

Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis

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Background: Risk factors for increased anaphylaxis severity are poorly understood. Angiotensin-converting enzyme (ACE) inhibitors have been associated with severe anaphylactic reactions in patients with hymenoptera venom allergy. Studies evaluating the association between beta-blockers and severe anaphylaxis have been conflicting.

Objective: To evaluate the association between antihypertensive medication use and increased anaphylaxis severity.

Methods: We included emergency department anaphylaxis patients aged 18 years and older. Markers of severe anaphylaxis were defined as (1) syncope, hypotension, or hypoxia; (2) signs and symptoms involving 3 or more organ systems; and (3) hospitalization. Antihypertensive medications evaluated included beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, and diuretics. Simple and multiple logistic regression analyses were conducted to estimate the association between antihypertensive medication use and markers of increased anaphylaxis severity.

Results: Among 302 patients with anaphylaxis, 55 (18%) had syncope, hypoxia, or hypotension, 57 (19%) required hospitalization, and 139 (46%) had 3 or more organ system involvement. After adjusting for age, gender, suspected trigger, and preexisting lung disease, beta-blocker, ACE-inhibitor, diuretic, or antihypertensive medication use in aggregate remained associated with both 3 or more organ system involvement and need for hospital admission. The adjusted associations between antihypertensive medication use in aggregate and 3 or more organ system involvement yielded an odds ratio of 2.8 (95% CI, 1.5-5.2; $P = .0008$) and with hospitalization an odds ratio of 4.0 (95% CI, 1.9-8.4; $P = .0001$).

Conclusions: In emergency department anaphylaxis patients, antihypertensive medication use is associated with increased organ system involvement and increased odds of hospital admission, independent of age, gender, suspected trigger, or preexisting lung disease. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Anaphylaxis, antihypertensive medications, angiotensin-converting enzyme inhibitor, beta-blocker, risk factors, emergency department

Anaphylaxis is a systemic allergic reaction that is most commonly treated in the emergency department (ED).^{1,2} Signs and symptoms can vary from relatively mild to life-threatening.^{3,4} Brown⁴ developed a grading system linking clinical features with severity. Based on this grading system, severe anaphylaxis was defined as patients who experienced hypoxia, hypotension, or neurologic compromise, typically manifested by collapse.

Risk factors for severe anaphylaxis are poorly understood. In previous studies, ACE inhibitors have been associated with severe anaphylactic reactions in patients with hymenoptera venom allergy.⁵ There are numerous case reports of increased severity of anaphylaxis in patients taking beta-blockers.⁶⁻⁹ Beta-blocker use has been associated with an increased risk of an anaphylactic reaction to intravenous contrast, but not with an increased risk of anaphylaxis in patients receiving allergen immunotherapy injections.^{4,10,11} In multiple logistic regression analyses, however, ACE-inhibitor and beta-blocker use was not associated with severe anaphylaxis.⁴ Thus, the association of beta-blockers and ACE inhibitors with increased anaphylaxis severity has not been clearly established. Furthermore, the association of the use of diuretics or antihypertensive medications in general with anaphylaxis severity has not been reported.

We hypothesized that the use of beta-blockers, ACE inhibitors, or other antihypertensive medications including diuretics, calcium channel blockers (CCBs), and angiotensin receptor blockers is associated with markers of increased anaphylaxis severity. To test this hypothesis, we sought to estimate the association between antihypertensive medication use and markers of increased anaphylaxis severity.

METHODS

Study design and setting

The study had a retrospective observational cohort design. Patients were consecutively included at the Saint Mary's Hospital ED, a tertiary care academic ED with 72,000 annual patient visits.

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Abbreviations used

ACE: Angiotensin-converting enzyme

CCB: Calcium channel blocker

ED: Emergency department

NIAID/FAAN: National Institute of Allergy and Infectious Diseases/
Food Allergy and Anaphylaxis Network

OR: Odds ratio

SBP: Systolic blood pressure

Selection of participants

Electronic medical records of ED patients aged 18 years and older were electronically queried. Records of all patients who had any ED diagnosis containing “allergy,” “anaphy,” or “sting” were reviewed, and those who met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria for anaphylaxis were included. The study was conducted from April 2008 to July 2011. The Mayo Clinic institutional review board approved all study procedures.

