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# Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

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**Background:** Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are known to cause angioedema.

**Objective:** To evaluate the time to onset of angioedema and the subsequent episodes of angioedema in patients initially experiencing ACE-I- or ARB-induced angioedema.

**Methods:** A manual medical record review was conducted on 64 patients with a diagnosis of urticaria, angioedema, or anaphylaxis as a result of taking an ACE-I or ARB. Data recorded included demographic characteristics; time to onset of symptoms; concomitant medication use; laboratory test results; recurrent episodes of angioedema, urticaria, or anaphylaxis; and morbidity and mortality.

**Results:** The mean age of patients with angioedema was 60.2 years (age range, 32–92 years). Women (60%) and African Americans (69%) were affected more commonly. The primary location for angioedema was the lips and tongue. Sixty-one of 64 patients developed at least one episode of angioedema as the result of taking an ACE-I, and 3 patients had angioedema associated with an ARB. The mean time to onset of angioedema after initiation of therapy in 51 patients was 1.8 years, with 13 patients (25%) presenting within the first month and 6 patients (12%) developing angioedema in the first week. No patients required a tracheostomy or died. Also, none of the 6 patients, whose angioedema was attributed to an ACE-I who then received an ARB, developed recurrent angioedema in more than 8.1 patient-years of follow-up.

**Conclusions:** Angioedema attributable to an ACE-I or ARB resolves on discontinued use of the medication. It most commonly affects women and African Americans and did so in the first month of treatment in 25% of patients. Physicians should be aware but not deterred necessarily from recommending an ARB in patients with ACE-I-induced angioedema because of the benefits of control of hypertension or reducing albuminuria in selected patients.

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## INTRODUCTION

Angioedema is a deep swelling of the tissues just below the skin and mucous membranes. It is often characterized by nonpitting asymmetric swelling that is usually nonpruritic.<sup>1</sup> Most commonly, this swelling occurs in the perioral area, periorbital area, tongue, genital area, and extremities.<sup>1</sup>

Angiotensin-converting enzyme inhibitors (ACE-Is) are indicated in the treatment of hypertension, congestive heart failure, coronary artery disease, and diabetic nephropathy<sup>2</sup> and have been known to cause angioedema.<sup>3</sup> Various studies suggest that the incidence of angioedema is between 0.1% and 2.2%.<sup>4,5</sup> With increasing indications for these medications and their use becoming more widespread, the purpose of this study was to characterize the patients and their reactions to ACE-I- and angiotensin receptor blocker (ARB)-related angioedema at our institution during a 13-year period. We sought to determine the time to onset of angioedema and the

natural history of cases, including whether angioedema recurred or was associated with subsequent administration of an ACE-I or ARB.

## METHODS

Patients selected for the study were those with a diagnosis of adverse reaction or allergy to ACE-Is or ARBs as identified by an adverse reaction E-Code between January 1991 and May 2004 using the pharmacy database at Northwestern Memorial Hospital, a 1,106-bed academic tertiary care medical center in Chicago, IL. It is the responsibility of the Pharmacy and Therapeutics Committee at Northwestern Memorial Hospital to track adverse reactions for review and to implement changes to prevent or reduce future adverse reactions. The medical record coder reviews all hospital medical records and assigns all adverse reactions an E-code. The information suggestive of an adverse drug reaction (angioedema, urticaria, anaphylaxis, hyperkalemia, hypotension) is identified either from a physician or nurse entry into the medical record or, if not recorded as an adverse drug reaction, still identified by the medical records coder. For this study, the database of all adverse reactions (using E-codes) was analyzed to search for adverse reactions to ACE-Is and ARBs. This search identified 287 patients with adverse drug

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reactions suspected to be caused by ACE-Is and/or ARBs. These reactions consisted of decrease in renal function, hypotension, cough, near syncope, and hyperkalemia. The resulting list was refined based on limiting the analysis to cases labeled as angioedema, urticaria, or anaphylaxis. A manual review of the paper, microfiche electronic record, or electronic record was performed for all cases.

