Appendix A

Advanced Life Support – 2026 Evidence to Decision Tables

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Thrombolytics During Cardiac Arrest (ALS 3203)

QUESTION

Should thrombolytics vs. no thrombolytics be used for cardiac arrest in adults or children?	
POPULATION:	Adults of children in cardiac arrest
INTERVENTION:	Thrombolytics
COMPARISON:	No thrombolytics
MAIN OUTCOMES:	Survival to hospital discharge; Return of spontaneous circulation (ROSC); Any intracranial hemorrhage; Favourable Neurological Outcome at hospital discharge;
SETTING:	Any setting
PERSPECTIVE:	Individual Patient
BACKGROUND:	Pulmonary embolism and acute coronary syndrome are not uncommon etiologies of cardiac arrest. Thrombolytics are treatment options for these conditions for patients not in cardiac arrest. Some have questioned whether thrombolytics should be added to the routine / standard management algorithm for cardiac arrest.
CONFLICT OF INTERESTS:	One member was the lead author on the TROICA trial.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It is estimated that there are over 4 million cardiac arrests that occur per year globally. Acute coronary occlusion (ACS) and pulmonary embolisms (PE) are both common etiologies of cardiac arrest, for which treatment options may include thrombolytic medications. Although the etiology of cardiac arrest is rarely known at the time of treatment, given that ACS and PE are common etiologies, it has been suggested that intra-arrest thrombolysis may be an appropriate empiric treatment option for undifferentiated cardiac arrest.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	There have been three randomized clinical trials performed (one pilot trial and two clinical-effectiveness trials), randomizing individuals with cardiac arrest (primarily out-of-hospital cardiac arrest, but a small number of in-hospital cardiac arrest patients) to intra-arrest thrombolytics vs placebo. No trial reported a significant improvement of survival to hospital discharge or survival to hospital discharge with favourable neurological outcome. When examining subgroup analyses, among those with bystander CPR, treatment with thrombolysis (vs. placebo) resulted in a lower proportion with 30-day survival (RR 0.55, 95% CI 0.35, 0.87). Among those with initial shockable rhythms, data was suggestive that	

	thrombolysis (vs. placebo) may lead to worse outcomes (RR 0.80, 95% CI 0.60, 1.06) however this was not statistically significant.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The primary risk of thrombolysis is of bleeding complications. Two studies reported bleeding complications, which were consistently numerically higher for those treated with thrombolysis. However, the only bleeding complication that was statistically different between groups was "any intracranial hemorrhage" (RR 6.96, 95% CI 1.59, 30.41).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The research investigating thrombolysis for undifferentiated includes three randomized clinical trials. One trial was judged to have a high risk of bias, however was small and contributed a very small weight to the meta-analysis. Further, the results were not inconsistent with other data. Thus, we have not down-graded the overall certainty of evidence based on this single study. All data are consistent, with no evidence demonstrating a benefit of thrombolysis. However, the confidence intervals of the results are wide, and thus there may still be benefit or harm within these bounds.	

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 ○ No important uncertainty or variability	Previous data indicate that patients prioritize survival with intact neurological function, but also value survival.	

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	The available randomized clinical evidence did not detect a benefit of thrombolysis for undifferentiated out-of-hospital cardiac arrest. Among those with bystander CPR, a harmful effect was detected. Further, thrombolysis resulted in a higher proportion of cases with intracranial hemorrhage. Also worth considering is the task-saturated nature of cardiac arrest resuscitations, and that the deployment of additional interventions may interfere with or worsen the quality of standard resuscitation management. Overall, the balance between desirable and undesirable effects favour not administering thrombolytics. (See Appendix A "Evidence Table" below).

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Thrombolytics are expensive, often costing over $1000 USD per dose. The drugs typically need to be refrigerated (at 2-8 degrees C), which adds to the expense of storing on ambulances in the out-of-hospital setting. The drugs have a typical shelf-life of 3 years. Overall, the costs and logistical challenges of providing this therapy are not negligible.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies evaluating the resources required for this intervention.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	There are no studies which have examined cost-effectiveness. However given the cost of the intervention and lack of evidence of effectiveness, it is unlikely that the intervention would be cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given there was no benefit seen with thrombolytics, there is no expected impact on equity. If there was a benefit seen, monitoring efforts for inequitable access to this expensive treatment option would have been appropriate.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The available research did not include any assessments of acceptability. However, given that survival with favourable neurological outcomes is a prioritized outcome of patients, and that thrombolytic medications are administered while patients are unconscious, it is likely that the eventual neurological outcome data would govern acceptability. Overall, it is likely that this intervention would be acceptable to patients if it demonstrated effectiveness.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The cost for thrombolytics is not negligible, often costing over $1000 USD per dose. Thrombolytics require refrigerated storage (at 2–8 °C) and need to be reconstituted prior to administration. Overall, thrombolytic use is potentially feasible, but does add to healthcare costs, as well as resulting in additional tasks to perform during cardiac arrest resuscitations.	

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	Trivial	Small	**Moderate**	Large		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
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

We recommend against the routine administration of thrombolytics during cardiopulmonary resuscitation for the treatment of cardiac arrest (strong recommendation, moderate certainty of evidence).

