ALS 2025 CoSTR Appendix A – Evidence to Decision Tables

Mechanical vs. Manual CPR – IHCA Load distributing band (ALS 3002)

QUESTION

Should a load-distributing band mechanical CPR device vs. manual CPR be used for IHCA?	
POPULATION:	IHCA
INTERVENTION:	a load-distributing band mechanical CPR device
COMPARISON:	manual CPR
MAIN OUTCOMES:	ROSC; survival to hospital discharge or 30 days or longer; survival with favorable neurological outcome at hospital discharge, 30 days or longer; resuscitation-related injuries
SETTING:	**IHCA**
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	High quality CPR is critical to improving cardiac arrest outcomes. Use of mechanical CPR has increased significantly since the COVID pandemic, although the existing treatment recommendation suggests against routine use.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There were no studies investigating desirable effects of load-distributing band mechanical CPR in IHCA.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Limited evidence (one small study) has not found a significant difference in CPR-related injuries from the load-distributing band mechanical CPR device compared with manual CPR, although the point estimate for CPR-related injuries was higher.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low	Very low certainty of effect was found from one small study.	

○ Moderate ○ High ○ No included studies		

Outcomes	With manual CPR	With
Serious resuscitation-related structural visceral damage (Koster 2017)	77 per 1,000	

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	Survival with favorable neurological outcome is widely regarded as the most critical outcome. Opinions vary on the relative importance of outcomes such as ROSC. The outcome of resuscitation-related injuries probably varies somewhat, in part based on whether increased survival with favorable neurological outcome is achieved or not.	

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 single trial of a load-distributing band CPR device compared with manual CPR did not show either benefit or increased harm from the use of mechanical CPR, although it was not powered for clinical outcomes. Indirect evidence from OHCA trials is mixed.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Cost depends on whether hospitals are already using one of these devices. No studies were identified.	

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		
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		
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	Because the evidence suggests neither benefit nor harm, whether or not use of these devices for OHCA is implemented likely would not impact equity, although purchasing these devices would be more difficult in low-resource settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	These devices are already in use in many healthcare settings.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies	Feasibility will depend on the financial and training resources of the healthcare system.	

o Don't know		

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 suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions for cardiac arrest (weak recommendation, very low-certainty evidence).

Automated mechanical chest compression devices may be a reasonable alternative to manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety (good practice statement).

Justification

This topic was prioritized by the ALS Task Force due to awareness of a marked increase in the use of mechanical CPR in several countries since the COVID-19 pandemic, and because the Task Force was aware of new trials. For the use of a load-distributing band for IHCA, only 1 study was identified and this showed neither benefit nor harm for the use of a mechanical device for CPR compared with manual CPR). The primary focus of that study was resuscitation-related injuries. The treatment recommendation and good practice statement are therefore based primarily on evidence from trials of mechanical CPR for OHCA, or for other types of mechanical CPR devices in the IHCA setting.

Subgroup considerations

Evidence not available, but consideration of avoiding delays in defibrillation, perhaps by not deploying mechanical CPR devices until after the first shock for shockable rhythms, is likely important.

Implementation considerations

Not addressed

Monitoring and evaluation

Mechanical CPR devices require training and regular practice to use efficiently.

Research priorities

· Whether mechanical CPR improves outcome from IHCA.
· Whether the possible benefit of mechanical CPR depends on timing of use, cardiac arrest rhythm, or setting.
· Whether one mechanical CPR device is superior to another
· Whether rates of CPR-related injuries from mechanical CPR vary by patients size and age
· The optimal approach to defibrillation (ie whether to pause the device for defibrillation, vs other approaches such as timing defibrillation with compression phase) when mechanical CPR devices are used

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Mechanical vs. Manual CPR – OHCA load-distributing band (ALS 3002)

QUESTION

Should Load-distributing band device vs. manual CPR be used for OHCA?	
POPULATION:	Adults with out-of-hospital cardiac arrest
INTERVENTION:	Mechanical CPR with a load-distributing band device
COMPARISON:	manual CPR
MAIN OUTCOMES:	ROSC, survival to hospital discharge, 30 days or longer, favorable neurologic outcome at hospital discharge, 30 days or longer, CPR-related injuries
SETTING:	OHCA
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	High quality CPR is critical to improving cardiac arrest outcomes. Use of mechanical CPR has increased significantly since the COVID pandemic, although the existing treatment recommendation suggests against routine use.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One large randomized controlled trial found no benefit to neurologic outcome or survival using mechanical CPR whereas another large trial found worse outcomes. One small trial identified a survival benefit from using mechanical CPR.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One small study and one large RCT found no increased harm from use of mechanical CPR.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

Question: Does CPR with a load-distributing band device compared to manual CPR improve outcomes for OHCA
Setting: OHCA
Bibliography: Wik 2014, Gao 2016, Hallstrom 2006, Koster 2017

Certainty assessment						
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Survival to hospital discharge (Hallstrom 2006, Wik 2014, Gao 2016)						
3	randomised trials	serious[A,B,C,J]	serious[E,I]	not serious	not serious[K]	none
Favourable neurological outcome at discharge (Hallstrom 2006, Wik 2014, Gao 2016) (assessed with: CPC 1/2 or mRS 0-3)						
3	randomised trials	serious[A,B,C,J]	serious[A,I]	not serious	not serious[K]	none
Injuries after resuscitation (Wik 2014, Koster 2017) (assessed with: Any injury or Serious resuscitation-related structural visceral damag						
2	randomised trials	serious[A,K]	not serious	not serious	serious[I]	none

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	Survival with favorable neurological outcome is widely regarded as the most critical outcome. Opinions vary on the relative importance of outcomes such as ROSC. The outcome of resuscitation-related injuries probably varies somewhat, in part based on whether increased survival with favorable neurological outcome is achieved or not.	

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 were four trials of load-distributing band devices for OHCA; two were large-scale randomized controlled trials which were powered for clinical outcomes, one was a small randomized controlled trial not powered for outcomes and one focused primarily on adverse events (not powered for outcomes). The additional cost of these devices likely favors use of manual CPR when feasible.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs	Mechanical CPR devices are expensive, and having enough to be present at every OHCA	Some health care systems are already using these devices, so

○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	event may not be warranted based on the lack of proven benefit.	costs of implementation will vary based on what local practice is currently.
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	We did not look specifically for studies of resources required.	
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		
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	Because the evidence suggests neither benefit nor harm, whether or not use of these devices for OHCA is implemented likely would not impact equity, although purchasing these devices would be more difficult in low-resource settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	These devices are already in use in many healthcare settings.	
Feasibility Is the intervention feasible to implement?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility will depend on the financial and training resources of the healthcare system.	

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 suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions for out-of-hospital cardiac arrest (weak recommendation, very low to moderate certainty evidence).

We suggest that automated mechanical chest compression devices are a reasonable alternative to manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety (weak recommendation, very low certainty evidence).

Justification

This topic was prioritized by the ALS Task Force due to awareness of a marked increase in the use of mechanical CPR in several countries since the COVID-19 pandemic, and because the Task Force was aware of new trials. Although there have now been several trials, the Task Force agreed that meta-analysis would not provide clinically reliable information, due to the heterogeneity of the trials available. Discussion and rationale for the treatment recommendations included the following:

· The 3 largest trials, which provide the highest-certainty evidence, were all neutral overall when reporting risk ratios, showing no benefit or harm from mechanical CPR, compared with manual CPR. One of these trials found a small significant different in neurological outcome when using an adjusted odds ratio (aOR), with worse outcome in the group assigned to piston-based mechanical CPR, compared with those assigned to manual CPR.10 The authors reported this result as both an unadjusted OR (0.77 [0.59-1.02]) and an aOR (0.72 [0.52-0.99]), and it was not clear which of these was primary. We therefore chose to report the RR for the main result reporting. The task force discussed that all of these results are very similar. A fourth large trial was stopped early due to decreased survival to discharge with favorable neurologic outcome.4

· Lower-certainty evidence from other smaller trials was conflicting, with some showing benefit and some showing harm from mechanical CPR.

· Most trials were done in the out-of-hospital setting. The more limited data for IHCA is also inconsistent. Both trials were small, with one designed to test feasibility and one to look at adverse effects; thus neither was designed to compare critical clinical outcomes.

· The task force discussed the pros and cons of pooling studies in meta-analysis extensively, in the end deciding that heterogeneity was too marked (including devices used, timing of use, and protocols included with use of mechanical CPR) that pooling results could be misleading.

· For each critical outcome, the lowest certainty of evidence was very low certainty for both IHCA and OHCA. GRADE advice is to use the lowest certainty of evidence included when wording the treatment recommendation. In this case, since the amount of higher certainty evidence (moderate and low) for OHCA far outweighed that for IHCA, the task force did not think using very low certainty as the sole designation for the evidence was appropriate, and therefore ranges are provided separately for IHCA and OHCA.

· The Task Force discussed concern about the potential for delays in initial defibrillation when attempting to use mechanical CPR for cardiac arrest with shockable rhythm. One trial conducted subgroup analyses by initial rhythm, finding that patients with an initial shockable rhythm had lower survival at 30 days if they were randomized to mechanical CPR with a piston-based device, compared with manual CPR.10 This concern could be avoided by not deploying a mechanical device until after a first shock (if indicated) is delivered.

· The task force discussed the lack of justification for the cost of mechanical CPR devices and the training required for their use to be implemented, in light of the evidence suggesting no benefit. However, as there is also no convincing evidence for, there is insufficient evidence to suggest that healthcare systems already using mechanical CPR routinely need to change practice.
· The Task Force was in agreement that mechanical CPR is useful in settings where manual CPR either risks provider safety (eg during transport) or interferes with other potentially life-saving procedures (eg in the cardiac catheterization lab or during ECMO cannulation).
· There are several mechanical CPR devices available currently, and there is no evidence to favor one over the other at present.
· The Task Force discussed the importance of training when mechanical CPR devices are used, to minimize pauses in compressions during placement and to ensure proper placement so that visceral injuries are minimized.

Subgroup considerations

The task force was interested in the effect of CPR devices by initial rhythm, but not studies were identified looking at this specifically with the load-distributing band devices.

Implementation considerations

Training is crucial when implementing use of these devices, with a focus on minimizing interruptions to CPR when deploying the device.
Systems should consider cost and the lack of proven benefit in routine use when considering use of mechanical CPR devices.

Monitoring and evaluation

Research priorities

· Whether the possible benefit of mechanical CPR depends on timing of use, cardiac arrest rhythm, or setting.
· Whether one mechanical CPR device is superior to another
· Whether rates of CPR-related injuries from mechanical CPR vary by patients size and age
· The optimal approach to defibrillation (ie whether to pause the device for defibrillation, vs other approaches such as timing defibrillation with compression phase) when mechanical CPR devices are used

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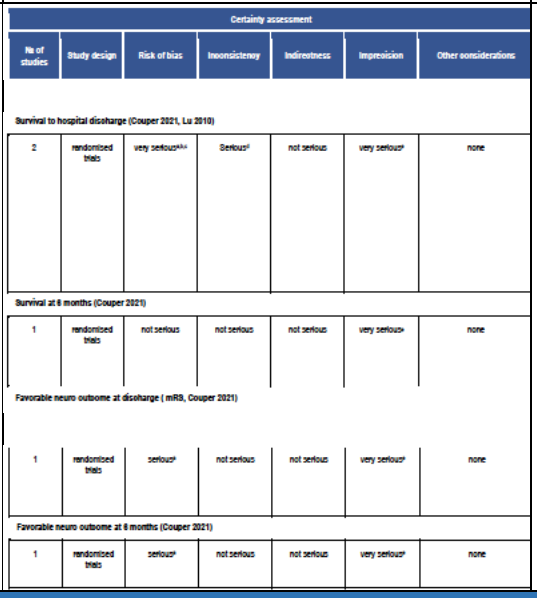
Mechanical vs. Manual CPR – IHCA PISTON (ALS 3002)

QUESTION

Should a piston-based mechanical CPR device vs. manual CPR be used for IHCA?	
POPULATION:	IHCA
INTERVENTION:	a piston-based mechanical CPR device
COMPARISON:	manual CPR
MAIN OUTCOMES:	ROSC ; survival to hospital discharge, 30 days or longer; favorable neurological outcome at hospital discharge, 30 days or longer; CPR-related injuries
SETTING:	**IHCA**
CONFLICT OF INTERESTS:	TF member K Couper was an author of one of the included trials

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	High quality CPR is critical to improving cardiac arrest outcomes. Use of mechanical CPR has increased significantly since the COVID pandemic, although the existing treatment recommendation suggests against routine use.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We identified 4 studies that addressed outcomes of PISTON-based mechanical CPR devices. Two of these used a LUCAS device and found no evidence of benefit for mechanical CPR vs manual. 1 small trial used the "thumper" device which suggested improved outcomes,. The 4th study only addressed outcomes of injury and found no difference between a mechanical device and manual CPR.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One small study directly assessed the incidence of injuries using a piston-based mechanical CPR device compared with manual CPR and found no difference.	
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		

Certainty assessment						
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Survival to hospital discharge (Couper 2021, Lu 2010)						
2	randomized trials	very serious[AA]	Serious[#]	not serious	very serious[a]	none
Survival at 6 months (Couper 2021)						
1	randomized trials	not serious	not serious	not serious	very serious[a]	none
Favorable neuro outcome at discharge (mRS, Couper 2021)						
1	randomized trials	serious[a]	not serious	not serious	very serious[a]	none
Favorable neuro outcome at 6 months (Couper 2021)						
1	randomized trials	serious[a]	not serious	not serious	very serious[a]	none

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	Survival with favorable neurological outcome is widely regarded as the most critical outcome. Opinions vary on the relative importance of outcomes such as ROSC. The outcome of resuscitation-related injuries probably varies somewhat, in part based on whether increased survival with favorable neurological outcome is achieved or not.	

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	None of the trials of the piston-based mechanical CPR in the IHCA setting found a benefit over manual CPR, but there was no harm detected either. The one small study identified that used the 'Thumper" mechanical CPR device IHCA suggested better outcomes with mechanical CPR. The additional cost of these devices likely favors use of manual CPR when feasible.	

Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings	Mechanical CPR devices are expensive, and having enough to be present at every IHCA event may not be warranted based on the lack	

○ Moderate savings ○ Large savings ○ Varies ○ Don't know	of proven benefit. There is also a cost associated both with training people to use the devices, and maintenance of the devices.	
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		
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		
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	Because the evidence suggests neither benefit nor harm, whether or not use of these devices for IHCA is implemented likely would not impact equity, although purchasing these devices would be more difficult in low-resource settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	These devices are already in use in many healthcare settings.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	Feasibility will depend on the financial and training resouirces of the healthcare system.	

○ Probably yes ○ Yes ● Varies ○ Don't know		

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 suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions for cardiac arrest (weak recommendation, very low certainty evidence)

We suggest that automated mechanical chest compression devices are a reasonable alternative to manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety (good practice statement).

Justification

None of the trials of the piston-based mechanical CPR device (LUCAS) in the IHCA setting found a benefit over manual CPR, but there was no harm detected either. These were all small and weren't powered to clinical outcomes. One small study was identified that used the 'Thumper" mechanical CPR device IHCA, and this suggested better outcomes with mechanical CPR. Overall, the evidence is of very-low certainty. Based on this, and on the higher-certainty OHCA data also showing not benefit, the Task Force opinion is that manual CPR is likely favored over mechanical CPR.

Mechanical CPR is reasonable when prolonged resuscitation is needed, or when manual CPR is difficult due to lack pf personnel or need for transport or procedures during CPR.

Subgroup considerations

No data available

Implementation considerations

Training is crucial when implementing use of these devices, with a focus on minimizing interruptions to CPR when deploying the device.

Systems should consider cost and the lack of proven benefit in routine use when considering use of mechanical CPR devices.

Monitoring and evaluation

Research priorities

-Whether devices should be paused for defibrillation, when in use
-Whether outcomes with mechanical CPR vary with institutional experience with the device

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Mechanical vs. Manual CPR – OHCA PISTON (ALS 3002)

QUESTION

Should a piston-based mechanical CPR device vs. manual CPR be used for OHCA?	
POPULATION:	Adults with out-of-hospital cardiac arrest
INTERVENTION:	Mechanical CPR with a piston-based mechanical CPR device
COMPARISON:	manual CPR
MAIN OUTCOMES:	ROSC; survival to discharge, 30 days or later; survival with favorable neurologic outcome at hospital discharge, 30 days or later, CPR-related injuries.
SETTING:	OHCA
CONFLICT OF INTERESTS:	Helen Pocock was a co-author on one of the randomized controlled trials considered as part of this systematic review, and therefore did not conduct bias assessment for that trial.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	High quality CPR is critical to improving cardiac arrest outcomes. Use of mechanical CPR has increased significantly since the COVID pandemic, although the existing treatment recommendation suggests against routine use.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	All studies suggest no benefit to survival with mechanical CPR. The largest trials providing the highest-certainty evidence show neither benefit nor harm for most outcomes, and worse 12 month neurological outcome when using statistical method of aOR.	

