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Incidence and Predictors of Angioedema in Elderly Hypertensive Patients at High Risk for Cardiovascular Disease: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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Angioedema is a rare, potentially life-threatening condition that has been associated with angiotensin-converting enzyme inhibitors since their introduction in the 1980s. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest antihypertensive study conducted to date, randomized 42,418 participants to a diuretic (chlorthalidone), a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an α-blocker (doxazosin). Patients who developed angioedema were compared for baseline characteristics and changes in antihypertensive drug administration. Fifty-three participants developed angioedema during active follow-up: 55% were black, 60% men, and 70% were assigned to lisinopril (including 62% of black participants with angioedema), 15% to chlorthalidone, 9% to doxazosin, and 6% to amlodipine. Six percent occurred within a day of randomization and 23% within the first week. Over half did not have an increase in their assigned (blinded) antihypertensive drug before angioedema onset; 3 (6%) had a dose increase within a week before onset. One patient died following an angioedema episode. The occurrence of angioedema in the angiotensin-converting enzyme inhibitor arm corresponds with previously reported angioedema–angiotensin-converting enzyme inhibitor associations. (J Clin Hypertens. 2006;8:649–656) ©2006 Le Jacq

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Angioedema, first described over a century ago, manifests as a nonpruritic swelling that is of sudden onset and is often restricted to the skin and mucous membrane of the face. It can be serious and life-threatening when the upper airways, especially the larynx, are involved.[1–3] Angioedema has been associated with consumption of certain foods, injury from insect bites, and use of certain medicines (including antihypertensive drugs,

specifically angiotensin-converting enzyme [ACE] inhibitors). Although rare, angioedema is a well-known adverse reaction associated with the use of ACE inhibitors, one of the antihypertensive drug classes utilized in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[4] a large, randomized, double-blind clinical trial conducted in a diverse clinical care community setting.

Drugs, specifically antihypertensive drugs, that are known to be associated with angioedema are so labeled; however, there is a paucity of data on the incidence rates of this event, its magnitude among chronically treated hypertensive individuals, and the relationship of time of onset to initiation of use. One reason for the scant data may be the lack or limited availability of a sizable cohort of hypertensive individuals with a known denominator who are treated and followed for a long duration.

ALLHAT, a multicenter clinical trial of 42,418 adults, was designed to determine whether the occurrence of cardiovascular events was lower in older hypertensive patients treated with a calcium channel blocker (amlodipine), an ACE inhibitor (lisinopril), or an α-blocker (doxazosin) compared with those treated with a diuretic (chlorthalidone).[4] ALLHAT, with its large cumulative patient years of follow-up, enables the observation of the occurrence of this potentially life-threatening adverse drug event in hypertensive patients being treated with commonly prescribed antihypertensive medicines and under the care of a wide range of clinical specialties and care providers.

In this paper, we report the incidence and predictors of angioedema among elderly hypertensive patients who are at high risk for cardiovascular disease.

METHODS

ALLHAT was sponsored by the National Heart, Lung, and Blood Institute and enrolled its 42,418 participants in 623 clinical centers in the United States, Canada, Puerto Rico, and the US Virgin Islands.[5] The doxazosin arm was stopped prematurely in March 2000.[6,7] Results of the antihypertensive trial were published in December 2002.[8]

The design of ALLHAT has been described in detail elsewhere.[4] Briefly, those eligible for randomization were 55 years or older, had systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg or took medication for hypertension, and had at least one other risk factor for coronary heart disease (CHD) events. Risk factors included previous myocardial infarction or stroke, left ventricular hypertrophy by electrocardiogram or echocardiogram, history of type 2 diabetes, current cigarette smoking, and low high-density lipoprotein cholesterol level. Potential participants for whom there was a contraindication for one of the blinded drug classes, or whose clinical status required one of the blinded drugs, were not enrolled. The primary end point for the antihypertensive trial was the composite of nonfatal myocardial infarction and fatal CHD.

