
Increasing hospitalizations due to angioedema in the United States

Robert Y. Lin, MD,*† and Shaili N. Shah, BA†

Background: Angioedema may occur in patients taking angiotensin-converting enzyme inhibitors. With the more prevalent use of this class of medications in the United States, it is not known whether angioedema hospitalizations have increased nationally in recent years.

Objectives: To profile the trends in angioedema hospitalizations and to examine associated demographic factors and comorbid diseases in the United States.

Methods: A national database of hospitalizations in the United States was queried for hospitalizations with a principal diagnosis of angioedema and other major acute allergic disorders (anaphylaxis, urticaria, and allergy unspecified). Subsequent analysis was performed to determine the current angioedema hospitalization trends (1998–2005) and to examine clinical and demographic variables that distinguished angioedema from the other allergic disease admissions.

Results: The angioedema hospitalization rate was 3.3 in 100,000 in 1998 and rose to 4.0 in 100,000 in 2005. In contrast, the combined hospitalization rate for nonangioedema allergic disorders showed an overall decline and was exceeded by angioedema hospitalization rates after 2000. African American patients had consistently higher hospitalization rates (≥ 2 times) for angioedema compared with non-African American patients. Hypertension, increasing age, and African American ethnicity were associated with angioedema hospitalizations. Twenty-four percent of hospitalizations for angioedema were coded for an adverse effect due to cardiovascular or antihypertensive agents.

Conclusions: Angioedema has become the dominant allergic disorder that results in hospitalization in the United States. Angioedema hospitalizations have a distinct epidemiologic pattern that differs from that observed in other atopic disease hospitalizations.

Ann Allergy Asthma Immunol. 2008;101:185–192.

INTRODUCTION

Angioedema manifests as a deep swelling of the tissues just below the skin and mucous membranes. It is characterized by nonpitting, asymmetrical swelling that is generally nonpruritic and forms mostly around the perioral area, periorbital area, tongue, genitals, and extremities.¹ Angioedema can be life threatening and even fatal, with respiratory involvement leading to asphyxiation.

Because angiotensin-converting enzyme (ACE) inhibitors are indicated in the management of several chronic conditions,² including hypertension, heart failure, post-myocardial infarction, diabetes mellitus, and chronic kidney disease, the use of this class of drugs is quite prevalent.^{3,4} Angioedema is a frequent adverse effect noted in patients taking ACE inhibitors.⁵ Therefore, one might expect that the incidence of angioedema, and in severe cases, angioedema hospitalizations, has also become prevalent along with the increased use of ACE inhibitors. Indeed, in other parts of the world, such as South Australia, researchers have found an increase in angio-

edema admissions attributable to the increased use of ACE inhibitors.⁶

The incidence of certain types of allergic disorders in the United States has been described. Neugut et al⁷ determined that 1.21% to 15.04% of the US population may be affected by anaphylaxis. In 2005, Lin et al⁸ reported that angioedema has become the most common nonasthmatic acute allergic disorder resulting in hospitalization in New York State. However, the incidence of angioedema hospitalizations in the entire United States has not, to our knowledge, been previously reported. In this article, the national incidences of, trends in, and characteristics of angioedema-related hospitalizations are, thus, described for recent years in the United States. We hypothesized that patients with angioedema would be different from patients with other allergic diseases. Thus, we also compared characteristics of patients admitted with angioedema with those of patients admitted with other allergic diseases using analytical models.

METHODS

Data Sources

The Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project, funded by the US government's Agency for Healthcare Research and Quality, contains annual hospital discharge data from a stratified, random sample of hospitals across the United States.⁹ Each NIS hospital discharge record includes data fields consisting of demographic,

Affiliations: * Department of Medicine, St Vincent's Hospital Manhattan, Saint Vincent Catholic Medical Centers, New York, New York; † New York Medical College, Valhalla, New York.

Disclosures: Authors have nothing to disclose.

Funding Sources: Ms Shah was supported by an intramural fellowship provided by New York Medical College.

Received for publication October 25, 2007; Received in revised form February 8, 2008; Accepted for publication February 11, 2008.

clinical, and financial information. These fields include primary and secondary diagnostic fields, procedure codes, age, sex, race, total charges, length of stay, and disposition status. Each hospital discharge record also includes a discharge weight to allow for national estimates.¹⁰ The study years of 1998 through 2005 were chosen for analysis based on improved national representation and more thorough database field listings for these years. Each year's database contains hospital discharges from approximately 1,000 hospitals that, when weighted, ranged from 34,874,001 (in 1998) to 39,163,834 (in 2005).

