Literature Review and Grading

GRAD	QUALITY	COMMENTS
E		
E	OUTSTANDING	Case report on FFP
E	ADEQUATE	Case 1: ACE-induced angioedema that responded to icatibant. Case 2: patient on ACEi but the authors called it idiopathic and icatibant did not help
F	UNSATISFACTOR HY	Letter to the editor. No methodology
E	OUTSTANDING	Case report of 76F. Treated with icatibant. Dyspnea relieved within minutes. Swelling almost
		disappeared after 30m
	E E F	E OUTSTANDING E ADEQUATE F UNSATISFACTOR HY

 BaÅŸ M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, Veit J, Schossow B, Hapfelmeier A, Kehl V, Kojda G, Hoffmann TK. A randomized trial of icatibant in ACE- inhibitor-induced angioedema. N Engl J Med. 2015 Jan 29;372(5):418-25. doi: 10.1056/NEJMoa1312524 	A	Adequate	Industry-sponsored, multicenter, phase 2, double blind, double dummy design. 27 patients included in analysis. 8.0 hours vs 27.1 hours for median time to complete resolution
 6. Bernstein JA, Moellman JJ, Collins SP, Hart KW, Lindsell CJ. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor- induced angioedema in the emergency department. Ann Allergy Asthma Immunol. 2015 Mar;114(3):245-9. doi: 10.1016/j.anai.2014.12.007. Epub 2015 	A	Adequate	Industry- sponsored, 2- center, phase 2, triple blind design. 50 patients included in analysis. Discharge criteria met in < 4 hours in 31% of ecallantide patients and 21%
Jan 16.			of placebo
 7. Bolton MR, Dooley-Hash SL. Angiotensin-converting enzyme inhibitor angioedema. J Emerg Med. 2012 Oct;43(4):e261-2. doi: 10.1016/j.jemermed.2011.03.029. Epub 2011 May 7. No abstract available. 	E	Poor	Case report of 76M. Treated with FFP. Nearly complete resolution over the next 2h
 8. Bova M, Guilarte M, Sala-Cunill A, Borrelli P, Rizzelli GM, Zanichelli A. Treatment of ACEI-related angioedema with icatibant: a case series. Intern Emerg Med. 2015 Apr;10(3):345-50. doi: 10.1007/s11739-015-1205-9. Epub 2015 Feb 10 	D.	Adequate	All patients received standard of care treatment. After treatment with icatibant symptom relief was reported at 30 min (IQR 27.5-70 min). Complete resolution of sx at 5h (IQR 4-7h). A comparison was made to to the 10

9. Chan NJ, Soliman AM. Angiotensin converting enzyme inhibitor- related angioedema: onset, presentation, and management. Ann Otol Rhinol Laryngol. 2015 Feb;124(2):89-96. doi: 10.1177/0003489414543069. Epub 2014 Jul 24.	D.	Outstanding	patients who had previously had angioedema where complete resoluation was at 54h (IQR 33-63h) Retrospective analysis of 88 patients. Looked at Onset and symptoms. Minimal discussion regarding treatment
 10. Charmillon A, Deibener J, Kaminsky P, Louis G. Angioedema induced by angiotensin converting enzyme inhibitors, potentiated by m-TOR inhibitors: successful treatment with icatibant. Intensive Care Med. 2014 Jun;40(6):893-4. doi: 10.1007/s00134-014-3290-z. Epub 2014 Apr 16. No abstract available. 	E.	Poor	65F on quinapril and everolimus for breast cancer. Regression of swelling 1 hour after administration of icatibant
11. Cheong E, Dodd L, Smith W, Kleinig T.			52M on perindipril who received alteplase. Icatibant