Data collection and outcome measures

Data were collected by using a standardized data abstraction form. We collected data on daily medication use, medical history, suspected triggers of the anaphylaxis episode (based on documented trigger at the time of the ED evaluation), clinical signs and symptoms, ED management, and disposition. Markers of increased anaphylaxis severity included the following: (1) signs and symptoms of syncope, hypotension, or hypoxia; (2) signs and symptoms involving 3 or more organ systems; and (3) hospital admission. Hypotension was defined according to the NIAID/FAAN criteria as a 30% drop in systolic blood pressure (SBP) from baseline; or: SBP less than 70 mm Hg for children 1 month to 1 year, or less than (70 mm Hg + [2 × age]) for children 1 to 10 years, or less than 90 mm Hg for children 11 to 17 years and adults.

Statistical analysis

We present all continuous data as medians with interquartile range as appropriate for the distribution of the data. Categorical data are presented as percent frequency of occurrence. Simple (univariate) and multiple (multivariable) logistic regression models were fit to estimate the association between antihypertensive medication use and markers of increased severity of anaphylaxis. Because previous studies demonstrated potential associations between age, gender, the suspected trigger of the reaction, and underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and anaphylaxis severity, we adjusted for these confounders in multiple logistic regression analyses. Cardiovascular disease was highly correlated with antihypertensive medication use and was therefore dropped from the multiple logistic regression analysis to avoid the problem of collinearity.

Odds ratios (ORs) with corresponding 95% CIs were calculated for each association. *P* values represent 2-sided hypothesis testing unless otherwise noted, and *P* value of .05 or less was considered statistically significant. Statistical analyses were performed by using JMP software, version 9.0 (SAS Institute, Inc, Cary, NC).

RESULTS

From April 2008 to July 2011, we included 302 adults who met NIAID/FAAN diagnostic criteria for anaphylaxis. Baseline characteristics, suspected triggers of anaphylaxis, underlying lung disease, and outcomes of the study cohort are summarized in Table I. Median age of the study sample was 44.3 years (interquartile range, 31.5–58.0). Two hundred four patients (68%) were female, and 91% were white, reflecting the relatively small proportion of minorities in the community. Eighty-seven (29%) patients were on at least 1 antihypertensive medication, 49

TABLE I. Patient characteristics and outcomes in 302 ED patients with anaphylaxis

Variable	Finding, n (%)
Females	204 (68)
Age (y)	
Median (IQR)	44.3 (32–58)
Race	
White	274 (91)
Hispanic	0
Black	9 (3)
Asian/Pacific islander	4 (1)
Other	13 (4)
Unknown	2 (1)
Inciting allergen	
Food	82 (27)
Medication	78 (26)
Venom	29 (10)
Latex	2 (1)
Contrast	17 (6)
Other	14 (5)
Unknown	80 (27)
Lung disease	
Asthma	75 (25)
COPD	9 (3)
Antihypertensive agents	
Beta-blockers	49 (16)
ACE inhibitors	34 (11)
CCBs	22 (7)
ARBs	8 (3)
Diuretics	45 (15)
Any antihypertensive	87 (29)
Outcomes	
Intubation	8 (3)
Syncope, hypotension, hypoxia	55 (18)
≥3 Organ system involvement	139 (46)
Hospital admission	57 (19)

ARBs, Angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

(16%) were on beta-blockers, 34 (11%) were on ACE inhibitors, 22 (7%) were on CCBs, 8 (3%) were on angiotensin receptor blockers, and 45 (15%) were on diuretics.

Fifty-five patients (18%) had signs or symptoms of syncope, hypoxia, or hypotension. One hundred thirty-nine patients (46%) had 3 or more organ system involvement, and 57 (19%) patients required hospital admission, including 27 to the intensive care unit and 30 to the ward. To establish the association between hospital admission and anaphylaxis severity, we analyzed the association between hospital admission and symptom severity (presence of syncope, hypoxia, hypotension) as well as the association between hospital admission and the administration of more than 1 dose of epinephrine by performing multiple logistic regression analysis. We found (after adjusting for age, gender, trigger, and underlying cardiovascular or lung disease) that both the presence of syncope, hypotension, or hypoxia (OR, 4.5; 95% CI, 2.2–9.2; *P* < .0001) and the administration of more than 1 dose of epinephrine (OR, 17.3; 95% CI, 7.0–46.4; *P* < .0001) were associated with hospital admission, indicating that admission was likely to be based on the severity of anaphylaxis.

