

Patients Taking β -Blockers Do Not Require Increased Doses of Epinephrine for Anaphylaxis



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What is already known about this topic? Risk factors for increased anaphylaxis severity are numerous, and some evidence suggests that β -blocker use may predispose patients to more severe anaphylaxis.

What does this article add to our knowledge? β -Blocker use was not associated with a significantly increased need for any epinephrine or repeat epinephrine dosing among patients seen in an emergency department with anaphylaxis.

How does this study impact current management guidelines? β -Blocker use may not be clinically significant with regard to epinephrine responsiveness among patients with anaphylaxis.

BACKGROUND: β -Blocker use has been associated with increased anaphylaxis severity.

OBJECTIVE: We aimed to assess for an association between β -blocker use and requirement for more than 1 dose of epinephrine for anaphylaxis management.

METHODS: We conducted a retrospective observational study of patients seen in our emergency department for anaphylaxis between April 2008 and January 2015. The primary outcome measure was the number of doses of epinephrine. Associations with repeat epinephrine administration (>1 vs ≤ 1 dose of epinephrine) and associations with any epinephrine administration (>0 vs 0 dose) were evaluated using logistic regression models and summarized as odds ratio (OR) and 95% CIs. The study was powered to detect a 10% or greater difference in need for repeat epinephrine administration between patients who were and were not taking β -blocker medications.

RESULTS: Of 789 patient visits with a documented medication history included in the study, 63 (8%) required more than 1 epinephrine dose and 83 (11%) were on β -blocker therapy. Among patients who required more than 1 epinephrine dose,

8 (13%) were taking a β -blocker, compared with 75 patients (10%) who received 0 or 1 dose of epinephrine (OR, 1.26; 95% CI, 0.58-2.75). Among patients who required at least 1 epinephrine dose, 41 (9%) were taking a β -blocker, compared with 42 patients (12%) who received no epinephrine (OR, 0.73; 95% CI, 0.46-1.14).

CONCLUSIONS: β -Blocker use may not be clinically significant with regard to the need for epinephrine dosing among emergency department patients with anaphylaxis. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1553-8)

Key words: Anaphylaxis; β -Blocker; Emergency department; Epinephrine

INTRODUCTION

Visits to the emergency department (ED) for anaphylaxis have recently doubled.¹ Risk factors for increased severity of anaphylaxis are numerous, and there is evidence that β -blocker use may predispose a patient toward more severe anaphylaxis.²⁻⁴ However, the clinical significance of this increased risk with regard to the need for increased doses of epinephrine has not been demonstrated.

The pathophysiology and pharmacodynamics of β -blocker effects on anaphylaxis have been demonstrated by animal studies.⁴ Several different models could explain the association of β -blockers and increased anaphylaxis severity, including the priming of mast cells for mediator release and the blunting of the physiologic response to endogenously produced or exogenously administered catecholamines.⁵ Another important consideration is that most patients taking β -blockers are being treated for cardiovascular disease. This potentially confounds the data because patients with known cardiovascular disease may independently have poorer outcomes in the setting of anaphylaxis.^{6,7}

Although studies have demonstrated an association between β -blocker use and increased anaphylaxis severity, as evidenced by increased organ system involvement and hospital admission, an association with the need for increased epinephrine dosing has

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Abbreviations used

ACE- Angiotensin-converting enzyme
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
ICU- Intensive care unit
OR- Odds ratio

not been established. The primary objective of our study was to determine whether the risk of requiring more than 1 dose of epinephrine for the treatment of anaphylaxis is increased among ED patients taking β -blocker medications. A secondary outcome of interest was to determine whether patients using β -blockers were more likely to require any epinephrine compared with those not using β -blockers.