Icatibant as a Potential Treatment of Life-Threatening Alteplase-Induced Angioedema. J Stroke Cerebrovasc Dis. 2018 Feb;27(2):e36-e37. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.0 39. Epub 2017 Oct 31.	E.	Poor	given. Upper airway edema visibly improved within 15 min complete resolution within 2 hours
12. Curtis RM, Felder S, Borici-Mazi R, Ball I. ACE-I Angioedema: Accurate Clinical Diagnosis May Prevent Epinephrine- Induced Harm. West J Emerg Med. 2016 May;17(3):283- 9. doi: 10.5811/westjem.2016.2.29224. Epub 2016 Apr 26.	D.	Poor	Retrospective chart review of cases of AAE (includes ACEi and ARB induced angioedema) 2 patients who received epinephrine had morbidity
 13. Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. Intern Med J. 2015 Aug;45(8):821-7. doi: 10.1111/imj.12799. 	D.	Good	13 patientsreceived icatibant.4 patientsintubated
 14. Gallitelli M, Alzetta M. Icatibant: a novel approach to the treatment of angioedema related to the use of angiotensin-converting enzyme inhibitors. Am J Emerg Med. 2012 Oct;30(8):1664.e1-2. doi: 10.1016/j.ajem.2011.09.014. Epub 2011 Nov 17. 15. Greve J, Bas M, Hoffmann TK, Schuler PL Weller P. Koida G. 	E.	Adequate	76M with 3 previous presentations (4 total). On 4th presentation after getting icatibant his swelling almost resolved completely by 10 hours. Prospective case series of 10
Schuler PJ, Weller P, Kojda G, Strassen U.			series of 10 subjects

Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor- induced angioedema. Laryngoscope. 2015 Jun;125(6):E198-202. doi: 10.1002/lary.25113. Epub 2015 Jan 13.	C.	Adequate	compared to historical cohort of 47 patients. Compared treatment with C1- INH concentrate. 10.1 hours vs 33.1h
 16. Hahn J, Trainotti S, Hoffmann TK, Greve J. Drug-Induced Inhibition of Angiotensin Converting Enzyme and Dipeptidyl Peptidase 4 Results in Nearly Therapy Resistant Bradykinin Induced Angioedema: A Case Report. Am J Case Rep. 2017 May 25;18:576-579. 	E.	Adequate	83F on ACEi and DPP-IV. Treated with C1-INH and icatibant with slow response
· · · · · ·			54F on ACEi who
 17. Hannoodi F, Sabbagh H. ACE Inhibitor-Induced Angioedema following Cervical Spine Surgery. Case Rep Cardiol. 2017;2017:4268962. doi: 10.1155/2017/4268962. Epub 2017 Mar 1. 	E.	Good	was intubated for neck surgery. Unable to be extubated due to edema at the level of the arytenoids. Treated with dexamethasone for 4 days. After Acei stopped she was extubated the next day.
 18. Hassen GW, Kalantari H, Parraga M, Chirurgi 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. Review. 	E.	Outstanding	7 cases of presumed ACEi- induced angioedema that all improved in temporal association to administration of FFP.

19. Howarth D. ACE inhibitor angioedema - a very late presentation. Aust Fam Physician. 2013 Dec;42(12):860-2.	E.	Good	77M intubated after failing steroids, antihistamines and epi
20. Illing EJ, Kelly S, Hobson JC, Charters S. Icatibant and ACE inhibitor angioedema. BMJ Case Rep. 2012 Aug 30;2012. pii: bcr2012006646. doi: 10.1136/bcr-2012- 006646.	E.	Adequate	62M with tongue swelling. Tx with hydrocortisone, chlorphenamine with no improvement. Given epi nebs and then a single dose of icatibant. Intubated. Extubated 48 hours later.
 21. Jackeviciute J, Pilvinis V, Pilviniene R. Fatal outcome of late-onset angiotensin- converting enzyme inhibitor induced angioedema: A case report. Medicine (Baltimore). 2018 Aug;97(31):e11695. doi: 10.1097/MD.00000000011695. 	E.	Adequate	89F intubated. Extubated. Reintubated with difficulty. ETT narrow due to edema. Cardiac arrest. ROSC. Blood clot at distal end of tube removed. FFP given with no improvement. Angioedema resolved 13 days later. Death at 24 days
22. Jacob J, Bardes I, Palom X, Carrizosa M, Fuentes E.			Letter to the editor about Fok article. 10 patients treated