Justification

· There were three RCT's which examined the benefit of thrombolytics (vs. no thrombolytics) for cardiac arrest. Overall, available data did not demonstrate a benefit of thrombolytics for any clinical outcome, however data indicated a risk of harm due to an increased risk of intracranial bleeding.
· Although studies had specific inclusion criteria (presumed cardiac origin [i.e. no obvious non-cardiac cause], witnessed arrest, or PEA), these categories were still broadly undifferentiated.
· Risk of bias was judged to be low for two large RCT's, and high for a small pilot study. However, we elected not to downgrade the certainty of evidence based on the high risk of bias for the single study, given that: (1) in the meta-analysis the small study had minimal impact on the overall results; (2) results were consistent after removal of the small study; and (3) the results of the small study were consistent with the two larger studies.
· All safety outcomes examining bleeding were suggestive of an increased risk of bleeding from thrombolytic therapy. A single outcome of "any intracranial hemorrhage" showed a statistically significant harm. We classified safety outcomes at a high risk of bias (specifically verification bias), given that all cases were not evaluated for the outcome of interest. For example, patients that died early in the course of treatment did not survive long enough to be evaluated. Even those that survived initial treatment did were not all evaluated for bleeding complications. It is likely that bleeding (even life-threatening bleeding) was missed given that all patients were critically ill and did not all undergo evaluation for bleeding. However, the direction of bias would likely be in underestimating the harms of thrombolytics, and thus a comprehensive evaluation of bleeding would likely only increase the current findings which already suggest a risk of increased bleeding.

Subgroup considerations

· Although analyses examining subgroups should be considered exploratory and at risk of type I error given multiple comparisons, it is notable that among cases with bystander CPR, thrombolytic therapy (in comparison to no thrombolytic therapy) resulted in an lower proportion of survivors. The subgroup of cases with initial shockable rhythms was also suggestive of harm.

Implementation considerations

· We considered the resource implications of administering this therapy, which were not negligible. The therapy often costs >$1000 USD, require refrigerated storage, and need to be reconstituted prior to administration.

Monitoring and evaluation

· Not applicable

Research priorities

· Our review examined cases of undifferentiated cardiac arrest, which were largely out-of-hospital cardiac arrests
· Future research may be warranted to examine the benefit of thrombolytics among: (1) those with an increased risk of PE; (2) in-hospital cardiac arrest.

Appendix A: Evidence Table

Certainty assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of	Study event rates (%)		Relative effect (95	Anticipated absolute effects	
							With no thrombolytics	With thrombolytics		Risk with no	Risk difference with

Follow-up						evidence			% CI)	thrombolytics	thrombolytics
Survival to hospital discharge											
1299 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Moderate[a,b]	91/646 (14.1%)	79/653 (12.1%)	**RR 0.86** (0.65 to 1.14)	91/646 (14.1%)	**20 fewer per 1,000** (from 49 fewer to 20 more)
Return of spontaneous circulation (ROSC)											
1294 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Moderate[a,b]	307/643 (47.7%)	316/651 (48.5%)	**RR 1.04** (0.72 to 1.51)	307/643 (47.7%)	**19 more per 1,000** (from 134 fewer to 243 more)
Any intracranial hemorrhage											
1032 (1 RCT)	serious[c]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low[b,c]	2/514 (0.4%)	14/518 (2.7%)	**RR 6.95** (1.59 to 30.41)	2/514 (0.4%)	**22 more per 1,000** (from 2 more to 111 more)
Favourable Neurological Outcome at hospital discharge											
1299 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Moderate[a,b]	55/653 (8.4%)	55/646 (8.5%)	**RR 1.00** (0.70 to 1.41)	55/653 (8.4%)	**0 fewer per 1,000** (from 25 fewer to 35 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias for Fatovich 2024 was judged to be high, however given the small sample size and low weight on the results, we did not downgrade the overall certainty of evidence based on this single study.
b. Confidence interval are wide, including both clinically important potential benefit and harm.
c. Bleeding outcomes were not consistent across studies. Verification bias was a concern

References:

1. Abu-Laban RB, Christenson JM, Innes GD, van Beek CA, Wanger KP, McKnight RD, MacPhail IA, Puskaric J, Sadowski RP, Singer J, Schechter MT and Wood VM. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. *N Engl J Med*. 2002;346:1522–1528.
2. Bottiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, Carli PA, Adgey JA, Bode C and Wenzel V; on behalf of the Troica Trial Investigators and the European Resuscitation Council Study Group. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med*. 2008;359:2651–2662.
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Intramuscular Epinephrine (ALS 3212)

QUESTION

SHOULD INTRAMUSCULAR EPINEPHRINE BE USED DURING CARDIAC ARREST IN ADULTS?	
POPULATION:	Adult patients who suffer a cardiac arrest in any setting.
INTERVENTION:	Intramuscular (IM) route of epinephrine administration.
COMPARISON:	IV/IO epinephrine administration.
MAIN OUTCOMES:	Any clinical outcome.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival for cardiac arrest remains poor despite advances in resuscitation. IM epinephrine is a relatively inexpensive intervention that can be delivered by a variety of first responders and enable earlier administration of epinephrine.	This topic was chosen for review because it has never been systematically reviewed by ILCOR. It was prioritized by the ALS Task Force as there is great interest in the topic after a recent publication. This topic was completed using the adolopment process, leveraging a recently published systematic review.[1]

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Only one clinical study was identified.[2] The study was single-center study comparing patient outcomes before and after implementation of an early, first-dose IM epinephrine EMS protocol for adult OHCA patients. In both groups epinephrine 1 mg IV or IO was provided every 3–5 min once vascular access was established. The pre-intervention period took place between January 2010 and October 2019. The post-intervention period was between November 2019 and May 2024. 5 animal studies were identified.[3-7] The animal studies were heterogenous with regards to methodology and interventions precluding any meaningful synthesis of the results	If the effect of IM epinephrine is similar or attenuated compared to IV/IO epinephrine the desirable effect on clinical important outcomes is likely small.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○Trivial ○ Varies ○ Don't know	There was no sign of a potential undesirable effect of IM epinephrine in the one clinical study that was identified.	The potential undesirable effects include necrosis and infection at the injection site. Furthermore, it is unclear whether prioritizing IM epinephrine could potentially delay other important interventions.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence was judged very low-certainty (downgraded for risk of bias and imprecision)	

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 ○ No important uncertainty or variability	The importance of survival and neurologically intact survival is generally agreed upon.	