METHODS

This study adheres to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) Statement.⁸ We conducted a single-center retrospective observational study of ED patients who met the diagnostic criteria for anaphylaxis. Our electronic records system was searched to identify patients who sought care between April 2008 and January 2015 at Mayo Clinic Hospital—Rochester, Saint Marys Campus, Rochester, Minnesota—a tertiary care academic ED with approximately 73,000 visits per year.

Selection of participants

All patients who provided research consent and who met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis⁹ were included. Detailed methods on patient selection have been previously published.¹⁰ The Mayo Clinic Institutional Review Board approved the study.

Data collection and outcome measures

We collected data using a previously piloted and developed standardized data collection form. Data collection was performed by 2 resident physicians who received training before the beginning of this study, and variables were clearly defined before data abstraction. Questions that arose during the data abstraction process were discussed with the primary investigators. A sample of charts was reviewed by both reviewers. Reviewers were not blinded to the study hypothesis. Patients were excluded from the primary and secondary outcome analysis if they did not have a documented medication list in the electronic health record within 3 months of the ED visit date.

Data collected included demographic characteristics, specification of anaphylactic symptoms and trigger (if known), medications, medical history including cardiovascular disease and chronic obstructive pulmonary disease (COPD), dosages of epinephrine administered, and disposition after ED evaluation. Cardiovascular disease was defined as coronary artery disease, myocardial infarction, angina, heart failure, valvular heart disease, arrhythmia syndromes, and congenital heart disease. Routes of epinephrine administration included subcutaneous, intramuscular, and intravenous. Nebulized epinephrine administration was not included.

Statistical analysis and sample size calculation

Continuous data are summarized as median (interquartile range), and categorical data are summarized as number (percentage). Comparisons of variables between patient visits with and without

documentation of medication history were evaluated using Wilcoxon rank sum, chi-square, and Fisher exact tests. Associations with repeat epinephrine administration (>1 vs ≤ 1 dose of epinephrine) and associations with any epinephrine administration (>0 vs 0) were evaluated using logistic regression models and summarized as odds ratio (OR) and 95% CI. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). All tests were 2-sided, and P values of less than .05 were considered statistically significant.

Sample size calculations were performed on the basis of a 2-sided chi-square test assuming 80% power and a significance level of .05. Assumptions for expected results were based on an estimation that approximately 8% of ED patients with anaphylaxis require more than 1 dose of epinephrine and that approximately 10% are taking a β -blocker medication.¹⁰ To detect an absolute increase in need for more than 1 dose of epinephrine from 7% to 17%, a sample size of 790 patients would be required. To detect an increase of 20% (50% vs 70%) in the need for any epinephrine dosing would require a sample size of 530 patients.

RESULTS

During the study period, 885 ED visits occurred among 819 patients who granted permission for review of their medical records and met diagnostic criteria for anaphylaxis.⁹ Of these patient visits, 789 (89%) had documentation of medication history. There were no significant differences with regard to repeat epinephrine administration (>1 vs ≤ 1 dose of epinephrine) or need for any epinephrine administration (>0 vs 0 dose of epinephrine) between those with and without a documented medication history (Table I). However, those without a documented medication history were more likely to be male and to be discharged home, and less likely to have respiratory and mucocutaneous symptoms and to have a history of several prior allergic conditions. Because the primary outcome used to power the study during the design phase was repeat epinephrine use, this was the primary outcome chosen for analysis.

Analysis of patients with documented medications

Among the 789 patient visits with documented medication history, 63 (8%) resulted in repeat epinephrine administration and 83 (11%) were taking β -blockers. β -Blockers were used by 8 patients (13%) who required more than 1 dose of epinephrine, versus 75 patients (10%) who received 0 or 1 dose of epinephrine (OR, 1.26; 95% CI, 0.58-2.75; $P = .56$) (Table II). The association of β -blocker use with repeat epinephrine administration remained statistically nonsignificant after adjusting for age, sex, precipitating allergen, COPD, and cardiovascular disease in a multivariable setting (OR, 1.51; 95% CI, 0.66-3.42; $P = .33$). In addition, 41 patients (9%) who required at least 1 epinephrine dose were on a β -blocker, compared with 42 patients (12%) who received no epinephrine (OR, 0.73; 95% CI, 0.46-1.14; $P = .17$) (Table III).