Of the 4 classes of antihypertensive drugs used in ALLHAT, the ACE inhibitor lisinopril was the most well known to cause angioedema, albeit infrequently. Consequently, the use of ACE inhibitors in ALLHAT mandated careful observation of the entire participant cohort for possible signs of angioedema. Site physicians were required to report all cases of angioedema among ALLHAT participants. Both the ALLHAT *Manual of Operations* and the ALLHAT *Training Manual* instructed that the ALLHAT medication be immediately and permanently discontinued if angioedema developed. Angioedema surveillance by the site physicians was stressed throughout the trial, through specific instructions (including reiteration of signs and symptoms that might suggest angioedema) via mailings and discussions at the annual investigators meetings and articles in the staff bulletin. Specifically, physicians and coordinators were reminded to monitor for swelling of the lips, tongue, skin, subcutaneous tissue, and mucous membranes, as well as possible, albeit less frequent, involvement of internal organs, particularly the gastrointestinal tract. Warnings of the possibility of airway obstruction and the potential for death were repeatedly enumerated. Doctors were admonished to immediately request unmasking of the blinded drug and to immediately and permanently discontinue the use of any ACE inhibitor,[9] and any other suspected causative agent, in cases of possible angioedema. Finally, the patients, their families, and other physicians involved in the patients' care were to be clearly told of these instructions, and the patients' charts were to be so marked. When unmasking of blinded drugs was requested due to suspected angioedema, the ALLHAT Clinical Trials Center physician contacted the site investigator to obtain further information and to ensure immediate discontinuation of the study drug and formal reporting of the episode. These reports were reviewed on a case-by-case basis by the ALLHAT Clinical Trials Center, Project Office leadership, and the independent Data Safety and Monitoring Board.

For this report, data were analyzed by blinded antihypertensive treatment groups for all

angioedema events occurring between randomization and final study visits. Baseline data and timing of onset of angioedema relative to randomization, dose increases, and month and season of occurrence were examined. Descriptive statistics of the aforementioned items were tabulated.

For each baseline characteristic, 2-proportion or 2-sample mean difference tests were performed comparing each of the 3 nondiuretic groups to chlorthalidone.

RESULTS

Angioedema was reported in 53 of 42,418 (0.12%) ALLHAT participants: 37 of 9054 (0.41%) assigned to lisinopril and 16 to the other 3 treatment groups (8 of 15,255 [0.05%] to chlorthalidone; 3 of 9048 [0.03%] to amlodipine; and 5 of 9061 [0.06%] to doxazosin). Events occurred throughout the year, with a slight, although clinically insignificant, preponderance during the summer and fall. Baseline characteristics over the total cohort with and without angioedema are given in Table I. Baseline characteristics of the angioedema cohort are as follows: over half (55%) were black and 40% were women. Mean age at study entry was 66 years, 36% were current smokers, 11% had a history of diabetes, and 30% had a history of CHD. Mean baseline serum levels were as follows: potassium, 4.1 mEq/dL; fasting glucose, 111.2 mg/dL; creatinine, 1.03 mg/dL; and total cholesterol, 209.4 mg/dL. Aspirin use was reported in 36% (19 of 52) of patients. Estrogen was used in 48% (10 of 21) of women. Angioedema patients in the lisinopril group were more likely to be black, male, without a history of CHD, and have a lower fasting glucose and total serum cholesterol compared with the non–lisinopril-assigned participants. Overall, comparisons of baseline characteristics between those who did and did not develop angioedema showed those without angioedema trended toward being non-black (36% in those without vs 55% in those with angioedema) and nonsmokers (22% in those without vs 36% in those with angioedema) and had more diabetes at baseline (36% in those without vs 11% in those with angioedema).

The cumulative incidence of angioedema events by follow-up month and baseline characteristics is shown in Table II, and the time from randomization to onset of angioedema in Table III. Two thirds of angioedema events, including the majority from all treatment groups except chlorthalidone, occurred during the first year. The overall 0.12% cumulative incidence largely followed the lisinopril group, whose annual cumulative incidence ranged from 0.29% at Year 1 to 0.39% at Year 4 and 0.41% at Year 6.

Three (6%) angioedema cases occurred within 1 day of randomization and initiation of the blinded ALLHAT medication; 12 (23%) occurred within the first week and 18 (34%) within the first month following randomization. Two thirds (36 of 53) of participants with angioedema first developed it in the year following randomization; 8 (15%) cases occurred within the next 2 years and 1 case developed after 6 years. As expected, the lisinopril group, which constituted the majority of cases, reflected a similar time to onset; numbers in the other treatment groups were too small to individually characterize.

