

Age-related cardiovascular outcomes in older adults receiving epinephrine for anaphylaxis in the emergency department



Michael E. O'Brien, PharmD^a, Jennifer L. Koehl, PharmD^a, Ali S. Raja, MD^{b,c}, Timothy B. Erickson, MD^{c,d}, and Bryan D. Hayes, PharmD^{a,c}

Clinical Implications

- Epinephrine for patients with anaphylaxis is a life-saving intervention; however, there is a risk of adverse cardiac events. An analysis of cardiac outcomes based on age in patients treated for anaphylaxis with epinephrine showed that patients older than 80 years should be closely monitored for adverse cardiac events.

TO THE EDITOR:

Anaphylaxis is defined as a serious and possibly life-threatening systemic allergic reaction; the most commonly administered treatment is intramuscular (IM) epinephrine.^{1,2} Several adverse effects are related to epinephrine administration, and the most concerning are ischemic cardiac events and tachydysrhythmias. Certain patient populations may be at a higher risk of cardiac events, particularly older adults.³⁻⁵

In a study of 220 patients with anaphylaxis, patients older than 50 years ($n = 54$) or older than 65 years ($n = 28$) were more likely to have adverse cardiac events following the administration of epinephrine for anaphylaxis versus younger patients.⁶ In another study of 492 patients with anaphylaxis, those older than 50 years ($n = 122$) were less likely to receive epinephrine but more likely to be overdosed and experience a cardiac adverse event.⁷ Therefore, the purpose of this study was to determine the odds of an adverse cardiac event occurring following the administration of epinephrine in patients older than 50 years during the treatment of anaphylaxis.

This retrospective cohort study, conducted in a large health care system, was approved by the institutional review board and informed consent was deemed not necessary. The health care system contains 9 emergency departments (EDs) with more than 350,000 combined ED visits per year.

Eligible patients included those presenting to any ED within the study health care system who received epinephrine for concern of anaphylaxis between April 1, 2016, and August 1, 2018. Patients were excluded if they were younger than 50 years or received an epinephrine continuous infusion. All visits for each patient during this study period were included, and each was considered a unique patient encounter.

A comprehensive chart review was performed for each eligible patient by a study author (M.E.O.). Cardiovascular disease history was defined as a documented history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting.

The primary outcome was adverse cardiac effects of epinephrine during the treatment of anaphylaxis. Patients aged 50 to 59 years were selected as the reference group to compare to the older patients. The primary outcome was a composite measure of elevated troponin within 8 hours of epinephrine administration (using the fourth-generation troponin T assay), ischemic electrocardiogram (ECG) changes (defined as acute ST changes, T-wave inversions, pathological Q-wave changes, or new left-bundle branch block) within 2 hours of epinephrine administration, or new tachydysrhythmia (defined as ventricular tachycardia or fibrillation, atrial flutter or fibrillation, or multifocal tachycardia) within 2 hours of epinephrine administration, based on a previous study.⁷ Each ECG was interpreted by 2 board-certified emergency medicine physicians (A.S.R. and T.B.E.) who reached a consensus regarding evidence of ischemia.

Secondary outcomes included the prescribing rate of epinephrine autoinjectors upon hospital discharge and changes in systolic blood pressure values preepinephrine and highest/lowest within 2 hours postepinephrine.

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the study facility. All statistical analyses were performed by using the Statistical Program for Social Sciences (SPSS for Windows 22.0; SPSS, IBM Corp, Armonk, NY).

There were 389 patients identified during this study period, and 296 patients were ultimately included in this analysis. The median age was 60 years, and 163 (55%) patients were female. Baseline characteristics (Table I) were similar across ages, with an increase in history of cardiovascular disease in the older groups. Ninety-eight percent of the epinephrine doses were administered intramuscularly and 2% were administered subcutaneously. There were 27 troponin values and 56 ECGs available for evaluation.

Ten unique patients (3%) experienced the primary composite outcome. Patients 80 to 89 years old had higher odds of experiencing an adverse cardiac effect compared with those 50 to 59 years old (odds ratio, 8.8; 95% CI, 1.2-67.1; Table II). Only 3 patients older than 90 years were included in this study, with none of them experiencing the primary outcome.

Fifty-eight of 296 patients (20%) had a documented prescription for an epinephrine autoinjector at presentation to the ED and 205 patients (69%) had a documented prescription upon discharge. The median systolic blood pressure values were comparable before and after the administration of epinephrine.

Studies suggest that patients older than 50 years are at a higher risk of adverse cardiac events.^{6,7} In our study, patients were stratified by age to assess if older patients were at a higher risk of adverse cardiac events. Patients 80 to 89 years old had a higher risk of having an adverse cardiac event than those aged 50 to 59 years.