Northwestern Memorial Hospital uses 2 electronic medical records, Cerner PowerChart (Kansas City, MO) and Epic (Madison, WI). Cerner PowerChart is used primarily to record data on inpatients. Dictations were implemented to interface with this system in April 1998 and daily medical progress notes in July 2004. The general medicine clinic began using Epic in 1996; this system was implemented in the Division of Allergy-Immunology in February 2004.

For each case, data were recorded, including demographic characteristics, time to onset of symptoms, concomitant medication use, laboratory tests (with emphasis on complement), indication for ACE-I or ARB use, and particular medication causing the adverse drug reaction. The medical records from the hospital and outpatient electronic records were reviewed to search for subsequent episodes of angioedema, urticaria, or anaphylaxis and future use of ACE-Is or ARBs. Mortality and morbidity also were recorded. Approval for this study was obtained from the Office for the Protection of Research Subjects at Northwestern University.

## RESULTS

### *Patient Characteristics*

All 64 patients presented to the emergency department with angioedema of whom 2 patients also had localized urticaria. The mean age of patients was 60.2 years, with a range of 32 to 92 years (Table 1). Sixty percent of patients were women. Patients of African American descent (69%) were more commonly affected with angioedema than whites (23%) and Hispanics (2%). However, African Americans constituted only approximately 20% of the patients admitted to our hospital during this 13-year period. Sixty-one of 64 patients experienced angioedema associated with an ACE-I, and 3 patients developed angioedema from an ARB. It was not possible to determine if any of these 3 patients had previously experienced angioedema from an ACE-I.

Concomitant use of a nonsteroidal anti-inflammatory medication or aspirin was found in 24 (38%) of the 64 patients who developed angioedema attributed to an ACE-I or ARB. Two patients were identified as previously having had a cough while taking an ACE-I (the first patient had a cough the day before developing angioedema, and the second patient had experienced angioedema attributable to fosinopril and then received ramipril, which induced cough). One patient had experienced angioedema in the absence of an ACE-I or ARB and then developed it again from an ACE-I.

A history of angioedema attributed to an ACE-I was identified in 4 patients. Two patients had 2 prior episodes, and 2 patients had 1 prior episode. Similar to a prior study, 22% of

Table 1. Characteristics of 64 Patients With ACE-I- or ARB-Induced Angioedema

Characteristics	No. (%) of patients*
Age, y	
Mean	60.2
Median	59
Range	32–92
Sex	
Male	26 (40)
Female	38 (60)
Race	
African American	44 (69)
White	15 (23)
Hispanic	2 (3)
Other and unknown	3 (5)
Indication for use of ACE-I or ARB	38
Hypertension alone	19
Hypertension and diabetes	9
Coronary artery disease or congestive heart failure	10
Unspecified	26
Concomitant specific medication use	31
NSAID or aspirin	24 (38)
Cyclo-oxygenase 2 inhibitor	4 (6)
Opiate	3 (5)
Other medication allergy	14†
Penicillin	9 (14)
Clindamycin	2 (3)
Sulfonamide	2 (3)
Radiocontrast material	2 (3)
Rofecoxib	1 (2)
Azithromycin	1 (2)
Cough with ACE-I	2
Previous episodes of angioedema while receiving ACE-I	4
Previous episode of angioedema before use of ACE-I	1

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

\* Data are presented as number (percentage) of patients unless otherwise indicated.

† Some patients were labeled as allergic to more than one medication.

our patients reported an allergy to other medications, of which penicillin was the most common<sup>6</sup> (Table 1).

### *Treatment*

Nine patients (14%) received epinephrine administered as 0.3 mg subcutaneously in the emergency department. Two patients from this group received a second dose. All 9 patients received methylprednisolone, 60 mg, and diphenhydramine, 50 mg, intravenously. Overall, 63 patients (98%) received either intravenous or oral corticosteroids and diphenhydramine.