Half (27 of 53) of the total (20 of 37 in the lisinopril group) of participants did not have a dose escalation before onset of angioedema (Table IV). In the remainder, the time from increase in dosage to onset ranged from 3 days to 3–4 years. Approximately 6% of participants with angioedema had a dose increase within the week before onset, 17% within the month before onset, and 36% within the previous year. Further, 7% (4 of 53) of the total and 5% (2 of 37) of the lisinopril participants had previously discontinued, and subsequently restarted, the blinded medication before the onset of angioedema (data not shown).

At the time of the report of the angioedema, full recovery was reported in 46 (87%) patients, and 6 (11%) were alive with or being treated for sequelae (data not shown). One death associated with angioedema occurred in a white man in the lisinopril group in whom the study drug had been discontinued more than 3 years earlier; this was also the only case in which intubation was reported. The patient's death occurred 5 months following reinstitution of the drug.

COMMENTS

The 0.12% of the ALLHAT population experiencing angioedema was largely driven by the 0.41% of participants assigned to the ACE inhibitor lisinopril who developed it. Angioedema has previously been attributed to such drugs as aspirin, nonsteroidal anti-inflammatory agents, penicillin,[10–12] and angiotensin II receptor antagonists,[13–15] as well as foods (peanut products) and radiocontrast media.[10] The largest group of angioedema cases is thought to be idiopathic.[10] However, ACE inhibitors are believed to be responsible for 25%–38% of all cases of angioedema.[13] The reaction appears to be specific to this class rather than to individual drug members of the class.[12]

It is not surprising to have had such an incidence among ALLHAT patients receiving an ACE

Table I. Selected Baseline Characteristics of Angioedema Participants Assigned to Lisinopril vs Those Assigned to the Non-Lisinopril Treatment Groups

	Participants With Angioedema* Assigned Treatment Group			Participants Without Angioedema†
Baseline characteristics	Lisinopril	Non-lisinopril‡	Total	Total
Number	37	16	53	42,365
Angioedema cohort, %	69.81	30.19	100.00	—
ALLHAT cohort, %	0.087	0.038	0.12	99.88
Age, mean (SD), y	66.6 (8.35)	65.1 (6.81)	66.2 (7.88)	66.9 (7.72)
Age group, n (%), y				
55–65	19 (51.35)	9 (56.25)	28 (52.83)	20,099 (47.44)
66–75	11 (29.73)	7 (43.75)	18 (33.96)	16,182 (38.20)
Women, n (%)	13 (35.14)	8 (50.00)	21 (39.62)	19,820 (46.78)
Race, n (%)				
Black	23 (62.16)	6 (37.50)	29 (54.72)	15,055 (35.54)
Nonblack	14 (37.84)	10 (62.50)	24 (45.28)	27,309 (64.46)
On blood pressure treatment ≥2 mo	31 (83.78)	14 (87.50)	45 (84.91)	36,791 (86.84)
On blood pressure treatment <2 mo	3 (8.11)	0 (0.00)	3 (5.66)	1425 (3.36)
Untreated at baseline	3 (8.11)	2 (12.50)	5 (9.43)	4148 (9.79)
Current smoker	14 (37.84)	5 (31.25)	19 (35.85)	9250 (21.84)
History of diabetes	4 (10.81)	2 (12.50)	6 (11.32)	15,277 (36.06)
History of CHD	10 (27.03)	6 (37.50)	16 (30.19)	10,750 (25.37)
Aspirin use§	14 (37.84)	5 (31.25)	19 (35.85)	15,204 (35.89)
Estrogen use (women)	9 (69.23)	1 (12.5)	10 (47.62)	3491 (17.59)
Visit 1 blood pressure, mean (SD)				
Treated ≥2 mo				
SBP, mm Hg	139.3 (15.71)	142.0 (10.65)	140.2 (14.26)	142.7 (12.96)
DBP, mm Hg	82.1 (8.10)	84.9 (5.32)	82.9 (7.41)	82.3 (9.52)
Treated <2 mo				
SBP, mm Hg	167.3 (7.09)	—	167.3 (7.09)	158.1 (13.32)
DBP, mm Hg	92.7 (11.24)	—	92.7 (11.24)	89.4 (9.76)
BMI, mean (SD) (kg/m^2)	29.4 (7.61)	29.5 (6.66)	29.4 (7.27)	29.7 (6.15)
Serum potassium, mean (SD) (mEq/dL)§	4.1 (0.50)	4.1 (0.44)	4.1 (0.47)	4.3 (0.51)
Fasting glucose, mean (SD) (mg/dL)	106.7 (28.72)	121.0 (60.90)	111.2 (41.41)	123.0 (57.06)
Creatinine, mean (SD) (mg/dL)§	1.08 (0.33)	0.92 (0.13)	1.03 (0.29)	1.02 (0.30)
Total cholesterol, mean (SD) (mg/dL)§	204.4 (33.27)	220.7 (36.50)	209.4 (34.74)	215.9 (43.2)