The US Census Bureau data were accessed to obtain national resident population estimates for 1998 to 2005.¹¹ For calculations related to race after 1999, the population estimates used were based on 5 race categories (white alone or in combination, African American alone or in combination, American Indian or Alaskan native alone or in combination, Asian alone or in combination, and Hawaiian native/other Pacific Islander alone or in combination).¹² For the years after 1999, the African American alone or in combination population estimate was increased by 3.5% to adjust for the anticipated underreporting of this group¹³ due to differences in the 2000 census. This study was given exemption from institutional review board approval by the Saint Vincent Catholic Medical Centers Integrated Scientific and Ethical Review Board.

Case Selection and Data Elements

The NIS databases for 1998 to 2005 were queried for *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes relating to various acute allergic disease categories present in the principal diagnosis. These codes included 4 major principal allergy diagnoses: angioedema (code 995.1); allergy unspecified (code 995.3); anaphylaxis due to food (code 995.6*), nonfood (code 995.0), or serum (code 999.4); and urticaria (code 708.*). These hospitalizations were, thus, considered to be the cohort of all patients admitted for an acute, nonasthmatic allergic disease.

For this selected cohort, cases were examined for secondary diagnoses, including asthma (code 493.*), and several comorbid conditions with the potential for being associated with ACE inhibitor treatment, including hypertension (code 401.*), ischemic heart disease (codes 410.*–414.*), chronic kidney disease (code 585.*), congestive heart failure (code 428.*), and diabetes mellitus (code 250.*). External injury codes were examined for adverse effects due to drug therapy, including antihypertensive agents (code E942.6); other, unspecified cardiovascular agents (code E942.9); aspirin and aspirin derivatives (code E953.3); antirheumatic agents (code E953.6); and unspecified antipyretics and analgesics (code E953.9). Finally, procedure fields were examined for *Current Procedural Terminology* codes pertaining to respiratory interventions that may be performed in acute allergic hospitalizations, including laryngoscopy and tracheoscopy (code 31.42), endotracheal intubation (code 96.04), and mechanical ventilation (code 96.71).

Race was first determined by the hospital providing the data and was then adjusted by the Healthcare Cost and Utilization Project, which formed 1 element for race and ethnicity. If the source provided both race and ethnicity, ethnicity took precedence over race in the final reported race.⁷

Statistical Analysis

Data analysis was performed using a software package (JMP version 5.1; SAS Institute Inc, Cary, North Carolina). National estimates of angioedema hospitalization rates were derived by summing each patient record's discharge weight and dividing by the population estimate for the relevant years.¹⁴ Estimates of angioedema hospitalizations were compared with estimates of the other acute allergic disorders, and the general characteristics of the admissions for each of these disorders were tabulated.

Univariate and multivariate logistic regression models were used to examine for distinct angioedema associations of variables in the entire allergic disease cohort. The dependent binomial outcome was defined using angioedema hospitalizations vs nonangioedema allergic disease hospitalizations in the cohort. Clinical predictor variables analyzed included secondary diagnoses of urticaria, asthma, hypertension, chronic kidney disease, ischemic heart disease, diabetes mellitus, and congestive heart failure. Other predictor variables included age, sex, race, year of discharge, month of admission, weekend admission, region of the country, hospital characteristics, and expected payer being Medicare or Medicaid. Discharge weights were used for adjustment in all regression models. Significant predictors of angioedema being the principal diagnosis in the cohort of all allergic disease hospitalizations were identified by means of stepwise logistic regression. The probability required for a covariant to enter the model was .25, and the probability at which a covariant was removed from the model was .10. All significant variable factors were held constant in adjusted models examining for the independent predictor effects of specific variables of interest. Hospital charges and length of stay were also characterized for the different allergic disease admission groups.

RESULTS

General Characteristics

The 1998 to 2005 NIS databases include 35,444 hospital admissions for patients with a primary diagnosis of angioedema, anaphylaxis, urticaria, or allergy unspecified. The applications of the appropriate sampling weights for the NIS resulted in an estimate of 86,738 hospitalizations in the United States for a primary diagnosis of angioedema during the study period (Table 1). There were consistently more angioedema admissions each year than admissions for any of the other acute allergic nonasthmatic disorders. The median age of patients with angioedema was approximately 60 years compared with younger than 50 years for the other allergic disease hospitalization groups. African Americans constituted 27% of angioedema admissions but only 8% to 11% of the other allergic disease admission groups. Whereas 58% of

