

Cardiovascular and Diabetic Medications That Cause Bradykinin-Mediated Angioedema



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Medication-induced angioedema is a bradykinin-mediated process that results from increased production or decreased degradation of bradykinin. These reactions are documented for several cardiac medications including blockers of the renin-angiotensin-aldosterone system (RAAS). Other cardiovascular and diabetes medications further increase the risk of medication-induced angioedema, particularly with concomitant use of RAAS inhibitors. Dipeptidyl peptidase IV inhibitors are a class of oral diabetic agents that affect bradykinin and substance P degradation and therefore can lead to angioedema. Neprilysin inhibitors are a separate class of cardiac medications, which includes sacubitril, and can lead to drug-induced angioedema especially when used in combination with RAAS inhibitors. This article discusses the proposed mechanisms by which these medications cause angioedema and how medication-induced angioedema differs from mast cell-mediated angioedema. It also details how to recognize medication-induced angioedema and the treatment options available. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:610-5)

Key words: Angioedema; Bradykinin; ACE inhibitors; ARBs (angiotensin receptor blockers); Dipeptidyl peptidase IV inhibitors; Neprilysin inhibitors; Icatibant

CASE

Mr. C was a 76-year-old man who presented to the emergency department with a chief complaint of “sore throat and shortness of breath.” Two hours after he took his morning medications, he felt a “burning” sensation in his posterior pharynx, became short of breath, and noted a change in his ability to talk. Medications included fluoxetine, metoprolol, fosinopril, and pravastatin. He had a history of benign essential hypertension, hyperlipidemia, depression, and coronary artery disease. Otherwise, his medical, surgical, social, and family histories and review of symptoms were noncontributory.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 19, 2017; revised February 18, 2017; accepted for publication March 21, 2017.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.03.017>

His vital signs were normal except for a pulse oximetry of 85% to 86% on room air. He was noted to have audible stertor (low-pitched snoring or rumbling sound). There was no lip, tongue, uvula, or facial swelling. Lungs were clear. The rest of the physical examination was unremarkable.

Laboratory studies revealed a mild leukocytosis, normal differential, normal C4, and were otherwise normal. Chest x-ray was unremarkable and a computed tomography scan of the neck showed edema of the aryepiglottic folds and lateral hypopharyngeal wall bilaterally, with a reduced airway caliber. Laryngoscopy confirmed moderate edema of the arytenoids and aryepiglottic folds and poor visualization of the vocal cords.

Differential diagnosis included a systemic allergic reaction causing laryngeal edema, severe laryngitis, idiopathic angioedema, angiotensin converting enzyme inhibitor (ACEi)-mediated angioedema, and acquired C1 inhibitor deficiency.

Elective intubation was performed approximately 4 hours after his arrival. He was admitted to the intensive care unit where he received 2 units of fresh frozen plasma, methylprednisolone 125 mg IV every 8 hours, and famotidine 20 mg IV every 12 hours. He remained intubated for 1 week, after which he was weaned off the ventilator. The diagnosis was ACEi-induced angioedema secondary to fosinopril.

OVERVIEW OF ANGIOEDEMA

Angioedema is nonpitting swelling of subcutaneous and submucosal tissues due to vascular dilation and increased permeability of arterioles and venules. Mast-cell histaminergic and bradykinin-mediated etiologies are 2 mechanisms that are described below.

Mast cell-mediated angioedema

Mast cells, when perturbed, release mediators including histamine, tryptase, prostaglandin D2, and leukotriene C4, resulting in subcutaneous and cutaneous edema. Urticaria and pruritus usually accompany mast cell-mediated angioedema. It can be triggered in an allergic individual by foods, drugs, insect stings, and other allergens via IgE mediation and manifests rapidly after allergen exposure. It usually resolves over 24 to 48 hours. In systemic allergic reactions, serum tryptase, a marker of mast cell activation, may be elevated. An elevated tryptase can also be an indication of mast cell activation syndrome, or even mastocytosis, and it is used as a screening tool for these conditions in cases of unexplained anaphylaxis. Tryptase is used clinically by measuring serum levels in patients with angioedema to clarify the mechanism of the reaction.