### *Incriminated ACE-Is or ARBs*

As indicated in Table 2, we found that lisinopril (50%), enalapril (20%), and quinapril (6%) were incriminated as causes of angioedema in 76% of the patients with ACE-I

Table 2. ACE-Is and ARBs Considered to Cause Angioedema From 1991 to 2004\*

Drug	No. (%) of patients with angioedema
Lisinopril	32 (50)
Enalapril	12 (20)
Quinapril	4 (6)
Ramipril	4 (6)
Fosinopril	4 (6)
Benazepril	2 (3)
Captopril	2 (3)
Enalapril	2 (3)
Irbesartan	1 (2)
Candesartan	1 (2)
Losartan	1 (2)

Abbreviations: ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

\* At Northwestern Memorial Hospital, lisinopril has been the most commonly prescribed ACE-I for inpatients (29%) followed by ramipril (15%) and enalapril (13%) during 2001 to 2003.

angioedema at Northwestern Memorial Hospital. Lisinopril was the ACE-I most commonly prescribed to inpatients. This observation may account for the increased prevalence of angioedema from this medication at this hospital.

#### *Clinical Features of Reactions Attributed to an ACE-I or ARB*

Our analysis shows that from the time an ACE-I or ARB is initiated to the time of presentation for angioedema to a hospital varied from 1 day to more than 10 years. The mean time for 51 patients, in whom data were available, was 1.8 years. Angioedema presented within the first month in 25% of cases, of which 12% of cases occurred within the first week.

As presented in Table 3, 41 (64%) of the 64 patients had isolated angioedema at presentation. The most commonly affected area of angioedema was above the neck. In our patient population, 61% of cases had angioedema of the lips and 33% had angioedema of the tongue. One person had swelling of the feet in association with facial and hand swelling. This 45-year-old African American man had been using enalapril and received ibuprofen 15 minutes before the onset of acute swelling of the feet, face, and hands. Pruritus and urticaria were extremely uncommon, being present in 2 patients who also had angioedema.

Thirteen patients (20%) were admitted to the medical intensive care unit. Of these patients, 2 were intubated, and no patients required a tracheostomy to maintain their airway. There were no fatalities from the episode of acute angioedema attributable to an ACE-I or ARB.

#### *Follow-up of Patients Who Received an ACE-I or ARB*

Follow-up information from electronic and paper records was available for 28 patients whose initial reaction was considered attributable to an ACE-I or ARB. Seventeen patients, whose initial reaction was associated with an ACE-I, never received another ACE-I or an ARB for more than 2.8 patient-years. None of these patients developed angioedema accord-

Table 3. Clinical Features of Acute Angioedema Attributed to an ACE-I or ARB

Features	No. (%) of patients*
Time to angioedema presentation after starting ACE-I or ARB therapy	
Range	1 day to >10 y
Mean for 51 patients, y	1.8
≤1 month	13 (25)
First week	6 (12)
1 mo to 1 y	18 (35)
>1 y	14 (28)
Locations of isolated angioedema (n = 64)	
Lips	21
Tongue	13
Face	3
Throat	4
Feet	0
Hands	0
Unknown	1/42
Other locations of angioedema (n = 64)	
Lips	18
Tongue	8
Face	12
Throat	8
Feet	1
Hands	2
Unknown	0/49
Urticaria and angioedema	2
Pruritus and angioedema	5
Admissions to the medical intensive care unit	13
Intubated	2
Tracheostomy	0
Deaths	0
Follow-up after the presenting episode	28
Not receiving ACE-I or ARB	20
Using an ARB	6
Episodes of subsequent angioedema	0 (8.1 patient-years)
Using another ACE-I	2
Episodes of subsequent angioedema	0 (0.6 patient-years)
Complement assessed and found to be normal	11

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

\* Data are presented as number (percentage) of patients unless otherwise indicated.

ing to the records. Six patients who developed angioedema to an ACE-I received an ARB, and none developed angioedema after 8.1 patient-years. Two additional patients received a different ACE-I, and neither patient developed angioedema after 7 months. None of the 3 patients who had an episode of angioedema believed to be attributable to an ARB received another ARB or an ACE-I for more than 1.3 patient-years. These patients did not have additional angioedema according to the medical record review.