For each characteristic, 2-proportion or 2-sample mean difference tests were performed comparing each of the 3 nondiuretic groups with chlorthalidone, respectively. ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; and BMI, body mass index. *Two participants with angioedema reported open-label (nonassigned study drug) angiotensin-converting enzyme inhibitor use: one was assigned to step 1 chlorthalidone and one to step 1 lisinopril. †Comparisons between treatment groups of baseline characteristics among those without angioedema showed no significant differences. ‡Non-lisinopril treatment groups included chlorthalidone, amlodipine, and doxazosin. §Aspirin use was available for 52 participants; serum potassium, creatinine, and total cholesterol were available for 50 participants; and fasting glucose was available for 41 participants; there were no statistically significant differences (type 1 error probability of .05) between lisinopril and non-lisinopril groups.

inhibitor. Approximately 0.1%–0.7% of patients receiving ACE inhibitors experience angioedema.[11,12,14,16,17] The rate of this adverse effect among users of ACE inhibitors has been reported to be 3 times that of users of calcium channel blockers.[15] Among African Americans taking ACE inhibitors, the rate may be 5 times that of whites.[18]

One ALLHAT participant of Asian/Pacific Islander descent and assigned to lisinopril experienced angioedema. It is commonly held that ACE inhibitor intolerance occurs more frequently among Asians, particularly Chinese patients. While several small studies have documented an increase in the frequency of cough among Chinese patients and

Table II. Cumulative Incidence of Angioedema by Follow-Up Month

Baseline characteristics	Sample Size*	Cumulative Incidence, n (%) Follow-Up, mo 12	24	36	48
Number (% of ALLHAT cohort)	42,418	35 (0.08)	39 (0.09)	43 (0.10)	49 (0.12)
Step 1 (assigned) treatment group					
Chlorthalidone	15,255	2 (0.01)	2 (0.01)	3 (0.02)	6 (0.04)
Amlodipine	9048	3 (0.03)	3 (0.03)	3 (0.03)	3 (0.03)
Lisinopril	9054	26 (0.29)	29 (0.32)	32 (0.35)	35 (0.39)
Doxazosin	9061	4 (0.04)	5 (0.06)	5 (0.06)	5 (0.06)
Age group, y					
55–65	20,127	18 (0.09)	21 (0.10)	22 (0.11)	26 (0.13)
66–75	16,200	12 (0.07)	12 (0.07)	14 (0.09)	16 (0.10)
>75	6091	5 (0.08)	6 (0.10)	7 (0.11)	7 (0.11)
Gender					
Male	22,577	19 (0.08)	22 (0.10)	26 (0.12)	29 (0.13)
Female	19,841	16 (0.08)	17 (0.09)	17 (0.09)	20 (0.10)
Race					
Black	15,084	23 (0.15)	25 (0.17)	26 (0.17)	27 (0.18)
Nonblack	27,333	12 (0.04)	14 (0.05)	17 (0.06)	22 (0.08)
On BP treatment ≥2 mo	36,836	32 (0.09)	36 (0.10)	38 (0.10)	42 (0.11)
On BP treatment <2 mo	1428	1 (0.07)	1 (0.07)	3 (0.21)	3 (0.21)
Untreated at baseline	4153	2 (0.05)	2 (0.05)	2 (0.05)	4 (0.10)
Current smoker	9269	14 (0.15)	16 (0.17)	16 (0.17)	18 (0.19)
History of diabetes	15,283	5 (0.03)	5 (0.03)	5 (0.03)	6 (0.04)
History of coronary heart disease	10,766	8 (0.07)	10 (0.09)	11 (0.10)	15 (0.14)
Aspirin use	15,223	10 (0.07)	12 (0.08)	15 (0.10)	17 (0.11)

Participants randomized late did not have follow-up beyond 48 months. ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Sample size drops off with time.

have demonstrated somewhat different pharmacokinetics and pharmacodynamics,[19,20] a true increase in the level of ACE inhibitor intolerance among Asians has not been documented. Data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) documents the increase in cough but not a true increase in intolerance by any other measure (S. MacMahon, DSc, PhD, personal oral and e-mail communication, March 2006).