Table 1. Cohort Characteristics

Characteristics	Angioedema	Anaphylaxis	Urticaria	Allergy unspecified
1998 hospitalizations				
No.	8,839	5,583	4,238	912
Costs, \$	48,099,043	32,395,350	16,461,638	3,529,356
1999 hospitalizations				
No.	9,336	5,863	3,700	980
Costs, \$	49,637,654	31,906,641	14,169,379	3,981,988
2000 hospitalizations				
No.	9,724	5,938	3,960	1,169
Costs, \$	61,305,246	44,294,000	16,553,775	4,042,900
2001 hospitalizations				
No.	11,311	5,681	4,057	952
Costs, \$	76,571,723	45,281,919	20,552,804	4,569,845
2002 hospitalizations				
No.	11,808	5,907	3,805	1,056
Costs, \$	97,146,947	52,528,244	25,065,432	6,741,386
2003 hospitalizations				
No.	11,531	5,807	4,062	966
Costs, \$	108,246,835	63,373,821	30,531,254	5,957,006
2004 hospitalizations				
No.	12,265	6,365	3,796	1,122
Costs, \$	117,523,704	67,740,423	25,977,943	5,895,815
2005 hospitalizations				
No.	11,925	6,670	3,718	898
Costs, \$	123,390,211	76,201,286	29,099,577	5,412,552
Total hospitalizations (1998–2005)				
No.	86,738	47,813	31,336	8,055
Costs, \$	681,921,363	413,721,684	178,411,802	40,130,849
Age, median, y	60.46	45.93	42.14	45.01
Length of stay, median, d	1.57	1.1	1.93	1.13
African American race, %	26.49	9.94	7.59	10.79
Laryngoscopy/tracheoscopy, endotracheal intubation, mechanical ventilation, %	9.84	8.81	0.3	1.0
Hypertension, %	57.97	23.64	20.63	24.35
Urticaria in any secondary diagnosis, %	2.88	8.22	0.61	10.32
Asthma, %	8.54	16.22	8.85	8.91
Medicare, %	45.61	23.81	21.72	25.04
Medicaid, %	10.45	11.13	15.07	14.24
Adverse effects due to cardiovascular/antihypertensive agent, %	24.23	1.6	1.36	0.62
Adverse effects due to aspirin, antirheumatic, or unspecified antipyretic/analgesic, %	2.7	6.0	2.3	0.5
Death, %	0.33	0.93	0.08	0.11
Female sex, %	63.39	59.11	64.39	63.61
Total charge, median, US \$	4,228.12	4,562.65	3,658.95	3,386.66

angioedema hospitalizations had a diagnosis of hypertension, the proportion of other allergic disease hospitalizations with hypertension was less than 25%. An adverse effect due to a cardiovascular or antihypertensive agent was observed in 24% of patients with angioedema but in less than 2% of each of the other allergic disease admission groups. Adverse effects due to aspirin, antirheumatics, and unspecified antipyretics and analgesics were most frequently observed in anaphylaxis hospitalizations. Anaphylaxis hospitalizations also had a higher proportion of asthma than the other allergic disease admission groups. Laryngoscopy, tracheoscopy, en-

dotracheal intubation, and mechanical ventilation were more common in the angioedema and anaphylaxis cases.

Overall Trends

There was an overall increase in the angioedema hospitalization rate during the study period. In 1998, the hospitalization rate for angioedema was 3.3 per 100,000. In 2005, the angioedema hospitalization rate rose to 4.0 per 100,000 (Fig 1). By 2001, the angioedema hospitalization rate exceeded the combined hospitalization rates for all other allergic diseases. After 2001, angioedema continued to dominate allergic dis-