Angiotensin-converting enzyme inhibitor- induced angioedema and icatibant: a new hope. Intern Med J. 2015 Oct;45(10):1093-4.	F.	Unsatisfactory	with icatibant who improved within 12 hours
doi: 10.1111/imj.12849. No abstract available.			
 23. Javaud N, Achamlal J, Reuter PG, Lapostolle F, Lekouara A, Youssef M, Hamza L, Karami A, Adnet F, Fain O. Angioedema Related to Angiotensin- Converting Enzyme Inhibitors: Attack Severity, Treatment, and Hospital Admission in a Prospective Multicenter Study. Medicine (Baltimore). 2015 Nov;94(45):e1939. doi: 10.1097/MD.00000000001939. 	C.	Outstanding	prospective, multicenter, observational study in 4 French hospitals and call center. 62 patients enrolled. Symptom relief occurred significantly earlier in patients receiving specific treatment than in untreated patients (0.5 [0.5–1.0] versus 3.9 [2.5– 7.0] hours
24. Kaufman MB. ACE Inhibitor-Related Angioedema: Are Your Patients at Risk?	E.	Adequate	All 4 cases treated with standard therapy
P T. 2013 Mar;38(3):170-2.			
 25. Korzeniowska K, Cielewiczi A, Pawlaczyk M, Motowidlo K, Andrys-Wawrzyniak I, Jablecka A. ANGIOEDEMA AFTER ANGIOTENSIN- CONVERTING ENZYME INHIBITORS. Acta Pol Pharm. 2017 May;74(3):983- 986. 	E.	Adequate	2 cases. Treated with steroids and antihistamines
26. Krogh Nielsen T, Bygum A, Rye Rasmussen E.			60F. Neither adrenaline inhalations, intravenously

Life-threatening angio-oedema after the first dose of an ACE inhibitor-not an anaphylactic reaction. BMJ Case Rep. 2016 May 26;2016. pii: bcr2016214364. doi:10.1136/bcr-2016- 214364.	E.	Adequate	administrated corticosteroids, atropine nor furosemide were effective and the patient soon become bradycardic. A tracheotomy was performed and the patient was placed on a ventilator.
27. Kuhlen JL Jr, Forcucci J. Angiotensin-converting enzyme inhibitor- induced unilateral tongue angioedema. Am J Med Sci. 2012 Nov;344(5):416-7. doi: 10.1097/MAJ.0b013e318258317f.	E.	Good	62M. Unilateral tongue angioedema. Improved then worsened. Tx with steroids and antihistamines. Intubated.
28. Leibfried M, Kovary A. C1 Esterase Inhibitor (Berinert) for ACE Inhibitor-Induced Angioedema: Two Case Reports. J Pharm Pract. 2017 Dec;30(6):668-671. doi: 10.1177/0897190016677427. Epub 2016 Nov 11.	E.	Adequate	2 cases of ACEi- Induced Angioedema. Treated with berinert. Case 1 treated with antihistamine, methylprednisolon e, epinephrine, and fresh frozen plasma. When symptoms did not resolve, intravenous C1 peptide esterase inhibitor (C1INH) was administered, with clinical improvement. Four hours later, symptoms returned and the patient underwent emergency

			tracheostomy. Case 2: received conventional treatment. Endo- tracheal tube placement was unsuccessful. While the patient was undergoing intubation in the operating room, intravenous C1INH was administered resulting in quick improvement of symptoms.
29. Leung E, Hanna MY, Tehami N, Francombe J.			Female with ACEi- angioedema. Tx
Isolated unilateral tongue oedema: the			with meds
adverse effect of Angiotensin converting	Ε.	Adequate	
enzyme inhibitors.			
Curr Drug Saf. 2012 Nov 1;7(5):382-3.			
30. Lewis LM, Graffeo C,			multicenter, phase
Crosley P, Klausner HA,			2, double-blind
Clark CL, Frank A, Miner J,			study with subjects
larrobino R, Chyung Y.			randomized to
Ecallantide for the acute treatment of	٨	Outstanding	receive a single
angiotensin-converting enzyme inhibitor-	А.	Outstanung	subcutaneous
induced angioedema: a multicenter,			dose of ecallantide
randomized, controlled trial.			(10, 30, or 60 mg)
			or placebo plus physician-directed
Ann Emerg Med. 2015 Feb;65(2):204-13.			conventional
doi:			therapy. discharge
10.1016/j.annemergmed.2014.07.014.			eligibility endpoint
Epub 2014 Aug 30.			was met by 72%
			of the placebo group and 85%,
			89%, and 89% of
			the ecallantide 10-
			, 30-, and 60-mg