Most cases of angioedema are thought to occur within hours to a week following the initiation of the medication, but there have been rare instances of drug-related angioedema years after first taking the drug.[12,16,21] In ALLHAT, relatively few cases of angioedema occurred within the first day of using the blinded medication (including lisinopril), although one fifth of all cases occurred within the first week. Cases continued to occur sporadically throughout the 6 years of the trial. Late-onset angioedema has been reported in users of ACE inhibitors, although it frequently is not recognized as such.[22] The vast majority of cases in ALLHAT did not involve a prior discontinuation and subsequent restarting of the drug and, of those, only one patient had restarted the drug within 15–30 days of the onset of the angioedema. Half of the patients had a prior dose increase of their study medication, but only 3 events in the total group, including 2 in the lisinopril group, had occurred within the week following the dose increase. In the other cases, the events occurred up to 3–4 years following the dose increase. Two of the affected participants reported nonstudy (open-label) ACE inhibitor use: one, assigned to step 1 chlorthalidone, had a single report of ACE inhibitor use nearly 3 years before the angioedema; the other, assigned to step 1 lisinopril, reported open-label ACE inhibitor use for approximately 16 months before onset.

A spectrum of symptoms associated with angioedema includes well-demarcated swelling of the tongue, lips, or face as well as edema of the mucous membranes of the mouth, throat, and nose. Involvement of the upper respiratory tract can lead to acute respiratory distress and airway obstruction, from which death may occur.[16,23] ACE

Table III. Time From Randomization to Onset of Angioedema in ALLHAT Participants*

	Number (%) of Participants With Angioedema				
Time from Randomization to Onset of Angioedema	C	A	L	D	Total
<1 d	1	0	2	0	3
1–7 d	1	0	6	2	9
Total within first wk†	2 (25)	0	8 (22)	2 (40)	12 (23)
8–14 d	0	0	1	0	1
15–30 d	0	0	4	1	5
Total within first mo†	2 (25)	0	13 (35)	3 (60)	18 (34)
31–60 d	0	0	3	1	4
61–90 d	0	1	2	0	3
Total within first 3 mo†	2 (25)	1 (33)	18 (49)	4 (80)	25 (47)
91–182 d	0	1	3	0	4
6 mo–1 y	0	1	6	1	7
Total within first year†	2 (25)	3 (100)	27 (73)	5 (100)	36 (68)
1–2 y	0	0	3	0	4
>2–3 y	1	0	3	0	4
>3–4 y	3	0	2	0	5
>4–5 y	0	0	1	0	1
>5–6 y	1	0	1	0	2
>6 y	0	1	0	0	1

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; C, chlorthalidone; A, amlodipine; L, lisinopril; and D, doxazosin. *For participants who experienced more than one episode of angioedema, only the first is considered. †Values are cumulative.

inhibitor-induced angioedema may occur more frequently than is reported due to lack of recognition of relatively mild symptoms by the patient or physician[24] or lack of documentation on the part of the physician.[13,14] An unrecognized case of angioedema may result in continued use of the ACE inhibitor and a subsequent, more severe event; it is thus imperative that patients with even mild angioedema not be restarted on ACE inhibitors.[15,23]

Due to the nature of this "large and simple" trial,[4] additional clinical information including allergies, diet, and use of non-ALLHAT medications was not available. Physicians were urged to report all suspected cases of angioedema in their ALLHAT participants, regardless of other possible etiologies. It is thus likely that some of the reported cases were associated with other causes. In an effort not to underestimate this potentially life-threatening illness, all cases were considered, for purposes of analyses and safety, to be associated with the blinded medication. It is also likely that, as in the general community, some mild cases of angioedema were not recognized and thus not reported.[22,24,25] With each report of angioedema, physicians were unblinded to the identity of the study medication and instructed to permanently discontinue that drug class and ACE inhibitor (whether or not implicated) in the affected patient.

