



EDUCATIONAL OBJECTIVE: Readers will weigh the risks and possible benefits of substituting an angiotensin receptor blocker for an angiotensin-converting enzyme inhibitor after angioedema



**BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS**

Q: Can an ARB be given to patients who have had angioedema on an ACE inhibitor?

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A: CURRENT EVIDENCE SUGGESTS no absolute contraindication to angiotensin receptor blockers (ARBs) in patients who have had angioedema attributable to an angiotensin-converting enzyme (ACE) inhibitor. However, since ARBs can also cause angioedema, they should be prescribed with extreme caution after a thorough risk-benefit analysis and after educating the patient to watch for signs of angioedema while taking the drug.

■ A GROWING PROBLEM

Angioedema is a potentially life-threatening swelling of the skin and subcutaneous tissues, often affecting the lips and tongue (FIGURE 1), and in some cases interfering with breathing and requiring tracheostomy.¹ The incidence rate of angioedema in patients taking ACE inhibitors ranges from 0.1% to 0.7%.²⁻⁴ Although this rate may seem low, the widespread and growing use of ACE inhibitors and ARBs in patients with diabetes, diabetic nephropathy, and congestive heart failure⁵ makes angioedema fairly common in clinical practice.

ACE inhibitor-induced angioedema most commonly occurs within days of initiating therapy, but it also may occur weeks, months, or even years after the start of treatment.¹ Patients who are over age 65, black, or female are at higher risk, as are renal transplant recipients taking mTOR inhibitors such as sirolimus. Diabetes appears to be associated with



FIGURE 1. Angioedema affecting the tongue in a man taking an angiotensin-converting enzyme inhibitor. Involvement of the lips and the tongue can be life-threatening, requiring tracheostomy.

a lower risk.^{4,6,7} This adverse reaction to ACE inhibitors is thought to be a class side effect, and the future use of this class of drugs would be contraindicated.^{8,9}

ACE inhibitors cause angioedema by direct interference with the degradation of bradykinin, thereby increasing bradykinin levels and potentiating its biologic effect, leading to increased vascular permeability, inflammation, and activation of nociceptors.⁸

■ EVIDENCE TO SUPPORT THE USE OF ARBs

ACE inhibitors and ARBs both block the renin-angiotensin-aldosterone pathway and confer similar advantages in patients with congestive heart failure, renal failure, and diabetes. But since ARBs directly inhibit the

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angiotensin receptor and do not interfere with bradykinin degradation, how they cause angioedema is unclear, and clinicians have questioned whether these agents might be used safely in patients who have had angioedema on an ACE inhibitor.

In a large meta-analysis of randomized clinical trials, Makani et al² investigated the risk of angioedema with ARB use in 35,479 patients and compared this with other commonly used antihypertensive drugs. The weighted incidence of angioedema was 0.30% with an ACE inhibitor, 0.11% with an ARB, and 0.07% with placebo.² In seven trials included in this study that compared ARBs with placebo, there was no significant difference in the risk of angioedema. Even in such a large study, the event rate was small, making definite conclusions difficult.

In a retrospective observational study of 4 million patients by Toh et al,³ patients on beta-blockers were used as a reference, and propensity scoring was used to estimate the hazard ratio of angioedema separately for drugs targeting the renin-angiotensin-aldosterone system, including ACE inhibitors and ARBs. The risk of angioedema, as measured by the cumulative incidence and incidence rate, was highest for ACE inhibitors and was similar between ARBs and beta-blockers. The risk of serious angioedema was three times higher with ACE inhibitors than with beta-blockers, and there was no higher risk of serious angioedema with ARBs than with beta-blockers.³

Looking specifically at the use of ARBs in patients who developed angioedema on an ACE inhibitor, Haymore et al¹⁰ performed a meta-analysis evaluating only three studies that showed the estimated risk of angioedema with an ARB was between 3.5% and 9.4% in patients with a history of ACE inhibitor-induced angioedema. Later, when the results of the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease trial¹¹ were published, the previous meta-analysis was updated¹²: the risk of angioedema with an ARB was only 2.5% (95% confidence interval 0%–6.6%), and there was no statistically significant difference in the odds (odds ratio 1.1; 95% confidence interval 0.07–17) of angioedema between ARBs and placebo.^{10,12} Again, these results

should be interpreted with caution, as only two patients in the ARB (telmisartan) group and three patients in the placebo group developed angioedema.