For a sensitivity analysis, we evaluated associations of β -blocker use with epinephrine use using generalized estimating equations, and none of the associations was statistically significant. The associations (ORs) of β -blocker use with repeat epinephrine administration, before and after multivariable adjustment, were 1.71 (95% CI, 0.73-3.95; $P = .22$) and 1.72 (95% CI, 0.66-4.51; $P = .27$). The association (OR) of β -blocker use with any epinephrine administration was 0.74 (95% CI, 0.47-1.15; $P = .18$).

TABLE I. Comparison of features between patient visits with and without documentation of medication history (N = 885)

Feature	Documented medication history		P
	No (n = 96)	Yes (n = 789)	
Age at visit (y)	33 (15-49)	34 (18-53)	.15
Age at visit (y)			.34
<18	28 (29)	195 (25)	
≥18	68 (71)	594 (75)	
Sex			.04
Male	50 (52)	323 (41)	
Female	46 (48)	466 (59)	
Race	(n = 95)	(n = 780)	.42
White	80 (84)	680 (87)	
All others	15 (16)	100 (13)	
Symptoms in ED			
Mucocutaneous	89 (93)	782 (99)	<.001
Gastrointestinal	33 (34)	311 (39)	.34
Respiratory	71 (74)	664 (84)	.01
Cardiovascular	32 (33)	326 (41)	.13
Suspected precipitating allergen			.52
Food	29 (30)	276 (35)	
Medication	16 (17)	157 (20)	
Venom	17 (18)	96 (12)	
Latex	0	2 (<1)	
Contrast	7 (7)	38 (5)	
Other	3 (3)	40 (5)	
Unknown	24 (25)	180 (23)	
Personal history			
Anaphylaxis	20 (21)	238 (30)	.06
Medication allergy	39 (41)	404 (51)	.05
Food allergy	26 (27)	299 (38) (n = 784)	.03
Insect sting allergy	8 (8) (n = 95)	98 (12) (n = 786)	.25
Asthma	16 (17) (n = 95)	226 (29) (n = 788)	.02
Seasonal allergy	13 (14) (n = 95)	191 (24)	.02
Atopic dermatitis	7 (7) (n = 95)	74 (9) (n = 788)	.52
Disposition			.002
Home	57 (59)	360 (46)	
Observation unit	25 (26)	328 (42)	
Admitted to hospital	11 (11)	46 (6)	
Admitted to ICU	3 (3)	55 (7)	
Epinephrine doses			.16
0	35 (36)	343 (43)	
1	51 (53)	383 (49)	
>1	10 (10)	63 (8)	
Epinephrine doses			.41
≤1	86 (90)	726 (92)	
>1	10 (10)	63 (8)	

Values are median (interquartile range) or no. of visits (%).

Analysis in adult patients

A comparison of medication use by patient age revealed that none of the 195 patients younger than 18 years had a history of β -blocker, angiotensin-converting enzyme (ACE) inhibitor, calcium channel blocker, or angiotensin receptor blocker use. Thus, the associations with epinephrine administration were repeated

in the subset of 594 patient visits among adults only (Table III). History of anaphylaxis was similar between adult patients who were and were not taking β -blockers (29% vs 30%; $P = .79$). There was no significant association between β -blocker use and epinephrine administration for more than 1 versus 0 or 1 dose of epinephrine (OR, 1.22; 95% CI, 0.55-2.71; $P = .62$) or for 1 or more versus 0 doses of epinephrine (OR, 0.76; 0.48-1.20; $P = .24$) in adult patients. The association of β -blocker use with repeat epinephrine administration among adults remained statistically nonsignificant after adjusting for sex, precipitating allergen, COPD, and cardiovascular disease in a multivariable setting (OR, 1.64; 95% CI, 0.72-3.71; $P = .24$) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Furthermore, the association of β -blocker use with any epinephrine administration also was not statistically significant among adult patients after similar adjustments (OR, 0.96; 95% CI, 0.57-1.62; $P = .87$).