## DISCUSSION

The major findings in our study were as follows: (1) female and African American patients had an increased predomi-

nance of angioedema from an ACE-I or ARB, (2) the location of angioedema was above the neck and predominantly the tongue and lips, (3) urticaria and pruritus were rare clinical findings in patients with ACE-I- and ARB-induced angioedema and did not occur without angioedema, (4) only 25% of patients presented with angioedema within the first month of initiating an ACE-I or ARB, (5) just one patient had a history of angioedema before initiation of an ACE-I or ARB, (6) none of the 6 patients who had developed ACE-I-associated angioedema experienced angioedema from an ARB, and (7) there were no fatalities or tracheostomies performed at our institution in the 13 years that were reviewed in this study.

The mechanism of angioedema from an ACE-I or ARB has been elucidated in part. Substrates for ACE include angiotensin I, bradykinin, and substance P. It has been thought that the angioedema is attributable to an increase in bradykinin and its reactive metabolite, des-Arg bradykinin.<sup>7</sup> In the kinin pathway, high-molecular-weight kininogen comes into contact with a negatively charged surface. Activated Hageman factor then cleaves kininogen to form kallikrein, which degrades high-molecular-weight kininogen to form bradykinin, which activates bradykinin 2 receptors to induce vessel dilation and increase vascular permeability.<sup>8</sup> Bradykinin is degraded via its major pathway to inactive byproducts by both angiotensin-converting enzyme (ACE) and x-pro aminopeptidase (APP). If ACE is not present, then a minor pathway uses carboxypeptidase N to degrade bradykinin to des-Arg bradykinin.<sup>7</sup> The des-Arg bradykinin acts on inducible bradykinin 1 receptors to cause vasodilation and is degraded to its inactive byproducts using ACE and APP<sup>9</sup> (Fig 1). In ACE-I-induced angioedema, Molinaro et al<sup>7</sup> reported that the half-life of des-Arg bradykinin is increased and may contribute to angioedema. The half-life in patients who had experienced ACE-I angioedema was 60 minutes compared with 37 minutes in patients who had not developed angioedema.<sup>7</sup> In addition, Adam et al<sup>9</sup> demonstrated that APP activity was reduced in patients with ACE-I-associated angioedema. Both of these mechanisms could lead to accumulation of des-Arg bradykinin, which can cause the angioedema that occurs in patients with ACE-I-induced angioedema.<sup>7,9</sup>

Anderson and de Shazo<sup>10</sup> reported the importance of bradykinin as a key mediator of ACE-I angioedema using *in vivo* studies. Healthy subjects were skin tested with histamine, codeine, and bradykinin before and 1 hour after administration of captopril, 25 mg. There was no change in the wheal or erythema for histamine, but the wheal size was increased with codeine and bradykinin.<sup>10</sup> Five of 10 subjects developed transient facial flushing that began 2 to 3 minutes after the bradykinin injections.<sup>10</sup>

Lefebvre et al<sup>11</sup> suggested that bradykinin may not be the only mediator responsible for ACE-I angioedema. Levels for dipeptidyl peptidase IV were significantly decreased in patients with ACE-I-induced angioedema.<sup>11</sup> This enzyme degrades substance P, and its reduced activity may lead to an

accumulation of substance P, causing increased vascular permeability and leakage of plasma proteins.<sup>11</sup>

Our study showed that females and African Americans were more commonly affected by angioedema from an ACE-I or ARB. Similar results have been reported by Sondhi et al,<sup>12</sup> who found that 64% of patients with ACE-I angioedema were female and 91% were African American. The higher incidence of angioedema in African Americans might be due to having lower levels of bradykinin than whites as shown by decreased urinary kallikrein<sup>13</sup> but greater sensitivity to bradykinin.<sup>14</sup>