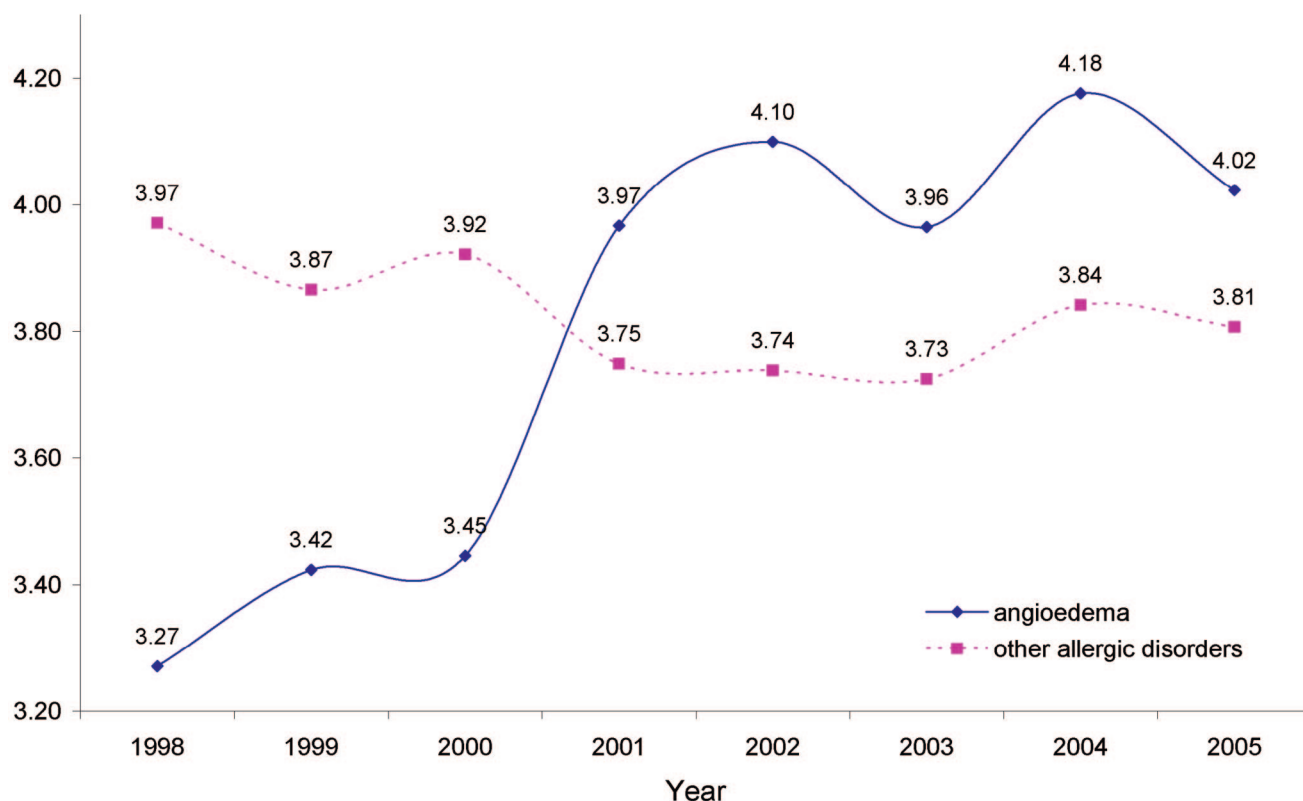


Figure 1. Hospitalization rates for angioedema and other allergic disorders.

ease admissions. The combined hospitalizations rates for other allergic diseases showed a slight decline with time. The yearly angioedema hospitalization rates were consistently higher for African American patients than for patients not coded as African American (Fig 2). The 1998 angioedema hospitalization rate for African American patients was 6.7 per 100,000 compared with the 2004 rate of 8.9 per 100,000 and the 2005 rate of 7.0 per 100,000 (Fig 2).

Multivariate Factors Associated With Angioedema Admission

In a univariate analysis, having a diagnosis of hypertension or being of African American ethnicity was associated with angioedema admission in the cohort of allergic disease admissions (Table 2). Stepwise selection showed that hypertension, increasing age, and African American race had the strongest associations with angioedema admission in logistic regression modeling. Factors also entering the prediction model for angioedema admission included urban location of the hospital, region of the hospital, month of admission, not having asthma, weekend admission, female sex, not having Medicaid, diabetes mellitus, not having urticaria (as a secondary diagnosis), increased year of discharge, teaching status of the hospital, type of ownership of the hospital, congestive heart failure, largest hospital bed size, chronic kidney disease, and Medicare. Ischemic heart disease had positive

predictor effects only if time-related factors were not included in the model. Even after adjusting for all the significant variables in multivariate analysis, acute allergic disease admissions had an increased likelihood of having angioedema as the principal diagnosis if there was African American ethnicity (adjusted odds ratio, 3.3; 95% confidence interval, 3.1–3.5) or hypertension (adjusted odds ratio, 2.4; 95% confidence interval, 2.3–2.5) ($P < .001$ for both variables) (Table 2). The adjusted odds ratios for other categorical factors, including comorbidities and temporal factors, hospital aspects, and demographic features, ranged from 0.7 (urticaria in nonprincipal diagnosis) to 1.3 (chronic kidney disease).