Univariable associations of repeat epinephrine administration with cardiovascular symptoms, including hypotension, chest pain, presyncope, syncope, or incontinence, were not statistically significant. The OR for hypotension, specifically, was 1.98 (95% CI, 0.89-4.39; $P = .09$).

A total of 55 patients were admitted to the intensive care unit (ICU). Patients taking β -blockers were significantly more likely than those not taking β -blockers to be admitted to the ICU (14% vs 6%; $P = .005$), although when adjusting for admission to the ICU, the association of β -blocker use with repeat epinephrine administration was still not statistically significant (OR, 0.89; 95% CI, 0.38-2.08; $P = .79$).

DISCUSSION

In this study of 789 ED patient visits for anaphylaxis, we did not find a significant association between β -blocker use and the need for increased epinephrine dosing. This suggests that the effects of β -blockers may not be as clinically significant as previously thought. Patients who required more than 1 dose of epinephrine were not significantly more likely to be taking a β -blocker than those who required 0 or 1 dose of epinephrine. Furthermore, those who required any epinephrine for the management of their anaphylactic reaction were also not more likely to be taking a β -blocker.

Physiologically, β -receptor signaling mediates catecholamine response and is, thus, essential to survival during anaphylaxis via downstream effects on vasomotor tone, cardiac inotropy and chronotropy, pulmonary vascular resistance, bronchodilation, and endothelial function.¹¹ Despite the physiologic rationale, the clinical evidence cited in guidelines to support a negative effect of β -blockade on anaphylaxis is only observational.¹² A 1987 review by Toogood¹³ describes case reports and case series showing increased severity of anaphylactic reactions among patients treated with β -blockers. Lang¹² reported 2 large case-control studies of patients with anaphylactic reactions to contrast media demonstrating that those taking β -blockers have an increased risk of bronchospasm (OR, 3.73). Although patients taking β -blockers also were slightly more likely to be hospitalized after such reactions, the association was not statistically significant.¹²

Previous studies in our ED demonstrated an association between the use of multiple antihypertensive drugs by a given person (β -blockers, ACE inhibitors, calcium channel blockers, and diuretics) and increased anaphylaxis severity independent of age, sex, or suspected trigger.¹⁰ Among a cohort of 302 patients,

TABLE II. Univariable associations with repeat epinephrine administration (N = 789)

