PGY-4

**Critical Review Form**

 **Meta-Analysis**

[Holmberg MJ, Issa MS, Moskowitz A, et al. Vasopressors during adult cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2019;139:106‐121.](http://pmid.us/30980877)

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**Objectives: "to commission a systematic review and meta-analysis of vasopressors during cardiac arrest to inform an updated Consensus on Science and Treatment Recommendation (CoSTR)." (p. 107)**

**Methods: This systematic review and meta-analysis was commissioned by the** [**International Liaison Committee on Resuscitation (ILCOR)**](https://www.ilcor.org/) **to further understand the effects of vasopressors given during cardiac arrest on patient outcomes. Following** [**PRISMA guidelines**](http://www.prisma-statement.org/)**, the authors searched the literature for randomized controlled trials and observational studies with a comparison group that enrolled adults (> 18 years) in any setting, and compared IV or IO vasopressors with different vasopressors, combinations of vasopressors, or no vasopressor. The outcomes of interest included short-term survival (return of spontaneous circulation [ROSC], survival to hospital admission), mid-term survival (survival to hospital discharge and at 28 days, 30 days, or 1 month), mid-term neurologic outcomes (**[**Cerebral Performance Category [CPC] score**](https://www.azdhs.gov/documents/preparedness/emergency-medical-services-trauma-system/save-hearts-az-registry-education/cerebral-performance-categories-scale.pdf) **1-2 or** [**modified Rankin Scale [mRS]**](https://www.mdcalc.com/modified-rankin-scale-neurologic-disability) **0-3 at 28 days, 30 days, or 1 month), and long-term outcomes (>1 month).**

**On November 23, 2018, investigators searched Medline, Embase, WebofScience, CINAHL, and the Cochrane Library, with no language restriction, to identify relevant articles. The bibliographies of included articles were also reviewed to identify additional, potentially relevant articles.** [**The Clinical Trials Registry Platform**](https://www.who.int/ictrp/en/) **was searched on January 24, 2019 to identify ongoing trials.**

**Out of 4142 records identified, 3938 were excluded, leaving 204 articles for review. Of these, 89 were eventually included in the systematic review. There were 22 controlled trials and 67 observational studies. Seven controlled trials were further excluded as they evaluated the utility of high-dose epinephrine, which has been assessed in a prior ILCOR-commissioned systematic review, leaving 15 controlled trials (82 total trials).**

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| **Critical Review Form: Meta-Analysis** |
| Guide | Comments |
| **Are the results valid?** |
| Did the review explicitly address a sensible question? | Yes. Given changing recommendations regarding the use of epinephrine and vasopressin in cardiac arrest, a systematic review of all studies evaluating the efficacy of vasopressors in this setting seems appropriate and potentially practice changing. |
| Was the search for relevant studies detailed and exhaustive? | Yes. The authors searched all of the major databases (Medline, Embase, WebofScience, CINAHL, and the Cochrane Library), and searched the Clinical Trials Registry Platform to identify ongoing trials. They did not search conference abstracts or the [gray literature](http://pmid.us/15088074), but it is unlikely that doing so would have revealed additional articles. This review was at low risk of [publication bias](http://pmid.us/10729693). |
| Were the primary studies of high methodological quality? | No. Of the controlled trials, three trials were rated as having high risk of bias, two were rated as having concerns for risk of bias, and only two were rated as low risk of bias. Risk of bias in these studies was primarily due to concerns with the randomization process and deviations from the intended intervention.All of the observational studies were rated as critical or serious for risk of bias, largely due to issues with [confounding](https://www.ejves.com/article/S1078-5884%2818%2930126-6/fulltext) or [selection bias](http://pmid.us/21491415). |
| Were the assessments of the included studies reproducible? | Yes. Two authors assessed risk of bias using the [revised Cochrane risk-of-bias tool](https://research.monash.edu/en/publications/a-revised-tool-for-assessing-risk-of-bias-in-randomized-trials) for controlled trials and the [Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool](https://www.bmj.com/content/355/bmj.i4919) for observational studies. |
| **What are the results?** |
| What are the overall results of the study? | Two controlled trials evaluated the use of epinephrine compared to placebo for OHCA:* Pooled results revealed increases in ROSC (RR 3.09, 95% CI 2.82-3.39), survival to hospital admission (RR 2.88, 95% CI 2.57-3.22), and survival to hospital discharge (RR 1.44, 95% CI 1.11-1.86) in favor of epinephrine.
* There was no benefit to epinephrine with regards to survival to hospital discharge with a favorable neurologic outcome (RR 1.21, 95% CI 0.90-1.62).
* One of the two studies looked at 3-month outcomes and found an increased rate of survival (RR 1.40, 95% CI 1.07-1.84) but no improvement in favorable neurologic outcome at 3 months (RR 1.30, 95% CI 0.94-1.80).
* Pooled results separated by initial rhythm demonstrated an increase in ROSC for both shockable (RR 1.68, 95% CI 1.48-1.92) and nonshockable rhythm (RR 4.45, 95% CI 3.91-5.08), as well as increased survival to hospital discharge for nonshockable rhythms (RR 2.56, 95% CI 1.37-4.80).
	+ There was no difference in survival to hospital discharge for shockable rhythms (RR 1.23, 95% CI 0.94-1.62).
* In the one study looking at 3-month outcomes, there was no difference in survival with good neurologic outcome at 3 months for those with nonshockable rhythms, but among those with shockable rhythms the results approached statistical significance (RR 3.03, 95% CI 0.98-9.38).