The physiologic mechanism of ACE inhibitor-induced angioedema is thought to be predominantly nonimmunologic and related to increased levels of bradykinin secondary to inhibition of ACE-induced bradykinin degradation.[18,26–28] Bradykinins are potent vasodilators that produce hypotension when given to humans.[11] Thus, the result of bradykinin accumulation due to ACE inhibition is vasodilation, capillary leakage, and edema.[14,21] Substance P, a neuropeptide whose degradation is also inhibited by ACE inhibitors, may be involved.[11] Histamine and C1 esterase have further been suggested as possible targets of investigation.[12]

Molinaro and colleagues[28] have suggested a multifactorial mechanism of ACE inhibitor-associated angioedema involving pharmacologic, metabolic, and other triggering factors. Genetic factors, including deficiencies of carboxypeptidase N (kininase) and C1 esterase inhibitor, have been suggested as having possible etiologic roles. Genetic studies are currently underway for ALLHAT participants[29]; separate analyses of multiple genes in the subset of participants with angioedema have thus far failed to identify specific genetic associations (E. Boerwinkle, PhD, oral and e-mail communication, November 2004).

The largest series of angioedema cases associated with ACE inhibitors was reported in the

Table IV. Time From Most Recent Increase in Dose of Step 1 (Blinded) Antihypertensive Medication Prior to Onset of Angioedema in ALLHAT Participants*

Time from Most Recent Step 1 Dose Increase to Onset of Angioedema	Number (%) of Participants With Angioedema				
	C	A	L	D	Total
No dose increase†	4 (50)	0	20 (54)	3 (60)	27 (51)
1–2 d	0	0	0	0	0
3–7 d	0	1	2	0	3
Total with dose increase within first week†	0	1 (33)	2 (5)	0	3 (6)
8–14 d	0	0	2	0	2
15–30 d	0	1	2	1	4
Total with dose increase within first month†	0	2 (66)	6 (16)	1 (20)	9 (17)
31–60 d	0	0	0	0	0
61–90 d	0	0	1	0	1
Total with dose increase within first 3 months†	0	2 (66)	7 (19)	1 (20)	10 (19)
91–182 d	1	1	1	0	3
6 mo–1 yr	1	0	4	1	6

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; C, chlorthalidone; A, amlodipine; L, lisinopril; D, doxazosin. *For participants who experienced more than one episode of angioedema, only the first is considered. †Values are cumulative.

Omapatrilat Cardiovascular Treatment vs Enalapril (OCTAVE) trial,[30,31] a 24-week, randomized, double-blind trial in which 12,634 of 25,302 hypertensive participants were assigned to the ACE inhibitor enalapril. Angioedema was a study end point, actively sought out for reporting and adjudication, and occurred in 0.68% (86 of 12,634) of those treated with the ACE inhibitor. It also occurred in 2.17% of those treated with the neutral endopeptidase/ACE inhibitor omapatrilat; these cases were more likely to occur early following administration of the first dose and were more likely to be severe. The increased incidence of angioedema with this newer agent contributed to its Food and Drug Administration denial.[32] The increased incidence in the enalapril arm compared with the ALLHAT ACE inhibitor arm (0.68% vs 0.41%) may reflect underreporting in ALLHAT and reinforces the need for physicians to more aggressively look for angioedema in patients with even minimal symptoms during ACE inhibitor use.

ALLHAT provided the second largest series of cases of angioedema associated with ACE inhibitor use and confirms that this adverse effect more frequently occurs in blacks and, further, is a measurable risk of treatment. Physicians must be sensitive to even the mildest symptoms of angioedema in all patients taking ACE inhibitors. These symptoms, frequently missed or attributed to other causes, may foretell a more severe episode with the continuation of ACE inhibitors in these patients.

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CME Questions

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INSTRUCTIONS FOR COMPLETING THIS FORM: Read the selected paper and answer all the questions that follow. After each question there is a series of possible correct answers. Please select the one best answer for each and place your selection on the answer grid. **YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION** and return the form within 6 months of the paper's publication to receive credit. Letters of credit will be mailed to participants biannually.