Feature	No. of epinephrine doses		OR (95% CI)	P
	≤1 (n = 726)	>1 (n = 63)		
Age at visit (y)*	34 (18-53)	36 (18-47)	1.00 (0.99-1.01)	.73
Sex				.12
Male	303 (42)	20 (32)	Reference	
Female	423 (58)	43 (68)	1.54 (0.89-2.67)	
Race	(n = 717)	(n = 63)		.67
White	624 (87)	56 (89)	Reference	
All others	93 (13)	7 (11)	0.84 (0.37-1.90)	
Symptoms in ED				
Mucocutaneous†	719 (99)	63 (100)	1.32 (0.06-28.50)	.86
Gastrointestinal	288 (40)	23 (37)	0.87 (0.51-1.49)	.62
Respiratory	604 (83)	60 (95)	4.04 (1.25-13.09)	.02
Cardiovascular	298 (41)	28 (44)	1.15 (0.68-1.93)	.60
Suspected precipitating allergen†				
Food	255 (35)	21 (33)	Reference	
Medication	145 (20)	12 (19)	1.02 (0.49-2.12)	.96
Venom	87 (12)	9 (14)	1.29 (0.58-2.89)	.53
Latex	2 (<1)	0	2.38 (0.06-100.50)	.65
Contrast	36 (5)	2 (3)	0.81 (0.21-3.21)	.77
Other	36 (5)	4 (6)	1.47 (0.50-4.34)	.49
Unknown	165 (23)	15 (24)	1.11 (0.56-2.20)	.76
Personal history				
Anaphylaxis	205 (38)	33 (52)	2.80 (1.66-4.70)	<.001
Medication allergy	363 (50)	41 (65)	1.86 (1.09-3.19)	.02
Food allergy	267 (37) (n = 721)	32 (51)	1.76 (1.05-2.94)	.03
Insect sting allergy	92 (13) (n = 723)	6 (10)	0.72 (0.30-1.72)	.46
Asthma	199 (27) (n = 725)	27 (43)	1.98 (1.17-3.35)	.01
Seasonal allergy	171 (24)	20 (32)	1.51 (0.86-2.64)	.15
Atopic dermatitis	71 (10) (n = 725)	3 (5)	0.46 (0.14-1.51)	.20
Medications				
β-Blockers	75 (10)	8 (13)	1.26 (0.58-2.75)	.56
ACE inhibitors	57 (8)	4 (6)	0.80 (0.28-2.27)	.67
Calcium channel blockers	33 (5)	5 (8)	1.81 (0.68-4.81)	.23
ARBs	19 (3)	1 (2)	0.60 (0.08-4.56)	.62
Diuretics	77 (11)	11 (17)	1.78 (0.89-3.56)	.10
Other antihypertensive medication†	14 (2)	0	0.39 (0.02-7.24)	.53
Any antihypertensive medication	163 (22)	16 (25)	1.18 (0.65-2.13)	.59
Medical history	(n = 718)			
COPD	15 (2)	1 (2)	0.76 (0.10-5.82)	.79
Cardiovascular disease	62 (9)	4 (4)	0.72 (0.25-2.04)	.53
Disposition				
Home	345 (48)	15 (24)	Reference	
Observation unit	308 (42)	20 (32)	1.49 (0.75-2.97)	.25
Admitted to hospital	39 (5)	7 (11)	4.13 (1.59-10.74)	.004
Admitted to ICU	34 (5)	21 (33)	14.21 (6.71-30.09)	<.001

ARB, Angiotensin receptor blocker.

Values are median (interquartile range) or no. of visits (%).

*OR and CI represent a 1-y increase in age.

†ORs, CIs, and P values estimated using Firth's penalized maximum likelihood method.

those taking antihypertensive medications had increased severity of anaphylaxis, as evidenced by increased organ system involvement and hospital admission. Sixteen percent of patients were using β-blockers alone. Although β-blocker use was associated with increased organ system involvement and hospitalization, it was not significantly associated with an increased rate of syncope,

hypoxia, or hypotension.^{3,14} This finding is in contrast to our previous study of antihypertensive medications and anaphylaxis severity in which ACE inhibitors were associated with increased hospital admission.³ In that study, however, we were unable to adjust for cardiovascular disease because of collinearity between antihypertensive agents and cardiovascular disease.

TABLE III. Univariable associations between antihypertensive medications and increased epinephrine administration