On simple logistic regression analyses, beta-blocker, ACE-inhibitor, diuretic, or antihypertensive medication use in

TABLE II. Simple logistic regression associations (n = 302)

Medication	Syncope, hypotension, hypoxia, n (%)		OR (95% CI), <i>P</i> value	>3 Systems, n (%)		OR (95% CI), <i>P</i> value	Hospital admission, n (%)		OR (95% CI), <i>P</i> value
	Yes	No		Yes	No		Yes	No	
	(n = 55)	(n = 247)		(n = 139)	(n = 163)		(n = 57)	(n = 245)	
Beta-blockers	13 (24)	36 (15)	1.8 (0.9-3.7), .1	31 (22)	18 (11)	2.3 (1.2-4.4), .01	20 (35)	29 (12)	4.0 (2.1-7.9), <.0001
ACE inhibitors	8 (15)	26 (11)	1.5 (0.6-3.4), .4	22 (16)	12 (7)	2.4 (1.1-5.0), .02	16 (28)	18 (7)	4.9 (2.3-10.4), <.0001
CCBs	5 (9)	17 (7)	1.4 (0.5-3.8), .6*	12 (9)	10 (6)	1.4 (0.6-3.5), .4	8 (14)	14 (6)	2.7 (1.1-6.8), .04*
ARBs	1 (2)	7 (3)	0.6 (0.1-5.3), 1.0*	4 (3)	4 (3)	1.2 (0.3-4.8), 1.0*	3 (5)	5 (2)	2.7 (0.62-11.5), .2*
Diuretics	11 (20)	34 (14)	1.6 (0.7-3.3), .2	28 (20)	17 (10)	2.2 (1.1-4.2), .02	20 (35)	25 (10)	4.8 (2.4-9.4), <.0001
Any	20 (36)	67 (27)	1.5 (0.8-2.8), .2	54 (39)	33 (20)	2.5 (1.5-4.2), .0004	32 (56)	55 (23)	4.4 (2.4-8.1), <.0001

ARBs, Angiotensin receptor blockers.

*Two-tailed Fisher exact test.

aggregate was significantly associated with 3 or more organ system involvement (Table II). Furthermore, these medications as well as CCBs were associated with hospitalization (Table II). The unadjusted associations between antihypertensive medication use in aggregate and 3 or more organ system involvement yielded an OR of 2.5 (95% CI, 1.5-4.2; *P* = .0004) and with hospitalization an OR of 4.4 (95% CI, 2.4-8.1; *P* < .0001). Simple logistic regression analysis also showed that chronic obstructive pulmonary disease, but not asthma, was associated with hospital admission. However, after adjusting for age, the association was no longer significant. Simple logistic regression analysis did not reveal any significant associations between individual antihypertensive medications and hypotension or the requirement for repeat epinephrine dosing, or continuous inotrope infusion (data not shown).

After adjusting for age, gender, suspected trigger, and lung disease, none of the antihypertensive medications was significantly associated with presenting signs of syncope, hypotension, or hypoxia (Fig 1, A), with an adjusted OR of 1.3 (95% CI, 0.61-2.7; *P* = .51) for antihypertensive medication use in aggregate. However, beta-blocker, ACE-inhibitor, diuretic, and antihypertensive medication use in aggregate was significantly associated with 3 or more organ system involvement (Fig 1, B) and hospitalization (Fig 1, C). The adjusted association between antihypertensive medication use in aggregate and 3 or more organ system involvement was significant (OR, 2.8; 95% CI, 1.5-5.2; *P* = .0008), as was the adjusted association with hospitalization (OR, 4.0; 95% CI, 1.9-8.4; *P* = .0001).

DISCUSSION

In our cohort we observed that antihypertensive medication use was associated with increased organ system involvement and hospital admission after adjusting for age, gender, suspected trigger, and preexisting lung disease. Although the associations between ACE inhibitors and beta-blockers and anaphylaxis severity have been evaluated previously, our study includes a larger spectrum of potential markers of increased severity and collected data on additional antihypertensive medications.