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	The one study that was identified[2] showed a clear effect of IM epinephrine, however the study was single-center study comparing patient outcomes before and after implementation of an early, first-dose IM epinephrine EMS, making it at serious risk of confounding.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	IM epinephrine is low-cost in most settings and possibly at a lower cost that IV/IO epinephrine.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant studies were identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	No cost-effectiveness data were identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○Probably no impact ●Probably increased ○ Increased ○ Varies ○ Don't know	IM epinephrine is low-cost in most settings and possibly lower cost than IV/IO epinephrine. However, whether IM epinephrine is effective, compared with no epinephrine, is unknown.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were identified.	There is great public interest in the intervention, and it is likely acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○Probably yes ● Yes ○ Varies ○ Don't know	IM administration of epinephrine is standard practice for the treatment of anaphylaxis.	

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
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

There is insufficient evidence to recommend adding intra-arrest intramuscular epinephrine to standard resuscitation care for cardiac arrest. (weak recommendation, very-low certainty of evidence).

Justification

- The TF recognized that intramuscular epinephrine is an interesting area of research and has gained increased attention. It is a relatively inexpensive intervention that can be delivered by a variety of first responders and could therefore enable earlier administration of epinephrine. In the management of cardiac arrest, earlier epinephrine is associated with improved clinical outcomes, however these studies are confounded by resuscitation time bias. Additionally, in a secondary analysis of the PARAMEDIC2 study, shorter time to treatment, whether treatment was adrenaline or placebo, was also associated with improved outcome.
- The key historical concern regarding IM epinephrine has been uncertainty regarding its absorption in cardiac arrest. The limited available data suggest that IM epinephrine may be associated with earlier administration, but the clinical effect on outcomes remains uncertain. However, the Task Force felt that it would be premature to recommend the use of IM epinephrine at this stage given that evidence is limited to a single observational study and extrapolation of potential benefit from studies exploring the association between time to drug administration and clinical outcome. The task force highlighted the need for randomized controlled trials to evaluate IM epinephrine in cardiac arrest, with a focus on shortening the time to first dose by administering epinephrine IM compared with IV/IO. The ALS TF considered that some patients receiving CPR may have been in a low flow state and they may be a group that potentially would benefit from early IM epinephrine.
- Only one observational study was identified that evaluated a first-dose intramuscular (IM) epinephrine protocol for adult out-of-hospital cardiac arrest (OHCA) patients, followed by advanced life support and intravenous/intraosseous (IV/IO) epinephrine administration. Consequently, the treatment recommendation does not extend to settings where subsequent advanced life support and IV/IO epinephrine administration are not available. The task force discussed the possibility that IM epinephrine could be useful in such settings, but the evidence is too sparse (no human data comparing IM with IV/IO) to support a recommendation. In addition, the task force discussed whether focus on IM epinephrine could result in delay of standard resuscitation interventions, including IV/IO epinephrine, which could inadvertently cause harm.
- Finally, the taskforce discussed whether the slower absorption of IM epinephrine compared to IV could be beneficial in the early post-resuscitation phase where hypotension is common and associated with poor outcomes, however this remains unknown.
- The relevance of the current topic is unknown for patients with in-hospital cardiac arrest where time to drug administration is shorter due to the high prevalence of pre-existing vascular access and earlier initiation of advanced life support.
- Animal studies were included in the systematic review but the results should be interpreted with caution due to risk of bias and generalizability to humans. In addition, time to drug administration in animals does not reflect the human clinical experience, where epinephrine administration is often delayed compared to animal studies.

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3. Lim D, Lee SH, Kim DH, Kang C, Jeong JH, Lee SB. The effect of high-dose intramuscular epinephrine on the recovery of spontaneous circulation in an asphyxia-induced cardiac arrest rat model. BMC Cardiovasc Disord. 2021;21(1):113.
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7. Redding JS, Asuncion JS, Pearson JW. Effective routes of drug administration during cardiac arrest. Anesth Analg. 1967;46(2):253-8.

Intra-Arrest Volume Therapy During Nontraumatic Cardiac Arrest (ALS 3207, part 1)