Medication	All patients					Adults (≥18 y) only				
	No. of epinephrine doses (n = 789)*			No. of epinephrine doses (n = 594)*			No. of epinephrine doses (n = 594)*			P
	0 (n = 343)	>0 (n = 446)	OR (95% CI)	≤1 (n = 545)	>1 (n = 49)	OR (95% CI)	0 (n = 265)	>0 (n = 329)	OR (95% CI)	
β-Blockers	42 (12)	41 (9)	0.73 (0.46-1.14)	75 (14)	8 (16)	1.22 (0.55-2.71)	42 (16)	41 (12)	0.76 (0.48-1.20)	.24
ACE inhibitors	34 (10)	27 (6)	0.59 (0.35-0.99)	57 (10)	4 (8)	0.76 (0.26-2.19)	34 (13)	27 (8)	0.61 (0.36-1.04)	.07
Calcium channel blockers	21 (6)	17 (4)	0.61 (0.32-1.17)	33 (6)	5 (10)	1.76 (0.66-4.74)	21 (8)	17 (5)	0.63 (0.33-1.23)	.18
ARBs	13 (4)	7 (2)	0.41 (0.16-1.03)	19 (3)	1 (2)	0.58 (0.08-4.40)	13 (5)	7 (2)	0.42 (0.17-1.07)	.07
Diuretics	40 (11)	48 (11)	0.91 (0.59-1.43)	76 (14)	11 (22)	1.79 (0.88-3.65)	40 (15)	47 (14)	0.94 (0.59-1.48)	.78
Other antihypertensive medication	9 (3)	5 (1)	0.44 (0.15-1.31)	12 (2)	0	0.43 (0.02-8.29)†	7 (3)	5 (2)	0.58 (0.18-1.86)	.36
Any antihypertensive medication	85 (25)	94 (21)	0.81 (0.58-1.13)	160 (29)	16 (33)	1.17 (0.63-2.18)	83 (31)	93 (28)	0.86 (0.61-1.23)	.42

ARB, Angiotensin receptor blocker.

*Values are no. of visits (%).

†ORs, CIs, and P values estimated using Firth's penalized maximum likelihood method.

Although definitive clinical evidence is lacking to show that β-blocker monotherapy enhances the risk of more aggressive therapy for anaphylaxis, accumulating data suggest that people using multiple antihypertensive medications are at a higher risk for severe anaphylaxis. To specifically examine the combinatorial effect of ACE inhibitors and β-blockers on anaphylaxis severity, Nassiri et al⁴ graded 4,783 cases of anaphylaxis reported to the anaphylaxis registry from Germany, Switzerland, and Austria. When adjusted for age and sex, the results showed a modest but significant increase in risk of severe anaphylaxis in patients taking both ACE inhibitors and β-blockers. Notably, the effect remained significant in the setting of monotherapy with either agent. In the same study,⁴ the authors designed a murine model of anaphylaxis to support their observation. Results showed that β-blockers and ACE inhibitors indeed synergistically exacerbated anaphylactic symptoms via decreasing the threshold of mast cell activation *in vitro*.

These animal experiments add support to clinical observations,⁴ but it remains critical to consider the high correlation of antihypertensive use and underlying cardiovascular disease in studied patient populations. Observations of increased severity of anaphylaxis with antihypertensive use may at least partly result from the underlying cardiovascular disease and not the medication alone. Both the above studies were unable to control for underlying cardiovascular disease.

Clinically, β-blockers are common in the ED patient population; they are prescribed for indications including hypertension, coronary artery disease, migraines, essential tremor, and, in children, congenital and/or inherited cardiac disorders. The benefit of long-standing β-blockade in certain patients has been well established, and the risk of undertreating these conditions on a daily basis is likely greater than that of life-threatening anaphylaxis. Still, the belief that patients taking β-blockers, particularly as monotherapy, should be counseled and treated differently has been supported by limited data originating from case series and case reports. The risk of withdrawing a β-blocker in patients with cardiovascular disease to prevent the relatively rare occurrence of anaphylaxis must be carefully weighed.

The results of this study suggest that patients with anaphylaxis on β-blocker therapy may not require more intensive anaphylactic treatment. Although the pharmacodynamics and pathophysiology associated with β-blocker use in the setting of anaphylaxis support withholding β-blockade in patients with allergies, the effects of β-blockers on epinephrine use for anaphylaxis may not be clinically significant.¹⁵ Importantly, an increased need for repeat epinephrine or any epinephrine in our patient population was not identified.