Antihypertensive medications could potentiate anaphylaxis, leading to increased organ system involvement and increased likelihood of hospital admission in numerous ways. ACE inhibitors competitively inhibit the ACE, which is a nonspecific enzyme involved in the metabolism of several small peptides including bradykinin.¹² ACE is responsible for 70% to 90% of bradykinin catabolism.¹² Bradykinin stimulates the synthesis of

nitric oxide, which enhances vasodilatation. In addition, bradykinin and other mediators that accumulate in the setting of ACE inhibition can stimulate bronchospasm.¹³ Furthermore, acute elevations in bradykinin levels can cause severe oropharyngeal angioedema, such as that seen in hereditary angioedema.¹⁴ Thus, physiologically, ACE inhibition could increase levels of bradykinin and subsequently lead to angioedema, hypotension, and bronchospasm. Likewise, the increased anaphylaxis severity of patients taking beta-blockers may be related to an exacerbation of bronchospasm, decreased cardiac contractility, or a blunted response to the epinephrine used for treatment. Diuretics may contribute to relative intravascular depletion and decreased cardiovascular reserve in the setting of an anaphylactic reaction.

Summers et al¹⁵ studied the association between serum ACE levels and pharyngeal edema in patients with peanut and tree nut allergy presenting to an allergy clinic. Although none of the patients was on ACE inhibitors, patients with severe pharyngeal edema (as defined by association with drooling or dyspnea) had significantly lower serum ACE levels than did those without pharyngeal edema. Furthermore, patients with serum ACE levels in the lowest quartile were 9.7 times more likely to have severe pharyngeal edema than were patients with higher ACE levels after correcting for age, gender, and atopic diseases. In contrast, there was no significant association between serum ACE level and severe bronchospasm, reduced consciousness, urticaria, and nonpharyngeal angioedema. These results suggest that a lower serum ACE activity level, which may also be seen in patients taking ACE inhibitors, increases the risk of severe pharyngeal edema. In our cohort we found an association between ACE-inhibitor use and 3 or more organ system involvement and hospitalization. We did not find an association between ACE-inhibitor use and oropharyngeal edema (data not shown), suggesting that the increased severity may be related to a variety of mechanisms. Larger studies are needed to more precisely determine the mechanism responsible for increased anaphylaxis severity in ED patients taking ACE inhibitors.

The association between beta-blockers and ACE inhibitors was evaluated in an observational cohort study of patients with known bee or vespid venom allergy presenting to 14 allergy clinics.⁵ Twenty-one percent of the patients experienced a severe reaction defined as anaphylactic shock, loss of consciousness, or cardiopulmonary arrest. Although beta-blocker use was significantly associated with severe anaphylaxis on only simple logistic regression analysis, ACE-inhibitor use remained associated with increased anaphylaxis severity in a multiple logistic regression model. Because only 5% of the patients in the cohort were on