DISCUSSION

This study demonstrates that hospitalizations for angioedema in the United States have increased in recent years, with a concomitant increase in health care expenditures. The small decreases in other acute allergic disease hospitalizations, which do not seem to offset the much larger increase in angioedema hospitalizations, and the lack of new allergy disease *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes, which might promote alternative diagnostic categorization during the study period, speak against simple coding shifts among the major allergic diseases as an explanation for the angioedema hospitalization

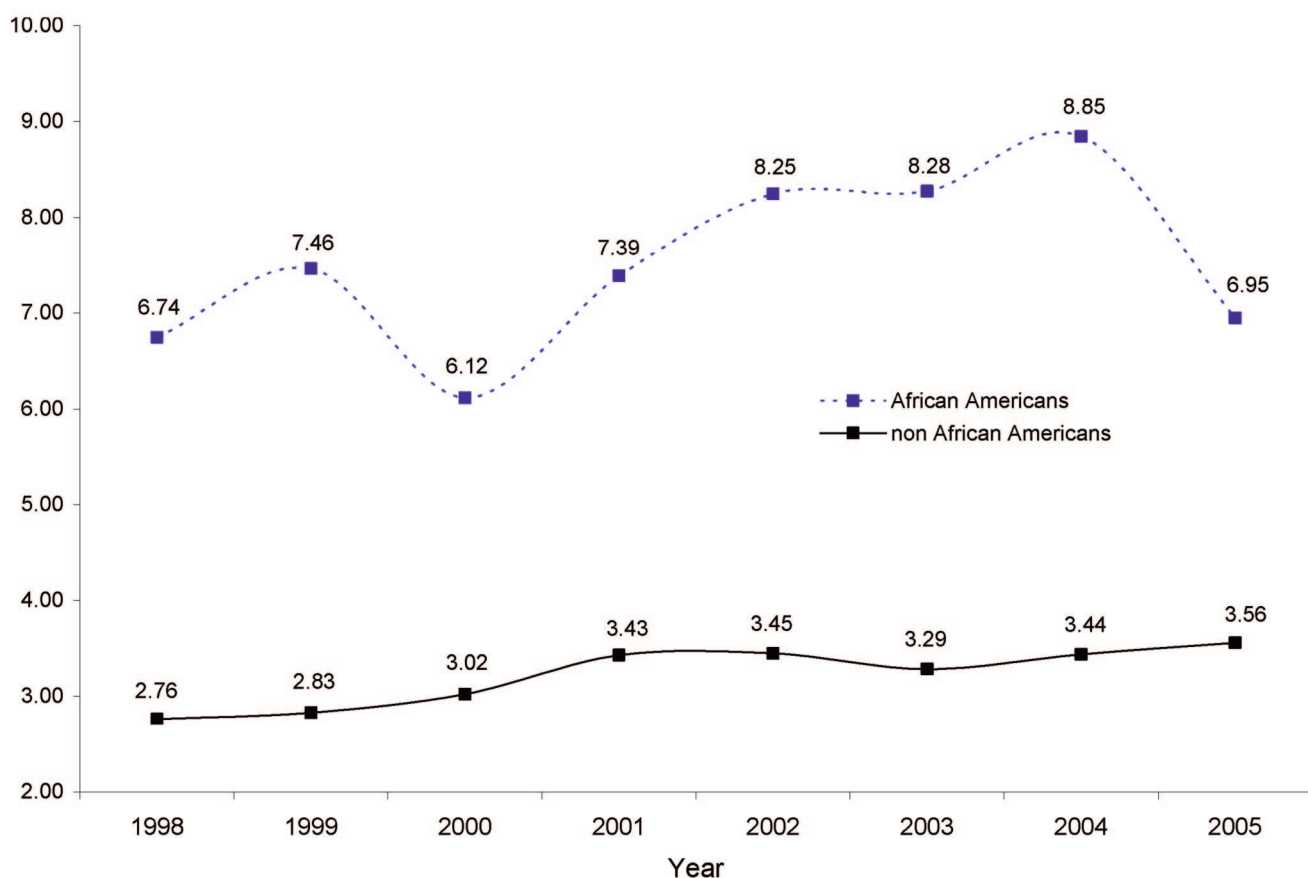


Figure 2. Angioedema hospitalization rates in African American vs non-African American patients.