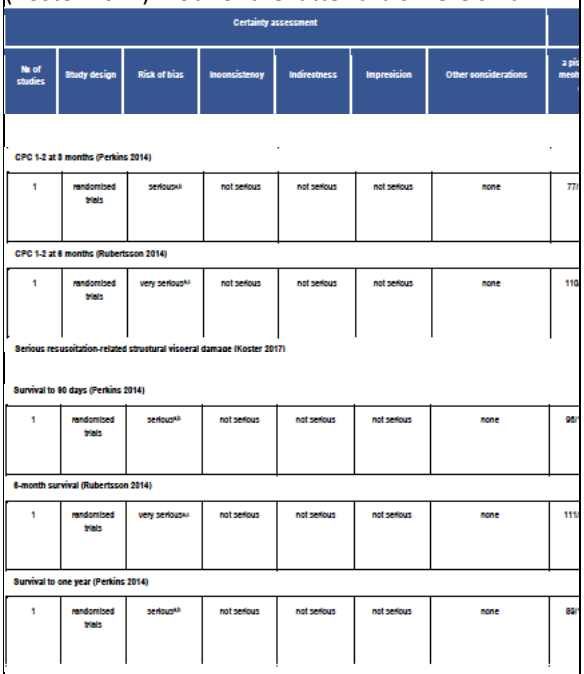
Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The largest trials providing the highest-certainty evidence show neither benefit nor harm for most outcomes, apart from 12 month neurological outcome where, when thte CACE2 statistical method of data analysis was used (giving an aOR), the outcome with mechanical CPR was worse . One small study found more serious resuscitation-related structural visceral injury with mechanical CPR.	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low	Certainty of evidence varies from very low to moderate and meta-analysis was not possible due to	

○ Moderate ○ High ○ No included studies	significant heterogeneity. There were five studies in OHCA; three were large-scale randomized controlled trials (Rubertsson 2014; Perkins 2014; Anantharaman 2017), one was a pilot study (Smekal 2011) and one focused primarily on adverse events (Koster 2017). Both of the latter trials were small.	



Certainty assessment							
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a pri meth
CPC 1-2 at 3 months (Perkins 2014)							
1	randomised trials	serious[A,b]	not serious	not serious	not serious	none	77
CPC 1-2 at 6 months (Rubertsson 2014)							
1	randomised trials	very serious[A,c]	not serious	not serious	not serious	none	110
Serious resuscitation-related structural visceral damage (Koster 2017)							
Survival to 90 days (Perkins 2014)							
1	randomised trials	serious[A,b]	not serious	not serious	not serious	none	95
6-month survival (Rubertsson 2014)							
1	randomised trials	very serious[A,c]	not serious	not serious	not serious	none	111
Survival to one year (Perkins 2014)							
1	randomised trials	serious[A,b]	not serious	not serious	not serious	none	89

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	Survival with favorable neurological outcome is widely regarded as the most critical outcome. Opinions vary on the relative importance of outcomes such as ROSC. The outcome of resuscitation-related injuries probably varies somewhat, in part based on whether increased survival with favorable neurological outcome is achieved or not.	

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	None of the trials of piston-based mechanical CPR in the OHCA setting found a benefit over manual CPR, but two suggested possible harm (one large study found worse 12 month neurological outcome when the CACE2 statistical method of data analysis was used, and one small study found more injuries associated with mechanical CPR). The additional cost of these devices likely favors use of manual CPR when feasible.	

○ Varies ○ Don't know		
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Mechanical CPR devices are expensive, and having enough to be present at every OHCA event may not be warranted based on the lack of proven benefit.	
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	This SR didnot include analysis of cost of devices, but an cost-effective analysis of the Paramedic 2 trial by Wik, 2017 looked at this.	
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	This systematic review didn't include any studies looking at cost-effectiveness as an outcome, but a cost effective analysis of the Paramedic trial was done by Wik, 2017. This demonstrated that patients in the LUCAS-2 group had poorer health outcomes (i.e. lower QALYs) and incurred higher health and social care costs than those in the manual CPR group.	
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	Purchasing these devices would be more difficult in low-resource settings. However, as most of the evidence suggests neither benefit nor harm for the majority of outcomes, whether or not use of these devices for IHCA is implemented likely would not impact equity.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes	These devices are already in use in many healthcare settings.	

○ Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility will depend on the financial and training resources of the healthcare system.	

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 suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions for out-of-hospital cardiac arrest (weak recommendation, very low to moderate certainty evidence). Automated mechanical chest compression devices may be a reasonable alternative to manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety (good practice statement).

Justification

This topic was prioritized by the ALS Task Force due to awareness of a marked increase in the use of mechanical CPR in several countries since the COVID-19 pandemic, and because the Task Force was aware of new trials. Although there have now been several trials, the Task Force agreed that meta-analysis would not provide clinically reliable information, due to the heterogeneity of the trials available. Discussion and rationale for the treatment recommendations included the following:

· The 3 largest trials, which provide the highest-certainty evidence, were all neutral overall when reporting risk ratios, showing no benefit or harm from mechanical CPR, compared with manual CPR. One of these trials found a small significant different in neurological outcome when using an adjusted odds ratio (aOR), with worse outcome in the group assigned to piston-based mechanical CPR, compared with those assigned to manual CPR.10 The authors reported this result as both an unadjusted OR (0.77 [0.59-1.02]) and an aOR (0.72 [0.52-0.99]), and it was not clear which of these was primary. We therefore chose to report the RR for the main result reporting. The task force discussed that all of these results are very similar. A fourth large trial was stopped early due to decreased survival to discharge with favorable neurologic outcome.4

· Lower-certainty evidence from other smaller trials was conflicting, with some showing benefit and some showing harm from mechanical CPR.

· Most trials were done in the out-of-hospital setting. The more limited data for IHCA is also inconsistent. Both trials were small, with one designed to test feasibility and one to look at adverse effects; thus neither was designed to compare critical clinical outcomes.

· The task force discussed the pros and cons of pooling studies in meta-analysis extensively, in the end deciding that heterogeneity was too marked (including devices used, timing of use, and protocols included with use of mechanical CPR) that pooling results could be misleading.

· For each critical outcome, the lowest certainty of evidence was very low certainty for both IHCA and OHCA. GRADE advice is to use the lowest certainty of evidence included when wording the treatment recommendation. In this case, since the amount of higher certainty evidence (moderate and low) for OHCA far outweighed that for IHCA, the task force did not think using very low certainty as the sole designation for the evidence was appropriate, and therefore ranges are provided separately for IHCA and OHCA.

· The Task Force discussed concern about the potential for delays in initial defibrillation when attempting to use mechanical CPR for cardiac arrest with shockable rhythm. One trial conducted subgroup analyses by initial rhythm, finding that patients with an initial shockable rhythm had lower survival at 30 days if they were randomized to mechanical CPR with a piston-based device, compared with manual CPR.10 This concern could be avoided by not deploying a mechanical device until after a first shock (if indicated) is delivered.

· The task force discussed the lack of justification for the cost of mechanical CPR devices and the training required for their use to be implemented, in light of the evidence suggesting no benefit. However, as there is also no convincing evidence for, there is insufficient evidence to suggest that healthcare systems already using mechanical CPR routinely need to change practice.
· The Task Force was in agreement that mechanical CPR is useful in settings where manual CPR either risks provider safety (eg during transport) or interferes with other potentially life-saving procedures (eg in the cardiac catheterization lab or during ECMO cannulation).
· There are several mechanical CPR devices available currently, and there is no evidence to favor one over the other at present.
· The Task Force discussed the importance of training when mechanical CPR devices are used, to minimize pauses in compressions during placement and to ensure proper placement so that visceral injuries are minimized.

Subgroup considerations

· The Task Force discussed concern about the potential for delays in initial defibrillation when attempting to use mechanical CPR for cardiac arrest with shockable rhythm. One trial conducted subgroup analyses by initial rhythm, finding that patients with an initial shockable rhythm had lower survival at 30 days if they were randomized to mechanical CPR with a piston-based device, compared with manual CPR. This concern could be avoided by not deploying a mechanical device until after a first shock (if indicated) is delivered.

Implementation considerations

Implementation difficulty would be variable, as several systems already use these devices. Training is important to minimize interruptions to CPR.

Monitoring and evaluation

Not addressed

Research priorities

· Whether the possible benefit of mechanical CPR depends on timing of use, cardiac arrest rhythm, or setting.
· Whether one mechanical CPR device is superior to another
· Whether rates of CPR-related injuries from mechanical CPR vary by patients size and age
· The optimal approach to defibrillation (ie whether to pause the device for defibrillation, vs other approaches such as timing defibrillation with compression phase) when mechanical CPR devices are used

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Oxygen Dose after ROSC in Adults (ALS 3517)

QUESTION

Oxygenation strategy after return of spontaneous circulation (ROSC) in adults with cardiac arrest	
Population:	Unresponsive adults with sustained return of spontaneous circulation (ROSC) after cardiac arrest in any setting.
Intervention:	A ventilation strategy targeting specific SpO2 and PaO2 targets.
Comparison:	Treatment without specific targets or with an alternate target to the intervention.
Main outcomes:	Clinical outcome including survival/survival with a favorable neurological outcome at hospital discharge/30 days, and survival/survival with a favorable neurological outcome after hospital discharge/30 days (e.g., 90 days, 180 days, 1 year).
Setting:	Pre-hospital and ICU settings

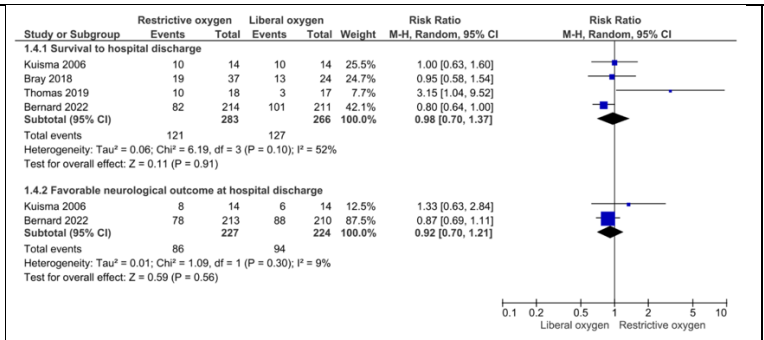
ASSESSMENT

Problem
Is the problem a priority?

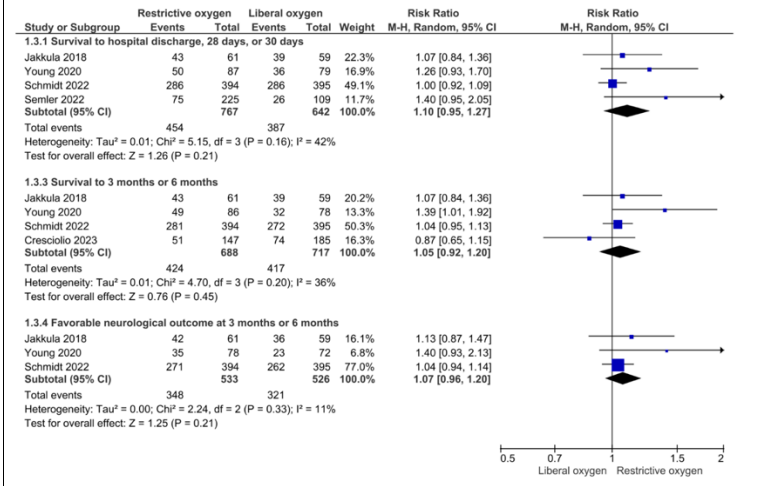
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest, both in and out-of-hospital, is relatively common and has a very high mortality. Previously, both hypoxemia and hyperoxia have been reported to be associated with worse outcome in patients who are post-cardiac arrest. Hypoxemia may worsen ischemic brain injury and injury to other organs, while hyperoxia may lead to increased oxidative stress and organ damage after reperfusion. New randomized trials have been published since this topic was last updated in 2020.	

Desirable Effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The evidence on the effect of different oxygen target on survival and neurologic outcome is mixed, with inconsistencies across observational studies and randomized trials in both methodology and results. Observational studies, identified in the previous review from 2020, were all at serious or critical risk of bias, reporting a mix of positive and negative results. Trials conducted in the hospital setting have generally been more suggestive of benefit from normoxia than trials conducted in the pre-hospital setting, although many individual trials have been limited by a small sample size. The pooled results and the most comprehensive randomized trials in the prehospital {Bernard 2022 1818} and hospital {Schmidt 2022 1467} settings, which compared an oxygen saturation of 90-94% to 98-100% and a PaO_2 of 9-10 kPa to 13-15 kPa, found no significant evidence favoring either the higher or lower oxygen targets. One new study identified this year {Meyer 2024 1} reported 1-year outcomes from the Schmidt 2022 trial and also found no difference. Meta-analyses for oxygen targets in the pre-hospital setting	



Meta-analyses for oxygen targets in the ICU setting



Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Although the evidence is of low certainty, it is likely that the undesirable effects of hypoxia are significant. Furthermore, the largest randomized trial to inform oxygenation targets in the pre-hospital setting (comparing oxygen saturation targets of 90-94% to 98-100%) suggests that early titration to a lower oxygen target is harmful {Bernard 2022 1818}. The undesirable effects of hyperoxia are uncertain due to mixed results showing either harm (in observational studies included in the 2020 systematic review) or no benefit (in randomized trials).	

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 varies across the included studies from very low to moderate.	

Oxygenation Targets in the Prehospital Setting

Certainty assessment						Patients		Effect		Certainty
N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive oxygen	Liberal oxygen	Relative (95% CI)	Absolute (95% CI)	
Survival to hospital discharge (Kuisma 2006, Bray 2018, Thomas 2019, Bernard 2022)										
4	not serious	not serious	not serious	serious[b]	none	121/283 (42.8%)	127/266 (47.7%)	**RR 0.98** (0.70 to 1.37)	**10 fewer per 1,000** (from 143 fewer to 177 more)	⊕⊕⊕◯ Moderate
Favorable neurological outcome at hospital discharge (Kuisma 2006, Bernard 2022)										
2	not serious	not serious	not serious	serious[b]	none	86/227 (37.9%)	94/224 (42.0%)	**RR 0.92** (0.70 to 1.21)	**34 fewer per 1,000** (from 126 fewer to 88 more)	⊕⊕⊕◯ Moderate
Survival to 3 months (Thomas 2019)										
1	not serious	serious[a]	not serious	very serious[c]	none	10/18 (55.6%)	3/17 (17.6%)	**RR 3.15** (1.04 to 9.52)	**379 more per 1,000** (from 7 more to 1,000 more)	⊕◯◯◯ Very low
Survival to 12 months (Bernard 2022)										
1	not serious	not serious	not serious	serious[b]	none	72/208 (34.6%)	81/193 (42.0%)	**RR 0.82** (0.64 to 1.06)	**76 fewer per 1,000** (from 151 fewer to 25 more)	⊕⊕⊕◯ Moderate
Favorable neurological outcome at 12 months (Bernard 2022)										
1	not serious	not serious	not serious	serious[b]	none	54/203 (26.6%)	58/186 (31.2%)	**RR 0.85** (0.62 to 1.17)	**47 fewer per 1,000** (from 118 fewer to 53 more)	⊕⊕⊕◯ Moderate

[a] Results differ from RCTs with similar intervention
[b] Confidence interval included both possible benefit and possible harm
[c] Confidence interval included clear benefit, but the sample size did not meet the optimal information size