The rate of overall cardiac complications was 3.4% (10 of 296), more than twice the rate reported in previous studies (0.9%-1.3%).^{5,7} This may be due to the older population of patients included within our study or potentially a higher rate of obtaining ECGs and troponin levels. Previous studies did not include the number of ECGs or troponin levels evaluated and

TABLE I. Characteristics of study cohort patients

Characteristic	All (n = 296)			50-59 y (n = 134)			60-69 y (n = 108)			70-79 y (n = 34)			80-89 y (n = 17)			>90 y (n = 3)		
	Median/n	IQR/%		Median/n	IQR/%		Median/n	IQR/%		Median/n	IQR/%		Median/n	IQR/%		Median/n	IQR/%	
Age (y)	60	55-68		54	52-56		64	62-67		72	71-77		86	83-87		91	91-94	
Male	133	45		55	41		54	50		16	47		7	41		1	33	
Female	163	55		79	59		54	50		18	53		10	59		2	67	
White	218	74		97	72		82	76		23	68		13	76		3	100	
Black	32	11		15	11		9	8		6	18		2	12		0	0	
Hispanic	22	7		10	7		8	7		4	12		0	0		0	0	
Asian	15	5		7	5		6	6		1	3		1	6		0	0	
Other	8	3		5	4		2	2		0	0		1	6		0	0	
Unknown	1	0.3		0	0		1	0.9		0	0		0	0		0	0	
Height (cm)	n = 276	168	160-175	n = 123	168	160-175	n = 101	170	163-175	n = 32	163	160-173	n = 17	162	157-175	n = 3	158	158-161
Weight (kg)	n = 282	79	68-93	n = 126	80	68-95	n = 103	81	69-94	n = 33	83	68-90	n = 17	66	59-77	n = 3	62	57-67
BMI (kg/m ²)	n = 276	28	25-32	n = 123	28	25-32	n = 101	28	25-32	n = 32	30	26-32	n = 17	24	21-29	n = 3	25	24-26
Cardiovascular disease history	23	8		3	2		11	10		5	15		4	24		0	0	
Troponin within 8 h of epinephrine	27	9		9	7		9	8		5	15		4	24		0	0	
ECG within 2 h of epinephrine	56	19		21	16		23	21		7	21		3	18		2	67	
Prehospital epinephrine	20	7		8	6		4	4		7	21		1	6		0	0	

BMI, Body mass index; ECG, electrocardiogram; IQR, interquartile range.

TABLE II. Adverse cardiac effects of epinephrine by age

Age (y)	N	Incidence (n)	Incidence (%)	OR	95% CI
50-59	134	2	1.5	—	—
60-69	108	4	3.7	2.5	0.5-14.1
70-79	34	2	5.9	4.1	0.6-30.4
80-89	17	2	11.8	8.8	1.2-67.1
>90	3	0	0	NA	NA

NA, Not applicable/available.

they were obtained only if the patient experienced anginal chest pain.^{5,7}

This assessment was limited to medication orders and any associated documentation; therefore, the dose or route of administration may have differed in actuality. Data on patient comorbidities and prescription medication use could not be collected because of inconsistent documentation and availability of this data. The increased risk of cardiac events may have resulted from anaphylaxis or other confounders we were unable to measure and not necessarily from epinephrine. Use of the 50- to 59-year-old reference group may have decreased the sensitivity of the analysis because this group is already at a higher risk of adverse cardiac events as compared with those younger than 50 years. Also, the rarity of our outcomes limits our statistical power. To more fully understand the risk of epinephrine in older adults, future studies should address the above limitations by prospectively enrolling a larger cohort of patients with a broad spectrum of age groups.

In this retrospective study evaluating 296 patients receiving epinephrine for anaphylaxis, patients 80 to 89 years old were more likely to experience an adverse cardiac event than those aged 50 to 59 years. These results emphasize the necessity of increased monitoring for adult patients older than 80 years receiving epinephrine for anaphylaxis.

^aDepartment of Pharmacy, Massachusetts General Hospital, Boston, Mass^bDepartment of Emergency Medicine, Massachusetts General Hospital, Boston, Mass^cHarvard Medical School, Boston, Mass^dDivision of Medical Toxicology, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, Mass

This study received no specific grant or funding from any agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 12, 2019; revised April 26, 2019; accepted for publication April 26, 2019.

Available online May 10, 2019.

Corresponding author: Michael E. O'Brien, PharmD, Department of Pharmacy, Massachusetts General Hospital, 55 Fruit St, GRB005, Boston, MA 02114. E-mail: Mobrien56@mgh.harvard.edu.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.04.040>**REFERENCES**

1. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J* 2015;8:32.
3. Nakazato R, Arsanjani R, Achenbach S, Gransar H, Cheng VY, Dunning A, et al. Age-related risk of major adverse cardiac event risk and coronary artery disease extent and severity by coronary CT angiography: results from 15 187 patients from the International Multisite CONFIRM Study. *Eur Heart J Cardiovasc Imaging* 2014;15:586-94.
4. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67-492.
5. Campbell RL, Bellolio MF, Knutson BD, Bellamkonda VR, Fedko MG, Nestler DM, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 2015;3:76-80.
6. Campbell RL, Hagan JB, Li JTC, Vukov SC, Kanthala AR, Smith VD, et al. Anaphylaxis in emergency department patients 50 or 65 years or older. *Ann Allergy Asthma Immunol* 2011;106:401-6.
7. Kawano T, Scheuermeyer FX, Stenstrom R, Rowe BH, Grafstein E, Grunau B. Epinephrine use in older patients with anaphylaxis: clinical outcomes and cardiovascular complications. *Resuscitation* 2017;112:53-8.