QUESTION

SHOULD INTRAVASCULAR VOLUME THERAPY BE USED DURING CPR FOR NON-TRAUMATIC CARDIAC ARREST?	
POPULATION:	Adults with non-traumatic cardiac arrest in any setting.
INTERVENTION:	Intravascular volume therapy during cardiac arrest.
COMPARISON:	No intravascular volume therapy or a different intravascular volume therapy during cardiac arrest (a different type, volume, or timing).
MAIN OUTCOMES:	Any clinical outcome.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival from cardiac arrest remains poor despite advances in resuscitation. Optimal fluid management during cardiac arrest is uncertain.	This topic was prioritized given evolving evidence.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Prehospital hypertonic saline with HES** Small RCTs of hypertonic saline plus hydroxyethyl starch (HES) compared to HES alone showed no benefit in survival to hospital admission, survival to hospital discharge, and favorable neurological outcome.[1,2] **Prehospital infusion of cold normal saline** RCTs of prehospital infusion of cold normal saline compared to standard care showed no benefit in return of spontaneous circulation, survival to hospital discharge, favorable neurological outcome, and survival at one year.[3,4]	No randomized trials directly evaluated routine volume therapy versus no volume therapy as a resuscitation strategy. The trials that were identified evaluated specific interventions such as hypertonic saline with hydroxyethyl starch or rapid infusion of ice-cold crystalloids during cardiopulmonary resuscitation. The cold crystalloid trials were designed to induce therapeutic hypothermia rather than for volume resuscitation purposes. The interpretation of these trials was limited by the control group often receiving ambient temperature fluids in addition to ice-cold crystalloids.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	**Prehospital hypertonic saline with HES** No adverse events relevant to the PICOST question were reported in these trials.[1,2] **Prehospital infusion of cold normal saline** One RCT reported higher rates of pulmonary edema with prehospital infusion of cold normal saline compared to standard care (62/207 [10%] vs 26/227 [4.5%]; P < 0.05), whereas another RCT reported no difference (7/41 [17%] vs 8/36 [22%]; P = 0.59).[3,4]	Physiological concerns exist that fluid boluses during chest compressions may increase right atrial pressure, impair venous return, and consequently reduce coronary perfusion pressure. Evidence for hypertonic solutions with hydroxyethyl starch has limited relevance as hydroxyethyl starch solutions has been withdrawn from or heavily restricted in most countries because an increased risk of coagulopathy, acute kidney injury, and mortality in multiple large trials of critically ill patients.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence for trials ranged from very low to low across different comparisons and outcomes downgraded for risk of bias, indirectness, and imprecision. The observational studies addressing non-traumatic intra-arrest volume therapy were highly heterogeneous and at serious or critical risk of bias, precluding meaningful meta-analysis.	

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 ○ No important uncertainty or variability	The importance of survival and neurologically intact survival is generally agreed upon.	

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	The available evidence does not show any benefit from routine intravascular volume therapy during CPR for non-traumatic cardiac arrest.	Physiological concerns about impaired coronary perfusion with fluid boluses during chest compressions, combined with lack of benefit, suggest the balance probably favors no routine volume therapy in normovolemic patients.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Crystalloid solutions are low-cost in most settings.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant studies were identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	No cost-effectiveness data were identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were identified.	Most interventions considered are currently used in clinical practice and are likely acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

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
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest against the routine use of intravascular volume therapy during cardiopulmonary resuscitation in patients with undifferentiated non-traumatic cardiac arrest (weak recommendation, very low-certainty evidence).

We recommend against the use of hydroxyethyl starch solutions during cardiopulmonary resuscitation or after return of spontaneous circulation (strong recommendation, very low-certainty evidence).
If clinical circumstances indicate that the patient was hypovolemic prior to the cardiac arrest, volume therapy may be reasonable (Good Practice Statement).

Justification

- The systematic review identified no randomized trials that directly evaluated routine volume therapy versus no volume therapy as a resuscitation strategy. The trials that were identified evaluated specific interventions such as hypertonic saline with hydroxyethyl starch or rapid infusion of ice-cold crystalloids during cardiopulmonary resuscitation.
- There are physiological concerns that fluid boluses during chest compressions may increase right atrial pressure, impair venous return, and consequently reduce coronary perfusion pressure.
- Trials evaluating rapid infusion of ice-cold crystalloids were designed to induce therapeutic hypothermia rather than evaluate volume resuscitation. The interpretation of these trials was limited by the control group often receiving ambient temperature fluids in addition to ice-cold crystalloids.
- Hydroxyethyl starch solutions, regardless of their formulation (such as Hespan, HAES-steril, and Voluven), have been withdrawn from or heavily restricted in most countries because of an increased risk of coagulopathy, acute kidney injury, and mortality in multiple large trials of critically ill patients.
- The observational studies were all at serious or critical risk of bias and evaluated highly heterogeneous populations and interventions. These studies generally found no consistent association between volume therapy and outcomes.

References:

1. Bender R, Breil M, Heister U, Dahmen A, Hoeft A, Krep H, et al. Hypertonic saline during CPR: Feasibility and safety of a new protocol of fluid management during resuscitation. Resuscitation. 2007;72(1):74-81.
2. Breil M, Krep H, Heister U, Bartsch A, Bender R, Schaefers B, et al. Randomised study of hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest. Resuscitation. 2012;83(3):347-52.
3. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). Circulation. 2016;134(11):797-805.
4. Debaty G, Maignan M, Savary D, Koch FX, Ruckly S, Durand M, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med. 2014;40(12):1832-42.

Intravascular Volume Therapy During Traumatic Cardiac Arrest (ALS 3207, part 2)

QUESTION

SHOULD INTRAVASCULAR VOLUME THERAPY BE USED DURING CPR FOR TRAUMATIC CARDIAC ARREST?	
POPULATION:	Adults with traumatic cardiac arrest in any setting.
INTERVENTION:	Intravascular volume therapy during cardiac arrest.
COMPARISON:	No intravascular volume therapy or a different intravascular volume therapy during cardiac arrest (a different type, volume, or timing).
MAIN OUTCOMES:	Any clinical outcome.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival for cardiac arrest remains poor despite advances in resuscitation. Optimal fluid management during cardiac arrest is uncertain.	This topic was prioritized given evolving evidence.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Prehospital blood products** One subgroup analysis within an RCT[1] of prehospital blood products compared to normal saline administration showed no difference in in-hospital mortality or impaired lactate clearance (test for subgroup differences, P = 0.32).	Direct evidence from traumatic cardiac arrest trials was limited to a small subgroup analysis within a study evaluating blood products in patients with hemorrhagic shock.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	**Prehospital blood products** No adverse events relevant to the PICOST question were reported.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence was very low, downgraded for risk of bias and imprecision. The observational studies addressing volume therapy for traumatic cardiac arrest were highly heterogeneous and at serious or critical risk of bias, precluding meaningful meta-analysis.	