Table 2. Logistic Regression Models: Univariate and Multivariate Associations Between Hypertension and African American Race as Related to Angioedema Hospitalizations

Dependent Variable	Independent Variable	Adjusting Variables	Odds Ratio (95% CI)
Angioedema	African American	None	3.6 (3.5–3.7)
Angioedema	Hypertension	None	4.3 (4.2–4.4)
Angioedema	African American	Hypertension	2.9 (2.8–3.0)
Angioedema	Hypertension	African American	3.9 (3.8–4.0)
Angioedema	African American	Hospital characteristics, ^a region, ^b Medicare, Medicaid, demographics, ^c time variables, ^d and comorbidities ^e	3.3 (3.1–3.5)
Angioedema	Hypertension	Hospital characteristics, ^a region, ^b Medicare, Medicaid, demographics, ^c time variables, ^d and comorbidities ^e	2.4 (2.3–2.5)
Angioedema	African American	Demographics, ^c time variables, ^d and comorbidities ^e	3.3 (3.2–3.4)
Angioedema	Hypertension	Demographics, ^c time variables, ^d and comorbidities ^e	2.4 (2.3–2.5)
Angioedema	African American	Demographics ^c and comorbidities ^e	3.3 (3.2–3.4)
Angioedema	Hypertension	Demographics ^c and comorbidities ^e	2.3 (2.3–2.4)

Abbreviation: CI, confidence interval.

^a Hospital characteristics include hospital bed size, teaching status of the hospital, hospital location (rural or urban), and type of ownership of the hospital.

^b Region refers to the 4 US Census–defined regions.

^c Demographics include sex, age, and African American ethnicity (for models examining hypertension as the independent variable of interest).

^d Time variables include year of discharge, month of admission, and whether admission was on the weekend.

^e Comorbidities include chronic kidney disease, asthma, urticaria (in secondary diagnosis), congestive heart failure, ischemic heart disease, and diabetes mellitus. Ischemic heart disease was not included as a comorbidity in the fullest model. African American ethnicity was included in models examining hypertension as the independent variable of interest.

increases. Angioedema hospitalizations were infrequently associated with additional diagnoses of urticaria, which suggests that these were, by and large, not chronic urticaria cases, which often can also manifest angioedema.¹⁵ Because patients with angioedema had differing associated disease comorbidities and were older, this suggests a distinct group of patients with allergic disease, not the same patients with nonangioedema allergic disease who were coded differently. The presence of a significant year effect in multivariate analyses with adjustment for age and factors more typically characterizing atopic disease (asthma and urticaria) also points toward angioedema truly being more predominant in more recent years. This national trend contrasts with that observed in Australia, where anaphylaxis hospitalizations have recently surpassed angioedema hospitalizations.¹⁶

With a reported prevalence of hypertension in the United States of close to 30%¹⁷ and with more than 30% of antihypertensive drug prescriptions being written for ACE inhibitors,⁴ it is reasonable to assume that ACE inhibitor therapy is prevalent in the American population. The presence of hypertension in most angioedema admissions also suggests a possible role of ACE inhibitor use. Angioedema related to ACE inhibitor use rarely presents with urticaria,^{18,19} and the small proportion of patients with angioedema in the present study who also manifested urticaria is similar to that reported in ACE inhibitor-associated angioedema series.^{18,19}

Older patients may be at risk for adverse reactions to medications as a result of polypharmacy.²⁰ Nonsteroidal anti-inflammatory drugs are another potential cause of allergic reactions in older patients.²¹ However, possible codes for adverse reactions to nonsteroidal anti-inflammatory drugs, including adverse reactions to aspirin, antirheumatics, and unspecified antipyretics and analgesics, were not more common in angioedema hospitalizations but instead were observed more often in anaphylaxis admissions. In contrast, many angioedema hospitalizations had additional codes for an adverse effect due to a cardiovascular or antihypertensive agent, which suggests that the angioedema was recognized as a complication of drug therapy, possibly an ACE inhibitor.

The ethnic disparity in the burden of disease related to angioedema hospitalizations is apparent in this study. Even after controlling for other factors, including hypertension, African American race was still a strong predictor of hospital admission due to angioedema in the allergic disease hospitalizations cohort. Investigators have postulated a role of increased sensitivity to bradykinin in African American patients who develop angioedema while taking ACE inhibitors.²² These findings underscore the need to develop alternative, effective treatments that do not carry a significant risk of angioedema, especially in high-risk patients, such as African Americans, who also have a higher prevalence of hypertension.²³ Compared with the New York State study by Lin et al,⁸ this national study showed a stronger effect (higher odds ratio) of race on angioedema hospitalizations. This may be due to different racial coding in the national database compared with the SPARCS (Statewide Planning and Re-

search Cooperative System) database used in the New York State study.