Oxygenation Targets in the Hospital Setting

Certainty assessment						Patients		Effect		Certainty
N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restrictive oxygen	Liberal oxygen	Relative (95% CI)	Absolute (95% CI)	
Survival to hospital discharge, 28 days, or 30 days (Jakkula 2018, Young 2020, Schmidt 2022, Semler 2022)										
4	serious[a]	not serious	not serious	serious[b]	none	454/767 (59.2%)	387/642 (60.3%)	**RR 1.10** (0.95 to 1.27)	**60 more per 1,000** (from 30 fewer to 163 more)	⊕⊕◯◯ Low
Favorable neurological outcome at hospital discharge (Schmidt 2022)										
1	not serious	not serious	not serious	serious[b]	none	268/394 (68.0%)	261/395 (66.1%)	**RR 1.03** (0.93 to 1.14)	**20 more per 1,000** (from 46 fewer to 93 more)	⊕⊕⊕◯ Moderate
Survival to 3 months or 6 months (Jakkula 2018, Young 2020, Schmidt 2022, Cresciolio 2023)										
4	serious[a]	not serious	not serious	serious[b]	none	424/688 (61.6%)	417/717 (58.2%)	**RR 1.05** (0.92 to 1.20)	**29 more per 1,000** (from 47 fewer to 116 more)	⊕⊕◯◯ Low
Favorable neurological outcome at 3 months or 6 months (Jakkula 2018, Young 2020, Schmidt 2022)										
3	serious[a]	not serious	not serious	serious[b]	none	348/533 (65.3%)	321/526 (61.0%)	**RR 1.07** (0.96 to 1.20)	**43 more per 1,000** (from 24 fewer to 122 more)	⊕⊕◯◯ Low
Survival at 1 year (Meyer 2024)										
1	Serious[c]	not serious	not serious	serious[b]	none	259/394 (66%)	249/395 (63%)	**RR 1.04** (0.94-1.16)	**25 more per 1,000** (from 38 fewer to 101 more)	⊕⊕◯◯ Low
Favorable neurologic outcome at 1 year (Meyer 2024)										
1	Serious[c]	not serious	not serious	serious[b]	none	246/385 (64%)	233/386 (60%)	**RR 1.06** (0.94-1.18)	**36 more per 1,000** (from 36 fewer to 109 more)	⊕⊕◯◯ Low

[a] Included subgroup analyses of RCTs
[b] Confidence interval included both possible benefit and possible harm
[c] Post hoc 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	Survival with favorable neurologic outcome and survival are critical outcomes.	

variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ 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	For hyperoxia, studies generally show either association with harm or no association, but do not generally show association with benefit. The balance of evidence therefore slightly favors a benefit from normoxia in comparison with hyperoxia. For hypoxemia, limited evidence favors avoiding hypoxemia, with a benefit from normoxia. Moreover, some of the randomized trials conducted in the pre-hospital setting reported more desaturation of arterial blood in the lower oxygen target groups, and the largest trial in the pre-hospital setting to inform oxygenation targets (comparing oxygen saturation targets of 90-94% to 98-100%) suggests that early titration to a lower oxygen target is harmful {Bernard 2022 1818}.	
Resources required How large are the resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	We did not identify any studies evaluating the cost of an oxygen strategy targeting a specific oxygen level. However, as it is the current standard of care to measure an oxygen saturation continuously in post-arrest, critically-ill patients, and since a titrated oxygen approach would lead to the same or decreased oxygen use, it is likely that an intervention to avoid hyperoxia would not incur significant cost.	In lower resource settings where pulse oximetry and arterial blood gas analysis are not routinely available, titration of oxygen may be less feasible.
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	We did not identify any studies specifically comparing resources including costs between the two interventions.	

● No 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	We did not identify any studies addressing cost-effectiveness.	
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 identify any studies addressing the effect of titration of oxygen to specific targets on health equity in post-arrest patients. In resource-poor settings where ICU equipment and oxygen may be of limited supply, titrating to the minimum amount of oxygen needed to maintain a saturation in the normal range could increase equity by reserving oxygen for other patients.	
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, but these treatment recommendations do not include any substantial changes compared to 2020.	Although we did not identify any studies addressing acceptability, it is common practice to decrease FiO_2 for other critically ill patients once reliable monitoring of oxygenation is available.
Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed by this review. However, avoiding hyperoxia should be feasible in most ICU settings where patients are continually monitored. Decreasing FiO_2 in the pre-hospital setting or in the immediate post-arrest period may be less feasible as measurement of arterial oxygen may be hard to obtain reliably and could potentially lead to hypoxemia. Some pre-hospital systems utilize transport ventilators that do not have the capacity to adjust the fraction of inspired oxygen, which may also limit feasibility in the pre-hospital setting. There may be significant limitations to feasibility for many aspects of post-arrest care in resource-poor settings, but this is not specific to oxygen titration.	

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

Recommendations

Oxygen targets

We recommend the use of 100% inspired oxygen until the arterial oxygen saturation, or the partial pressure of arterial oxygen can be measured reliably in adults with ROSC after cardiac arrest in the pre-hospital setting (strong recommendation, moderate certainty evidence) and in-hospital setting (strong recommendation, low certainty evidence).

We recommend avoiding hypoxemia in adults with ROSC after cardiac arrest in any setting (strong recommendation, very low certainty evidence).

We suggest avoiding hyperoxemia in adults with ROSC after cardiac arrest in any setting (weak recommendation, low certainty evidence).

Following reliable measurement of arterial oxygen levels, we suggest targeting an oxygen saturation of 94-98% or a partial pressure of arterial oxygen of 75-100 mm Hg (approximately 10-13 kPa) in adults with ROSC after cardiac arrest in any setting (good practice statement).

When relying on pulse oximetry, health care professionals should be aware of the increased risk of inaccuracy that may conceal hypoxemia in patients with darker skin pigmentation (good practice statement).

Justification

Since the prior review, the only new evidence identified was a reporting of one-year outcomes from a previously-included trial. These results were consistent with the shorter-term outcomes included in the prior CoSTR. Therefore, the ALS Task Force did not think any change to the treatment recommendations was indicated. The main discussion points informing these treatment recommendations are included below.

The task forces felt that oxygen titration should not be attempted until oxygen levels (arterial oxygen saturation with a pulse oximeter or partial pressure of oxygen in arterial blood) can be measured reliably. This is most likely to be an important consideration in the prehospital setting where arterial blood gas analysis is rarely available and peripheral oxygen saturation may be difficult to obtain consistently. Some of the RCTs conducted in the prehospital setting reported more desaturation of arterial blood in the lower oxygen target groups, and the largest RCT to inform oxygenation targets (comparing oxygen saturation targets of 90-94% to 98-100%) suggests that early titration to a lower oxygen target is harmful {Bernard 2022 1818}. Most patients in the standard care arm of that RCT received 100% oxygen prior to hospital arrival, rather than titrated levels, due to the introduction of air-mix mechanical ventilators. Hence, the task forces deemed it acceptable to temporarily target a higher oxygen range to mitigate the risk of hypoxemia. The task forces discussed whether the evidence favored avoiding any titration of oxygen in the prehospital setting since most patients in the EXACT trial {Bernard 2022 1818} received 100% oxygen without titration. However, most thought that once reliable measurement of oxygenation was available, the evidence only supported not titrating to a lower target range of 90-94%. The separate recommendations for

different settings, with a stronger recommendation for the prehospital setting, were influenced by the evidence of harm from that same RCT as well as the differing certainty of evidence in the prehospital and ICU studies.

In making the recommendation to avoid hypoxemia, the task forces acknowledges that the evidence is of very low certainty from observational studies. The task forces concluded that the physiologic basis for hypoxia being harmful justifies its avoidance, and detection of hypoxemia may be the best surrogate for true hypoxia.

The suggestion to avoid hyperoxemia is based on very low to moderate certainty evidence that showed either harm (in observational studies included in the 2020 systematic review) or no benefit (in RCTs) from **hyperoxemia.** It is important to consider that the RCTs generally compared a conservative oxygen strategy with a liberal oxygen strategy. Observational studies, which compared oxygen levels rather than strategies, generally defined the hyperoxemia group as those with PaO_2 > 300 mm Hg, a level above what many would consider usual care.

The variability in oxygenation targets across RCTs and observational studies makes it difficult to identify an evidence-based optimal range. However, the task forces recognized the need for more precise guidance than what has previously been provided. The most comprehensive RCTs in the prehospital {Bernard 2022 1818} and hospital {Schmidt 2022 1467} settings, which compared an oxygen saturation of 90-94% to 98-100% and a PaO_2 of 9-10 kPa to 13-15 kPa, don't identify a specific optimal arterial oxygen saturation or partial pressure of oxygen but support normoxemia being safe. Given the absence of conclusive evidence for specific oxygen levels outside the normoxemia range, the task force agreed that targeting an oxygen saturation of 94-98% or a PaO2 target of 75-100 mm Hg (10-13 kPa) is reasonable.

While studies evaluating the accuracy of pulse oximetry in people with different degrees of skin pigmentation were not part of this systematic review, the systematic review team and task forces are aware of and considered several such studies that have found a slightly higher risk of occult hypoxemia (pulse oximetry reading of greater than 90% saturation while arterial oxygen saturation by blood gas is < 88%) in people with darker skin. {Sjoding 2020 2477; Won 2021 e2131674; Jamali 2022 1951} While none of these studies were done in cardiac arrest patients, the task forces felt that this issue was important to make medical professionals treating cardiac arrest patients aware of, as this knowledge could inform decision making about whether to titrate supplemental oxygen. The task forces provided a good practice statement to highlight this issue, while acknowledging that this evidence was not formally evaluated as part of this systematic review.

Subgroup considerations

The studies available have included both cardiac arrests in the in-hospital and out-of-hospital seting, and generally have not analyzed patients separately. No evidence suggesting a differential effect was found.

Implementation considerations

These recommendations have not changed since 2024, so the task force did not think implementation would be a challenge.

Research priorities

The evidence regarding the effect of targeting different levels of oxygenation in post-arrest patients remains limited. The following knowledge gaps have been identified:

1. The optimal oxygen target for post-cardiac arrest patients
2. Whether there is a threshold at which hypoxemia or hyperoxemia become harmful
3. The optimal duration for specific oxygen strategies

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Ventilation ($PaCO_2$ targets) after ROSC from Cardiac Arrest (ALS 3516)

QUESTION

Carbon dioxide targets after return of spontaneous circulation (ROSC) in adults with cardiac arrest	
Population:	Unresponsive adults with sustained return of spontaneous circulation (ROSC) after cardiac arrest in any setting.
Intervention:	A ventilation strategy targeting specific PaCO2 targets.
Comparison:	Treatment without specific targets or with an alternate target to the intervention.
Main outcomes:	Clinical outcome including survival/survival with a favorable neurological outcome at hospital discharge/30 days, and survival/survival with a favorable neurological outcome after hospital discharge/30 days (e.g., 90 days, 180 days, 1 year).
Setting:	Pre-hospital and ICU settings

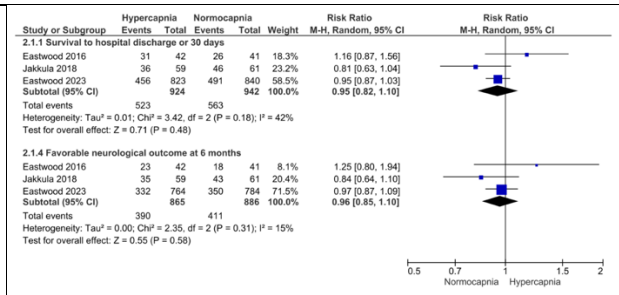
ASSESSMENT

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 and out-of-hospital, is relatively common and has a very high mortality. Both hypocapnia and hypercapnia have previously been thought to be associated with worse neurologic outcome in post-arrest patients. Hypocapnia can lead to cerebral vasoconstriction, which could lead to decreased perfusion in a brain already at risk for ischemic injury. Hypercapnia may increase cerebral blood flow, and thus has been posited as a possible way to mitigate hypoxic brain injury. However, the effect of hypercapnia in presence of cerebral edema due to hypoxic-ischemic brain injury is unclear.	

Desirable Effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The evidence from randomized trials and observational studies is inconsistent. Trials have failed to show any effect from different carbon dioxide targets. The largest trial to inform ventilation targets in the hospital setting found no significant differences in outcomes from targeting normocapnia ($PaCO_2$ of 35-45 mm Hg) and mild hypercapnia ($PaCO_2$ of 50-55 mm Hg). Observational studies have been evenly distributed in showing benefit, harm, or no effect associated with hypercapnia. Results for hypocapnia have also been inconsistent, although no studies have found an association with benefit.	



Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ○Varies ● Don't know	The available evidence on the effect of hypercapnia or hypocapnia is inconsistent. Trials have failed to show any effect from different carbon dioxide targets. Observational studies have been evenly distributed in showing benefit, harm, or no effect associated with hypercapnia. Results for hypocapnia have also been inconsistent, although no studies have found an association with benefit. Whether there is a threshold at which hypocapnia and hypercapnia becomes harmful remains a knowledge gap.	

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 from randomized trials is moderate with the largest trial to-date including 1700 patients in the hospital setting comparing normocapnia ($PaCO_2$ of 35-45 mm Hg) to mild hypercapnia ($PaCO_2$ of 50-55 mm Hg) {Eastwood 2023 45}.	

Ventilation Targets in the Hospital Setting

Certainty assessment						Patients		Effect		Certainty
N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Hypercapnia	Normocapnia	Relative (95% CI)	Absolute (95% CI)	
Survival to hospital discharge (Eastwood 2016, Jakkula 2018, Eastwood 2023)										
3	not serious	not serious	not serious	serious[a]	none	523/924 (56.6%)	563/942 (59.8%)	**RR 0.95** (0.82 to 1.10)	**30 fewer per 1,000** (from 108 fewer to 60 more)	⊕⊕⊕◯ Moderate
Survival to 6 months (Eastwood 2023)										
1	not serious	not serious	not serious	serious[a]	none	423/816 (51.8%)	450/832 (54.1%)	**RR 0.96** (0.88 to 1.05)	**22 fewer per 1,000** (from 65 fewer to 27 more)	⊕⊕⊕◯ Moderate
Favorable neurological outcome at 6 months (Eastwood 2016, Jakkula 2018, Eastwood 2023)										
3	not serious	not serious	not serious	serious[a]	none	390/865 (45.1%)	411/886 (46.4%)	**RR 0.96** (0.85 to 1.10)	**19 fewer per 1,000** (from 70 fewer to 46 more)	⊕⊕⊕◯ Moderate

[a] Confidence interval included both no benefit and possible harm

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	Survival with favorable neurologic outcome and survival are critical outcomes.	

● Probably no important uncertainty or variability ○ 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	The balance of effects favors the comparison (normocapnia) when compared to hypocapnia. The balance of effects favors neither the comparison nor the intervention when comparing normocapnia to mild to moderate hypercapnia. This balance is determined by the failure of randomized trials to show any difference between carbon dioxide targets, and observational data that is neutral on hypercapnia compared to normocapnia, and favors normocapnia over hypocapnia.	
Resources required How large are the resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	We did not identify any studies evaluating the cost of a ventilation strategy targeting one carbon dioxide range over another, but a significant cost seems unlikely, except in settings where the costs blood gas analysis are high for the available resources.	
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	We did not identify any studies specifically comparing resources including costs between the two interventions.	
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	We did not identify any studies addressing cost-effectiveness.	

○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		
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	Targeting a specific carbon dioxide value may be difficult in settings where blood gas analysis is not available. However, as measuring carbon dioxide values is not a change from previous recommendations, we do not think that recommending a specific target will change existing equity or inequity.	
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, but these treatment recommendations do not include any substantial changes compared to 2020.	
Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed by this review but should be feasible in most settings given that this is not a significant change in recommendation.	

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

Recommendations

We suggest targeting normocapnia (a partial pressure of carbon dioxide of 35-45 mm Hg or approximately 4.7-6.0 kPa) in adults with ROSC after cardiac arrest (weak recommendation, moderate certainty evidence).

Justification

The evidence from RCTs and observational studies is inconsistent. RCTs have failed to show any effect from different CO2 targets. The largest RCT to inform ventilation targets in the hospital setting found no significant differences in outcomes from targeting normocapnia (PaCO2 of 35-45 mm Hg) and mild hypercapnia (PaCO2 of 50-55 mm Hg) {Eastwood 2023 45}. Observational studies have been evenly distributed in showing benefit, harm, or no effect associated with hypercapnia. Results for hypocapnia have also been inconsistent, although no studies have found an association with benefit.