ACCREDITATION STATEMENT: Winthrop-University Hospital (WUH) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. WUH designates this Continuing Medical Education activity for a maximum of 1 credit hour in Category 1 credit towards the AMA Physicians' Recognition Award. Each physician should claim only those hours of credit that he/she actually spent on the educational activity. WUH relies upon faculty participants in its CME programs to provide educational information that is objective and as free of bias as possible. In this spirit, and in accordance with the guidelines of the program sponsor, faculty participants are expected to indicate any commercial relationship that might be perceived as a real or apparent conflict of interest.

EDITOR DISCLOSURES: Todd C. Kerwin, MD: Aventis, Takeda Pharmaceuticals—Speakers' Bureau.

AUTHOR DISCLOSURES: The National Heart, Lung, and Blood Institute sponsored the study and was involved in all aspects other than direct operations of the study centers. This included collection, analysis, and interpretation of the data in addition to the decision to submit the manuscript for publication. Linda B. Piller, MD, MPH: none. Charles E. Ford, PhD: none. Barry R. Davis, MD, PhD: Takeda Pharmaceuticals, GlaxoSmithKline Inc., BioMarin Pharmaceutical Inc., Procter & Gamble Pharmaceuticals—Data and Safety Monitoring Board. Chuke Nwachuku, MA, DrPH: AstraZeneca LP—employee. Henry R. Black, MD: Novartis, Bristol-Myers Squibb, Sanofi-Aventis, Daiichi Sankyo, Merck Sharp & Dohme, Myogen, Gilhead, Pfizer—consultant; Novartis, Bristol-Myers Squibb, Sanofi-Aventis, Daiichi Sankyo, Pfizer—Speakers' Bureau. Suzanne Oparil, MD: none. Tamrat M. Retta, MD, PhD: none. Jeffrey L. Probstfield, MD: Boehringer-Ingelheim Pharmaceuticals, Kos Pharmaceuticals, Inc., Sanofi-Aventis, King Pharmaceuticals—research grant; King Pharmaceuticals—consultant.

OBJECTIVE AND TARGET AUDIENCE: All clinicians are eligible to receive credit. At the conclusion of this activity, participants should be able to: (1) summarize the important points discussed in the paper reviewed, (2) identify patients to whom the paper is relevant, (3) modify management practices as new information is learned, and (4) identify deficiencies in their knowledge base.

Please Select the One Best Answer for Each and Place Your Selection on the Answer Grid.

1. Questions the investigators hoped to answer in this study included which of the following:
   - A __ Which of the antihypertensive agents studied in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were associated with angioedema
   - B __ The time course of developing angioedema
   - C __ The relationship between age and sex and the development of angioedema
   - D __ All of the above

2. Angioedema occurring with angiotensin-converting enzyme (ACE) inhibitor use is thought to result from:
   - A __ Impurities in the manufacturing process
   - B __ A direct immunologic reaction
   - C __ An increase in the level of bradykinin
   - D __ All of the above

3. Angioedema occurs more often in:
   - A __ White men
   - B __ Black men
   - C __ White women
   - D __ Asian men

4. The overall incidence of angioedema in patients taking lisinopril was approximately:
   - A __ 0.4%
   - B __ 1%
   - C __ 3%
   - D __ None of the above

5. Which of the following statements regarding the conclusions of this study is false?
   - A __ Angioedema occurs more commonly with ACE inhibitors than with the other antihypertensive medications used in ALLHAT.
   - B __ Angioedema occurs most commonly in blacks.
   - C __ Angioedema resulting from ACE inhibitor use will occur only within 48–72 hours of starting the medication.
   - D __ The incidence of angioedema seen in ALLHAT was consistent with that seen in prior studies.

CME Answers are available from *The Journal of Clinical Hypertension* page at www.lejacq.com

CME Answer Grid

Answer the questions from the previous page by selecting the best choice of A, B, C, or D.

Questions: 1.__ 2.__ 3.__ 4.__ 5.__

CME Evaluation

	Agree				Disagree
1. My knowledge was enhanced by this activity.	1.__	2.__	3.__	4.__	5.__
2. The activity helped to clarify issues specific to hypertensive patients.	1.__	2.__	3.__	4.__	5.__
3. The information obtained from this exercise will have an impact on my care of patients.	1.__	2.__	3.__	4.__	5.__
4. The format of the exercise was useful.	1.__	2.__	3.__	4.__	5.__

5. Suggestions for future topics:

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