It is possible that some dampening in the increase in angioedema-related hospitalizations for more recent years may have been due to an increased awareness of angioedema as a complication of antihypertensive drug treatment and the resulting shift in preferences for alternative treatments that do not pose as great a risk of angioedema in high-risk patients. One alternative treatment that could potentially be considered is the angiotensin II receptor blocker (ARB) class of antihypertensive drugs, which is increasingly being used to treat hypertension.⁴ In a clinical trial by Granger et al²⁴ of patients with congestive heart failure, candesartan was studied as an alternative treatment in patients who had previously experienced ACE inhibitor-induced angioedema. Three of 39 patients (8%) who had been intolerant of ACE inhibitors due to angioedema also experienced non-life-threatening angioedema from the ARB, but only 1 patient discontinued ARB use as a result. This was in contrast to the complete lack of angioedema developing in the 40 patients in the placebo group who previously experienced ACE inhibitor-related angioedema. However, several case reports^{25,26} have noted recurrence of angioedema (including angioedema of the pharynx) after treatment with an ARB in patients who have had previous ACE inhibitor-induced angioedema. Because ARBs have no effect on bradykinin activity, it is unclear how angioedema is promoted in this setting. It has been theorized that angiotensin II receptor stimulation may increase kinin production or may reduce non-ACE kinin-degrading enzymes.²⁷ The key role of the kinin class of mediators in angioedema is evidenced by the recent therapeutic developments of a kallikrein inhibitor²⁸ and a bradykinin receptor 2 antagonist²⁹ for hereditary C1 esterase inhibitor deficiency (hereditary angioedema).

Angioedema, as related to kinin metabolism, can be a significant factor in drug development. The vasopeptidase inhibitor omapatrilat was tested in large clinical trials for congestive hypertension and congestive heart failure.^{30,31} However, this potent inhibitor of ACE was associated with a 3-fold higher incidence of angioedema compared with enalapril (the comparator drug). Omapatrilat was subsequently abandoned for clinical development despite superior treatment effects in hypertension and congestive heart failure.^{30,31} Other medications can affect enzymes, such as dipeptidyl-peptidase IV, which have effects on kinin metabolism. Because dipeptidyl-peptidase IV activity decreases have been noted in patients who had ACE inhibitor-associated angioedema compared with controls,³² it raises the possibility of angioedema developing in patients treated with sitagliptin, which inhibits dipeptidyl-peptidase IV.³³ Sitagliptin, a drug in a new class of antidiabetic medications,³³ was recently approved for use in the United States.

There have been reports of anaphylaxis and other serious allergic reactions associated with venom immunotherapy in patients taking ACE inhibitors.³⁴ To our knowledge, the risk of more severe allergic reactions to any form of immunother-

apy in patients taking ACE inhibitors has not been systematically quantified or established in case-control studies despite published concerns.³⁵ In the present study, the proportion of patients with anaphylaxis who were coded as having an adverse reaction to a cardiovascular or antihypertensive agent was less than one-tenth of the proportion of patients with angioedema. This finding suggests that anaphylaxis is a much less common adverse effect than is angioedema.

One limitation of this study relates to the use of an administrative database, where factors such as incomplete records, variability in coding, miscoding, and differences in verification procedures may contribute to decreased accuracy of findings.³⁶ Clinical details, such as the actual time sequence of clinical events, the actual listing of all administered medications, and the precise manifestations of the angioedema, also were not available. Because the earlier years of the NIS data include fewer participating states, there may be some variability in these national data. However, the NIS is designed to achieve a representative sample of patients from the entire country, making it a valuable source of information despite some inconsistencies, and it has been used in numerous publications during the past decade to define specific important clinical patterns and outcomes.^{37,38} In this study, the NIS database allowed for examination of a large sample of patients admitted to the hospital for allergic diseases to estimate the incidence and characterize the epidemiologic patterns of angioedema hospitalizations in the United States.

ACKNOWLEDGMENTS

We thank Ariel Teitel, MD, and Charles Carpati, MD, for their help.