Although the known benefits of β-blocker therapy in the setting of many cardiovascular diseases may outweigh the risk of interaction of β-blockers and epinephrine during anaphylaxis, we do not suggest generalizing these results to patients on immunotherapy. Such patients may represent a select cohort of atopic patients at a higher risk for adverse events, including severe anaphylaxis or epinephrine-refractory anaphylaxis.

Patients with cardiovascular disease may also be at risk for adverse outcomes secondary to an exaggerated unopposed α response when already on β-blockade. The severity of the interaction between epinephrine and β-blockers likely varies with β-receptor selectivity, dose, and length of time on β-blockade. Physiology studies have demonstrated that epinephrine, when given to healthy volunteers 5 minutes after a single intravenous

dose of propranolol, results in hypertension and reflexive bradycardia.¹⁶ This interaction is largely due to the blockade of β -2 receptors in the peripheral vasculature, because these effects are generally smaller than those due to metoprolol, a cardioselective β -blocker.¹⁷ In contrast to acute β -blockade, a more recent study by Pong et al¹⁸ of patients on chronic β -blockade demonstrated less consistent hemodynamic responses to epinephrine challenge. Although most patients in that study were taking cardioselective β -blockers, chronic β -blockade likely results in long-term regulatory changes at the receptor level that affect response to adrenergic challenges.^{19,20} Patients in the Pong et al¹⁸ study were older but were free of cardiovascular disease; thus, the authors were unable to report adverse events in that population. Although the physiologic mechanisms are clear,²¹ the frequency of severe interactions between epinephrine and β -blockers reported in the literature has been low,^{22,23} which suggests that mild responses may remain unnoticed. In any case, the interaction remains important to consider. In our study, a small subset of patients was admitted to the ICU, and those taking β -blockers were significantly more likely to be admitted to the ICU. ICU admission could be interpreted as a surrogate marker of anaphylaxis severity, although the subset in our study is too small to evaluate. Alternatively, the finding could be related to patients on β -blockers having multiple comorbid conditions requiring a higher level of care during or after anaphylaxis.

Our study has several limitations. Retrospective chart review has inherent data quality issues, including retrospective study design and data quality being dependent on the original provider's documentation. Also, despite this being a large cohort of patients with anaphylaxis, the cohort that received more than 1 dose of epinephrine was relatively small. Because we studied patients with anaphylaxis only, we cannot say that β -blockade independently decreases the threshold for anaphylaxis, although a similar number of patients with or without β -blocker use in our study had anaphylaxis earlier. In addition, although it is unlikely to be statistically significant, 789 patient visits were included instead of the a priori sample size of 790.

In conclusion, our results demonstrate that after controlling for COPD and cardiovascular comorbid conditions, age, and sex, the use of β -blockers was not associated with at least a 10% increase in the need for more than 1 dose of epinephrine. Although it is possible that the risk of repeat epinephrine is smaller than 10%, the clinical significance of this is uncertain and may not outweigh the benefits of β -blockers for other conditions.