Considering the lack of evidence for benefit or harm from targeting CO2 levels above or below the normal range, the task forces deemed it reasonable to target normocapnia, generally defined as a PaCO2 of 35-45 mm Hg in both RCTs and observational studies. Notably, the task force is aware of unpublished data from one RCT {Bernard 2022 1818} and observational studies not included in this review {Moon 2007 219; Mueller 2022 120; Kim 2019 1;

Abrahamowicz 2022 3} suggesting that ETCO2 levels may not accurately reflect PaCO2 levels, which may be an important consideration in the prehospital setting. As with all critically ill patients, there may be specific scenarios in which CO2 levels may need to be higher or lower than normal to compensate for other illnesses (e.g., severe lung injury or metabolic acidosis).
The task forces discussed the possible complication of acidemia from hypercapnia. The presence or absence of metabolic acidosis requires consideration when choosing a ventilation strategy and PaCO2 target, and metabolic acidosis is common in post-arrest patients. Additionally, opinions vary on whether arterial blood gas analysis in patients receiving targeted temperature management should be adjusted for temperature. Approaches to blood gas interpretation regarding temperature varied across RCTs and observational studies. These variations in methodology and in definitions of target ranges prohibit the task forces from being able to recommend specific numbers or a specific method for blood gas analysis for systems implementing these recommendations.

Subgroup considerations

The task forces discussed whether cardiac arrest patients with baseline chronic lung disease and chronic CO2 retention might respond differently to different CO2 targets, however, no evidence addressing this subgroup was found. The task forces agreed that it would be reasonable to adjust PaCO2 targets in patients with known chronic CO2 retention (expert opinion).

Implementation considerations

These recommendations have not changed significantly compared to 2020, so the task force did not think implementation would be a challenge.

Monitoring and evaluation

Research priorities

The evidence regarding the effect of different ventilation targets in post-arrest patients remains limited. The following knowledge gaps have been identified:

1. Whether there is a threshold at which hypocapnia and hypercapnia becomes harmful
2. The accurate correlation of $ETCO_2$ with $PaCO_2$ levels
3. The effects of manipulating $PaCO_2$ on cerebral blood flow in post-cardiac arrest
4. How $PaCO_2$ targets should be adjusted in those with chronic CO_2 retention
5. Whether arterial blood gas analysis should be adjusted to 37°C or to a patient's current temperature

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IV vs. IO Drugs (ALS 3200)

QUESTION

Should Intraosseous vs. intravenous be used for Cardiac arrest?	
POPULATION:	Cardiac arrest
INTERVENTION:	Intraosseous
COMPARISON:	intravenous
MAIN OUTCOMES:	30-day survival; Return of spontaneous circulation (any); Return of spontaneous circulation (sustained); Survival (30-day/ discharge) with favourable neurological outcome; Survival at hospital discharge; Survival at 3-months; Survival at 6-months; Survival with favourable neurological outcome at 3-months; Survival with favourable neurological outcome at 6-months; Health-related quality of life at 3-months; Health-related quality of life at 6-months;
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	Drug therapy is a core component of Advanced Life Support. Current resuscitation guidelines recommend that drugs during cardiac arrest are given via the peripheral intravenous route, wherever feasible. The intraosseous route is recommended only when intravenous access cannot be rapidly achieved. Observational studies suggest the intraosseous route may facilitate more rapid drug administration. Over recent years, several studies have reported increased use of intraosseous access in adult cardiac arrest.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Drug therapy, particularly epinephrine, has been shown to have a large effect on return of spontaneous circulation and small-moderate effect on 30-day survival. The effect of a different drug route for administering cardiac arrest drugs is likely to be small. In our systematic review, point-estimate of each meta-analysis varied between favouring the intravenous or intraosseous route, but the findings were typically not statistically significant. The point estimate typically suggested a small effect.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate	In our systematic review, point-estimate of each meta-analysis varied between favouring the intravenous or intraosseous route, but the findings were typically not statistically	

○ Large ○ Varies ○ Don't know	significant. The point estimate typically suggested a small effect. For sustained return of spontaneous circulation, we found a statistically significant small effect in favour of the intravenous route.	
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	Across all outcomes (including the three critical outcomes), the certainty of evidence was ranked as low or moderate.	
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	Our list of incomes comprises all outcomes that were included in the Core Outcome Set for Cardiac Arrest, namely survival, survival with favourable neurological outcome, and health-related quality of life. These were outcomes that were prioritised by members of the public, cardiac arrest survivors, researchers and clinicians and are categorised as critical outcomes.	
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	In our systematic review, point-estimate of each meta-analysis varied between favouring the intravenous or intraosseous route, but the findings were typically not statistically significant. The point estimate typically suggested a small effect. For sustained return of spontaneous circulation, we found a statistically significant small effect in favour of the intravenous route.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs	There may be variability across settings.	

○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Across the world, intravenous vascular access is typically routinely available and is the default access route in emergency care. In many settings, clinicians will be skilled in securing intraosseous access and equipment will be routinely available. In these setting, a key consideration will be consumables required to secure intravenous and intraosseous access. An intraosseous needle is markedly more expensive than an intravenous cannula. In other settings, intraosseous equipment may not be available to clinicians. In these settings, there would be a need to provide training and purchase equipment and consumables.	
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	We did not specifically search for studies on costs. One trial (Couper et al 2024) will undertake a health economic analysis.	
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	We did not specifically search for studies on costs. One trial (Couper et al 2024) will undertake a health economic analysis.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased	In none of the included trials (or in our meta-analysis) did we identify any evidence that the effectiveness of the intervention might vary across population sub-groups.	

○ Varies ○ Don't know		
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both intravenous and intraosseous access are already used frequently in emergency care.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Intraosseous and intravenous access are already routinely available in many emergency care systems. There may be systems in which intraosseous has not yet been implemented and there may be some financial barriers that influence its implementation.	

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 suggest IV access, as compared to IO access, as the first attempt for vascular access during adult cardiac arrest (weak recommendation, low certainty evidence).

If IV access cannot be rapidly achieved within two attempts, it is reasonable to consider IO access as an alternative route for vascular access during adult cardiac arrest (good practice statement).

Justification

This topic was prioritized by the ALS Task Force based on the publication (or forthcoming publication) of three large randomised controlled trials evaluating the clinical effectiveness of an intraosseous vascular access strategy compared with an intravenous vascular access strategy in adult out-of-hospital cardiac arrest since the last ILCOR systematic review and CoSTR in 2020.

In considering the importance of this topic, the task force noted that several observational studies have reported marked increases in the use of the intraosseous route in adult out-of-hospital cardiac arrest over recent years, despite council guidelines continuing to recommend that the peripheral intravenous route should be the primary route for drug administration in adult cardiac arrest.

Given the availability of data from large RCTs and challenges in interpreting observational studies due to confounding and resuscitation time bias, the task force chose to consider only randomized controlled trials.

In making these recommendations, the ALS Task Force considered the following:

- The expected mechanism through which intraosseous drug administration might improve clinical outcomes is by facilitating faster administration of time-critical cardiac arrest drugs. However, whilst this effect was observed in an early randomized controlled trial, time to drug administration was similar between the intraosseous and intravenous groups in all three recent trials.

- The use of intraosseous access did not result in a statistically significant improvement in survival, survival with favourable neurological outcome, or health-related quality of life at any time-point, in comparison to intravenous access.
- The three trials were all superiority trial aiming to test the superiority of one group compared with the other group, such that the absence of an observed effect should not be interpreted as indicating that an intraosseous vascular access strategy is equivalent to an intravenous vascular access strategy.
- There was evidence that the use of intraosseous access reduced the odds of achieving sustained return of spontaneous circulation.
- In emergency care throughout the world, the intravenous route is the standard approach for administering drugs and fluid.
- There are important cost implications in relation to intraosseous access, both in terms of training and equipment. Even in settings where intraosseous access is routinely available, the costs of a single intraosseous needle is markedly higher than a peripheral intravenous cannula.
- Animal data provide some evidence that the pharmacokinetics of drugs administered via the intraosseous route may be influenced by insertion site (proximal humerus v proximal tibia). The findings of the systematic review sub-group analyses showed no evidence of an interaction between site and clinical outcome, with point estimates favoring the proximal tibial route, albeit with very wide confidence intervals.
- Previous data suggests that the benefit of amiodarone may be enhanced when given through the intravenous route. Experts have expressed concern that absorption of lipophilic drugs, such as amiodarone, may be particularly influenced by intraosseous administration. However, this effect has not been observed in animal studies.
- Trial sequential analyses suggest that the optimal information size has been reached for small sized effects (absolute difference of 2%), but not for very small effects.
- The good practice statement reflects the approach taken in two of the included trials, whereby patients in the intravenous group were protocolized to receive two intravenous vascular access attempts, and then the route for subsequent vascular access attempts was at the discretion of the attending clinician.
- There may be patients where IV access is not feasible due to specific patient factors (e.g. the patient is known to be very difficult to secure IV access) or environmental factors (e.g. very poor lighting; space constraints). For this small group of patients, it may be reasonable to attempt IO access first.
- There was an absence of direct evidence for the in-hospital setting, but it was noted that the question is likely of less relevance to the hospital setting as: 1) A high proportion of patients will likely have established intravenous access at the time of cardiac arrest, and, 2) For the minority of patients without established intravenous access, environmental conditions (e.g. space/ lighting) and the higher number of staff members would likely lead to a high rate of successful intravenous access attempts.

Research priorities

Where there is a need for intraosseous access, there are limited data on the optimum anatomical site for insertion.

There are limited data on patient outcome beyond hospital discharge/ 30-days.

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Vasopressors During Cardiac Arrest -Epinephrine vs Placebo (ALS 3208, 3211)

QUESTION

Vasopressors during adult cardiac arrest – Epinephrine vs. no epinephrine	
POPULATION:	Adult individuals with cardiac arrest in any setting (our-of-hospital or in-hospital).
INTERVENTION:	Epinephrine provided intravenously or intraosseously during cardiopulmonary resuscitation.
COMPARISON:	No epinephrine provided intravenously or intraosseously during cardiopulmonary resuscitation.
MAIN OUTCOMES:	Clinical outcome including survival, favorable neurological outcome, and health-related quality of life at hospital discharge, 30 days, 90 days, 180 days, and 1 year.

ASSESSMENT

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.	

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 return of spontaneous circulation and survival at hospital admission are substantial. The improvement in survival (hospital discharge, 30-days, 3 months, 6 months, and 12 months) is moderate. Whether there is improvement in survival with favorable neurological outcome remains uncertain. The desirable effects appear more pronounced in non-shockable compared with shockable rhythms.	Additional considerations that were raised included the impact of increased return of spontaneous circulation on organ donation.

Epinephrine compared to placebo – Any rhythm (Jacobs	
Outcome	**RR (95% CI)**
Return of spontaneous circulation	3.09 (2.82 to 3.39)
Survival at hospital discharge	1.44 (1.11 to 1.86)
Favorable neurological outcome at hospital discharge	1.21 (0.90 to 1.62)

Epinephrine compared to placebo – Shockable rhythms (	
Outcome	**RR (95% CI)**
Return of spontaneous circulation	1.68 (1.48 to 1.92)
Survival at hospital discharge	1.23

	(0.94 to 1.62)		(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 rhythms (Jacobs 2011, Perkins 2018)			
Outcome	**RR (95% CI)**		**RD (95% CI)**
Return of spontaneous circulation	4.45 (3.91 to 5.08)		254 more per 1,000 (from 214 more to 301 more)
Survival at 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)

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There is no evidence in clinical trials that epinephrine specifically contributes to cerebral injury beyond its effect of increasing overall survival, including in patients who may have sustained neurological damage.	Epinephrine likely increases the number of survivors with both favorable and unfavorable neurological outcomes, as observed in the PARAMEDIC2 trial.[1,2] This apparent increase in survivors with unfavorable neurological outcome should not be interpreted as epinephrine directly causing unfavorable neurological outcomes, but rather reflects its efficacy in restoring circulation in patients who may already have sustained significant cerebral injury due to prolonged cardiac arrest.

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

Outcome	RR (95% CI)	RD (95% CI)
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 1,000 (from 1 fewer to 13 more)
Favorable neurologic outcome at 6 months *	1.34 (0.96 to 1.88)	5 more per 1,000 (from 1 fewer to 13 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 of evidence for return of spontaneous circulation and survival at hospital admission; moderate certainty of evidence for survival at hospital discharge, 3 months, and 6 months; and low to moderate certainty of evidence for favorable neurological outcome at hospital discharge, 3 months, and 6 months.	The variation in the certainty of evidence by outcome was largely due to the event rate for each outcome. There was higher statistical power to evaluate differences in return of spontaneous circulation (a more common event) than survival with favorable neurological outcome (a much less common event). The certainty of evidence for favorable neurological outcome at 3 months and 6 months was also lessened by a loss to follow-up.

Comparison (OHCA)	Outcome

	Return of spontaneous circulation	Survival at hospital discharge	Favorable neurological outcome at hospital discharge
Epinephrine compared to placebo – Any rhythm	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate	⊕⊕⊕◯ Moderate
Epinephrine compared to placebo – Shockable rhythms	⊕⊕⊕◯ Moderate	⊕⊕⊕◯ Moderate	⊕⊕◯◯ Low
Epinephrine compared to placebo – Non-shockable rhythms	⊕⊕⊕⊕ 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 ○ No important uncertainty or variability	A study suggests that patients value survival with favorable neurological outcome most highly.[3]	The importance of neurological intact survival is generally agreed upon with recognition that survival without neurological recovery is an undesirable outcome for most patients.

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	See above summary of desirable and undesirable effects.	Although there was no statistically significant effect from epinephrine on survival with favorable neurological outcome, the significantly difference in return of spontaneous circulation and survival led to the conclusion that the balance of effects favors the intervention.

○ Varies ○ Don't know		
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Resources might need to be allocated to communities that do not currently have capacity for administration of epinephrine in the out-of-hospital setting.
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		
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	Epinephrine use was associated with increased donation rates in a recent cost-effectiveness analysis of the PARAMEDIC2 trial (99 recipients from 40 donors in the epinephrine group vs 67 recipients from 24 donors in the placebo group) (Achana 2020 579). The analysis, incorporating both direct economic effects of survivors and indirect economic benefits of organ donation, yielded an incremental cost-effectiveness ratio for epinephrine of GBP 16,086 per quality-adjusted life year gained.	Costs are likely to be healthcare system specific.
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		

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 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.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Currently the standard of care is to provide epinephrine during cardiac arrest.	

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	Very low	Low	Moderate	High			**No included studies**

REQUIRED RESOURCES							
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

CONCLUSIONS

Recommendation

We recommend administration of epinephrine during cardiopulmonary resuscitation (strong recommendation, low 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 or pulseless VT), we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during cardiopulmonary resuscitation (weak recommendation, very low certainty of evidence).

We suggest against the routine use of high-dose epinephrine in cardiac arrest (weak recommendation, very low certainty of evidence).

Justification

In making the recommendation for epinephrine during cardiopulmonary resuscitation, we considered the findings that epinephrine substantially improves both return of spontaneous circulation, mid-term survival, and long-term survival as compared to placebo. There appears to be a more pronounced effect of epinephrine on return of spontaneous circulation and survival to hospital discharge in non-shockable rhythms compared to shockable rhythms, but assessment of these sub-groups should be taken with caution. For non-shockable rhythms, we recommend administering epinephrine as soon as feasible, given limited alternative interventions in most cases and chances of survival decreasing rapidly over time. 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. While the optimal timing in relation to defibrillations remains unknown, we suggest administering epinephrine after initial defibrillation attempts have been unsuccessful.

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Vasopressors During Cardiac Arrest- Epinephrine vs. Vasopressin in Combination with Epinephrine (ALS 3208, 3212)

QUESTION

Vasopressors during adult cardiac arrest – Vasopressin or vasopressin plus epinephrine compared to epinephrine	
POPULATION:	Adult individuals with cardiac arrest in any setting (our-of-hospital or in-hospital).
INTERVENTION:	Vasopressor or a combination of vasopressors provided intravenously or intraosseously during cardiopulmonary resuscitation.
COMPARISON:	No vasopressor, a different vasopressor, a different combination of vasopressors, a different vasopressor dose, or a different timing of vasopressors provided intravenously or intraosseously during cardiopulmonary resuscitation.
MAIN OUTCOMES:	Clinical outcome including survival, favorable neurological outcome, and health-related quality of life at hospital discharge, 30 days, 90 days, 180 days, and 1 year.

ASSESSMENT

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.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	For both the vasopressin vs epinephrine and the vasopressin plus epinephrine vs epinephrine only comparisons, no study found a significant difference in any outcomes between groups.	Studies were underpowered preventing definitive conclusions from being drawn from results.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	One potential undesirable effect is an increasing complexity in the cardiac arrest treatment algorithm, which may not be warranted if there are no differences in outcomes.	
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 varies but is low or very low for all outcomes. **Comparison (OHCA)** / **Outcome**: **Return of spontaneous circulation** / **Survival at hospital discharge** / **Favorable neurological outcome at hospital discharge** Initial vasopressin compared to initial epinephrine: ⊕⊕◯◯ Low / ⊕◯◯◯ Very low / Not applicable Initial epinephrine plus vasopressin compared to epinephrine only: ⊕◯◯◯ Very low / ⊕◯◯◯ Very low / ⊕⊕◯◯ Low	The low to very low certainty of evidence is due largely to inadequate sample sizes and inconsistency of results across trials.