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 ○ No important uncertainty or variability	The importance of survival and neurologically intact survival is generally agreed upon.	

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	The available evidence does not clearly favor any specific volume therapy strategy over another for traumatic cardiac arrest.	Given the distinct pathophysiology of hemorrhagic shock and insufficient direct evidence, no recommendation for specific volume therapies in traumatic cardiac arrest could be made, and practitioners should follow local trauma resuscitation guidelines for managing trauma patients

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Crystalloid solutions are low-cost in most settings.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant studies were identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	No cost-effectiveness data were identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were identified.	Most interventions considered are currently used in clinical practice and are likely acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

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
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

There is insufficient direct evidence to recommend for or against the routine use of specific volume therapies during cardiopulmonary resuscitation in patients with traumatic cardiac arrest.

Justification

- Direct evidence from traumatic cardiac arrest trials was limited to a subgroup analysis within a study evaluating blood products in patients with hemorrhagic shock
- Given the distinct pathophysiology of hemorrhagic shock and insufficient direct evidence, no recommendation for specific volume therapies in traumatic cardiac arrest could be made, and practitioners should follow local trauma resuscitation guidelines for managing trauma patients
- The routine use of blood products in non-traumatic cardiac arrest remains uncertain and should be limited to the context of clinical trials

References:

1. Crombie N, Doughty HA, Bishop JRB, Desai A, Dixon EF, Hancox JM, et al. Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Haematol. 2022;9(4):e250-e61.

Intravascular Volume Therapy After Cardiac Arrest (ALS 3518)

QUESTION

SHOULD INTRAVASCULAR VOLUME THERAPY BE USED AFTER RETURN OF SPONTANEOUS CIRCULATION?	
POPULATION:	Adults with ROSC from cardiac arrest in any setting.
INTERVENTION:	Intravascular volume therapy after cardiac arrest.
COMPARISON:	No intravascular volume therapy or a different intravascular volume therapy after cardiac arrest (a different type, volume, or timing).
MAIN OUTCOMES:	Any clinical outcome.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival for cardiac arrest remains poor despite advances in resuscitation. Optimal fluid management after cardiac arrest is uncertain.	This topic was prioritized given evolving evidence.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Prehospital infusion of cold crystalloids:** RCTs of prehospital infusion of cold normal saline compared to standard care showed no benefit in survival to hospital discharge and favorable neurological outcome.[1-8] Subgroup analyses stratified by fluid type showed no significant difference in treatment effect between cold normal saline and Ringer's solution (P = 0.47 for survival; P = 0.61 for favorable neurological outcome). **In-hospital balanced crystalloids vs normal saline** One RCT of in-hospital use of balanced crystalloids compared to normal saline showed no benefit in survival to hospital discharge, survival at 6 months, and favorable neurological outcome.[8] **In-hospital hypertonic saline with HES** One RCT of in-hospital use of hypertonic saline plus hydroxyethyl starch (HES) compared to crystalloids showed no benefit in survival at 1 year.[9]	The cold crystalloid trials were designed to induce therapeutic hypothermia rather than for volume resuscitation purposes. The interpretation of these trials was limited by the control group often receiving ambient temperature fluids in addition to ice-cold crystalloids.

Undesirable Effects

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	**Prehospital infusion of cold crystalloids** One RCT reported higher rates of pulmonary edema (256/631 [41%] vs 184/609 [30%]; P < 0.001) and re-arrest (176/686 [26%] vs 138/671 [21%]; P = 0.008) with prehospital infusion of cold normal saline compared to standard care **In-hospital balanced crystalloids** One RCT reported no difference in development of acute kidney injury (11/27 [41%] vs 7/26 [27%]; P = 0.29) or major adverse kidney events within 30 days (14/27 [52%] vs 7/26 [27%]; P = 0.06). **In-hospital hypertonic saline with HES** No adverse events relevant to the PICOST question were reported in a single trial.	Undesirable effects vary depending on the specific volume therapy strategy. Normal saline causes hyperchloremic acidosis and may be associated with increased risk of acute kidney injury in critically ill patients compared to balanced crystalloids. However, this evidence is not specific to cardiac arrest, and concerns have been raised about the lower tonicity of balanced fluids, which could potentially worsen cerebral edema. Evidence for hypertonic solutions with hydroxyethyl starch has limited relevance as hydroxyethyl starch solutions has been withdrawn from or heavily restricted in most countries because an increased risk of coagulopathy, acute kidney injury, and mortality in multiple large trials of critically ill patients.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence for trials ranged from very low to low across different comparisons and outcomes downgraded for risk of bias, indirectness, and imprecision. The observational studies addressing post-arrest volume therapy were highly heterogeneous and at serious or critical risk of bias, precluding meaningful meta-analysis.	
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 ○ No important uncertainty or variability	The importance of survival and neurologically intact survival is generally agreed upon.	

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	The available evidence does not clearly favor any specific volume therapy strategy over another for post-cardiac arrest care.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Crystalloid solutions are low-cost in most settings.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant studies were identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	No cost-effectiveness data were identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were identified.	Most interventions considered are currently used in clinical practice and are likely acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Standard crystalloid solutions are widely available in most prehospital and hospital settings.	

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
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We recommend against the use of hydroxyethyl starch solutions during cardiopulmonary resuscitation or after return of spontaneous circulation (strong recommendation, very low-certainty evidence).