Idiopathic angioedema is also likely histaminergic in etiology because it responds to antihistamines. Unlike bradykinin-mediated angioedema, which may be life threatening,

Abbreviations used

ACEi	Angiotensin-converting-enzyme inhibitor
ANP	A-type natriuretic peptide
APP	Aminopeptidase P
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AT2	Angiotensin type 2 receptor
B1	Bradykinin type 1 receptor
B2	Bradykinin type 2 receptor
CPN	Carboxypeptidase N
DPP-IV	Dipeptidyl peptidase IV
FFP	Fresh frozen plasma
HAE	Hereditary angioedema
NEP	Neutral endopeptidase (neprilysin)
PARADIGM-HF	Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure
RAAS	Renin-angiotensin-aldosterone system
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease

Idiopathic angioedema is usually not life threatening, even when it occurs in the laryngopharynx. However, precaution should still always be taken, as some individuals may have smaller anatomical upper airways, posing a higher potential risk of asphyxiation. It is commonly associated with urticaria.

Treatment for mast cell or histamine-mediated angioedema includes antihistamines, glucocorticoids, and also epinephrine, particularly when it is associated with the signs and symptoms of a systemic allergic reaction.

Bradykinin-mediated angioedema

This paper focuses on bradykinin-mediated angioedema, which results from the overproduction of bradykinin or the inhibition of bradykinin degradation. Mast cells are not the primary culprit, so urticaria and pruritus do not accompany this form of angioedema. The primary areas affected include the face, lips, tongue, and laryngopharynx. Bradykinin-mediated angioedema is unique in that it also may affect the gastrointestinal mucosa, causing bowel wall edema, presenting with abdominal pain, nausea, vomiting, and diarrhea.¹ This occurs in both hereditary and acquired angioedema. The 2 main etiologies of bradykinin-mediated angioedema are C1 inhibitor deficiency, either acquired or hereditary, or medication-mediated, the topic of this article.

Bradykinin and its physiologic roles

Bradykinin is a peptide composed of 9 amino acids and is a potent vasodilator, causing increased capillary permeability. It has 2 receptors, bradykinin type 1 receptor (B1) and bradykinin type 2 receptor (B2), the latter of which is constitutively expressed and participates in bradykinin's vasodilatory role. When bradykinin binds its receptor B2, downstream signaling pathways ultimately release mediators, including nitric oxide and prostaglandins. These potentiate increased vascular permeability and plasma extravasation into submucosal tissues, resulting in angioedema.^{2,3} Bradykinin is broken down by ACE, neutral endopeptidase (NEP), aminopeptidase P (APP), carboxypeptidase N (CPN), dipeptidyl peptidase IV (DPP-IV), and kininase I. One of the metabolites of bradykinin, des-Arg9-bradykinin,

stimulates the B1 receptor, which is upregulated in inflammatory states and perpetuates the effects of bradykinin.⁴ Substance P is an undecapeptide belonging to the "tachykinin" family, but like bradykinin it has vasodilatory effects.^{5,6} Figure 1 depicts pathways involved in bradykinin-mediated angioedema and medications that affect these pathways.

MEDICATION-INDUCED BRADYKININ-MEDIATED ANGIOEDEMA

Renin-angiotensin-aldosterone system (RAAS) blocker-induced angioedema

RAAS blockers, most notably ACEi and angiotensin receptor blockers (ARBs), are prescribed worldwide and reduce the morbidity and mortality from hypertension, cardiovascular disease, and diabetes.⁷ However, ACEi have an uncommon but important side effect of drug-induced angioedema. The incidence is 0.1% to 0.7% among subjects who take these medications, with up to a 5 times greater risk in Americans of African heritage.⁸⁻¹⁰ Also, ACEi are contraindicated in subjects with a history of any form of angioedema. Two thirds of ACEi-induced angioedema occurs within the first 3 months of starting these medications, but reactions may occur after many years of use.⁸ If such a reaction is not properly identified and the medication is not discontinued, the angioedema may resolve, but can once again return and become a severe or life-threatening problem.^{11,12} The proposed mechanisms or pathways involved in RAAS blocker-induced angioedema are discussed below.