REFERENCES

1. Saltoun CA, Metzger WJ. Urticaria, AE, and hereditary angioedema. In: Grammer LC, Greenberger PA, eds. *Patterson'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. Stafford RS, Finkelstein SN, Cockburn IM, et al. National trends in antihypertensive prescribing patterns, 1990–2002. *J Gen Intern Med*. 2003;18(suppl 1):157.
4. Ma J, Lee KV, Stafford RS. Changes in antihypertensive prescribing during US outpatient visits for uncomplicated hypertension between 1993 and 2004. *Hypertension*. 2006;48:846–852.
5. Piller LB, Ford CE, Davis BR, et al. 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). *J Clin Hypertens (Greenwich)*. 2006;8:649–656.
6. Gabb GM, Ryan P, Wing LM, et al. Epidemiological study of AE and ACE inhibitors. *Aust N Z J Med*. 1996;26:777–782.
7. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med*. 2001;161:15–21.
8. Lin RY, Cannon AG, Teitel AD. Pattern of hospitalizations for AE in New York between 1990 and 2003. *Ann Allergy Asthma Immunol*. 2005;95:159–166.
9. Agency for Healthcare Research and Quality. *The HCUP Nationwide Inpatient Sample (NIS)*. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
10. Introduction to the HCUP Nationwide Inpatient Sample (NIS) 2005. http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2005.pdf. Accessed March 2, 2008.
11. Entire data set. US Census Bureau Web site. <http://www.census.gov/popest/datasets.html>. Accessed September 20, 2007.
12. Annual state population estimates by demographic characteristics with 5 race groups (5 race alone or in combination groups): April 1, 2000 to July 1, 2006. http://www.census.gov/popest/states/asrh/files/SC_EST2006_alldata5.doc. Accessed September 20, 2007.
13. Goldstein JR, Morning AJ. The multiple-race population of the United States: issues and estimates. *Proc Natl Acad Sci U S A*. 2000;97:6230–6235.
14. Foxman B, Klemstine KL, Brown PD. Acute pyelonephritis in US hospitals in 1997: hospitalization and in-hospital mortality. *Ann Epidemiol*. 2003;13:144–150.
15. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114:465–474.
16. Poulos LM, Waters AM, Correll PK, et al. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol*. 2007;120:878–884.
17. Centers for Disease Control and Prevention. Racial/ethnic disparities in prevalence, treatment, and control of hypertension—United States, 1999–2002. *MMWR Morb Mortal Wkly Rep*. 2005;54:7–9. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5401a3.htm>. Accessed September 21, 2007.
18. Sondhi D, Lippmann M, Murali G. Airway compromise due to angiotensin-converting enzyme inhibitor-induced AE: clinical experience at a large community teaching hospital. *Chest*. 2004;126:400–404.
19. Malde B, Regalado J, Greenberger PA. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Ann Allergy Asthma Immunol*. 2007;98:57–63.
20. Lampela P, Hartikainen S, Sulkava R, Huupponen R. Adverse drug effects in elderly people: a disparity between clinical examination and adverse effects self-reported by the patient. *Eur J Clin Pharmacol*. 2007;63:509–515.
21. Jenerowicz D, Czarnecka-Operacz M, Gorecka A, Stawny M. Drug-related hospital admissions: an overview of frequency and clinical presentation. *Acta Pol Pharm*. 2006;63:395–399.
22. Gainer JV, Nadeau JH, Ryder D, et al. Increased sensitivity to bradykinin among African Americans. *J Allergy Clin Immunol*. 1996;98:283–287.
23. Ferdinand KC, Armani AM. The management of hypertension in African Americans. *Crit Pathw Cardiol*. 2007;6:67–71.
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. 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.
26. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother*. 2000;34:526–528.
27. Roskiewicz F, Andriamanana I, Gras-Champel V, et al. Iatrogenic angioedema: the role of angiotensin converting enzyme inhibitor and angiotensin II receptor blockers [in French]. *Nephrol Ther*. 2007;3:89–95.
28. Schneider L, Lumry W, Vegh A, et al. Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol*. 2007;120:416–422.
29. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol*. 2007;119:1497–1503.
30. 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.
31. Solomon SD, Skali H, Bourgoun M, et al. Effect of angiotensin-

-
- converting enzyme or vasopeptidase inhibition on ventricular size and function in patients with heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) echocardiographic study. *Am Heart J*. 2005;150:257–262.
32. Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension*. 2008;51:141–147.
33. Ahrén B. DPP-4 inhibitors. *Best Pract Res Clin Endocrinol Metab*. 2007;21:517–533.
34. Stumpf JL, Shehab N, Patel AC. Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother*. 2006;40:699–703.
35. Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol*. 2003;112:1008–1009.
36. Iezzoni LI. Assessing quality using administrative data. *Ann Intern Med*. 1997;127:666–674.
37. MacMullen NJ, Tymkow C, Shen JJ. Adverse maternal outcomes in women with asthma: differences by race. *MCN Am J Matern Child Nurs*. 2006;31:263–268.
38. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *JAMA*. 2007;298:423–429.
- Requests for reprints should be addressed to:*
Robert Y. Lin, MD
Department of Medicine
St Vincent's Hospital Manhattan
Saint Vincent Catholic Medical Centers
153 W 11th St
New York, NY 10011
E-mail: robert_lin@nymc.edu
-