			groups,
			• .
 31. Lipski SM, Casimir G, Vanlommel M, Jeanmaire M, Dolhen P. Angiotensin-converting enzyme inhibitors-induced angioedema treated by C1 esterase inhibitor concentrate (Berinert®): about one case and review of the therapeutic arsenal. Clin Case Rep. 2015 Feb;3(2):126-30. doi: 10.1002/ccr3.171. Epub 2014 Dec 5. 	E.	Good	respectively. 77F tongue angioedema administered 125 mg of methylprednisolon e and 0.5 mg of epinephrine subcutaneously. Fresh frozen plasma was administered but there was no improvement after 4 h. Berinert four ampoules were injected (20 Ul/Kg). In less than an hour, the swelling was absorbed and the patient remained in hospital for 48 h observation
 32. Millot I, Plancade D, Hosotte M, Landy C, Nadaud J, Ragot C, Graffin B, Drouet C, Kanny G. Treatment of a life-threatening laryngeal bradykinin angio-oedema precipitated by dipeptidylpeptidase-4 inhibitor and angiotensin-I converting enzyme inhibitor with prothrombin complex concentrates. Br J Anaesth. 2012 Nov;109(5):827-9. doi: 10.1093/bja/aes371. No abstract available. 	E.	Adequate	67M on ACEi and DPP-4. 3rd presentation for angiodema. treated with epinephrine aerosols, i.v. dex- chlorpheniramine 5 mg, and methylprednisolon e 120 mg. The patient showed no improvement in the next hour. AVK antagonist, Kanokadw (LFB, France) 1500 IU, was adminis- tered. Dyspnoea and dysphonia regressed within

			20 min, and symptoms completely disappeared within 8 h. Further episodes treated with berinert and icatibant.
 33. Okumu M, Ochola F, Bodo C, Apuoyo K, Odhiambo N, Ng'ong'a A. Enalapril-Induced Angioedema: Two Case Reports in a Rural Health Facility in Kenya. Cureus. 2018 May 2;10(5):e2572. doi: 10.7759/cureus.2572. 	E.	Adequate	Case 1: 58F. Given IV dose of hydrocortisone and a 20 mg stat dose of intravenous chlorpheniramine were administered and the patient was observed for one hour. The edema was noted to subside Case 2: 55M. 4 mg intravenous dexamethasone injection and monitored for one hour. A gradual decrease in the swelling was observed about two hours after
34. Pucar PA, O'Sullivan M, Goudie A, Marr T, Brusch A. Successful treatment of ACE inhibitor- induced angioedema with icatibant, a bradykinin B2 receptor antagonist. Med J Aust. 2015 Jun 15;202(11):596-7. No abstract available.	E.	Adequate	65F. Treated with icatibant. On repeat FNE 10 minutes later, there was a significant improvement in her condition.

35. Rasmussen ER, Mey K, Bygum A. Isolated oedema of the uvula induced by intense snoring and ACE inhibitor. BMJ Case Rep. 2014 Aug 21;2014. pii: bcr2014205585. doi: 10.1136/bcr-2014- 205585.	E.	Adequate	50M. received complement C1- inhibitor concentrate ~15 units/kg injected intravenously over 10 min. Within about 40 min significant improvement of the oedema was observed and the patient's voice had normalised
36. Rasmussen ER, Bygum A. ACE-inhibitor induced angio-oedema treated with complement C1-inhibitor concentrate. BMJ Case Rep. 2013 Oct 4;2013. pii: bcr2013200652. doi:10.1136/bcr-2013- 200652.	E.	Adequate	63M. He was treated with drugs for anaphylaxis (epinephrine, antihista- mine and corticosteroid), but the angio-oedema progressed and also began to involve the soft palate and uvula. 1000 units (11 units/kg) of Berinert (complement C1- inhibitor concentrate) had already been administered intra- venously over 10 min and the angio- oedema had regressed significantly.

37. Raval P. A case report looking at ACE inhibitors as the cause of angioedema during dental treatment. Br Dent J. 2014 Jan;216(2):73-5. doi: 10.1038/sj.bdj.2014.2.	E.	Adequate	77M. Adrenaline and an antihistamine were administered to the patient
38. Shahani L. ACE inhibitor-induced intestinal angio- oedema: rare adverse effect of a common drug. BMJ Case Rep. 2013 Jul 22;2013. pii: bcr2013200171. doi: 10.1136/bcr-2013- 200171.	E.	Adequate	50F. Hx of Crohns presenting with abdo pain. Lisinopril was discontinued and the patient was treated with antihistamines
 39. 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. 	A.	Outstanding	phase III, 2- armed, randomized double-blind clinical trial was conducted at 59 centers severity of the ACE-leinduced angioedema attack was determined by the subject's worst severity rating at baseline among 4 clinical domains (difficulty breathing, difficulty swallowing, voice changes, and tongue swelling) Conventionally administered drugs, namely, antihistamines, corticosteroids, and epinephrine,