There is insufficient direct evidence to recommend for or against the use of specific volume therapies immediately after return of spontaneous circulation in patients with undifferentiated non-traumatic cardiac arrest.

Justification

- Trials evaluating rapid infusion of ice-cold crystalloids were designed to induce therapeutic hypothermia rather than evaluate volume resuscitation. The interpretation of these trials was limited by the control group often receiving ambient temperature fluids in addition to ice-cold crystalloids.
- Only one small trial (Woo et al., 2023) directly compared balanced crystalloids to normal saline in the post-arrest setting. Normal saline causes hyperchloremic acidosis and may be associated with increased risk of acute kidney injury in critically ill patients compared to balanced crystalloids. However, this evidence is not specific to cardiac arrest, and concerns have been raised about the lower tonicity of balanced fluids, which could potentially worsen cerebral edema.
- Hydroxyethyl starch solutions, regardless of their formulation (such as Hespan, HAES-steril, and Voluven), have been withdrawn from or heavily restricted in most countries because of an increased risk of coagulopathy, acute kidney injury, and mortality in multiple large trials of critically ill patients.
- The observational studies were all at serious or critical risk of bias and evaluated highly heterogeneous populations and interventions. These studies generally found no consistent association between volume therapy and outcomes.
- Given the lack of direct evidence comparing different fluid strategies in the post-arrest setting, the task force could not make a recommendation for any specific volume therapy.

References

1. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). Circulation. 2016;134(11):797-805.
2. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737-42.
3. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest*. Crit Care Med. 2012;40(3):747-53.
4. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand. 2009;53(7):900-7.
5. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014;311(1):45-52.
6. Kim F, Olsufka M, Longstreth WT, Jr., Maynard C, Carlbom D, Deem S, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation. 2007;115(24):3064-70.
7. Scales DC, Cheskes S, Verbeek PR, Pinto R, Austin D, Brooks SC, et al. Prehospital cooling to improve successful targeted temperature management after cardiac arrest: A randomized controlled trial. Resuscitation. 2017;121:187-94.
8. Woo JH, Lim YS, Cho JS, Yang HJ, Jang JH, Choi JY, et al. Saline versus Plasma Solution-A in Initial Resuscitation of Patients with Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. J Clin Med. 2023;12(15).
9. Heradstveit BE, Guttormsen AB, Langorgen J, Hammersborg SM, Wentzel-Larsen T, Fanebust R, et al. Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia - a prospective, randomised study. Scand J Trauma Resusc Emerg Med. 2010;18:29.

Video Laryngoscopy vs Direct Laryngoscopy During Cardiac Arrest (ALS 3308)

QUESTION:

Video laryngoscopy vs. laryngoscopy without video for endotracheal intubation?	
POPULATION:	Adults with cardiac arrest in any setting
INTERVENTION:	Video Laryngoscopy
COMPARISON:	Laryngoscopy without Video
MAIN OUTCOMES:	First Pass Success (RCT); Intubation Success (RCT); Time to Intubation; Esophageal Intubation;
SETTING:	Any (in-hospital or out-of-hospital)
CONFLICT OF INTERESTS:	none

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Advanced airway management is critical in advanced life support for individuals suffering cardiac arrest in order to provide effective ventilation to protect against aspiration of gastric contents. The 2019 ILCOR Consensus on Science and Treatment Recommendations (CoSTR) recommends either supraglottic airway or tracheal intubation when performing advanced airway management in cardiac arrest. Tracheal intubation during cardiac arrest presents unique challenges including challenges related to both patient-factors (e.g. shock, aspiration risk), scene-factors (e.g. intubation in non-intensive care or operating room settings), and resuscitation factors (e.g. ongoing chest compressions complicating laryngoscopic view). These unique challenges increase the risk of adverse effects of tracheal intubation including failed intubation attempts, excess pauses on chest compressions, and complications including esophageal intubation. Identifying the optimal approach to tracheal intubation during cardiac arrest resuscitation is a priority.	The ILCOR Advanced Life Support Task Force identified this question as critical following an evidence update. Data from cardiac arrest registries in the United States finds that most patients who suffer cardiac arrest undergo tracheal intubation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large	Across 3 RCTs[1-3] (n = 331) and 13 observational studies[4-16] (n ≈ 30,000) of adults undergoing tracheal intubation during cardiac arrest, the use of video laryngoscopy (VL) compared with direct	Given the overall burden of cardiac arrest globally, even modest desirable impacts could be large on the population scale.

○ Varies ○ Don't know	laryngoscopy (DL) was associated with improved procedural outcomes but no demonstrated difference in patient-centered outcomes. For **first-pass tracheal intubation success**, pooled RCT evidence[1-3] (very low certainty, downgraded for risk of bias, inconsistency, indirectness, and imprecision) showed no difference between VL and DL (RR 0.88, 95% CI 0.63–1.22). Observational data generally favored VL, with 8 of 12 studies reporting statistically significant higher success rates with VL. For **overall intubation success**, very low–certainty evidence from 3 RCTs[1-3] showed no difference (RR 1.00, 95% CI 0.90–1.12), while 5 of 6 observational studies favored VL. For **esophageal intubation**, rates were consistently lower with VL (1 RCT[3]: 4.3% vs 0%; pooled observational data: 5.6% vs 1.4%), a clinically meaningful absolute risk reduction (~4%, NNT ≈ 25). No benefit of VL over DL was demonstrated for **ROSC, survival,** or **survival with good neurologic** outcome in any observational study. These outcomes were not reported in any RCT. The potential desirable effects of VL are primarily procedural (improved first-pass and overall success, reduced esophageal intubation, better glottic view, and fewer compression interruptions). These may translate into safer airway management and improved team efficiency, particularly among less experienced operators or in difficult airway conditions. However, since improvements have not been shown to extend to patient-important outcomes (ROSC or survival), the overall magnitude of benefit is judged **moderate**.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Across 3 RCTs and multiple observational studies of adult cardiac arrest, there was no consistent evidence of increased harm with VL compared to DL. Two RCTs[1,3] found no difference in time to intubation between VL and DL and one RCT[3] reported fewer chest-compression interruptions with VL. Observational studies were mixed for time to intubation (some faster with VL), and no study identified higher rates of complications	