Angiotensin-converting enzyme inhibitors. The classic example of drug-induced angioedema occurs with ACEi. The mechanism involves the inhibition of bradykinin degradation, leading to activation of vascular B2 receptors. Excessive amounts of bradykinin cause overactivation of B2.¹³ When ACE is inhibited, as in the use of ACEi, the other degrading enzymes play a larger role in the breakdown of bradykinin. Therefore, individuals who have decreased activity in one or more of these enzymes (ie, APP, dipeptidyl peptidase IV) have a higher risk for ACEi-induced angioedema.¹⁴ Genetic polymorphisms in these degradation enzymes may explain why Americans of African heritage are at increased risk for angioedema.¹⁵

Angiotensin II receptor blockers. A complete understanding of how ARBs cause angioedema is still uncertain. Research in human subjects suggests that ARBs increase bradykinin levels via indirect mechanisms. ARBs prevent angiotensin II from binding the angiotensin type 1 receptor, resulting in elevated angiotensin II levels. Elevated angiotensin II may stimulate angiotensin type II (AT2) receptors, which normally reduce ACE activity. Stimulation of AT2 receptors therefore may reduce ACE activity and result in increased bradykinin levels.¹⁶ ARBs are thought to cause considerably less angioedema than ACEi perhaps because they increase only bradykinin levels, whereas ACEi increase both bradykinin and kallidin levels.¹⁶ Bradykinin and kallidin are very similar molecules both derived from kininogens. Plasma kallikrein forms bradykinin from kininogens, whereas tissue kallikrein forms kallidin from kininogens. Improved endothelial function in coronary artery disease is attributed to increased levels of bradykinin and nitric oxide.^{16,17} The TRANSCEND trial ("Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease") was designed to evaluate the effectiveness of