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	A study suggests that patients value survival with favorable neurological outcome most highly.[1]	The importance of neurological intact survival is generally agreed upon with recognition that survival without neurological recovery is an undesirable outcome for most patients.

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	Given the neutral results and the presumed benefit of keeping the recommendations for treating cardiac arrest as simple as possible, the balance of favorable and unfavorable effects slightly favors epinephrine.	As the studies on these comparisons are likely underpowered, even when pooled, further research should not be precluded in this area.

○ Varies ○ Don't know		
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		
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		
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		
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		

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 vasopressin is currently not the standard of care and would likely not be acceptable.	The provision of vasopressin is not currently part of the algorithm for treatment of cardiac arrest internationally, so the education and associated cost of introducing this change would likely not be acceptable, given the neutral results of available studies.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Vasopressin was previously used more broadly during cardiopulmonary resuscitation but is currently not the standard of care.	Implementing the addition of vasopressin to the treatment algorithm would require some cost for both medication and training, which might be burdensome for some healthcare systems.

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	Probably favors the intervention	Favors the intervention	Varies	Don't know

			intervention or the comparison				
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

CONCLUSIONS

Recommendation

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

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

Justification

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

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Buffering Agents for Cardiac Arrest (ALS 3205)

QUESTION

Should Buffering agents vs. Standard resuscitation (no buffering agents) be used for Cardiac Arrest?	
POPULATION:	Cardiac Arrest
INTERVENTION:	Buffering agents
COMPARISON:	Standard resuscitation (no buffering agents)
MAIN OUTCOMES:	Long Term Survival with Favorable Neurologic Outcome (clinical trials); Long Term Survival (at time of hospital discharge or later) (clinical trials); Long Term Survival (at time of hospital discharge or later) (propensity-matched observational studies); Short Term Survival (survival to hospital admission (clinical trials); Short Term Survival (survival to hospital admission (propensity-matched observational studies);
SETTING:	OHCA
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	Although not recommended in current guidelines, buffering agents are frequently administered in cardiac arrest.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	If buffering agent administration improved the likelihood of successful resuscitation (particularly long term survival with favorable neurologic outcomes), this would be highly desired by most people.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	If buffering agent administration reduced the likelihood of successful resuscitation (particularly long term survival with or without favorable neurologic outcomes), this would be strongly not desired by most people.	

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	Although the data are overall of low certainty, the results of clinical trials and propensity-matched observational studies consistently show no benefit from buffering agent administration, though there may be subgroups who benefit or are harmed.	
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	Most people value survival with good neurologic outcome. Agreement is likely less for survival with poor neurologic outcome, or short-term survival without long term 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	Based on current evidence, buffering agent administration likely has little effect on the desirable outcome (long term survival with favorable neurologic outcome). The effect on short-term outcomes is uncertain, and it is unclear whether people would prefer or prefer not to have short term survival without long term survival.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Buffering agents are commonly administered for patients in cardiac arrest, despite not being included in current guidelines.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Buffering agents are commonly administered for patients in cardiac arrest. The cost is low, particularly if these agents need to be stocked in resuscitation boxes / carts for special circumstances, such as hyperkalemia or sodium channel blocker poisoning.

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

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 administration of buffering agents such as sodium bicarbonate in the treatment of out-of-hospital cardiac arrest, unless a special circumstance for its use is present (weak recommendation, low certainty of evidence).

We suggest against the administration of buffering agents such as sodium bicarbonate in the treatment of in-hospital cardiac arrest, unless a special circumstance for its use is present (weak recommendation, very low certainty of evidence).

Justification

In making this recommendation we place a higher value on not allocating resources to an ineffective intervention, which may divert rescuer time from more beneficial interventions.

Subgroup considerations

This evaluation is not intended to address the use of buffering agents / sodium bicarbonate in the treatment of hyperkalemia (covered by PICO ALS 456) or sodium channel blocker / tricyclic antidepressant poisoning (ALS 429).

Implementation considerations

Current ILCOR guidance (Morrison 2010 S345, PMID 20956256) and international resuscitation council guidelines and training materials already recommend against the routine administration of buffering agents in cardiac arrest. Significant re-education would likely be required to change practice. Given that a large clinical trial is underway (the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) trial, Aarhus University Hospital, Denmark; NCT05564130), it may be prudent to defer this action until the results of the trial are known.

Research priorities

Appropriately sized modern RCTs in both the out-of-hospital cardiac arrest and in-hospital cardiac arrest settings are needed. The BIHCA trial, currently underway, will be the first clinical trial of buffering agent administration for in-hospital cardiac arrest.

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Cardiac Arrest associated with Hyperkalemia – Bicarbonate (ALS 3403)

QUESTION

Should Insulin vs. no treatment be used for the treatment of acute hyperkalemia?	
POPULATION:	Adults with cardiac arrest and hyperkalemia
INTERVENTION:	Bicarbonate as an acute pharmacological intervention with the aim of mitigating the harmful effect of hyperkalaemia or with the aim of lowering potassium levels
COMPARISON:	compared to either no intervention, a different intervention (including a different dose), or placebo
MAIN OUTCOMES:	Clinical outcomes (see below), potassium levels, or ECG findings
SETTING:	Adults
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o **Yes** o Varies o Don't know	Hyperkalaemia is a common electrolyte disturbance that is potentially life-threatening. The topic of acute treatment of hyperkalaemia was formally reviewed almost a decade ago	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o **Moderate** o Large o Varies o Don't know	Guidelines for the treatment of hyperkalemia both in non-arrested and arrested patients is very limited. Hyperkalemia is life-threatening, why any pharmacological intervention with the potential to mitigate the effects of hyperkalemia will have a moderate effect.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o **Small** o Moderate o Large o Varies o Don't know	None	

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	**Table 2. GRADE Overview**				In general there was a lack of studies including clinical relevant outcomes and a lack of studies conducted. Only a limited number of studies has compared different treatment strategies, providing little guidance to clinicians in prioritizing interventions
	Question	**Effect**	**Certainty of evidence**		
	Adults				
	Intravenous bicarbonate 50-390 mmol compared to no treatment for the treatment of acute hyperkalemia	mean.0.1 mmol/l lower (0.3 lower to 0.1 higher)	Very 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 ○ No important uncertainty or variability	The primary outcomes reported was change in potassium levels. Only a limited number of studies reported clinical relevant outcomes.	

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 rationale for recommending against the routine use of sodium bicarbonate in non-arrest patients is based on a meta-analysis of five studies, which showed no reduction in potassium levels with sodium bicarbonate. The decision that there is insufficient evidence to make a recommendation for or against the routine use of bicarbonate in cardiac arrest suspected to be caused by acute hyperkalemia was based on the lack of studies addressing this question and the general lack of effect of bicarbonate in cardiac arrest [3](CoSTR Buffering agents ALS TF 483). The decision not to recommend against bicarbonate was based on the lack of evidence for harm in the general cardiac arrest population.	

Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Bicarbonate is frequently used in clinical practice with a low cost	
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 cost-effectiveness 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	There is no evidence.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased	No studies identified	The drugs are widely available at a low costs.

○ Varies ○ Don't know		
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Yes. The recommendation is in line clinical practice.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	No evidence but the drugs are already used clinically.	

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

Patients Without Cardiac Arrest

For the treatment of acute hyperkalemia, we suggest against the routine use of IV sodium bicarbonate (weak recommendation, low-certainty evidence).

Patients With Cardiac Arrest

For the treatment of cardiac arrest suspected to be caused by acute hyperkalemia, there is insufficient evidence to make a recommendation for or against the use of IV sodium bicarbonate (weak recommendation, very low–certainty evidence).

Justification

The recommendation regarding sodium bicarbonate is based on the lack of identified studies addressing this question and the general lack of effect of bicarbonate in cardiac arrest. The decision not to recommend against was based on the lack of evidence of harm in the general cardiac arrest population.

Research priorities

- The optimal treatment of hyperkalemia during cardiac arrest

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Cardiac Arrest associated with Hyperkalemia – Calcium (ALS 3403)

QUESTION

Should Insulin vs. no treatment be used for the treatment of acute hyperkalemia?	
POPULATION:	Adults with cardiac arrest and hyperkalemia
INTERVENTION:	Intravenous calcium to mitigate the harmful effect of hyperkalaemia on ECG changes or arrythmias
COMPARISON:	no intervention, a different intervention (including a different dose), or placebo
MAIN OUTCOMES:	Clinical outcomes (see below), potassium levels, or ECG findings
SETTING:	Adults
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o **Yes** o Varies o Don't know	Hyperkalaemia is a common electrolyte disturbance that is potentially life-threatening. The topic of acute treatment of hyperkalaemia was formally reviewed in 2015.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o **Moderate** o Large o Varies o Don't know	Guidelines for the treatment of hyperkalemia both in non-arrested and arrested patients is very limited. Hyperkalemia is life-threatening, why any pharmacological intervention with the potential to mitigate the effects of hyperkalemia will have a moderate effect.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small	In patients with cardiac arrest there is evidence to suggest potential harm of routine administration of calcium. Whether this is true for	

○ **Moderate** ○ Large ○ Varies ○ Don't know	both non-arrest and arrest patients with hyperkalemia is unknown.	
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	Only one retrospective observational study was identified investigating the effects of calcium on ECG changes in patients without cardiac arrest (critical risk of bias). Calcium was administered concurrently with other interventions such as insulin and glucose. When major rhythm disorders caused by hyperkalemia were evaluated individually, the administration of calcium did not show statistically significant improvements in any rhythm disorders. In the observational data identified in the systematic review results from two studies, not deemed suitable for meta-analysis, demonstrated that administration of calcium was associated with a higher mortality. (Critical risk of Bias).	In general there was a lack of studies including clinical relevant outcomes and a lack of studies conducted. There are case reports published demonstrating an effect of calcium administration.
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 primary outcome of calcium administration is ECG changes. Only a limited number of studies reported clinical relevant outcomes.	
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	The task-force decided to suggest against the routine use of calcium in patients with hyperkalemia induced cardiac arrest (weak-recommendation, very low certainty of evidence) based on no evidence of a protective effect and a potential harmful effect of routine use in cardiac arrest patients.	

intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know		
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o **Don't know**	The cost of calcium is low. The recommendation against the routine use will like save some resources.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o **Very low** o Low o Moderate o High o No included studies	There are no cost-effectiveness studies	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o **Favors the comparison** o Probably favors the comparison o Does not favor either the intervention or the	There is no evidence.	The task-force decided to suggest against the routine use of calcium in patients with hyperkalemia induced cardiac arrest (weak-recommendation, very low certainty of evidence) based on no evidence of a protective effect and a potential harmful effect of routine use in

comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies		cardiac arrest patients. This will reduce costs.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Reduced o Probably reduced o **Probably no impact** o Probably increased o Increased o Varies o Don't know	No studies identified	The drugs are widely available at a low costs.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o **Probably yes** o Yes o Varies o Don't know	Calcium has also been recommended in international guidelines for many years despite limited evidence. The decisions to suggest against the use of calcium for patients with hyperkalaemia as the cause of the arrest may therefor receive some attention.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o **Yes** o Varies o Don't know	It's a recommendation against routine use.	

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

Patients without cardiac arrest:

For the treatment of acute hyperkalemia, there is insufficient evidence to recommend for or against the use of calcium for the treatment of hyperkalemia (weak recommendation, very low–certainty evidence).

Patients with cardiac arrest:

For the treatment of cardiac arrest suspected to be caused by acute hyperkalemia, there is insufficient evidence to recommend for or against the use of calcium (weak recommendation, very low–certainty evidence).

Justification

The recommendation regarding calcium was based on several considerations:

- Only anecdotal evidence of a protective effect of calcium during hyperkalemia
- Current guidelines recommend the use of calcium for the treatment of hyperkalemia
- One observational study demonstrating a higher mortality in patients with cardiac arrest receiving calcium; the study was assessed as having critical risk of bias
- The potential harm of routine calcium administration during out-of-hospital cardiac arrest
- The general recommendation against routine use of calcium during cardiac arrest

The ALS Task Force acknowledges that not recommending calcium administration in cardiac arrest that is suspected to be caused by acute hyperkalemia challenges current guidelines. The task force recognizes that distinguishing between noncardiac arrest and cardiac arrest can be clinically challenging, especially for patients in the peri-arrest phase. The evidence for harm of calcium is based on out-of-hospital cardiac arrest, whereas the recommendation for in-hospital cardiac arrest patients is based on indirect evidence.

Research priorities

- The optimal treatment of hyperkalemia during cardiac arrest

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Cardiac Arrest associated with Hyperkalemia – Insulin, Glucose & Salbutamol (ALS 3403)

QUESTION

Should Insulin vs. no treatment be used for the treatment of acute hyperkalemia?	
POPULATION:	Adults with cardiac arrest and hyperkalemia
INTERVENTION:	Insulin in combination with glucose or salbutamol (inhaled or intravenous) with the aim of mitigating the harmful effect of hyperkalaemia or with the aim of lowering potassium levels
COMPARISON:	compared to either no intervention, a different intervention (including a different dose), or placebo
MAIN OUTCOMES:	Clinical outcomes (see below), potassium levels, or ECG findings
SETTING:	Adults
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o **Yes** o Varies o Don't know	Hyperkalaemia is a common electrolyte disturbance that is potentially life-threatening. The topic of acute treatment of hyperkalaemia was formally reviewed almost a decade ago	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Trivial o Small o **Moderate** o Large o Varies o Don't know	Guidelines for the treatment of hyperkalemia both in non-arrested and arrested patients is very limited. Hyperkalemia is life-threatening, why any pharmacological intervention with the potential to mitigate the effects of hyperkalemia will have a moderate effect.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Trivial o **Small** o Moderate o Large o Varies o Don't know	In the systematic review it was reported that hypoglycemia was undesirable effect of insulin administration while tachycardia was an undesirable effect of beta2-agonists.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o **Very low** o **Low**	**Table 2. GRADE Overview**	In general there was a lack of studies including clinical

○ Moderate ○ High ○ No included studies	**Question**	**Effect**	**Certainty of evidence**	relevant outcomes and a lack of studies conducted. Based on data from the current review, it is unclear if a higher dose of the included drugs results in a larger decrease in potassium levels. The doses of the individual drugs varied from study to study and only one meta-analysis compared two different doses of insulin with comparable effects. Only a limited number of studies has compared different treatment strategies, providing little guidance to clinicians in prioritizing interventions
	Adults			
	8-12 units of insulin in combination with glucose compared to no treatment for the treatment of acute hyperkalemia	mean 0.7 mmol/l lower (0.9 lower to 0.6 lower)	Low	
		mean 0.7 mmol/l lower (0.9 lower to 0.6 lower)	Low	
	5 vs. 10 units of insulin in combination with glucose for treatment of hyperkalemia	mean 0.0 mmol/l higher (0.0 lower to 0.1 higher)	Very low	
	Inhaled salbutamol compared to no treatment for the treatment of acute hyperkalemia	mean 0.9 mmol/l lower (1.2 lower to 0.7 lower)	Very low	
	Intravenous salbutamol 0.5mg dissolved with glucose compared to no treatment for the treatment of acute hyperkalemia	mean 1.0 mmol/l lower (1.4 lower to 0.6 lower)	Very low	
	Salbutamol 0.5mg dissolved in glucose and 10 units of insulin in combination with glucose compared to no treatment for the treatment of acute hyperkalemia	mean.1.2 mmol/l lower (1.5 lower to 0.8 lower)	Very low	
	Salbutamol 0.5mg dissolved in glucose, compared to 10 units of insulin in combination with glucose for the treatment of acute hyperkalemia	mean.0.3 mmol/l lower (0.5 lower to 0.01 lower)	Very low	
	Combination of 10 units of insulin and 0.5mg salbutamol compared to 0.5 mg salbutamol[a]	mean.0.2 mmol/l lower (0.5 lower to 0.06 higher)	Very low	
	Combination of 10 units of insulin and 0.5 mg of salbutamol compared to 10 units of insulin[a]	mean.0.45 mmol/l lower (0.7 lower to 0.2 lower)	Very low	
	a. Insulin was given in combination with glucose and salbutamol was dissolved in glucose.			

