mediated angioedema induced by ACE inhibitors. *Rev Med Interne*. 2018;39(10):772-776.
15. Martinez Manzano JM, Lo KB, Patarroyo-Aponte G, Azmaiparashvili Z. The use of intravenous tranexamic acid for patients with angiotensin-converting enzyme inhibitor-induced angioedema: A case series. *Ann Allergy Asthma Immunol*. 2021 Feb 14:S1081-1206(21)00129-0. doi: 10.1016/j.anai.2021.02.011. Epub ahead of print. PMID: 33592284.