Retrospective studies of epinephrine compared to placebo:* The vast majority of the 46 studies found that epinephrine, compared with no epinephrine, was associated with decreased survival and worse neurologic outcome at hospital discharge.
* Ten studies looking at discrete time intervals to epinephrine administration found higher rates of ROSC with earlier epinephrine administration.
* Four studies looking at time to epinephrine administration as a continuous variable found a slight decrease in odds of ROSC for each minute delay.

Vasopressin compared with epinephrine:* Meta-analysis of three controlled trials found no significant difference in ROSC (RR 1.05, 95% CI 0.80-1.39), survival to hospital admission (RR 1.17, 95% CI 0.82-1.66), survival to hospital discharge (RR 1.26, 95% CI 0.76-2.07), or survival to hospital discharge with a favorable neurologic outcome (RR 0.93, 95% CI 0.58-1.49).
	+ When looking at subgroups based on initial rhythm, there was still no statistically significant difference in outcome.

Initial epinephrine plus vasopressin compared to epinephrine only:* Meta-analysis of three controlled trials found no significant difference in ROSC (RR 0.97, 95% CI 0.87-1.08), survival to hospital admission (RR 0.95, 95% CI 0.83-1.08), or survival to hospital discharge (RR 0.76, 95% CI 0.47-1.22).
* Six observational studies also found no difference between vasopressin, vasopressin plus epinephrine, and epinephrine with regards to outcomes.
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| How precise are the results? | See above. |
| Were the results similar from study to study? | Mostly yes. I2 statistics were 0% for the majority of meta-analyses performed, and visual interpretation of [Forest plots](http://www.cebi.ox.ac.uk/for-practitioners/what-is-good-evidence/how-to-read-a-forest-plot.html) was consistent with low levels of [heterogeneity](http://handbook.cochrane.org/chapter_9/9_5_1_what_is_heterogeneity.htm). The I2 statistic was 77% for survival to hospital admission when comparing epinephrine to placebo, and was 56%, 58%, 29%, and 100% for ROSC, survival to hospital admission, survival to hospital discharge, and favorable neurologic outcomes, respectively, when comparing vasopressin to epinephrine. |
| **Will the results help me in caring for my patients?** |
| How can I best interpret the results to apply them to the care of my patients? | Based on the synthesis of the supplied evidence, there appears to be no difference in outcome when using epinephrine versus vasopressin for treatment of OHCA, and no benefit to using both vasopressors for the same patient. When comparing epinephrine to placebo, epinephrine seems to improve rates of survival, but not survival with a favorable neurologic outcome (both at time of hospital discharge and at 3 months). Given these conflicting results, further research into [patient preferences and values](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029304/) may help provide an ethically sound road forward with regards to use of vasopressors in cardiac arrest. In particular, some may consider a CPC score of 3 (conscious but severely disabled) to be a good outcome, while others would disagree. |
| Were all patient important outcomes considered? | Yes. The authors tried to look at long-term (3-month) neurologic outcomes (a [patient-centered outcome](http://omerad.msu.edu/ebm/Intro/Intro6.html) recommended by [experts when performing research on cardiac arrest](http://pmid.us/21969010)) when available. This was only available for the comparison of epinephrine and placebo; when comparing vasopressin with epinephrine, neurologic outcome at discharge was the most patient-centric outcome available, and neurologic outcomes were not available when comparing epinephrine alone to vasopressin plus epinephrine. |
| Are the benefits worth the costs and potential risks? | Uncertain. Again, while epinephrine does not appear to improve long-term neurologic outcomes in OHCA, patient values could potentially affect these findings. In general, epinephrine should not be prioritized when managing cardiac arrest, with more emphasis on early defibrillation and high-quality chest compressions with limited interruptions. When epinephrine is being considered, it should be given early. |

**Limitations:**

1. [**Long-term neurologic outcomes**](http://pmid.us/21969010) **were only available for the meta-analysis of studies comparing epinephrine to placebo.**
2. **Study quality was variable, with high risk of bias in many of the controlled trials and critical risk of bias in most of the observational studies.**
3. **Given large degrees of methodological heterogeneity between many of the studies, very few were actually pooled for meta-analyses.**
4. [**Publication bias**](http://pmid.us/10729693) **could not be assessed given the low number of studies included in the meta-analyses.**

**Bottom Line:**

**This methodologically sound systematic review and meta-analysis commissioned by ILCOR found no difference in outcome when epinephrine and vasopressin for treatment of OHCA, and no benefit to using both vasopressors at the same time. When comparing epinephrine to placebo, epinephrine seems to improve rates of survival, but not survival with a favorable neurologic outcome (both at time of hospital discharge and at 3 months).**