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 primary outcomes reported was change in potassium levels. Only a limited number of studies reported clinical relevant outcomes. However despite limited evidence for clinical outcomes, an initial treatment strategy aiming at acutely lowering extracellular potassium levels seems logical	
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 potential undesirable effects are minor compared to an increased risk of cardiac arrest. The recommended drugs insulin and beta2-agonists are frequently used in clinical practice with an acceptable safety profile compared to an increased risk of cardiac arrest.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ **Moderate savings** ○ Large savings ○ Varies ○ Don't know	The recommended drugs insulin and beta2-agonists are frequently used in clinical practice with a low cost compared to the costs of a patient developing cardiac arrest.	
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 cost-effectiveness 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	There is no evidence, but likely favours the intervention by reducing the risk of cardiac arrest.	
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	No studies identified	The drugs are widely available at a low costs.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Insulin and beta2-agonists have been recommended in international guidelines for many years despite limited evidence, why the recommendation for these drugs should be acceptable.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	No evidence but the drugs are already used clinically.	

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

Patients Without Cardiac Arrest

For the treatment of acute hyperkalemia, we suggest IV insulin in combination with glucose, and/or inhaled or IV beta2-agonists (weak recommendation, low-certainty evidence).

Patients With Cardiac Arrest

For the treatment of cardiac arrest suspected to be caused by acute hyperkalemia, we suggest IV insulin in combination with glucose (weak recommendation, very low–certainty evidence).

Justification

Treatment recommendations were divided into noncardiac arrest and cardiac arrest because the pathophysiology of the 2 conditions differs making the treatment effect likely different in each group. Additionally, almost all the evidence identified was in noncardiac arrest patients.

Patients without cardiac arrest: The rationale for combining insulin (and glucose) with inhaled or IV beta2-agonists is based on a meta-analysis of 50 patients that demonstrated a greater reduction of potassium values with a combination of therapies compared with insulin alone. Only a few studies compared different treatment strategies and doses. Specific recommendations on dosing and a ranking of specific interventions are not included.

Patients with cardiac arrest: The recommendation for insulin in combination with glucose is based on indirect evidence from noncardiac arrest patients.

Beta2-agonists were not recommended based on the following considerations:

- Beta-adrenergic activation is already provided by the administration of epinephrine
- The theoretical potential for harmful effects from excessive beta stimulation during cardiac arrest
- The difficulty of dose titration of IV beta2-agonists during a cardiac arrest
- The general recommendation against tracheal administration of drugs during cardiac arrest due to unpredictable drug delivery

Research priorities

- The optimal treatment of hyperkalemia during cardiac arrest

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Opioid Toxicity – Bicarbonate (ALS 3451)

QUESTION

Should Bicarbonate vs. No Bicarbonate be used for adults and children with cardiac arrest secondary to suspected opioid poisoning ?	
Population:	Adults and children with cardiac arrest secondary to suspected opioid poisoning
Intervention:	Bicarbonate
Comparison:	No Bicarbonate
Main outcomes:	Return of Spontaneous Circulation, Survival to Hospital Discharge or 30-days, Survival to Hospital Discharge or 30-days with Favourable Neurological Status, Long Term Survival, Long Term Survival with Favourable Neurological Status
Setting:	In-hospital or out-of-hospital
Background:	Opioid toxicity is a common cause of cardiac arrest.
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	Opioid toxicity is a major cause of death, and is responsible for approximately 10% of out-of-hospital cardiac arrests. The pathophysiology of opioid-associated cardiac arrest is systematically different from cardiac arrests due to primary cardiac etiologies, and thus may benefit from different interventions.	

Desirable Effects
How substantial are the desirable anticipated effects?

Judgement	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There are no randomized controlled trials evaluating bicarbonate (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. Evidence is limited to a single observational study, in which the association of bicarbonate administration with outcomes was evaluated with a large list of other factors.[1] Bicarbonate was found to be associated with a decreased odds of survival to hospital discharge.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

Judgement	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There have been no randomized controlled trials evaluating bicarbonate (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. The existing literature is limited to observational data, with substantial risk of bias.	

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 is very low for the single outcome evaluated in the single observational study, due to indirectness and high risk of bias.	

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 have shown that survival is an important outcome after cardiac arrest.	

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	Currently available data examining the use of naloxone for cardiac arrest resuscitations are of very low certainty, and thus the balance between desirable and undesirable effects is unclear. The single available study is highly confounded by resuscitation time bias.	

Certainty assessment							Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Survival to Hospital Discharge								
1	non-randomised studies	very serious[a]	not serious	serious[b,c]	not applicable[d]	none	⨁◯◯◯ Very low[a,b,c]	CRITICAL

	CI: confidence interval *Explanations* a. The time of the medication administration was not accounted for in the analysis. Given that longer durations of resuscitation are associated with worse outcomes, medications given later in the resuscitation will be associated with worse outcomes, even if the drug confers no material benefit (resuscitation time bias). b. The study was not limited to opioid-associated OHCA, but rather included a broader population adult EMS-treated OHCA precipitated by "suspected drug overdose" c. The single study identified was limited to adults in the out-of-hospital setting. Therefore, Indirectness is very serious when considering resuscitation of children and/or resuscitation from in-hospital cardiac arrest." d. Given the heterogeneity of the study populations and designs, data was not pooled and a pooled estimate was not calculated. Thus, imprecision is not applicable.	

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 no evidence to suggest that bicarbonate would not be 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	Bicarbonate is readily available to advanced life support resuscitation teams, and may be provided via the intravenous routes.	

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
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

During advanced life support for cardiac arrest due to opioid poisoning, there is insufficient evidence to recommend any additional opioid-specific therapies (e.g., naloxone), beyond standard resuscitation care.

Justification

- We identified a single observational study in our systematic review, which was limited by serious risk of bias and indirectness.
- Indirectness: There were no studies which actually examined the population of interest for this recommendation, i.e., those with opioid-associated OHCA. The single study identified included cases with "suspected drug overdose", including all cases with evidence of deliberate or accidental overdose of any prescribed or non-prescribed drugs, or ethanol. In addition, there were no studies examining in-hospital cardiac arrest or pediatrics cases, and thus for these populations the evidence is very indirect.
- Bias: Bicarbonate is a medication typically provided after initial resuscitative interventions have failed, and thus may be a marker of poor prognosis. The single study identified did not account for the specific timing of bicarbonate administration in analyses, and thus resuscitation time bias is a large limitation.[2]
- The single study reported that bicarbonate was associated with a decreased odds of survival to hospital discharge. We found no other evidence to support use of bicarbonate in opioid-associated OHCA resuscitation.

Subgroup considerations

- Subgroups will be important to evaluate in future randomized controlled trials, however evidence to consider effectiveness in various subgroups is not currently available.

Implementation considerations

- Further higher quality evidence is required prior to implementation plans.

Monitoring and evaluation

- Further higher quality evidence is required prior to developing plans for monitoring and evaluation.

Research priorities

- Further research to identify the optimal treatment for opioid-associated cardiac arrest is warranted, given the high incidence of this condition. Research should include in and out-of-hospital cardiac arrest, and adult and pediatric populations.

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Opioid Toxicity – Naloxone (ALS 3451)

QUESTION

Should Naloxone vs. No Naloxone be used for adults and children with cardiac arrest secondary to suspected opioid poisoning ?	
POPULATION:	Adults and children with cardiac arrest secondary to suspected opioid poisoning
INTERVENTION:	Naloxone
COMPARISON:	No Naloxone
MAIN OUTCOMES:	Return of Spontaneous Circulation, Survival to Hospital Discharge or 30-days, Survival to Hospital Discharge or 30-days with Favourable Neurological Status, Long Term Survival, Long Term Survival with Favourable Neurological Status
SETTING:	In-hospital or out-of-hospital
BACKGROUND:	Opioid toxicity is a common cause of cardiac arrest
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	Opioid toxicity is a major cause of death, and is responsible for approximately 10% of out-of-hospital cardiac arrests. The pathophysiology of opioid-associated cardiac arrest is systematically different from cardiac arrests due to primary cardiac etiologies, and thus may benefit from different interventions.	

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 no randomized controlled trials evaluating naloxone (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. Although there is a larger body of data demonstrating the benefit of naloxone for opioid-induced respiratory depression, the existing literature for management of opioid-associated cardiac arrest is limited to observational data, with substantial risk of bias. Naloxone may confer benefit for opioid-associated cardiac arrest and improve survival and favourable neurological outcomes, however this is unknown.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate	There have been no randomized controlled trials evaluating naloxone (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. The	

○ Large ○ Varies ● Don't know	existing literature is limited to observational data, with substantial risk of bias. There is evidence from animal data showing worsening neurological outcomes among cases treated with naloxone. Naloxone may also induce pulmonary edema. Finally, given the task-saturated nature of cardiac arrest resuscitations, the deployment of any additional interventions may interfere with or worsen the quality of standard resuscitation management. Naloxone may confer undesirable effects for opioid-associated cardiac arrest, however this is unknown.	
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 is very low for all outcomes evaluated (including favourable neurological outcome, survival to hospital discharge, and return of spontaneous circulation). Existing data are severely limited due to indirectness and high risk of bias.	
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 have shown that survival and neurological function are important outcomes after cardiac arrest.	
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	Currently available data examining the use of naloxone for cardiac arrest resuscitations are of very low certainty, and thus the balance between desirable and undesirable effects is unclear.	

Certainty assessment	Certainty	Importance

○ Favors the intervention
○ Varies
○ Don't know

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Survival to Hospital Discharge								
4	non-randomised studies	very serious[a,b]	serious[c]	serious[d,e]	not applicable[j]	none	⊕◯◯◯ Very low[a,b,c,d,e]	CRITICAL
Return of Spontaneous Circulation								
3	non-randomised studies	very serious[a,b]	serious[f]	serious[e,g]	not applicable[j]	none	⊕◯◯◯ Very low[a,b,e,f,g]	IMPORTANT
Favourable Neurological Status at Hospital Discharge								
3	non-randomised studies	very serious[a,b]	serious[h]	serious[e,i]	not applicable[j]	none	⊕◯◯◯ Very low[a,b,e,h,i]	CRITICAL

CI: confidence interval

Explanations

a. Given that study cases were not limited to those with opioid-associated cardiac arrest, there is substantial bias introduced by indication bias: it is likely that prehospital providers administered naloxone among OHCAs with evidence of opioid toxicity. Previous data has shown that OHCAs secondary to opioid toxicity have better outcomes than those with undifferentiated OHCA, and also those with non-opioid drug toxicity. Thus, results of the association of naloxone and outcomes may be simply be demonstrating an association of opioid-related OHCA and outcomes, as the drug was likely given to these selected individuals.

b. The time of the medication administration was not accounted for in the analysis. Given that longer durations of attempted resuscitation are associated with worse outcomes, medications given later in the resuscitation will be associated with worse outcomes, even if the drug confers no material benefit (resuscitation time bias).

c. Two reported that naloxone is associated with an improved odds of survival to hospital discharge, while two did not detect an association.

	d. No studies examining survival specifically included cases of suspected opioid-associated cardiac arrest. Dhillon included adult EMS-treated OHCA (with a subgroup of drug-related OHCA), Quinn included adult EMS-treated OHCA, Strong 2023 included adult OHCA due to presumed overdose, and Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms. e. All identified studies were limited to adults in the out-of-hospital setting. Therefore, Indirectness is very serious when considering resuscitation of children and/or resuscitation from in-hospital cardiac arrest." f. Two studies report that naloxone is associated with an improved odds of ROSC, while one did not detect an association. g. No studies examining ROSC specifically included cases of suspected opioid-associated cardiac arrest. Dhillon included adult EMS-treated OHCA (with a subgroup of drug-related OHCA), Quinn included adult EMS-treated OHCA, and Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms. h. One study reported that naloxone is associated with an improved odds of favourable neurological outcome at hospital discharge, while two studies did not detect an association. i. No studies examining favourable neurological outcomes specifically included cases of suspected opioid-associated cardiac arrest. Strong 2023 included adult OHCA due to presumed overdose, Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms, Love included adult EMS-treated OHCAs with a documented history or exam consistent with overdose, family report of overdose, or if the patient had a known history of substance use j. Given the heterogeneity of the study populations and designs, data was not pooled and a pooled estimate was not calculated. Thus, imprecision is not applicable.	
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 no evidence to suggest that naloxone would not be acceptable to stakeholders.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	Naloxone may be provided via intranasal, intramuscular, subcutaneous, intravenous, or intraosseous routes.	

● Probably yes ○ Yes ○ Varies ○ Don't know	Naloxone administration is feasible to implement, similarly to other pharmacological resuscitative interventions.	

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
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

During advanced life support for cardiac arrest due to opioid poisoning, there is insufficient evidence to recommend any additional opioid-specific therapies (e.g., naloxone), beyond standard resuscitation care. If rescuers are uncertain whether a patient with suspected opioid poisoning is actually in cardiac arrest, administration of an opioid antagonist (eg, naloxone) is warranted (good practice statement).

Justification

- Our aim was to evaluate the evidence of advanced treatments (e.g., intravascular naloxone) that may confer benefit for those with opioid toxicity and *confirmed* cardiac arrest. This recommendation is directed at providers of ALS,[1] including clinicians with expertise with ascertaining pulselessness. However, if it is there is uncertainty regarding whether a patient is indeed in cardiac arrest vs. respiratory depression/apnea, implementing recommended treatments for respiratory depression/apnea (eg. naloxone) is warranted
- This recommendation is not intended to inform the provision care by individuals without training to ascertain pulselessness. For these rescuers, when attending to patients with opioid toxicity it may be difficult or impossible to distinguish between an obtunded patient with respiratory depression/apnea vs. a patient in true cardiac arrest. In these scenarios, please refer to the ILCOR CoSTR "Resuscitation care for suspected opioid-associated emergencies (BLS #811)".[2]
- Opioids suppress the respiratory drive, leading to hypoxia, and subsequent cardiac arrest. Naloxone is an effective reversal agent for opioid-induced respiratory depression, however its effectiveness in cardiac arrest is unclear, particularly when artificial respiration is provided.[3] Animal models have shown that naloxone may improve the probability of ROSC over standard resuscitation (even in the absence of opioids),[4–6] however other data suggests opioid-reversal may worsen cerebral injury.[7,8]
- We identified several observational studies in our systematic review, however which were limited by serious risk of bias and indirectness.
- Indirectness: There were no studies which actually examined the population of interest for this recommendation, i.e., those with opioid-associated OHCA. Some studies included undifferentiated OHCAs, [9–11] and others included cases with suspected drug-overdose[12–14] (including a wide array of prescription and non-prescription drugs, as well as ethanol). In addition, there were no studies examining in-hospital cardiac arrest or pediatrics cases, and thus for these populations the evidence is very indirect.
- Bias: Previous studies have shown that drug-related OHCA is associated with improved outcomes compared to undifferentiated OHCA[15,16], and that opioid-related OHCA is associated with improved outcomes compared to other drug-related OHCAs[17]. Drug-related cases are more likely to be treated with naloxone than undifferentiated OHCA,[9] and opioid-related OHCA are more likely to be treated with naloxone than other drug-related cases.[17] Thus, treatment with naloxone may simply be a marker of opioid toxicity and its apparent superior prognosis, rather than providing any actual benefit. In addition, existing studies did not account for the specific timing of naloxone administration in analyses, and thus are limited by resuscitation time bias.[18]
- We acknowledged that cardiac arrest resuscitations are task-saturated endeavors with multiple competing priorities.[1] We did not believe that the very low certainty evidence regarding the benefit of any opioid-specific ALS intervention was sufficient to recommend incorporating into ALS algorithms, given the risk of interfering with other evidence-based interventions. Given the uncertain state of the evidence, there is also a possible risk of harm.

Subgroup considerations

- Subgroups will be important to evaluate in future randomized controlled trials, however evidence to consider effectiveness in various subgroups is not currently available.

Implementation considerations

- Further higher quality evidence is required prior to implementation plans.

Monitoring and evaluation

- Further higher quality evidence is required prior to developing plans for monitoring and evaluation.