A number of studies have reported that angioedema from an ACE-I or ARB predominantly affects the head and neck.<sup>4,12,15,16</sup> We found similar findings. In our study, the lips and tongue were affected most commonly. Pruritus and urticaria rarely occurred with angioedema secondary to an ACE-I or ARB,<sup>12</sup> and our data concurred. In addition, Chiu et al<sup>15</sup> reported that no patients demonstrated symptom progression after treatment was initiated, and within 48 hours, most patients' angioedema will resolve. Only cases with significant tongue and oropharyngeal edema take more than 48 hours to resolve.<sup>15</sup>

Unlike Vleeming et al<sup>4</sup> and Agah et al,<sup>17</sup> who reported that 60% and 53% of patients experienced angioedema in the first week of initiating use of an ACE-I, we found that to be the case in just 9% of cases. However, 25% of patients presented within 1 month of starting therapy with an ACE-I or ARB. This observation is similar to the findings of Brown et al,<sup>18</sup> who found 22% of patients developed angioedema within the first month of starting use of an ACE inhibitor.

In 1990, Orfan et al<sup>19</sup> reported 4 cases of ACE-I-induced severe angioedema in patients with a prior history of idiopathic angioedema. We found one similar case. Four patients had angioedema attributable to an ACE-I before the episode that brought them to the hospital. In one patient, other factors were thought to cause the angioedema, for example, fruit ingestion. In others, the reaction may have been mild and the patients did not seek medical attention. It is possible that in 2 cases, the lack of temporal relation between initiating use of an ACE-I and developing angioedema may have led to its use not being discontinued. This finding is similar to the observations of Brown et al.<sup>18</sup>

Some authors advocate not prescribing an ARB in patients with a history of angioedema attributable to an ACE-I.<sup>20-22</sup> The most convincing data come from patients who have experienced angioedema from both an ARB and ACE-I. Warner et al<sup>21</sup> reported that 32% of patients with angioedema attributable to an ARB had a previous reaction to an ACE-I. Their group therefore recommended extreme caution when prescribing an ARB to a patient with ACE-I-related angioedema. However, Cicardi et al<sup>23</sup> reported that only 2 patients (8%) developed angioedema from an ARB from a group of 26 patients with ACE-I-associated angioedema.<sup>23</sup> In a study of 2,028 patients with congestive heart failure, the ARB candesartan or placebo was administered to patients who had been intolerant of ACE-Is.<sup>24</sup> Thirty-nine (3.8%) of 1,013