	e allowed at
any	time before or
afte	r study drug
	ninistration.
	nary efficacy
	point was time
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	neeting
	harge criteria,
	ned as time
	n study drug
	ninistration to
earl	iest time that
diffic	culty breathing
	difficulty
	llowing were
	ent (rating of 0
	of 4), and
	e change and
	gue swelling
	e mild or
	ent (0 or 1).
	ween
	ember 2013
	August 2015,
121	subjects with
pres	sumed ACE-
leine	duced
ang	ioedema were
	domized at 31
	9 opened
site	
	statistically
	nificant
	erences
	veen the 2
	tment groups
	ne primary
	acy end point
	me to meeting
disc	harge criteria
(P 1	⁄4 .63), the key
	ondary end
	t of TOSR (P
	.57), or any
	er secondary
	point
enu	ροιπ

40. Stewart M, McGlone R. Fresh frozen plasma in the treatment of ACE inhibitor-induced angioedema. BMJ Case Rep. 2012 Aug 24;2012. pii: bcr2012006849. doi:10.1136/bcr-2012- 006849.	E.	Good	2 cases of angioedema that temporally improved with administration of FFP
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41. Urnoski E, Grillo A,			41M. treated
Rosini JM.			initially with
Use of C1 Inhibitor for			diphenhydramine
			25 mg i.v., meth-
Angiotensin-Converting Enzyme			ylprednisolone 125
(ACE) Inhibitor-Induced	_		mg i.v., and
Angioedema Decreases	E.	Good	ranitidine 50 mg i.v.
Mechanical Ventilation Time.			His edema rapidly
			progressed with left
J Emerg Med. 2015			lip and further
Dec;49(6):e173-5. doi:			tongue swelling. An
10.1016/j.jemermed.2015.06.076.			airway alert was
Epub 2015 Sep 26.			called and nebu-
			lized lidocaine
			started for
			anticipated
			intubation. The pa-
			tient was ordered
			C1 inhibitor 1500
			units (17 mg/kg) i.v.
			Intubated prior to
			receiving C1-INH.
			Received C1-INH
			at approximately
			6:00 PM, the
			patient responded
			with marked
			decreased
			angioedema. The
			angioedema was

Γ	1		wated to we ask a
			noted to resolve
42. Volans A, Ferguson R. Using a bradykinin blocker in ACE inhibitor-associated angioedema in the emergency department. BMJ Case Rep. 2013 Jan 31;2013. pii: bcr2012008295. doi: 10.1136/bcr-2012-008295.	E.	Good	Noted to resolve symmetrically Case 1: Intravenous chlorpheniramine and steroids were given shortly after arrival without apparent effect. Case 2: Intravenous chlorpheniramine was given, followed by tranexamic acid and nebulised epinephrine. Following epinephrine, she suffered tachycardia mild chest pain which settled with oxygen and showed no ischaemic change on ECG. both patients were offered 'off licence' icatibant At 20min after injection, both were able to close their mouths and swallow saliva. Case 1 had a return of his voice at 30 min and case 2 patient's tongue had settled to only half the tongue being swollen. By 4
			h both were symptom-free
			symptom-free

 43. Wagner JG, Bench EM, Plantmason L. An Unusual Case of Angiotensin- Converting-Enzyme Inhibitor- Related Penile Angioedema with Evolution to the Oropharynx. West J Emerg Med. 2015 Dec;16(7):1185-7. doi: 10.5811/westjem.2015.8.28061. Epub 2015 Nov 18. 	E.	Good	52M. Penile angioedema that progressed to involve oropharynx. given diphenhydramine 50mg IV, famotidine 40mg IV, and methylprednisolone 125mg IV for possible allergic reaction versus acute onset of angioedema. He was observed in the ED for six hours, without progression or significant improvement in symptoms, and discharged home 68M treated with
44. Nishad AAN, Arulmoly K, Priyankara SAS, Abeysundara PK. A Forgotten Cause of Allergy at ER That Is Still Difficult to Diagnose and Treat at Poor Resource Setting: Angioedema after Using Angiotensin Converting Enzyme Inhibitors for 4 Years. Case Reports Immunol. 2019 Jan 2;2019:1676391. doi: 10.1155/2019/1676391. eCollection 2019.	E.	Good	intramuscular Adrenaline 0.5 mg stat and intravenous hydrocortisone 200 mg. Discharged on prednisone.

cricothyrotomy was per- formed to secure the patient's airway.