Research priorities

- There were no randomized controlled trials that evaluated naloxone, in comparison to placebo, for suspected opioid-associated cardiac arrest. Given the equipoise and high incidence of cases, an RCT is urgently needed to answer this question

- There was no evidence available for in-hospital cardiac arrest or pediatric cardiac arrest

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Mechanical Circulatory Support Post-resuscitation (ALS 3505)

QUESTION

Mechanical circulatory support after return of spontaneous circulation following cardiac arrest: a systematic review	
POPULATION:	Adult individuals (≥ 18 years or as defined in individual studies) with circulatory shock after return of spontaneous circulation (ROSC) following cardiac arrest in any setting (in-hospital or out-of-hospital).
INTERVENTION:	Management with a mechanical circulatory support device
COMPARISON:	Management without a mechanical circulatory support device or usual post-resuscitation care
MAIN OUTCOMES:	Primary outcome: survival at hospital discharge/30 days and at the time of the longest follow-up. Secondary outcomes: favorable neurological outcome, quality of life, length of hospital and ICU stay, adverse events/complications (e.g., bleeding, limb ischemia, arrhythmias, recurrent cardiac arrest, acute kidney injury +/- renal replacement therapy, stroke, hemolysis) as defined by study authors.
SETTING:	In-hospital

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiogenic shock affects more than half of patients resuscitated from cardiac arrest and is associated with a high mortality, especially when the underlying cause is a myocardial infarction. In addition to inotropes, vasopressors and revascularization of the infarct-related coronary artery, mechanical circulatory support (MCS) devices can be used to support the circulation, improve cardiac output, and end-organ perfusion in these patients. MCS may also have a role in myocardial protection and limiting further secondary neurological injury from hypoperfusion. MCS devices are being increasingly used in the treatment of acute myocardial infarction-related cardiogenic shock, including patients resuscitated from cardiac arrest, despite conflicting evidence regarding their effect on mortality.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The evidence on mechanical circulatory support (MCS) in post-cardiac arrest patients with cardiogenic shock is very limited. Randomized trials have been conducted in patients with acute myocardial infarction complicated by cardiogenic shock (AMI-CS), and many of them included a large proportion of resuscitated cardiac arrest patients (up to 92% in one trial). The available randomized trials in AMI-CS were mostly neutral, showing inconsistent direction of effects across outcomes, studies, and types of MCS devices. Similar findings were reported for the subgroup of cardiac arrest patients included in these trials. Recently, a trial involving a microaxial flow pump (Impella CP®) plus standard care, compared to standard care alone, demonstrated its superiority (hazard ratio, 0.74; 95% confidence interval [CI], 0.55 to 0.99; P = 0.04)[1]. However, cardiac arrest patients who remained comatose after the return of spontaneous circulation were excluded from this trial. An individual patient data meta-analysis of 9 randomized trials that found a benefit of mechanical circulatory support devices in patients with ST-elevation myocardial	

infarction without resuscitation before arrival of the emergency medical service or only short duration of resuscitation (<10 minutes)[2]

Table 2. Pooled rates of primary and secondary outcomes in patients receiving mechanical circulatory support versus standard care.

Outcome Subgroup	N. of studies	MCS	Standard care	Odds Ratio (95% CI)	P for effect	I^2
Survival at the longest follow-up available, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	11*	190/406 (47%)	171/410 (42%)	1.21 (0.91–1.60)	0.19	0%
Cardiogenic shock with or without prior cardiac arrest	14	426/944 (45%)	385/931 (41%)	1.17 (0.97–1.42)	0.10	0%
Survival at hospital discharge or 30 days, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	6	208/380 (55%)	213/386 (55%)	0.97 (0.73–1.30)	0.85	0%
Cardiogenic shock with or without prior cardiac arrest	13	521/928 (56%)	479/914 (52%)	1.16 (0.97–1.40)	0.12	0%
Survival at 6 months or 1 year, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	10*	188/376 (50%)	174/381 (46%)	1.21 (0.87–1.68)	0.25	11%
Cardiogenic shock with or without prior cardiac arrest	10	427/871 (49%)	389/862 (45%)	1.18 (0.95–1.46)	0.11	8%
Survival with favourable neurological outcome at the longest follow-up available, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	0	-	-	-	-	-
Cardiogenic shock with or without prior cardiac arrest	3	116/281 (41%)	108/279 (39%)	1.11 (0.79–1.57)	0.53	0%
Survival with favourable neurological outcome at hospital discharge or 30 days, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	0	-	-	-	-	-
Cardiogenic shock with or without prior cardiac arrest	3	93/280 (33%)	103/280 (37%)	0.85 (0.60–1.21)	0.37	0%
Survival with favourable neurological outcome at 6 months or 1 year, n (%)						
Resuscitated cardiac arrest with cardiogenic shock	0	-	-	-	-	-
Cardiogenic shock with or without prior cardiac arrest	2	110/268 (41%)	104/266 (39%)	1.09 (0.77–1.54)	0.64	0%

Abbreviations: MCS, mechanical circulatory support; CI, confidence interval
*including pooled data of 6 randomized trials from an individual patient-data meta-analysis by Thiele et al. 2024.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies	The available randomized trials in AMI-CS were mostly neutral, showing inconsistent effects across outcomes, studies, and types of MCS devices. Similar findings were reported for the subgroup of cardiac arrest patients included in these trials. Recently, a trial involving a microaxial flow pump (Impella CP®) plus standard care, compared to standard care alone, demonstrated its superiority (hazard ratio, 0.74; 95% confidence interval [CI], 0.55 to 0.99; P = 0.04) (Moller 2024). However, cardiac arrest patients who remained comatose after the return of spontaneous	

○ Don't know	circulation were excluded from this trial. Complications such as bleeding, limb ischemia, hemolysis, the need for renal replacement therapy, and sepsis were more frequent in patients treated with MCS compared to standard care. The increased complication rates were consistent across studies and outcomes, especially in patients treated with active MCS (e.g., microaxial flow pump).	
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 across outcomes is low (downgraded due to indirectness).	
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	Survival and survival with favorable neurological outcome are generally accepted as critical outcomes in patients with cardiac arrest. However, some patients, relatives, or clinicians may prioritize neurological outcome and quality of life over 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 balance of effects favors standard care, especially when mechanical circulatory support devices are applied in unselected patients, given the increased risk of complications and the lack of demonstrated benefits with this approach. However, the balance of effects likely favors the intervention over standard care when mechanical circulatory support devices are used in selected patients, where the strategy may offer some survival benefits despite a higher occurrence of treatable or reversible complications.	

Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We found an economic evaluation from the IABP-SHOCK II trial,[3] which showed slightly higher but statistically significant healthcare costs. Nevertheless, given the generally high costs associated with therapy for patients requiring mechanical support and the relatively small contribution from intra-aortic balloon pump (IABP) therapy, IABP may still be considered an economically reasonable and safe strategy, especially if clinical scenarios where IABP provides a benefit can be identified.[3] We did not identify any other analysis from identified randomized trials evaluating the cost of a mechanical circulatory support (MCS) device compared to another MCS device or specifically in cardiac arrest patients. However, significant costs seem likely, especially if routinely applied and for active MCS devices as performed in most included randomized trials.	
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	The certainty of evidence of resource required is low for intra-aortic balloon pump (downgraded for indirectness). We have not identified any other research that assessed resource required.	
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	We found an economic evaluation from the IABP-SHOCK II trial,[3] which showed slightly higher but statistically significant healthcare costs. Nevertheless, given the generally high costs associated with therapy for patients requiring mechanical support and the relatively small contribution from intra-aortic balloon pump (IABP) therapy, IABP may still be considered an economically reasonable and safe strategy, especially if clinical scenarios where IABP provides a benefit can be identified.[3] We did not identify any other analysis from identified randomized trials evaluating the cost of a mechanical circulatory support (MCS) device compared to another MCS device or specifically in cardiac arrest patients. However, significant costs seem likely, especially if routinely applied and for active MCS devices as performed in most included randomized trials.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably	Treating patients with a mechanical circulatory support (MCS) device may be difficult in low-resource settings due to the high cost of devices and consumables and in setting without the expertise and resources needed.	

increased ○ Increased ○ Varies ○ Don't know	

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.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility was not specifically addressed by this review but in included trials mechanical circulatory support (MCS) was feasible. However, we recognize that performing MCS requires special resources and skills that may be not available or feasible in every setting.	

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 suggest against the routine use of mechanical circulatory support devices in patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation (weak recommendation, low certainty of evidence).
We suggest considering mechanical circulatory support devices in highly selected patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation, in settings where this can be implemented (weak recommendation, low certainty of evidence).
When a mechanical circulatory support device is used, we suggest monitoring for adverse events and complications to allow their rapid identification and treatment (good practice statement).

Justification

In making a weak recommendation against the routine use of mechanical circulatory support devices in patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation, the task force considered pooled analyses from up to 14 randomized trials showing no difference in survival at various follow-ups (30 days or hospital discharge, 6 months, 1 year, and the longest available) between early routine treatment with a temporary mechanical circulatory support device and standard care in patients with cardiogenic shock, with or without prior cardiac arrest. No randomized trials were specifically designed and powered to assess a benefit in term of critical outcomes (e.g., survival or survival with favorable neurological outcome) in a population of patients with return of spontaneous circulation after a cardiac arrest. All the evidence was indirect, coming from randomized trials in patients with cardiogenic shock (64% [95% CI, 45–80] of patients included were resuscitated from cardiac arrest), except a small (N=60) randomized trial enrolling only patients resuscitated from in-hospital cardiac arrest due to acute coronary syndrome[4].

Although overall evidence did not support routine use of mechanical circulatory support devices, there may be certain patients who may benefit, and the task force discussed whether a selected approach to mechanical circulatory support devices in patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation may be considered rather than an unselected approach and made a weak recommendation suggesting the use of mechanical circulatory support devices in highly selected patients. In making this recommendation, the task force considered:

- the results of a randomized trial comparing a microaxial flow pump with standard care alone in infarct-related cardiogenic shock which found improved survival at 180 days (hazard ratio, 0.74; 95% confidence interval, 0.55 to 0.99)[1] and the fact that, in this trial, patients resuscitated from cardiac arrest who remained comatose (Glasgow Coma Scale ≤ 8) at hospital arrival were excluded, leaving a 20% of conscious patients resuscitated from cardiac arrest[1]. Most other trials involving patients with acute myocardial infarction and cardiogenic shock, the prevalence of patients resuscitated from cardiac arrest was high (up to 95% in one trial) and not limited to conscious patients.
- An individual patient data meta-analysis of 9 randomized trials that found a benefit of mechanical circulatory support devices in patients with ST-elevation myocardial infarction without resuscitation before arrival of the emergency medical service or short duration of resuscitation (<10 minutes) but not in the overall population of cardiac arrest patients[2].

The task force discussed the lack of evidence on how to select patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation for mechanical circulatory support. Based on the low certainty of evidence from randomized trials and subgroup analyses, the subgroups of patients who may potentially benefit include those with a Glasgow Coma Scale ≤ 8 at hospital arrival, patients with ST-elevation myocardial infarction without prior resuscitation before the arrival of emergency medical services, or those with a short duration of cardiac arrest (<10 minutes). The discussion mentioned also that the cause of death differs in patients with cardiogenic shock, depending on whether they experienced prior cardiac arrest. Hypoxic brain injury is the leading cause of death in those with cardiac arrest, while persistent cardiac failure is the primary cause in those without cardiac arrest. Therefore, in patients at high risk of brain injury, which cannot be addressed by mechanical circulatory support devices, the benefit of these devices may be less apparent. In the CoSTR on predicting good neurological outcomes after cardiac arrest[5], the task force found one study that showed a Glasgow Coma Scale motor score of 4–5 assessed at intensive care unit admission predicted favorable outcomes at 3 months, with a specificity of 98% (95% CI 93–99%) and sensitivity of 12% (95% CI 7–17%)[6]. Other predictors of good neurological outcomes, though not available at admission, included normal neuron-specific enolase blood values at 24–72 hours, an somatosensory evoked potential N20 wave amplitude above 4 μV, a continuous electroencephalogram background without discharges within 72 hours, or the absence of diffusion restriction in the cortex or deep grey matter on magnetic resonance imaging between days 2–7.[7–10] The task force agreed that, based on the current level of available evidence, making clear recommendations on how to select patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation for mechanical circulatory support is challenging. There was also a discussion about the risk of prematurely ruling out interventions for patients with possible neurological recovery based solely on early coma, as done in one trial[11].

In making these recommendations, the task force also considered:

- that implementation of mechanical circulatory support may incur significant costs and require specialized resources and skills, which may not be available or feasible in all settings;
- the 2023 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes stating that in patients with acute coronary syndrome and severe/refractory cardiogenic shock, short-term mechanical circulatory support may be considered (class of recommendation IIb, level of evidence C) and that the routine use of an intra-aortic balloon pump in patients without mechanical complications is not recommended (class of recommendation III, level of evidence B) and the 2023 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support stating that acute mechanical circulatory support should be initiated as soon as possible in patients with cardiogenic shock who fail to stabilize or continue to deteriorate despite initial interventions[12].

Finally, while mechanical circulatory support devices may be considered for highly selected patients, the task force emphasized the need for caution until further evidence becomes available. Given the increased rates of complications—particularly bleeding and limb ischemia—in patients with infarct-related cardiogenic shock treated with mechanical circulatory support devices, especially when venoarterial extracorporeal membrane oxygenation or left ventricular assist devices are used, the task force found it reasonable to issue a good practice statement recommending close monitoring for adverse events and complications if mechanical circulatory support is employed.

Subgroup considerations

Although overall evidence did not support routine use of mechanical circulatory support devices, there may be certain patients who may benefit, and the task force discussed whether a selected approach to mechanical circulatory support devices in patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation may be considered rather than an unselected approach and made a weak recommendation suggesting the use of mechanical circulatory support devices in highly selected patients. In making this recommendation, the task force considered:

- the results of a randomized trial comparing a microaxial flow pump with standard care alone in infarct-related cardiogenic shock which found improved survival at 180 days (hazard ratio, 0.74; 95% confidence interval, 0.55 to 0.99)[1] and the fact that, in this trial, patients resuscitated from cardiac arrest who remained comatose (Glasgow Coma Scale ≤ 8) at hospital arrival were excluded, leaving a 20% of conscious patients resuscitated from cardiac arrest[1]. Most other trials involving patients with acute myocardial infarction and cardiogenic shock, the prevalence of patients resuscitated from cardiac arrest was high (up to 95% in one trial) and not limited to conscious patients.
- An individual patient data meta-analysis of 9 randomized trials that found a benefit of mechanical circulatory support devices in patients with ST-elevation myocardial infarction without resuscitation before arrival of the emergency medical service or short duration of resuscitation (<10 minutes) but not in the overall population of cardiac arrest patients[2].

The task force discussed the lack of evidence on how to select patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation for mechanical circulatory support. Based on the low certainty of evidence from randomized trials and subgroup analyses, the subgroups of patients who may potentially benefit include those with a Glasgow Coma Scale ≤ 8 at hospital arrival, patients with ST-elevation myocardial infarction without prior resuscitation before the arrival of emergency medical services, or those with a short duration of cardiac arrest (<10 minutes). The discussion mentioned also that the cause of death differs in patients with cardiogenic shock, depending on whether they experienced prior cardiac arrest. Hypoxic brain injury is the leading cause of death in those with cardiac arrest, while persistent cardiac failure is the primary cause in those without cardiac arrest. Therefore, in patients at high risk of brain injury, which cannot be addressed by mechanical circulatory support devices, the benefit of these devices may be less apparent. In the CoSTR on predicting good neurological outcomes after cardiac arrest[5], the task force found one study that showed a Glasgow Coma Scale motor score of 4–5 assessed at intensive care unit admission predicted favorable outcomes at 3 months, with a specificity of 98% (95% CI 93–99%) and sensitivity of 12% (95% CI 7–17%)[6]. Other predictors of good neurological outcomes, though not available at admission, included normal neuron-specific enolase blood values at 24–72 hours, an somatosensory evoked potential N20 wave amplitude above 4 μV, a continuous electroencephalogram background without discharges within 72 hours, or the absence of diffusion restriction in the cortex or deep grey matter on magnetic resonance imaging between days 2–7.[7–10] The task force agreed that, based on the current level of available evidence, making clear recommendations on how to select patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation for mechanical circulatory support is challenging. There was also a discussion about the risk of prematurely ruling out interventions for patients with possible neurological recovery based solely on early coma, as done in one trial[11].

Implementation considerations

The task force recognized that treating patients with a mechanical circulatory support devices may be not feasible in low-resource settings due to the high cost of devices and consumables. The task force also acknowledged that

treating patients with a mechanical circulatory support devices requires specialized resources and skills that may not be available or feasible in every setting.