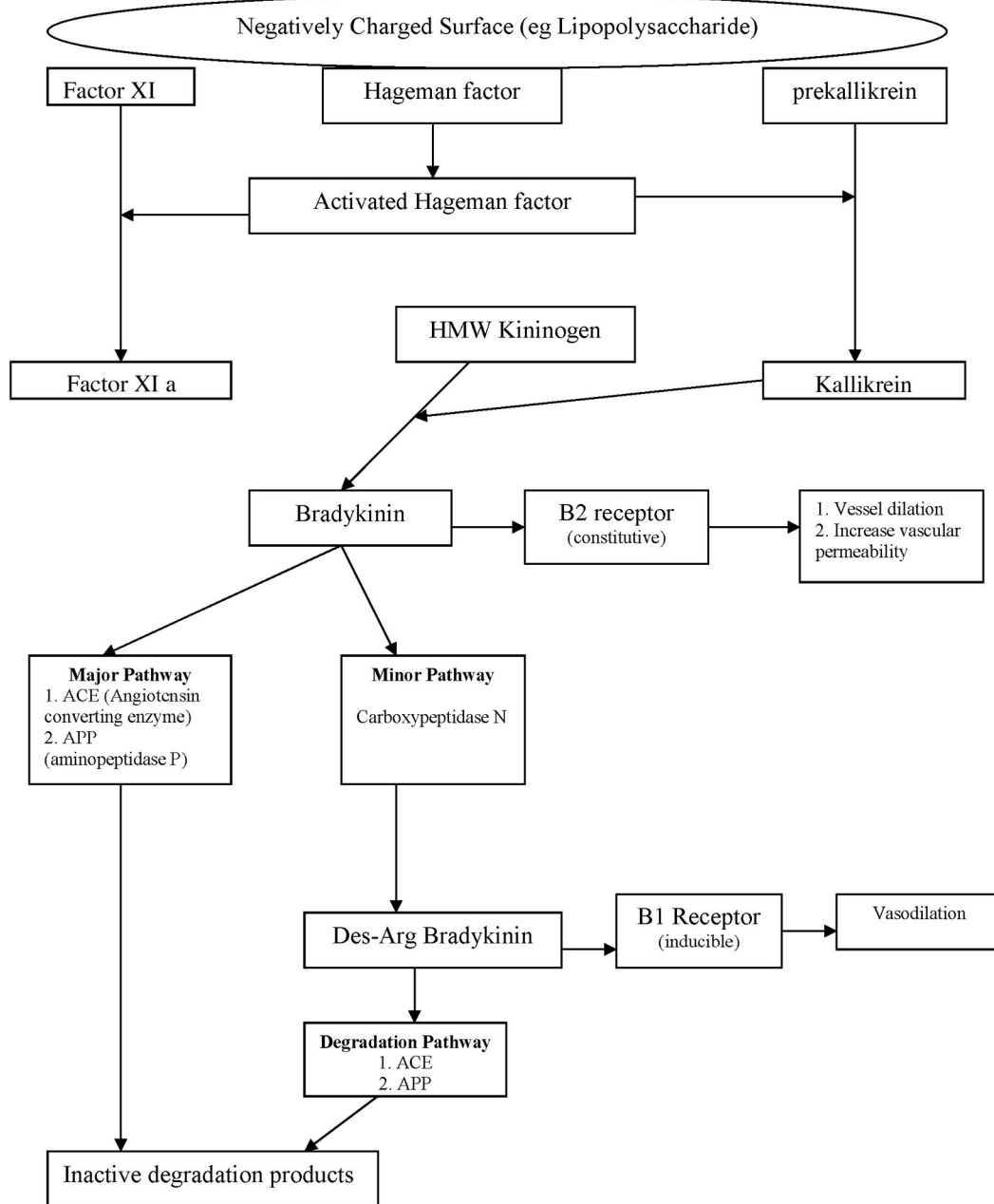


Figure 1. The bradykinin pathway. In the bradykinin pathway, Hageman factor is activated by interacting with a negatively charged surface, such as lipopolysaccharides from gram-negative organisms. The activated Hageman factor then converts factor XI to activated factor XI, thereby initiating the intrinsic pathway of the clotting cascade. Simultaneously, Hageman factor also converts prekallikrein to kallikrein, thereby initiating the bradykinin pathway. Kallikrein converts high-molecular-weight (HMW) kininogen to bradykinin.<sup>8</sup> Bradykinin acts on the bradykinin 2 receptors to cause vessel dilation and increased vascular permeability. Two pathways are present to degrade bradykinin to prevent uncontrolled swelling in the extravascular space. The major pathway uses angiotensin-converting enzyme (ACE) and aminopeptidase P (APP) to degrade bradykinin into inactive degradation products. In the minor pathway, carboxypeptidase N degrades bradykinin to des-Arg bradykinin, which acts on the inducible bradykinin receptors, causing vasodilation. The des-Arg bradykinin also uses ACE inhibitor and APP to convert des-Arg bradykinin to inactive degradation products.<sup>7</sup> Currently, there are at least 2 hypotheses regarding the mechanism whereby ACE inhibitors cause angioedema. One hypothesis is that the ACE inhibitors block the major pathway and shunt the degradation of bradykinin to the minor pathway, thereby increasing the formation of des-Arg bradykinin, which interacts with the inducible B1 receptor.<sup>7</sup> Another study also showed that patients susceptible to angioedema from an ACE inhibitor had lower levels of APP and thereby may accumulate des-Arg bradykinin.<sup>9</sup> Regardless, both hypotheses implicate the increased presence of des-Arg bradykinin as the protein responsible for causing angioedema from ACE inhibitors.