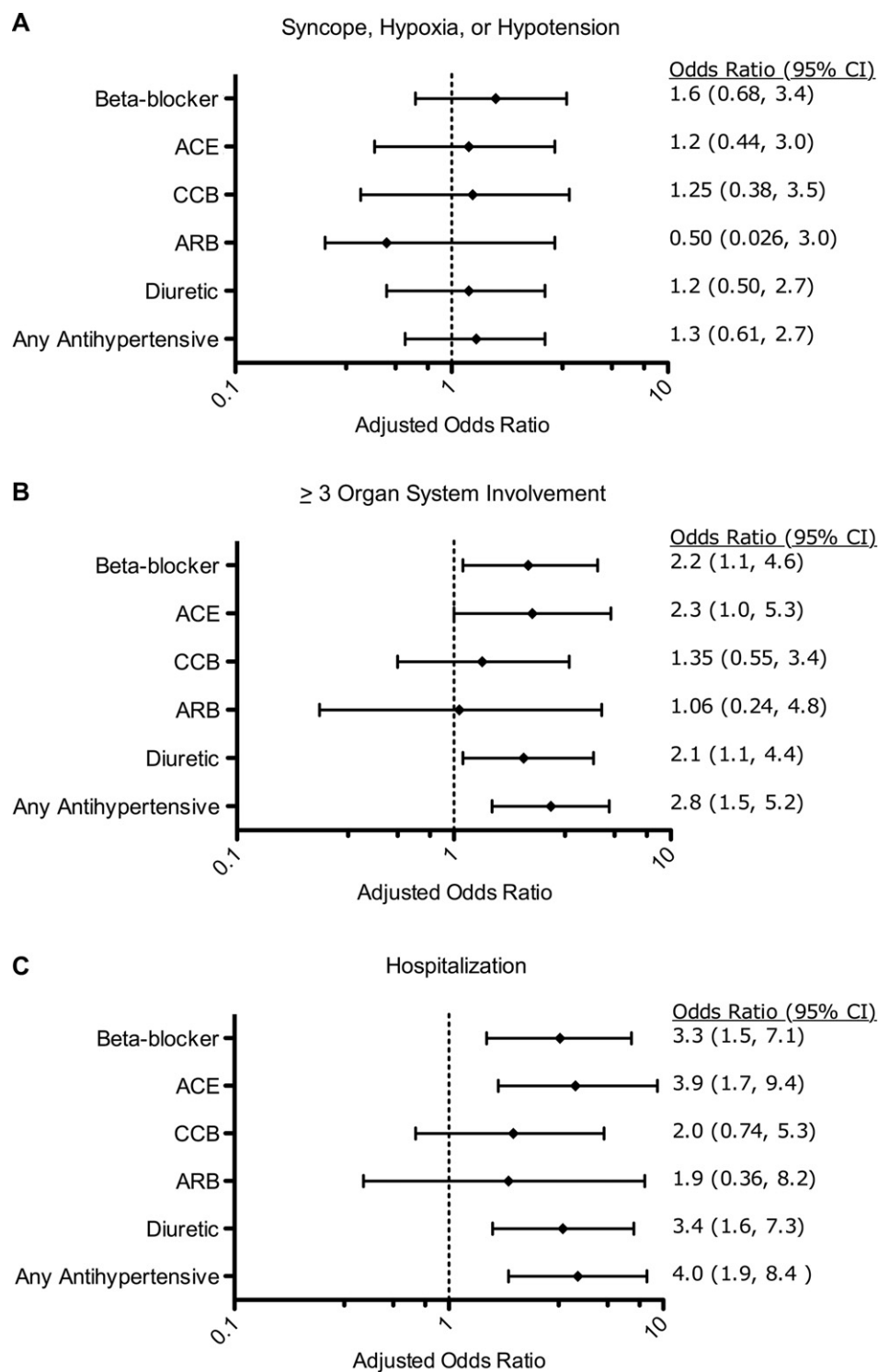


FIG 1. Multiple logistic regression analysis adjusted ORs (95% CI) for the association between antihypertensive medications and syncope, hypoxia, or hypotension (**A**); 3 or more organ system involvement (**B**); and hospitalization adjusted for gender, age, suspected trigger, and preexisting lung disease (**C**). *ARB*, Angiotensin receptor blocker.

beta-blockers, however, the authors concluded that their negative finding did not rule out the possibility of an association between beta-blockers and severe anaphylaxis.

The absence of an association between antihypertensive medications and severe anaphylaxis defined as syncope, hypoxia, or

hypotension in our cohort is consistent with the findings of Brown.⁴ Brown conducted a retrospective study of 1149 ED patients including children and adults designed to develop a clinical grading system for anaphylaxis, with a secondary aim to evaluate the predictors of severe anaphylaxis including associations with

beta-blocker or ACE-inhibitor use. The cohort included 21 patients (2%) on beta-blockers and 57 patients (5%) on ACE inhibitors. A total of 139 (12%) patients had severe anaphylaxis defined as signs and symptoms of hypotension, hypoxia, and collapse. Although both beta-blockers and ACE inhibitors were associated with reaction severity in simple logistic regression analyses, after adjusting for age, neither beta-blocker nor ACE-inhibitor use remained significantly associated. Based on the lack of a significant adjusted association, ORs were not presented in the article. In addition, a power calculation was not included.

