

Question: Vasopressors during cardiac arrest - vasopressin or vasopressin plus epinephrine compared to epinephrine

POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest from any etiology
INTERVENTION:	Vasopressors or a combination of vasopressors given IV or IO during CPR
COMPARISON:	No vasopressor or a different vasopressor or combination of vasopressors given IV or IO during CPR
MAIN OUTCOMES:	ROSC, survival (30-day, hospital discharge), survival with favorable neurological outcome at one month, 3 months or longer, survival with unfavorable neurologic outcome at 3 months or longer
SETTING:	1) Out-of-hospital cardiac arrest 2) In-hospital cardiac arrest

ASSESSMENT (VASOPRESSIN WITH OR WITHOUT EPINEPHRINE COMPARED TO EPINEPHRINE ONLY)

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Cardiac arrest, both in the out-of-hospital and in-hospital setting, is relatively common and carries a very high morbidity and mortality.	A recent large RCT on epinephrine vs placebo for cardiac arrest (Perkins 2018 711) has called attention to the general topic of vasopressors during cardiac arrest.
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input checked="" type="radio"/> Don't know	For both the vasopressin vs epinephrine and the vasopressin plus epinephrine vs epinephrine only comparisons, no study found a significant difference in any outcome between groups. Results from individual studies were inconsistent. Both individually and when pooled, confidence intervals included the null in all cases.	Studies were likely underpowered, preventing definitive conclusions from being drawn from results.
Undesirable Effects		
How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input type="radio"/> Trivial <input type="radio"/> Varies <input checked="" type="radio"/> Don't know	For both the vasopressin vs epinephrine and the vasopressin plus epinephrine vs epinephrine only comparisons, no study found a significant difference in any outcome between groups. Results from individual studies were inconsistent. Both individually and when pooled, confidence intervals included the null. One potential negative effect is increasing complexity in the cardiac arrest treatment algorithm, which may not be warranted if there are no differences in outcomes.	No additional perceived undesirable effects.
Certainty of evidence		
What is the overall certainty of the evidence of effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS															
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate (survival) ○ High ○ No included studies 	<p>The certainty of evidence varies, but is low or very low for all outcomes, very low in the majority.</p> <table border="1"> <thead> <tr> <th rowspan="2">Comparison (OHCA)</th> <th colspan="3">Outcome</th> </tr> <tr> <th>ROSC</th> <th>Survival to hospital discharge</th> <th>Favorable neurological outcome at hospital discharge</th> </tr> </thead> <tbody> <tr> <td>Initial vasopressin compared to initial epinephrine</td> <td>⊕⊕○○ LOW</td> <td>⊕○○○ VERY LOW</td> <td>NR</td> </tr> <tr> <td>Initial epinephrine plus vasopressin compared to epinephrine alone</td> <td>⊕○○○ VERY LOW</td> <td>⊕○○○ VERY LOW</td> <td>⊕⊕○○ LOW</td> </tr> </tbody> </table>	Comparison (OHCA)	Outcome			ROSC	Survival to hospital discharge	Favorable neurological outcome at hospital discharge	Initial vasopressin compared to initial epinephrine	⊕⊕○○ LOW	⊕○○○ VERY LOW	NR	Initial epinephrine plus vasopressin compared to epinephrine alone	⊕○○○ VERY LOW	⊕○○○ VERY LOW	⊕⊕○○ LOW	<p>The low to very low certainty of evidence is due largely to inadequate sample sizes and inconsistency of results across trials.</p>
Comparison (OHCA)	Outcome																
	ROSC	Survival to hospital discharge	Favorable neurological outcome at hospital discharge														
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>One study suggests that patients value survival with favorable neurologic outcome most highly.¹</p>	<p>We anticipate that survival with good neurological outcome would be most important. If that were unable to be determined, we anticipate that survival would be of value to patients.</p>

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	<p>Given the neutral results, and the presumed benefit of keeping the recommendations for treating cardiac arrest as simple as possible, the balance of favorable and unfavorable effects slightly favors epinephrine.</p>	<p>As the studies on these comparisons are likely underpowered, even when pooled, this should not preclude further research in this area.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We have not identified any research that assessed acceptability. However, vasopressin is not currently part of the algorithm for treatment of cardiac arrest internationally, so the education and associated cost of introducing this change would likely not be acceptable, given the neutral results of available studies.</p>	<p>No other considerations identified.</p>

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>Vasopressin was previously used more broadly during CPR, but is not the current standard.</p>	<p>Implementing the addition of vasopressin to the treatment algorithm would require some cost for both medication and training, which might be burdensome for some healthcare systems.</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Recommendation

We suggest against the administration of vasopressin in place of epinephrine during cardiopulmonary resuscitation (weak recommendation, very low certainty of evidence).

We suggest against the addition of vasopressin to epinephrine during cardiopulmonary resuscitation (weak recommendation, low certainty of evidence).

Justification

In suggesting that vasopressin not be used in place of or in addition to epinephrine, we are placing value on keeping the cardiac arrest treatment algorithm simpler when there is no evidence to support increasing complexity by adding additional medication options.

REFERENCES:

1. Haywood K, Whitehead L, Nadkarni V, Achana F, Beesems S, Bottinger B et al, COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. *Circulation* 137:e783–e801. April, 2018.