patients in the candesartan group experienced angioedema or anaphylaxis from an ACE-I; from this group; 3 (7.6%) developed angioedema from candesartan.<sup>24</sup> Use of the candesartan was discontinued in 1 patient and continued in the other 2 patients without additional angioedema or other untoward reaction. None of the 3 patients was hospitalized. Forty-four (4.3%) of 1,015 placebo-treated patients experienced angioedema or anaphylaxis from ACE-Is, but none of the 44 patients developed angioedema or anaphylaxis during the placebo treatment.<sup>24</sup> The authors concluded that "history of angioedema or anaphylaxis on an ACE inhibitor should prompt caution but does not seem to be a contraindication to use of an angiotensin-receptor blocker."<sup>24</sup> In our study, the 6 patients receiving an ARB had no subsequent angioedema after 97 patient-months. These data suggest that the use of an ARB in this population may not be as worrisome as previously described.

In our study, no patients required a tracheostomy or died. This observation may be due to early intervention and treatment. Using the grading system for generalized hypersensitivity reactions proposed by Brown,<sup>25</sup> 13 (20%) of 64 patients had grade 2 (moderate) reactions because of angioedema using acute dyspnea and stridor. In addition, some of our patients experienced drooling, garbled speech, and dysphagia, suggesting that these features should be added to the proposed grading system for grade 3 (severe). All patients received methylprednisolone and diphenhydramine in the emergency department on arrival. Most patients also received famotidine. At the earliest sign of throat tightness, the patients received subcutaneous or intramuscular epinephrine. Significant oropharyngeal swelling often led to an intubation unless refused by the patient. None of the patients in our study had refractory or progressive angioedema that required prolonged intubation and respiratory support. Karim and Masood<sup>26</sup> and Warriar et al<sup>27</sup> described the administration of fresh frozen plasma in these situations. The rationale is that the fresh frozen plasma may contain kininase II that can degrade the high levels of bradykinin thought to be responsible for ACE-I-induced angioedema.<sup>26,27</sup> Further data are needed regarding the administration of fresh frozen plasma.

One additional finding was the apparent reluctance to prescribe an ARB after angioedema from an ACE-I. Numerous studies have shown the efficacy of using an ARB to help manage hypertension, and if the data from ACE-I can be extrapolated to ARBs, then this medication class may be helpful in treating patients with concomitant hypertension and diabetes mellitus, congestive heart failure, and diabetic and nondiabetic nephropathy. Garg and Bakris<sup>28</sup> even concluded that ARBs may be used as first-line treatment in diabetic nephropathy. In our study, we identified 7 of 64 patients who may have benefited from a trial of an ARB. It is important to understand that the primary goal is blood pressure control with whatever agent necessary. However, there may be some added benefit of adding an ARB, because, like an ACE-I, it may improve endothelial dysfunction, cause regression of left ventricular hypertrophy, promote collateral

vessel development, and improve coronary revascularization as has been observed with the use of ACE-Is.<sup>29</sup>

ACE-I- and ARB-induced angioedema occurs predominately in women and African Americans. Only 28% of patients present within the first month of therapy; therefore, physicians must be aware that late reactions may occur. The data show that even severe angioedema appears to be an isolated event that resolves on discontinued use of an ACE-I or ARB. Physicians should be cautious, but not necessarily deterred, in prescribing an ARB to a patient with a history of ACE-I-induced angioedema, especially if the benefits of control of hypertension and decreased albuminuria may be helpful to the patient.