Despite finding an approximately 10% and 6% increase in the rates of syncope, hypoxia, or hypotension in patients taking beta-blockers and ACE inhibitors, respectively, these were not statistically significant differences. Our study was underpowered to detect differences of less than 20%. Thus, our results agree with those by Brown, but do not entirely exclude the possibility that beta-blockers and ACE inhibitors are predictors of an increased risk of hypoxia, hypotension, or syncope in ED anaphylaxis patients. Furthermore, certain medications may preferentially dispose particular patients to increased severity, such as patients on ACE inhibitors who have venom allergy.⁵ We are unable to determine the effects of antihypertensive medications in subpopulations because of the heterogeneity of our ED cohort; larger studies are needed.

The association between multiple antihypertensive medications and markers of anaphylaxis severity may support the theory that underlying cardiovascular comorbidities and not the individual antihypertensive medications predispose patients to more severe anaphylactic reactions. The consistent finding that age is an independent risk factor for increased anaphylaxis severity also supports this idea.^{4,5,15,16} Impaired endothelial vascular signaling and subsequent endothelial dysfunction is a putative mechanism underlying cardiovascular disease.¹⁷ Endothelial dysfunction results in systemic microvascular remodeling, impaired endothelium-dependent vasodilation, and augmented vasoconstriction. Mechanisms underlying endothelial dysfunction are complex and involve multiple vasoactive mediators including nitric oxide, prostacyclin, endothelin-1, thromboxane A2, and others.^{17,18} Dysfunction of these signaling pathways may result in exaggerated responses to the vasoactive mediators of anaphylaxis, impaired physiologic compensatory mechanisms, or potentially a blunted responsiveness to epinephrine administration, predisposing patients to more severe anaphylaxis. Furthermore, the interactions between the medications and the comorbidities may predispose patients to involvement of more organ systems and increased hospital admissions. We are unable to account for the effect of cardiovascular comorbidities on anaphylaxis severity in our cohort because of the high correlation between cardiovascular disease and antihypertensive medication use.

Although there have been no randomized trials or prospective studies on the effects of antihypertensive medications on anaphylaxis severity, a decision-analytic model was developed to guide clinicians to determine whether beta-blocker therapy would be beneficial in patients with peanut allergy.¹⁹ Based on this model, beta-blocker therapy would improve survival in patients with congestive heart failure or a history of myocardial infarction. Although we cannot draw definitive conclusions with regard to the long-term risks and benefits of antihypertensive medications in patients with anaphylaxis, our results indicate that beta-blockers, ACE inhibitors, and diuretics may increase the risk of

severe anaphylaxis. We did not identify statistically significant associations of angiotensin receptor blockers and CCBs with severe anaphylaxis after multivariable adjustment. Because of the relative rarity of these medications in the cohort studied, future studies are needed to determine whether these medications might be reasonable alternatives for patients with a history of anaphylaxis.

Our study has several limitations. Data quality is dependent on the accuracy of the medical record because of the retrospective study design. However, standardized data abstraction forms were used to reduce random and systematic errors and enhance the precision and accuracy of the variables collected. Furthermore, patients were included in the study as a consecutive cohort to decrease the impact of selection biases. The relatively small sample size prohibits additional subgroup analyses such as the association between groups of patients on multiple antihypertensive medications or effects on groups of patients with a particular trigger. In addition, as mentioned above, because of the collinearity between antihypertensive use and cardiovascular disease, we were unable to include cardiovascular disease in our multiple logistic regression model. Therefore, we cannot rule out the possibility that underlying cardiovascular comorbidity is a significant risk factor for more severe anaphylaxis. Finally, this study was performed at a single center with a predominantly white cohort, which may limit external validity.

In conclusion, beta-blocker, ACE-inhibitor, diuretic, or antihypertensive medication use in aggregate was associated with increased organ system involvement and hospital admission in ED patients with anaphylaxis. Based on the trend toward increased severity with multiple antihypertensive medications, it may be that cardiovascular comorbidities or the combination of these comorbidities and the medications used to treat them predispose patients to increased severity of anaphylaxis. Larger studies are needed to further define the effects of these medications with regard to specific symptoms or triggers.

Clinical implications: Patients on antihypertensive medications may be at risk for more severe anaphylaxis. Physicians should take this into consideration when caring for and counseling these patients.

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