	(e.g., esophageal intubation—actually lower with VL, a desirable effect). Undesirable effects specifically attributable to VL (e.g., prolonged attempts, CPR pauses, aspiration) were not consistently observed.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of evidence was assessed separately for randomized trials and for non-randomized studies. The certainty of evidence was judged to be very low across all outcomes assessed in both randomized trials and non-randomized studies, owing to a high risk of bias, unmeasured confounders, incomplete (or no) adjustment for measured potential confounders, and indirectness.	RCT data is limited to small, randomized trials with methodological concerns. All randomized trials were published between 2014 and 2017, when technology and training for video-assisted laryngoscopy was not as advanced.

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 ○ No important uncertainty or variability	We have not identified any cardiac arrest tracheal intubation studies that specifically addressed how patients valued the different outcomes.	The importance of the outcome of first pass success and overall success is uncertain. The COre Outcome Set for Cardiac Arrest (COSCA) identifies ROSC as an important outcome for efficacy studies. Survival and survival with good neurologic outcome are generally recognized as important by COSCA.

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	As above, the number and suspected importance of desirable outcomes likely favor the intervention.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No studies regarding the cost effectiveness of the intervention were identified.	Studies from the operating theatre have found that video laryngoscopy is cost-effective. Resources required likely depends upon training needs, and number of video-capable of laryngoscopes needed (e.g. for hospital settings vs. pre-hopsital settings), and whether a hospital system is currently already using video laryngoscopes.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No evidence identified.	The type of video-capable laryngoscope used varied substantially across included studies.

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ○ No included studies	No studies identified.	Studies from the operating theatre have found that video laryngoscopy is cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not find any studies regarding the impact of the intervention on health equity.	Although cost effectiveness studies have found video-laryngoscopy to be cost effective in some settings, the initial investment in supplies and training may be high for low resource settings.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies regarding acceptability identified.	Airway operators with less tracheal intubation experience may find video laryngoscopy to be more acceptable as compared to airway operators with more experience.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies regarding feasibility were identified.	

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
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

There is insufficient evidence to recommend video laryngoscopy in preference to direct laryngoscopy for tracheal intubation during CPR (weak recommendation, very low–certainty evidence).

To improve tracheal intubation first pass success, overall success, and to reduce rates of inadvertent esophageal intubation, it may be reasonable to perform video laryngoscopy during cardiac resuscitation in settings where this equipment is available and airway operators are well trained in the use of the device. (Good Practice Statement)

Justification

· This topic was prioritized by the Advanced Life Support Task Force given the expanded use of video laryngoscopy in cardiac arrest and other emergency airway management settings.
· Existing Consensus on Science and Treatment Recommendations for Advanced Airway Management During Adult Cardiac Arrest do not differentiate between video laryngoscopy and direct laryngoscopy.
· Airway management during cardiac arrest is uniquely challenging as a result of ongoing chest compressions, airway contamination, and restricted positioning, which may either enhance or diminish any performance advantages of video laryngoscopy.
· The Advanced Life Support Task Force included both randomized and non-randomized studies, recognizing that existing randomized trials remain few, small, and have numerous methodological flaws while non-randomized data provide important real-world information despite a very high risk of bias.
· Across included studies, there was substantial heterogeneity in video-capable laryngoscopy device type, operator experience, and arrest setting (OHCA vs IHCA), which were considered by the task force in arriving at treatment recommendations.
· In addition to studies of tracheal intubation during cardiopulmonary resuscitation, the Task Force considered indirect evidence comparing video laryngoscopy to direct laryngoscopy among patients not in cardiac arrest in the operating room and in non-elective and emergent tracheal intubations outside of the operating room. The indirect evidence considered generally matched findings from the cardiac arrest population, with a higher rate of first pass success and overall tracheal intubation success. In a Cochrane Review that included six randomized trials comparing video laryngoscopy to direct laryngoscopy in prehospital settings (including two in cardiac arrest populations), there was no benefit of video capable as compared to non-video capable laryngoscopy.
· No data was identified from cardiac arrest populations regarding the cost-effectiveness of video-capable laryngoscopes. Indirect evidence from tracheal intubation in the operating theatre suggest that video-laryngoscopy is cost effective.
· The Task Force noted potential procedural advantages (e.g., higher first-pass success, reduced esophageal intubation) when performing video laryngoscopy although these advantages do not currently translate into improved rates of ROSC, survival, or survival with good neurologic outcomes.
· The recommendation that there is insufficient evidence to recommend an approach to tracheal intubation using a laryngoscope with video capability over a laryngoscope without video capability during cardiac arrest resuscitation was arrived at by consensus of the Advanced Life Support Task Force, based upon mixed data when assessing proximal and procedural outcomes favoring video-capable laryngoscopy and no benefit to either approach when assessing more patient-important outcomes such as survival or survival with favorable neurologic outcome.
· The Task Force considered that in the absence of evidence supporting a different approach to tracheal intubation in the cardiac arrest population as compared to standard practice in non-elective tracheal intubation settings, it would be reasonable for airway operators to procced with their standard approach to laryngoscopy during cardiac arrest resuscitation.