In another review, Beavers et al¹³ advised that the prescribing practitioner should carefully perform a risk-benefit analysis before substituting an ARB in patients with ACE inhibitor-induced angioedema. They concluded that an ARB could be considered in patients who are likely to have a large clinical benefit from an ARB, such as those with heart failure. They also suggested that angioedema related to ARBs was less severe and occurred earlier than with that linked to ACE inhibitors.

No large clinical trial has yet been specifically designed to address the use of ARBs in patients with a history of ACE inhibitor-induced angioedema. The package insert for the ARB losartan mentions that the risk of this adverse reaction might be higher in patients who have had angioedema on an ACE inhibitor. However, the issue of recurrent angioedema is not further addressed for this or other commonly used ARBs.

GENERAL RECOMMENDATIONS

The mechanisms of ARB-induced angioedema are yet unknown. However, studies have shown that the incidence of angioedema while on an ARB is low and is probably comparable to that of placebo.^{2,3,12–14} And since ARBs share many of the cardiac and renal protective effects of ACE inhibitors, ARBs may be beneficial for patients who discontinue an ACE inhibitor because of adverse effects including angioedema.^{9,15,16} Based on the discussion above, there is no clear evidence to suggest that ARBs are contraindicated in such patients, especially if there is a compelling indication for an ARB.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines on hypertension in chronic kidney disease recommend caution when substituting an ARB for an ACE inhibitor after angioedema.¹⁵ The joint guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) for the diagnosis and management of heart failure in adults advise “extreme caution.”^{9,16}

The widespread use of ACE inhibitors makes angioedema fairly common in clinical practice

The risks and benefits of ARB therapy in this setting should be analyzed by the prescribing physician and discussed with the patient. The patient should be closely monitored for the recurrence of angioedema and should be given a clear plan of action should symptoms recur.

■ OUR ADVICE

In patients with ACE inhibitor-induced angioedema, we recommend the following:

- Determine that the patient truly has one of the evidence-based, compelling indica-

tions for an ARB. Carefully weigh the risks and benefits for the individual patient, and discuss the risk of angioedema based on age, race, sex, and medical history, and the availability of immediate medical care should angioedema occur.

- If there is an evidence-based indication for an ARB that outweighs the risk of angioedema, an ARB may be started with caution.
- Specifically discuss with the patient the possibility of recurrence of angioedema while on an ARB, and provide instructions on how to proceed if this should occur. ■

■ REFERENCES

1. Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005; 53:373–388.
2. 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; 110:383–391.
3. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012; 172:1582–1589.
4. Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med* 2005; 165:1637–1642.
5. Taylor AA, Siragy H, Nesbitt S. Angiotensin receptor blockers: pharmacology, efficacy, and safety. *J Clin Hypertens (Greenwich)* 2011; 13:677–686.
6. Duerr M, Glander P, Diekmann F, Dragun D, Neumayer HH, Budde K. Increased incidence of angioedema with ACE inhibitors in combination with mTOR inhibitors in kidney transplant recipients. *Clin J Am Soc Nephrol* 2010; 5:703–708.
7. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006; 26:725–737.
8. Inomata N. Recent advances in drug-induced angioedema. *Allergol Int* 2012; 61:545–557.
9. Hunt SA, Abraham WT, Chin MH, et al; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; 53:e1–e90.
10. 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; 101:495–499.
11. Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; 372:1174–1183.
12. Haymore BR, DeZee KJ. Use of angiotensin receptor blockers after angioedema with an angiotensin-converting enzyme inhibitor. *Ann Allergy Asthma Immunol* 2009; 103:83–84.
13. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. *Ann Pharmacother* 2011; 45:520–524.
14. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. *Am J Cardiovasc Drugs* 2012; 12:263–277.
15. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43(suppl 1):S1–S290.
16. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011; 58:2432–2446.

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Discuss with the patient the possibility of recurrence of angioedema while on an ARB