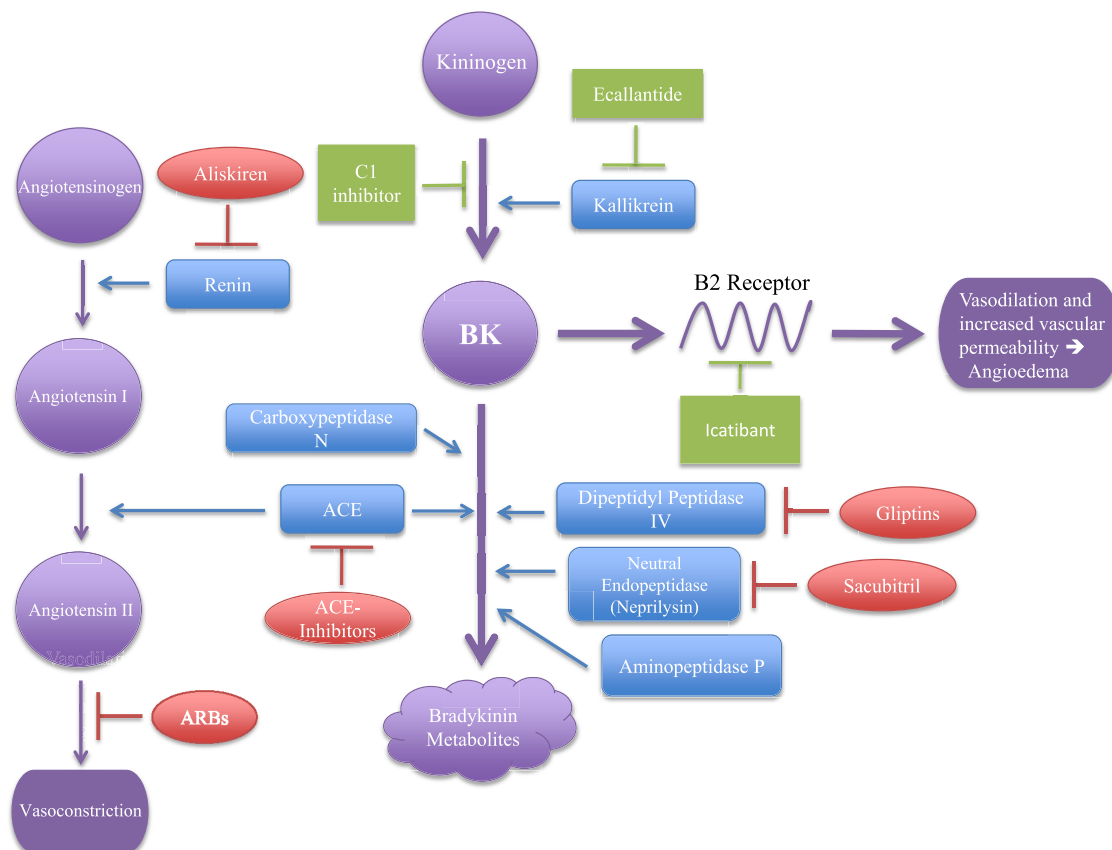


FIGURE 1. Demonstration of the pathways involved in bradykinin (BK)-mediated angioedema and the medications that target their peptidases. When the drugs in red inhibit these peptidases, they prevent the breakdown of bradykinin, allowing bradykinin to accumulate and stimulate its receptor B2, leading to vasodilation, increased vascular permeability, and angioedema. The drugs in green are inhibitors of bradykinin accumulation and can be used for the treatment of bradykinin-mediated angioedema. *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *B2*, bradykinin type 2 receptor.

ARBs in ACEi intolerant subjects.¹⁸ Subjects were deemed intolerant to ACEi for any documented reason, including angioedema and cough. The TRANSCEND trial revealed no difference in angioedema incidence among subjects taking ARBs versus other non-ACEi blood pressure medications. A meta-analysis found no significant differences in the incidence of angioedema with ARBs compared with placebo.^{18,19} Event rates of angioedema are low and difficult to measure even in large clinical trials, but a small case series of angioedema on ARBs is published.²⁰ The safety of switching subjects with ACEi-induced angioedema to an ARB is still in question. The American Academy of Allergy Asthma and Immunology practice parameters state that a “modest risk of recurrent angioedema exists” for subjects who experienced angioedema on an ACEi who are switched to an ARB.²¹ The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America “Focused Update on New Pharmacological Therapy for Heart Failure” recommends the use of ARBs in subjects with heart failure who cannot tolerate ACEi due to angioedema, but “...caution is advised because some subjects have also developed angioedema with ARBs.”²² Some studies find an increased risk of recurrence as high as 17%; however, this increased rate may be deceiving given the fact that recurrent episodes of angioedema

can occur even weeks to months after stopping ACEi.^{11,23} In addition, there is no test to distinguish between ACEi-induced angioedema and idiopathic angioedema, so a subject who experiences angioedema on both ACEi and ARBs may in fact have idiopathic angioedema.

Renin inhibitors. The renin inhibitor aliskiren, an antihypertensive agent, has a more global effect on the RAAS pathway by inhibiting the first step, the conversion of angiotensinogen to angiotensin I.¹⁹ It is not clear why aliskiren may cause angioedema. It decreases angiotensin I and II levels as a direct renin inhibitor, but it does not appear to affect bradykinin levels or ACE.²⁴ A meta-analysis found a 0.4% incidence of angioedema in subjects treated with aliskiren.^{25,26} Aliskiren is not commonly prescribed secondary to its side effect profile, which includes hyperkalemia, renal impairment, nonfatal stroke, and hypotension.²⁷

NEW DRUGS INDUCING ANGIOEDEMA VIA A BRADYKININ-ASSOCIATED MECHANISM

The process of bradykinin degradation involves more than just ACEi. Drugs that affect NEP, CPN, and DPP-IV also increase susceptibility to angioedema. Table 1 includes medications that

