Question: Vasopressors during cardiac arrest – epinephrine compared to placebo	
POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest from any etiology
INTERVENTION:	Vasopressor or a combination of vasopressors given IV or IO during CPR
COMPARISON:	No vasopressor given or a different vasopressor *or* a combination of vasopressors given IV or IO during CPR
MAIN OUTCOMES:	ROSC, survival (30-day, hospital discharge), favorable neurological outcome
SETTING:	1) Out-of-hospital cardiac arrest 2) In-hospital cardiac arrest

ASSESSMENT (VASOPRESSORS)

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ 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 (Perkins 2018 711) on the effect of epinephrine compared to placebo for out-of-hospital cardiac arrest has dramatically increased the amount of evidence on this topic, prompting an updated review.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate (survival) ○ Large ○ Varies ○ Don't know	For epinephrine compared with placebo, improvements in the short-term outcomes of ROSC and hospital admission are very substantial. The improvement in survival (30-day, discharge) is moderate yet still substantial, especially for initially nonshockable rhythms. Whether there is improvement in survival to discharge with good neurological outcome remains unclear. The desirable effects appear more pronounced in non-shockable compared with shockable rhythms (additional details are provided in the GRADE tables).	Additional considerations that were raised included the impact of increased ROSC on organ donation.

Epinephrine compared to placebo – Any rhythm (Jacobs 2011, Perkins 2018)		
Outcome	**Relative risk**	**Risk difference**
Return of spontaneous circulation	3.09 (2.82 to 3.39)	243 more per 1000 (from 211 more to 277 more)
Survival to hospital discharge	1.44 (1.11 to 1.86)	10 more per 1000 (from 2 more to 19 more)
Favorable neurological outcome at hospital discharge	1.21 (0.90 to 1.62)	4 more per 1,000 (from 2 fewer to 12 more)
Epinephrine compared to placebo – Shockable rhythm (Jacobs 2011, Perkins 2018)		
Outcome	**Odds ratio**	**Risk difference**
Return of spontaneous circulation	1.68 (1.48 to 1.92)	185 more per 1,000 (from 130 more to 250 more)
Survival to hospital discharge	1.23 (0.94 to 1.62)	22 more per 1,000 (from 6 fewer to 60 more)
Favorable neurological outcome at hospital discharge*	1.05 (0.76 to 1.45)	4 more per 1,000 (from 21 fewer to 39 more)
Epinephrine compared to placebo – Non-shockable rhythm (Jacobs 2011, Perkins 2018)		
Outcome	**Relative risk**	**Risk difference**
Return of spontaneous circulation	4.45 (3.91 to 5.08)	254 more per 1,000 (from 214 more to 301 more)
Survival to hospital discharge	2.56 (1.37 to 4.80)	7 more per 1,000 (from 2 more to 16 more)
Favorable neurological outcome at hospital discharge*	1.80 (0.80 to 4.07)	2 more per 1,000 (from 1 fewer to 9 more)

* Perkins 2018 only

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A potential undesirable outcome would be an increased number of survivors with severe neurological injury. Overall survival was increased with use of epinephrine, but there was no statistically significant increase in either survival to discharge or 3 months with a favorable neurologic outcome or survival to 3 months with an unfavorable neurologic outcome.	The task force decided *a priori* not to consider the outcome of survival with unfavorable neurologic outcome at less than 3 months after ROSC. This decision was based on the fact that in many cases the neurologic injury is still in the process of recovery at earlier time points, making assessing this outcome earlier than 3 months problematic.

Epinephrine compared to placebo – Any rhythm (Jacobs 2011, Perkins 2018)

Outcome	Relative risk	Risk difference
Favorable neurological outcome at hospital discharge	1.21 (0.90 to 1.62)	4 more per 1,000 (from 2 fewer to 12 more)
Favorable neurologic outcome at 3 months*	1.30 (0.94-1.80)	5 more per 1000 (from 1 fewer to 13 more)
Unfavorable neurological outcome at 3 months*	1.45 (0.67 to 3.12)	1 more per 1,000 (from 1 fewer to 6 more)

* Perkins 2018 only

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ●Moderate (survival) ○ High ○ No included studies	The certainty of evidence varies by outcome. There is high certainty for ROSC and hospital admission., moderate certainty for survival and low to moderate certainty for neurological outcomes.	The variation in certainty of evidence by outcome was largely due to the event rate for each outcome. There was more statistical power to evaluate differences in ROSC (a more common event) than survival with favorable neurologic outcome (a much less common event). Certainty for the outcomes of favorable or unfavorable neurologic outcome at 3 months was also lessened by loss to follow up for this outcome specifically.

Comparison (OHCA)	Outcome		
	ROSC	Survival to hospital discharge	Favorable neurological outcome at hospital discharge
Epinephrine comared to placebo – Any rhythm	⊕⊕⊕⊕ HIGH	⊕⊕⊕◯ MODERATE	⊕⊕⊕◯ MODERATE
Epinephrine comared to placebo – Shockable rhythm	⊕⊕⊕◯ MODERATE	⊕⊕⊕◯ MODERATE	⊕⊕◯◯ LOW
Epinephrine comared to placebo – Non-shockable rhythm	⊕⊕⊕⊕ HIGH	⊕⊕⊕◯ MODERATE	⊕⊕◯◯ LOW

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	One study suggests that patients value survival with favorable neurologic outcome most highly.[1]	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.

○ No important uncertainty or variability		

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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	See above summary of desirable and undesirable effects.	Althugh there was no statistically significant effect from epinephrine on survival with favorable neurologic outcome, the significant difference in ROSC and survival led to the conclusion that the balance of effects favors the intervention.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability. However, the provision of epinephrine is currently the standard of care and would therefore appear to be acceptable.	Currently the standard of care is to provide epinephrine during cardiac arrest. Differential recommendations based on rhythm are also somewhat incorporated into current practice with recommendations to provide defibrillation prior to epinephrine for patients with shockable rhythms. Resources might need to be allocated to communities that do not currently have capacity for administration of epinephrine in the out-of-hospital setting.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, current standard of care.	Yes, current standard of care.

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 recommend the administration of epinephrine during cardiopulmonary resuscitation (strong recommendation, low to moderate certainty of evidence).

For non-shockable rhythms (PEA/asystole), we recommend administration of epinephrine as soon as feasible during cardiopulmonary resuscitation (strong recommendation, very low certainty of evidence).

For shockable rhythms (VF/VT), we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during cardiopulmonary resuscitation (weak recommendation, very low certainty of evidence).

Justification

In making the recommendation for epinephrine during cardiopulmonary resuscitation we considered the findings that epinephrine improves ROSC, hospital admission and survival. The impact on neurologic outcome remains uncertain, with no statistically significant evidence of benefit or harm. There does appear to be a more pronounced effect of epinephrine in non-shockable rhythms compared to shockable rhythms but assessment of these sub-groups should be taken with caution. For non-shockable rhythms, there are limited alternative interventions in most cases and chances of survival decrease rapidly over time. Therefore, we recommend provision of epinephrine as soon as feasible. Exceptions may exist where a clear reversible cause can be rapidly addressed. For shockable rhythms, the studies evaluating administration of epinephrine included protocols for provision after the third defibrillation. Therefore, the optimal timing for epinephrine in relation to defibrillations remains unknown at this time but we suggest administering epinephrine after initial defibrillations have been unsuccessful.

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.