## REFERENCES

1. Saltoun CA, Metzger WJ. Urticaria, angioedema, and hereditary angioedema. In: Grammer LC, Greenberger PA, eds. *Patter-son's Allergic Diseases*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:239–256.
2. Burch S, Ou N. Current indications for ACE inhibitors and HOPE for the future. *Am J Manag Care*. 2002;8:478–490.
3. Sica DA, Black HR. Angioedema in heart failure: occurrence with ACE inhibitors and safety of angiotensin receptor blocker therapy. *Congest Heart Fail*. 2002;8:334–341.
4. Vleeming W, van Amsterdam JG, Stricker BH, deWildt DJ. ACE inhibitor-induced angioedema: incidence, prevention and management. *Drug Saf*. 1998;18:171–188.
5. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the omapatrilat cardiovascular treatment vs. enalapril (OCTAVE) trial. *Am J Hypertens*. 2004; 17:103–111.
6. Lee CE, Zembower TR, Fortis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med*. 2000;160:2819–2822.
7. Molinaro G, Cugno M, Perez M, et al. Angiotensin-converting enzyme inhibitor-associated angioedema is characterized by a slower degradation of des-arginine (9)-bradykinin. *J Pharmacol Exp Ther*. 2002;303:232–237.
8. Cunnion KM, Wagner E, Frank MM. Complement & kinin. In: Parlow TG, Stites DP, Imboden JB, eds. *Medical Immunology*. 10th ed. New York, NY: Lange Medical Books/McGraw Hill Medical Publishing Division; 2001:186–888.
9. Adam A, Cugno M, Molinaro G, et al. Aminopeptidase P in individuals with a history of angio-edema on ACE inhibitors. *Lancet*. 2002;359:2088–2089.
10. Anderson MW, de Shazo RD. Studies of the mechanism of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema: the effect of an ACE inhibitor on cutaneous responses to bradykinin, codeine, and histamine. *J Allergy Clin Immunol*. 1990;85:856–858.
11. Lefebvre J, Murphey LJ, Hartert TV, et al. Dipeptidyl peptidase IV activity in patients with ACE-inhibitor-associated angioedema. *Hypertension*. 2002;39:460–464.
12. Sondhi D, Lippmann M, Murali G. Airway compromise due to angiotensin-converting enzyme inhibitor angioedema: clinical experience at a large community teaching hospital. *Chest*. 2004; 126:400–404.
13. Margolius H. Urinary kallikreins and prostaglandins in blacks. *J Clin Hypertens*. 1987;3:51S–56S.

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14. Gainer JV, Nadeau JH, Ryder D, Brown NJ. Increased sensitivity to bradykinin among African Americans. *J Allergy Clin Immunol*. 1996;98:283–287.
  15. Chiu AG, Newkirk KA, Davidson BJ, et al. Angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter review and an algorithm for airway management. *Ann Otol Rhinol Laryngol*. 2001;110:834–840.
  16. Cohen EG, Soliman AM. Changing trends in angioedema. *Ann Otol Rhinol Laryngol*. 2001;110:701–706.
  17. Agah R, Bandi V, Guntupalli KK. Angioedema: the role of ACE inhibitors and factors associated with poor clinical outcome. *Intensive Care Med*. 1997;23:793–796.
  18. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. *JAMA*. 1997;278:232–233.
  19. Orfan N, Patterson R, Dykewicz MS. Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. *JAMA*. 1990;264:1287–1289.
  20. Kyrmizakis DE, Papadakis CE, Liolios AD, et al. Angiotensin-converting enzyme inhibitor and angiotensin II receptor antagonist. *Arch Otolaryngol Head Neck Surg*. 2004;130:1416–1419.
  21. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE-inhibitor-induced angioedema. *Ann Pharmacother*. 2000;34:526–528.
  22. Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. *Pharmacotherapy*. 2002;22:1173–1175.
  23. Cicardi M, Zingale LC, Bergamaschini L, Agostini A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med*. 2004;164:910–913.
  24. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362:772–776.
  25. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114:371–376.
  26. Karim MY, Masood A. Fresh-frozen plasma as a treatment for life-threatening ACE-inhibitor angioedema. *J Allergy Clin Immunol*. 2002;109:370–371.
  27. Warriar MR, Copilevitz CA, Dykewicz MS, Slavin RG. Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. *Ann Allergy Asthma Immunol*. 2004;92:573–575.
  28. Garg J, Bakris GL. Treatment of hypertension in patients with renal disease. *Cardiovasc Drugs Ther*. 2002;16:503–510.
  29. O’Keefe JH, Wetzel M, Moe RR, et al. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? *J Am Coll Cardiol*. 2001;37:1–8.

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