TABLE I. Medications that cause bradykinin-mediated angioedema

Category	Medications	Brand names
ACE inhibitors	Lisinopril	Prinivil (Merck, Whitehouse Station, NJ)
	Enalapril	Vasotec (Valeant, Bridgewater, NJ)
	Captopril	Capoten (Bristol-Myers Squibb, New York, NY)
	Fosinopril	Monopril (Bristol-Myers Squibb, New York, NY)
	Ramipril	Altace (Pfizer, New York, NY)
	Quinapril	Accupril (Pfizer, New York, NY)
	Benazepril	Lotensin (Validus, Parsippany, NJ)
	Perindopril	Aceon (Symplmed, Cincinnati, Ohio)
	Trandolapril	Mavik (AbbVie, Chicago, Ill)
	Moexipril	Univasc (UCB, Belgium)
DPP-IV inhibitors	Sitagliptin	Januvia (Merck, Whitehouse Station, NJ)
	Saxagliptin	Onglyza (AstraZeneca, Wilmington, Del)
	Vildagliptin	Galvus (Novartis, Switzerland)
	Linagliptin	Tradjenta (Boehringer Ingelheim, Germany)
	Alogliptin	Nesina (Takeda, Japan)
Neprilysin inhibitors	Sacubitril (used in combination with valsartan)	Entresto (Novartis, Switzerland)
ARBs	Losartan	Cozaar (Merck, Whitehouse Station, NJ)
	Valsartan	Diovan (Novartis, Switzerland)
	Telmisartan	Micardis (Boehringer Ingelheim, Germany)
	Candesartan	Atacand (AstraZeneca, Wilmington, Del)
	Irbesartan	Avapro (Bristol-Myers Squibb, New York, NY)
	Olmesartan	Benicar (Daiichi Sankyo, Japan)
	Azilsartan	Edarbi (Arbor, Atlanta, Ga)
	Eprosartan	Teveten (Abbott, Chicago, Ill)
Renin inhibitor combinations	Aliskiren/amlodipine	Tekamlo (Novartis, Switzerland)
	Aliskiren/valsartan	Valturna (Novartis, Switzerland)—off market
	Aliskiren/amlodipine/HCTZ	Amturnide (Novartis, Switzerland)

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-IV, dipeptidyl peptidase IV; HCTZ, hydrochlorothiazide.

can cause bradykinin-mediated angioedema. Several cardiovascular and diabetes medications interfere with these pathways. The DPP-IV inhibitors, as well as neprilysin inhibitors and combination agents, are discussed below.

Dipeptidyl peptidase IV inhibitors

DPP-IV inhibitors known as the “gliptins,” including sitagliptin, linagliptin, and saxagliptin, are oral agents used to manage type 2 diabetes. They inhibit the degradation of incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic peptide).²⁸ However, DPP-IV is also involved in the breakdown of substance P, and DPP-IV inhibition may cause angioedema. Many subjects with diabetes on these medications also have cardiovascular disease for which they take an ACEi. In a meta-analysis of subjects taking both vildagliptin and an ACEi, the risk of angioedema is amplified more than fourfold when compared with taking an ACEi alone.²⁹ Although the risk of angioedema is unknown using DPP-IV inhibitors alone, there may be an increased risk when combined with ACEi.^{30,31} Although DPP-IV plays a role in the breakdown of both bradykinin and substance P, studies suggest that when ACE is inhibited, DPP-IV plays a larger role in the inactivation of substance P.²⁹ DPP-IV inhibitors theoretically allow for more binding of substance P to its neurokinin receptor 1, resulting in increased vascular permeability.³²

Neprilysin inhibitors

Neprilysin, also known as NEP, is a zinc-dependent metalloprotease that breaks down multiple different peptides: endothelin, amyloid beta, angiotensin I and II, A-type natriuretic peptide (ANP), B-type natriuretic peptide, and kinins including bradykinin and substance P. Inhibitors of neprilysin are used for subjects with systolic heart failure.³³ The clinical trial PARADIGM-HF (“Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitors with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure”) demonstrates that the combination of an ARB, valsartan, with a neprilysin inhibitor, sacubitril, has superior outcomes to enalapril alone in subjects with systolic heart failure. Sacubitril/valsartan reduced the primary outcomes of hospitalization rates for heart failure and death by 20%.³³ However, sacubitril/valsartan also increased the risk of angioedema, almost double that observed in the enalapril group. This risk was also reflected in additional studies comparing sacubitril/valsartan with other ACEi and ARBs.³⁴⁻³⁶ As mentioned above, neprilysin has a role in the breakdown of bradykinin, so inhibitors of neprilysin theoretically could lead to increased bradykinin levels. The combination of valsartan with sacubitril may cause bradykinin overactivation via its receptor B2. Alternatively, neprilysin inhibitors may block the breakdown of ANP, which also may mediate nitric oxide release and vasodilation, leading to angioedema.³⁷

