CRITICAL REVIEW FORM:
THERAPY ARTICLES

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Citation: Kawano T, et al. Epinephrine use in older patients with anaphylaxis: Clinical outcomes and cardiovascular complications. Resuscitation. 2017 Mar;112:53-58

Study Objective: "Analyze the frequency of epinephrine administration and any cardiac complications between older (>50) and younger groups that presented to two urban ED's over a 5 year time span for anaphylaxis. Additionally, the study looked at routes of EPI administration, IM vs. IV, and characteristics of patients that received excessive dosing.

Study Methodology: Retrospective Cohort Study of a national healthcare database conducted at two urban academic teaching hospitals in Vancouver, British Columbia. (This database was the same as the Grunau study on steroid use presented by Dr. Rice). All patient's with a D/C diagnosis of "allergic reaction" were included. Excluded patients were those younger than 17 years, those with a primary diagnosis of asthma, those who left prior to assessment by a nurse or a physician, those whose allergen was an angiotensin-converting enzyme (ACE) inhibitor and those who had a past history of non-allergic angioedema. A comprehensive chart review was performed of each patient and the diagnosis of anaphylaxis was made using the National Institute of Allergy and Infectious Disease Anaphylaxis criteria

Primary outcome: the proportion of patients who were treated with epi.

Secondary outcome: the proportion of patients with pre-specified post-epi cardiovascular complications; further classified by route of administration (IV or IM).

Cardiovascular complications were defined as follows:
1. new onset of ventricular fibrillation or tachycardia
2. atrial flutter or fibrillation, or multifocal atrial tachycardia
3. acute stroke, defined as a new neurologic deficit
4. elevated cardiac troponin T with new ischemic ECG findings

Tertiary outcome: the proportion of patients who received an excessive dose of epi, defined as greater than 0.5 mg for intramuscular, or greater than 100ug for intravenous administration, respectively.

GUIDE	COMMENTS
I. Are the results valid?	
Did experimental and control groups begin the study with a similar prognosis (Table 1)	N/A (see question 4)
1. Were patients randomized?	Not applicable for retrospective cohort study

2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A Groups were determined by ICD discharge code and then further sorted based on age.
3. Were patients analyzed in the groups to which they were randomized?	N/A No intention-to-treat analysis in retrospective studies
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	(Table 1) described above. Older patients (≥ 50) represented 24.6% of cohort. They were more likely to have drugs as a precipitant, Only 6.5% of this cohort had any cardiac risk factors or hx. Older group was more likely to present with neuro symptoms, less likely to have hx. of asthma, less likely to have GI symptoms. Only 1/370 (0.3%) in the younger cohort had cardiac hx or RF.
5. Were patients aware of group allocation?	Study was retrospective, there was no group allocation at time of initial treatment
6. Were clinicians aware of group allocation?	N/A
7. Were outcome assessors aware of group allocation?	No. Three study investigators collected the data on groups for their allocation and identified PMHx, demographics, presentation, any epi treatment and route, length of stay –these investigators weren't aware of hypothesis and outcomes of study, they were only systematically collecting the data. 5% of charts were rechecked by a blinded reviewer. A separate investigator collected the data and information on cardiac risk factors and history. Another two independent reviewers determined the cardiac complications and disagreements were settled by a third blinded reviewer. Authors report a kappa score for agreement between reviewers of 0.9 which is excellent.
8. Was follow-up complete?	Yes, there was tracking of patient's outcomes for 7 days after their discharge. The study tracked any return ED visits and followed a national database to identify any mortality.
II What are the results ?	
1. How large was the treatment effect?	**Primary Outcome:** 269/492 patients (54.7%) received EPI 44/122 (36.1%) older patients and 225/370 (60.8%) younger Unadjusted OR 0.3 (CI 0.2-0.5) Older patients were more likely to receive intravenous epi (5/122 vs 2/370) and older patients were more likely to receive excessive dose of epi (7/44, 15.9% vs 2/225 0.9%) OR 20.7 (CI 3.8-211). Older patients by decades were less likely to get epi (16% at age >70) **Secondary and Tertiary Outcomes**: Only 5 patients had reportable complications 4/5 were > 50 OR 22.4 (CI 2.1-1129.8) **considered non-precise because of low numbers.** For cardiac complications in those that received epi: Older group: 9.1% (4/44) with a CI 2.5 -21.7

	Younger group: 0.4 % (1/225) with a CI <0.1-2.5 **It was noted in the potential limitations section that the small number of outcomes limited the overall statistical power for determining significant associations and could result in unreliable p values.** –
2. How precise was the estimate of the treatment effect? (CI's?)	See above.
III **How can I apply the results to patient care?**	
1. Were the study patients similar to my patient?	Yes and No I think the patients are probably healthier than our ER patients. It's difficult to assess similarities in our local patient populations and what the overall cardiac health was of the patients in this study compared to the generally large amount of patients seen in Sentara with a more significant cardiac and renal history. No racial demographics provided.
2. Were all clinically important outcomes considered?	The outcomes assessed were cardiac complications which included any type of ventricular arrhythmia, tachycardia, atrial fibrillation, ischemic changes on EKGS, elevated troponins, and stroke. I think that includes a wide spectrum of all the clinically important cardiac complication outcomes possible in these patients. No mention of need for resuscitation,
3. Are the likely treatment benefits worth the potential harm and costs?	Not enough data to draw conclusions. With how low the cardiac complication outcomes were between both groups, I think it makes it evident the treatment benefits with epinephrine for in the setting of anaphylaxis in an ER patient outweighs any potential harm, particularly cardiac complications in this study, and costs regardless of age group.

Limitations:

By far, the largest limitation of this study is its small sample size and inability to provide ANY conclusive evidence of anything other than older patients are less likely to get epi which could be detrimental.

Another limitation noted in the paper discussed the subjective clinical impressions that guided this study as well as a lack of clarity regarding how they qualified 25% of their patients (both groups) as having "severe anaphylaxis" yet the discharged over 95% of their patients

Limited the ICD code to "allergic reaction" however anaphylaxis can cover a very large spectrum of clinical scenarios. The management and characterization was not controlled for and physician dependent.

The cardiovascular "complications" were also an interesting area for limitations, on some of the recorded patient complications it was noted that their event was due to ischemic changes on their EKG however some of them continued to have those changes on repeat EKGS. It was never specified whether they had any pre-anaphylaxis EKGS that could have been compared to see what the patient's baseline was. This in turn would change the number of significant cardiac complications by epinephrine if some of the factors were already present at the patient's baseline.

Clinical Bottom Line: Epinephrine appears to commonly be withheld with progression in age over 50 in patients with anaphylaxis. IV epi should likely be avoided in the elderly. This study does not provide sufficient data regarding the potential harms of using epinephrine in this patient population.