Subgroup considerations

No specific subgroups were examined.

Implementation considerations

Implementation in settings where videolaryngoscopes are not already part of clinical practice would require training and monitoring, as well as additional resources to purchase equipment.

Monitoring and evaluation

While this topic was not specifically addressed, monitoring first pass success and overall intubation success rates, as well as clinical outcomes, is important to elucidate the benefit of different airway devices.

Research priorities

· There were no studies directly comparing different types of video-capable laryngoscopes, including no comparisons of hyperangulated vs. standard geometry laryngoscope bladers.
· There were limited studies directly assessing whether the impact of video laryngoscope use was different based upon the experience and skillset of the airway operator.
· The cost effectiveness of a switch to video-capable laryngoscopes is unknown. This is especially true for the pre-hospital setting and in low-resource settings.
· There was no study exploring tracheal intubation adjuncts (e.g. elastic bougie) as they related to video-capable vs. non-video-capable laryngoscopy.
· The training and experience requirements for each tracheal intubation laryngoscopic approach is uncertain.

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Supplemental Oxygen During CPR (ALS 3305)

QUESTION

Can the administration of maximal oxygen concentration improve survival?	
POPULATION:	Adults with cardiac arrest in any setting
INTERVENTION:	Administering a maximal oxygen concentration (e.g. 100% by face mask or closed circuit)
COMPARISON:	No supplemental oxygen (e.g. 21%) or a reduced oxygen concentration (e.g. 40-50%)
MAIN OUTCOMES:	Survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year, survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, ROSC?

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The brain is the most sensitive organ with regards to hypoxia and hypoxic brain injury is the major cause of death in patients with return of spontaneous circulation. The administration of supplemental oxygen appears intuitive. Studies (n = 6) generally find an association between higher PaO_2 during arrest and good outcome, but research evidence comparing different oxygen administration strategies is lacking.	All studies (n=6) suggest that a higher PaO_2 during CPR is associated with higher ROSC, hospital admission, or functional survival.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	In a large study on 16,013 out-of-hospital cardiac arrest patients, higher PaO_2 is associated with better functional survival (Adjusted ORs for favorable outcome were 2.09 (normoxia) and 5.04 (hyperoxia) vs hypoxia) (Izawa 2022). All six included studies have shown similar associations between higher PaO_2 and better outcome.	All the other included studies also showed that a higher PaO_2 is correlated to better outcomes (higher rate of ROSC with sustained ROSC, higher hospital admission, higher survival to hospital discharge/1 month, and better functional outcome)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH VIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Hyperoxemia during CPR is rare.	No studies report harm from hyperoxemia during CPR.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There are no studies that have compared different amounts of administered oxygen in patients undergoing CPR. In the identified studies all patients received 100% oxygen. The higher oxygen levels in some patients have likely been due to other patient or resuscitation factors such as lung function, etiology or arrest or quality of resuscitation, and not to the administration of oxygen. Therefore, the evidence is indirect and of very low certainty. On the other hand the consistent finding in the identified studies is that a higher PaO_2 is associated with better outcomes.	The observational studies addressing PaO_2 levels during cardiopulmonary resuscitation were highly heterogeneous and at serious or critical risk of bias, precluding meaningful meta-analysis.

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 ○ No important uncertainty or variability	The importance of survival and neurologically intact survival is generally agreed upon.	

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	There was no direct evidence favoring the intervention. The available evidence suggests better outcome with higher oxygen levels. No study found worse outcome with high intra-arrest oxygen levels.	Oxygen administration during CPR is **safe and likely beneficial**; monitoring ABG/PaO_2 can help optimize outcomes, especially in advanced care settings.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Oxygen is, in general, low-cost.	Resources/costs balance is not reported in the identified studies.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No relevant studies were identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention 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 ● No included studies	No cost-effectiveness data were identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Oxygen is widely available to advanced life support providers in most prehospital and hospital settings.	There are systems in lower-resource settings, in which oxygen is not readily available. The recommendation to provide oxygen during arrest and CPR has been in place for several years however, so this will not be a change.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No relevant studies were identified.	Oxygen is currently used during CPR in clinical practice in most healthcare systems, and is likely acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Oxygen is widely available to advanced life support providers in most prehospital and hospital settings.	There are systems in lower-resource settings, in which oxygen is not readily available. The recommendation to provide oxygen during arrest and CPR has been in place for several years however, so this will not be a change.

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
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	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

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest using the highest possible inspired oxygen concentration during CPR (weak recommendation, very-low-certainty evidence).

Justification

- The quality of evidence quality is very low with only prospective observational or registry studies of critical bias. No study has randomized patients into different levels of supplemental oxygen.
- All patients in the included studies received 100% oxygen. Therefore, the difference in oxygen levels between patients may be related to other things than the use of supplemental oxygen. Across all studies, oxygen administration during CPR appeared to be safe and was associated with improved early outcomes (ROSC, hospital admission, functional survival to hospital discharge/1 month).
- Hyperoxemia during CPR does not appear to be harmful.

Subgroup considerations

Oxygen is more likely to be less widely available in the prehospital setting but is available in most systems with ALS capabilities.

Implementation considerations

This recommendations has not changed, so the task force did not think implementation would be a challenge.

Monitoring and evaluation

Nothing additional was thought to be required.

Research priorities

The Task Force discussed that there are unlikely to ever be clinical trials on intra-arrest oxygen supplementation, given the consistency of the observational association between PaO_2 and short-term outcomes.

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