Other combination drugs

There are 2 additional combination drugs for hypertension that may be associated with an increased risk of angioedema. Aliskiren/amlodipine and aliskiren/valsartan are renin inhibitors combined with a calcium channel blocker or an angiotensin receptor blocker, respectively. Although there are no specific studies to indicate an increased risk of angioedema, aliskiren alone is implicated in an increased incidence of this complication.^{21,26} Therefore, physicians and other health care professionals should be aware that these combination drugs may also cause angioedema. Aliskiren/valsartan was removed from the US market in 2012 secondary to undesirable side effects unrelated to angioedema.

INTERVENTIONS

Management of bradykinin-mediated angioedema is different from mast cell-mediated angioedema. In severe cases, airway management may include intubation, as in the patient described in this report. Medications commonly used to treat histamine-induced angioedema include epinephrine, antihistamines, and glucocorticoids. These medications are not indicated in bradykinin-mediated angioedema, even though they are commonly prescribed, especially when idiopathic or mast cell-mediated angioedema cannot be ruled out.

Icatibant, a synthetic B2-receptor antagonist used to treat hereditary angioedema (HAE), can also be used to treat ACEi-induced angioedema.^{38,39} Although it is currently not licensed for this purpose, case reports as well as a phase II study of subjects who received icatibant for ACEi-induced angioedema had a similar time to reduction of symptoms as occurred with icatibant use in cases of HAE.³⁷ Additional large randomized phase III trials are underway. Ecallantide, which inhibits plasma kallikrein, thus decreasing the conversion of kininogen to bradykinin, is another medication FDA approved for HAE. However, good evidence for its use in ACEi-induced angioedema is lacking. Phase II and III studies found no benefit for its use compared with placebo in subjects with mild-to-moderate presentations of ACEi-induced angioedema.⁴⁰ Fresh frozen plasma (FFP), which contains kininase II (identical to ACE), degrades bradykinin, allowing for resolution of angioedema.¹⁵ Evidence for its benefit in ACEi-induced angioedema is supported by case reports and series; however, a lack of controlled data makes it difficult to state its efficacy. In the above case report, the patient received 2 units of FFP because icatibant was not available. FFP may have accelerated resolution of his angioedema, as a leak was noted around his endotracheal tube the following day, suggesting improvement. However, he was not able to be weaned off mechanical ventilation for several more days. Purified C1 inhibitor concentrate also has been investigated for use in bradykinin-mediated angioedema. It is approved for HAE and inhibits conversion of kininogen to bradykinin. Support for its use in ACEi-induced angioedema is only in case reports, but a phase III study is in progress.⁴⁰ In most cases of medication-induced bradykinin-mediated angioedema, discontinuing the medication and tincture of time are sufficient. Epinephrine, oral antihistamines, and glucocorticoids, as previously discussed, probably do not influence the outcome of bradykinin-mediated angioedema, although they are commonly utilized. Although not yet applied to practice, there are several studies utilizing the measurement of plasma bradykinin in subjects with ACEi-

induced angioedema. Circulating bradykinin levels were high while on therapy but decreased after discontinuation of the ACEi and recovery.⁴¹ Looking to the future, this could be a useful tool to diagnose and treat bradykinin-mediated angioedema.

CONCLUSIONS

Medication-induced angioedema is caused by increased production or decreased breakdown of vasoactive peptides including bradykinin and substance P. Medications increase vasoactive peptides in various ways. ACEi and neprilysin inhibitors prevent bradykinin breakdown. DPP-IV inhibitors reduce the breakdown of substance P and bradykinin. ARBs may indirectly increase bradykinin levels by increasing angiotensin II, which may decrease ACE activity. Aliskiren is a direct renin inhibitor, and the mechanism by which it may cause angioedema is unknown. The mechanisms of medication-induced angioedema require further research. As this case report illustrates, medication-induced angioedema can be severe. The patient showed response to FFP, but icatibant may have been a better alternative.

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