REFERENCES

- Clark S, Wei W, Rudders SA, Camargo CA Jr. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. *J Allergy Clin Immunol* 2014;134:1125-30.
- Shereff RH, Harwell W, Lieberman P, Rosenberg EW, Robinson H. Effect of beta adrenergic stimulation and blockade on immediate hypersensitivity skin test reactions. *J Allergy Clin Immunol* 1973;52:328-33.
- Lee S, Hess EP, Nestler DM, Bellamkonda Athmaram VR, Bellolo MF, Decker WW, et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. *J Allergy Clin Immunol* 2013;131:1103-8.
- Nassiri M, Babina M, Dolle S, Edenharter G, Rueff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. *J Allergy Clin Immunol* 2015;135:491-9.
- Matsumura Y, Tan EM, Vaughan JH. Hypersensitivity to histamine and systemic anaphylaxis in mice with pharmacologic beta adrenergic blockade: protection by nucleotides. *J Allergy Clin Immunol* 1976;58:387-94.
- Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol* 2007;7:337-41.
- Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993;153:2033-40.
- Benchimol EI, Smeeth L, Guttman A, Harron K, Hemkens LG, Moher D, et al, Record Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement [in German]. *Z Evid Fortbild Qual Gesundheitswes* 2016;115-116:33-48.
- Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium. Second symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2006;117:391-7.
- Campbell RL, Bashore CJ, Lee S, Bellamkonda VR, Li JT, Hagan JB, et al. Predictors of repeat epinephrine administration for emergency department patients with anaphylaxis. *J Allergy Clin Immunol Pract* 2015;3:576-84.
- Corbascio AN. Propranolol [correspondence]. *Clin Pharmacol Ther* 1971;12:559-61.
- Lang DM. Anaphylactoid and anaphylactic reactions: hazards of beta-blockers. *Drug Saf* 1995;12:299-304.
- Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988;81:1-5.
- Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
- Guinard JP, Mulroy MF, Carpenter RL, Knopes KD. Test doses: optimal epinephrine content with and without acute beta-adrenergic blockade. *Anesthesiology* 1990;73:386-92.
- Mackie K, Lam A. Epinephrine-containing test dose during beta-blockade. *J Clin Monit* 1991;7:213-6.
- Johnsson G. Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacol Toxicol (Copenh)* 1975;36:59-68.
- Pong RP, Bernards CM, Hejtmanek MR, Slee AE, Batra MS. Effect of chronic β -blockade on the utility of an epinephrine-containing test dose to detect intravascular injection in nonsedated patients. *Reg Anesth Pain Med* 2013;38:403-8.
- Hall JA, Petch MC, Brown MJ. In vivo demonstration of cardiac beta 2-adrenoreceptor sensitization by beta 1-antagonist treatment. *Circ Res* 1991;69:959-64.
- Motomura S, Deighton NM, Zerkowski HR, Doetsch N, Michel MC, Brodde OE. Chronic beta 1-adrenoceptor antagonist treatment sensitizes beta 2-adrenoceptors, but desensitizes M2-muscarinic receptors in the human right atrium. *Br J Pharmacol* 1990;101:363-9.
- Heilbrunn SM, Shah P, Bristow MR, Valantine HA, Ginsburg R, Fowler MB. Increased beta-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. *Circulation* 1989;79:483-90.
- Cunnington C, McDonald JE, Singh RK. Epinephrine-induced myocardial infarction in severe anaphylaxis: is nonselective β -blockade a contributory factor? *Am J Emerg Med* 2013;31:759.e1-2.
- Gandy W. Severe epinephrine-propranolol interaction. *Ann Emerg Med* 1989;18:98-9.

APPENDIX

TABLE E1. Multivariable associations with repeat (>1) epinephrine dose

Feature	All visits		Adult visits	
	OR (95% CI)	P	OR (95% CI)	P
Age ≥18 y	1.02 (0.51-2.01)	.97	NA	NA
Female	1.58 (0.89-2.81)	.12	1.90 (0.94-3.88)	.08
Suspected precipitating allergen				
Food	1.0 (reference)		1.0 (reference)	
Medication	0.91 (0.42-1.97)	.81	1.14 (0.48-2.68)	.77
Venom	1.31 (0.56-3.06)	.53	1.59 (0.60-4.19)	.35
Latex, contrast, or other	0.95 (0.36-2.51)	.92	1.25 (0.44-3.57)	.67
Unknown	1.05 (0.52-2.13)	.88	1.26 (0.54-2.97)	.60
COPD	0.75 (0.09-6.09)	.79	0.76 (0.09-6.17)	.80
Cardiovascular disease	0.64 (0.21-1.98)	.44	0.47 (0.13-1.68)	.24
β-Blockers	1.51 (0.66-3.42)	.33	1.64 (0.72-3.71)	.24

NA, Not applicable.