Monitoring and evaluation

Research priorities

The evidence regarding the role of mechanical circulatory support devices in patients with cardiogenic shock after cardiac arrest and return of spontaneous circulation remains limited. The following knowledge gaps have been identified:

1. No studies were identified that evaluated the effect of mechanical circulatory support devices on neurologically intact survival in patients with cardiac arrest.
2. Subpopulation of post-cardiac arrest patient in cardiogenic shock that might benefit from mechanical circulatory support
3. The value of mechanical circulatory support devices in patients without acute myocardial infarction-related cardiogenic shock or post-resuscitation shock following cardiac arrest of non-cardiac origin
4. The comparative effectiveness of different mechanical circulatory support devices or combinations of devices (e.g., ECPELLA, BIPELLA)
5. The optimal timing for initiating mechanical circulatory support after the return of spontaneous circulation
6. The ideal settings for implementing mechanical circulatory support in post-cardiac arrest patients
7. The cost-effectiveness of mechanical circulatory support in post-cardiac arrest patients

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Vasopressor Choice After ROSC from Cardiac Arrest (ALS 3528)

QUESTION

Should noradrenaline vs. adrenaline be used for low blood pressure after return of spontaneous circulation after cardiac arrest?	
POPULATION:	low blood pressure after return of spontaneous circulation after cardiac arrest
INTERVENTION:	noradrenaline
COMPARISON:	adrenaline
MAIN OUTCOMES:	Thirty day survival; Thirty day or hospital survival (pooled); Good functional outcome at thirty days or at hospital discharge ; Recurrent cardiac arrest; Recurrent cardiac arrest;
SETTING:	Pre-hospital or in-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	The majority of patients after cardiac require a vasopressor for the treatment of low blood pressure and achieve the currently recommended target of 60-65 mmHg. Many different vasopressor are used worldwide including noradrenaline, adrenaline, dopamine, and vasopressin. All these have slightly different effects. It is currently unclear if any one of these are preferable in patients after cardiac arrest given the combination of brain and cardiac injury.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Trivial • **Small** • Moderate • Large • Varies • Don't know	The systematic review identified 7 observational studies and one randomized study. Based one these it is difficult to assess the possible desirable effects. In general the larger RCT:s in patients cared for in the ICU have not shown any large difference in outcome depending on the choice of vasopressor. Based on the current evidence it is difficult to assess the desirable effects if there are any.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Trivial • **Small** • Moderate	It is possible that some vasopressors used could have significant side- effects. But based on the current evidence it is impossible to estimate.	

• Large • Varies • Don't know		

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 is one very small RCT. All the other studies are observational and it is clear that there is confounding by indication i.e. adrenaline may be used in the sicker patients. Even though there are aims to adjust for this but it is clear that there are residual confounding. The wat of adjusting for severity of illness is also very variable between studies.	

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	People will value long-term outcome, but we do not know if the choice of vasopressor really makes a difference on these. Another studied outcome is rearrest. This is also important but people would probably value long- term outcome more.	

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	Based on the current evidence we do not know what the optimal vasopressor is patients after cardiac arrest.	

• Don't know		
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • **Don't know**	All vasopressors are fairly cheap. But we found no study that has assessed costs of a specific vasopressor choice after cardiac arrest.	
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**	We found no studies that have assessed resources required based on the choice of vasopressor. The resources required are likely to be very similar between the drugs included in this review.	
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	We found no studies that have assessed resources required based on the choice of vasopressor. The resources required are likely to be very similar between the drugs included in this review.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• Reduced • Probably reduced • Probably no impact	It is likely that all it would be possible to use any of these vasopressor in most setting if there would be evidence to suggest superiority of a specific drug.	

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

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• No • Probably no • **Probably yes** • Yes • Varies • Don't know	The use of a vasopressor is standard practice in the ICU. For the patient the choice of which is probably not going to make any difference.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• No • Probably no • Probably yes • **Yes** • Varies • Don't know	The use of the type of vasopressors are probably feasible to implement in most hospitals. In the pre-hospital setting the situation may be a bit different.	

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
		•		

Recommendation

CONCLUSIONS

There is insufficient evidence to recommend a specific vasopressor to treat low blood pressure in patients after cardiac arrest.

Justification

There was disagreement among the ALS TF and therefore the type of TR was voted on. The TR that got the most votes was chosen. The voting was close with 9 votes favoring no recommendation and 7 votes favoring recommending the use of noradrenaline as the first choice.

Subgroup considerations

There is currently no evidence suggesting a different effect in a certain subgroup.

Implementation considerations

It would probably be easy to implement in most settings.

Monitoring and evaluation

Research priorities

There is limited data on this topic. There is a need for larger trials on this topic.

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Neuroprotective Drugs (ALS 3507)

QUESTION

Should [intervention] vs. [comparison] be used for [health problem and/or population]?	
POPULATION:	Patients with return of spontaneous circulation (ROSC) after cardiac arrest
INTERVENTION:	Any specific neuroprotective drug therapy administered after ROSC
COMPARISON:	Placebo or another drug
MAIN OUTCOMES:	Mortality at 30-days, hospital discharge or 180 days Functional outcome at 30-days, hospital discharge or 180 days
SETTING:	Out-of-hospital or in-hospital cardiac arrest
BACKGROUND:	Brain injury after cardiac arrest is a major problem. No treatment exists at the moment.
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	Cardiac arrest is a major health problem and many patients die in the intensive care unit or in the hospital with hypoxic brain injury. Currently there are no specific treatments available that alleviate brain injury and care is largely supportive. A treatment that alleviates brain injury would be of great importance.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• Trivial • **Small** • Moderate • Large • Varies • Don't know	According to the evidence no pharmacological treatment has been shown to have any beneficial effect on Neither survival nor functional outcome in patients after cardiac arrest. The conducted trials are fairly small and rule out fairly large effects. But the conducted trial sequential analyses have not identified any clear need to for larger trials on drugs such as steroids, coenzyme-Q10 and thiamine.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• Trivial • **Small** • Moderate • Large • Varies • Don't know	Thus far the conducted trials are small so whether these drugs have important side-effects are unknown. It is also possible that a drug that saves lives in a patient with severe brain injury can lead to the survival of patients with a poor functional	

	outcome. Whether this is true is not possible to know given the current available evidence.	
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	Most conducted studies are small and single center decreasing the certainty of evidence.	
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	As the current evidence suggest no effect there is probably no clear difference in how people value these results. This is especially true for coenxyme-Q10 which is currently not used in routinely in ICUs. With regards to steroids and thiamine the situation is different, these drugs are commonly used and these are cheap drugs. Therefore one could argue that why not use these even based on very limited evidence, if there is limited risk of harm. However, the risk of harm is possible with both steroids and thiamine and therefore probably most clinicians would favor not using these drugs routinely without better evidence.	
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 evidence does not suggest the beneficial effect of any neuroprotective drug on outcome in patients with ROSC after cardiac arrest. As these drugs are not routinely used in other critically ill patients, there is the possibility of harm most clinicians probably would favor the comparison i.e. not giving these drugs.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

• Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • **Don't know**	Poor neurologic recovery is costly after cardiac arrest. Most neuroprotective drugs included in the review are cheap and probably easy to administer favoring their use. But as side-effects and poor recovery is possible we do not know about the resources required.	
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 studies have assessed costs.	
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 have assessed cost-effectiveness.	
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 do not know as we have not identified any drug that improves outcome.	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• No • Probably no • Probably yes • Yes • Varies • **Don't know**	We do not know as we do not know if these drugs work.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• No • Probably no • **Probably yes** • Yes • Varies • Don't know	Most studies interventions involve the administration of intravenous drugs. It is likely that this therapy would be feasible in most 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	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
	•			
•		•	•	•

Recommendation

There is insufficient evidence to recommend the use of any specific drug therapy for comatose survivors of cardiac arrest. (weak recommendation, very low certainty evidence)

Justification

Our systematic review of the evidence has not identified any drug that improves outcome in patients after cardiac arrest.

Subgroup considerations

We have not identified any sub-group differences.

Implementation considerations

We have not identified any drug therapy that works and therefore we cannot evaluate implementation. But the administration of intravenous drugs is common practice and is likely to be easy to implement.

Monitoring and evaluation

Research priorities

There is a need for larger multicenter trial evaluating the effect of various drugs on outcome in patients with return of spontaneous circulation after cardiac arrest.

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Organ Donation After Cardiac Arrest (ALS 3600)

QUESTION

Organ Donation from Donors with Cardiac Arrest	
POPULATION:	Adults and children who are receiving solid organ transplantation in any setting
INTERVENTION:	Transplantation of an organ retrieved from a donor who, following cardiac arrest, received cardiopulmonary resuscitation (e.g., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation).
COMPARISON:	Transplantation of an oran retrieved from a donor who did not receive cardiopulmonary resuscitation.
MAIN OUTCOMES:	Primary outcome: graft function or recipient survival at the longest follow-up available. Secondary outcomes: graft function or recipient survival at 30 days and 1 year.
SETTING:	In-hospital or out-of-hospital cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is currently a mismatch between organ availability and demand worldwide. Only a minority of this demand can be met by donations from living donors, and only for some organs, such as kidneys. Therefore, the contribution from deceased donors is crucial. Patients who do not recover after cardiac arrest represent a potential source of organ donation. This can occur when patients die after initial successful resuscitation from cardiac arrest because of brain death (donors after death by neurological criteria, DBD) or following withdrawal of life-sustaining treatment (WLST) because of predicted poor outcome (controlled donors after cardiac death, cDCD)[1]. In other patients, cardiac death is pronounced at the end of an unsuccessful resuscitation attempt (uncontrolled donors after cardiac death uDCD). With organs from donors who have had cardiopulmonary resuscitation, there is concern that whole-body ischemia-reperfusion injury can result in significant extracerebral organ damage, making organs unsuitable for transplantation or at risk of worse outcomes and complications for the recipient. Given the important worldwide implications, we aim to assess whether organs retrieved from donors who died after sudden cardiac arrest and received cardiopulmonary resuscitation (i.e., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation) have comparable outcomes compared to organs retrieved from donors	

	who did not suffer a cardiac arrest (i.e., living donors or DBD donors). This topic had previously been reviewed for the 2010[2]and 2015[3] ILCOR COSTR. However, a recent ILCOR nonsystematic review[1] showed that a considerable amount of evidence needing assessment has been accumulated since then, and a new systematic review is desirable. The systematic review included evidence from studies conducted in adults or children. No date or language limits were imposed. The primary outcome measure was graft function or recipient survival at the longest available follow-up. The secondary outcome measures were graft function or recipient survival at 1 month and 1 year. Subgroup analyses were conducted based on the type or organ, outcome measure, and donor pathway (DBD or DCD). DCDs were further divided into uDCD (also classified as Maastricht category II donors) and cDCD (also classified as Maastricht category III) donors.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A total of 33 observational studies (25 retrospective and 8 prospective) were identified. Of these, 7 reported on heart donation, 14 on kidney donation, nine on liver donation, three on pancreas donation, one on lung donation, and one on intestine donation. Two studies reported more than one organ outcome. Twenty-six studies included adults, three included children, and four included a mix of adults and children. The risk of bias was assessed using the ROBINS-I tool. The outcomes of graft function or recipient survival at 30 days, 1 year, and the longest available follow-up are reported separately for each transplanted organ (heart, kidney, liver, lung, pancreas, intestine). The outcomes were compared in brain-dead donors (DBD) with prior cardiopulmonary resuscitation (CPR) vs. DBD without prior CPR in 22 studies, in donors from uncontrolled donation after circulatory death (uDCD) vs DBD without prior CPR in eight studies, in donors from uDCD vs donors from controlled donation after circulatory death (cDCD) without prior CPR in two studies, and in donors from cDCD with prior CPR vs DBDs. One study had two comparison groups (DBDs and cDCDs). **Heart**	Most of the evidence was on heart, liver and kidney transplantation. Limited evidence was available for lung, pancreas and intestine. Evidence for kidney and liver transplants showed worse 30-day and 1-year function or survival for grafts transplanted from uDCD donors compared to DBD donors who did not undergo CPR. However, we did not observe significant differences in organ function or survival at the longest available follow-up.

	For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,842 patients; six [4-9] enrolling 40,542 adults and one [10] enrolling 7300 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.27 [95% CI, 0.99 to 1.63]), in adults-only studies (OR 1.24 [95% CI, 0.93 to 1.64], and in children study (OR 1.41 [95% CI,1.19 to 1.68]). For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,854 patients; six [4-9] enrolling 40,554 adults and one [10] enrolling 7,300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.07 [95% CI, 0.97 to 1.18]), in adults-only studies (OR 1.06 [95% CI, 0.96 to 1.18], and in children study (OR 1.14 [95% CI, 0.85 to 1.53]). For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 6 studies (46,665 patients; five [4-8] enrolling 39,365 adults and one [10] enrolling 7300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.11 [95% CI, 0.96 to 1.28]), in adults-only studies (OR 1.11 [95% CI, 0.95 to 1.29], and in children study (OR 1.11 [95% CI, 0.70 to 1.74]). **Kidney** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low-certainty evidence (downgraded for inconsistency and indirectness) from 14 studies (17,839 patients; 12 studies [11-22] enrolling 4,459 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.96 [95% CI, 0.69 to 1.33]), in adults-only studies (OR 1.02 [95% CI, 0.69 to 1.49], and in mixed adults and children studies (OR 0,76 [95% CI, 0.27 to 2.17]).	

	For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 10 studies (15,758 patients; 8 studies [11, 12, 14, 15, 18-21] enrolling 2,378 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.89 [95% CI, 0.55 to 1.46]), in adults-only studies (OR 0.99 [95% CI, 0.55 to 1.77]).and in mixed adults and children studies (OR, 0.63 [95% CI, 0.14 to 2.73]). One [18] of these studies compared DBDs after ECPR with DBDs who did not receive ECPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 9 studies (3,279 patients), 8 studies [12, 13, 15, 16, 19-22] enrolling 2,994 adults and one study [23] enrolling 285 adults and children. These studies showed worse graft or recipient survival in organ recipients from donors who received CPR versus donors who did not (OR, 0.45 [95% CI, 0.25 to 0.81]). However, this was observed only when the comparison was made between uDCDs vs. DBDs, while it was not observed when it was made between uDCDs vs. cDCDs or DBDs after CPR vs. DBDs without CPR. **Liver** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness from 9 studies (3,739 patients; six [11, 25-29] enrolling 3,348 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.88 [95% CI, 0.68 to 1.15]), in adults-only studies (OR 0.81 [95% CI, 0.55 to 1.19], in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and in children studies (OR 0.95 [95% CI, 0.36 to 2.47]). However, in the subgroup analysis, we observed a worse outcome when comparing uDCDs to DBDs (OR 0.51 [95% CI, 0.32 to 0.83]), while this was not observed when comparing DBDs after CPR to DBDs without CPR. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for	

	inconsistency and indirectness) from 3 studies [11, 25, 27] in 469 adult patients, showing no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not (OR, 0.53 [95% CI, 0.27 to 1.02]). However, in the subgroup analysis, we observed a worse outcome when the comparison was made between uDCDs vs. DBDs (De carlis, Justo) (OR 0.42 [95% CI, 0.25 to 0.72]), while this was not observed when the comparison was made between DBDs after CPR vs. DBDs without CPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (3,610 patients; four [26-29] enrolling 3,219 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.84 [95% CI, 0.45 to 1.59]), in adults-only studies (OR 0.49 [95% CI, 0.18 to 1.30]), and in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and better in 1 pediatric study (OR 2.23 [95% CI, 1.07 to 4.67]). **Lung** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33] enrolling 236 adult patients, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 1.50 [95% CI, 0.77 to 2.90]). We found no studies reporting the critical outcome of **graft function or recipient survival at 1 year**. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33], which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 0.67 [95% CI, 0.38 to 1.19]). **Pancreas** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of	

	evidence (downgraded for indirectness) from 3 studies (14,043 patients; two [34, 35] enrolled 948 adults and one [24] enrolled 13,095 adults and children. The studies showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.83 to 1.23]), in adults-only studies (OR 1.03 [95% CI, 0.62 to 1.72], and in mixed adults and children studies (OR 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in children. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for indirectness) from one study [24] enrolling 13,095 adults and children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in adults only or in children. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for indirectness) from one study [35] enrolling 606 adults, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 0.60 [95% CI, 0.24 to 1.50]). We found no studies reporting this outcome in children. **Intestine** For the critical outcome of **graft function or recipient survival at the longest follow-up available**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [36] enrolling 67 adults. The study showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus those who did not in all studies (OR, 1.11 [95% CI, 0.21 to 5.88]). We found no studies reporting this outcome for the critical outcome of **graft function or recipient survival at 1 year** or for the critical outcome of **graft function or recipient survival at 30 days**.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We could not identify any remarkable undesirable effect for organ donation from DBDs. For organ donation from uDCD donors, there is potentially an increased risk of graft failure.	Given the alternatives of not having a solid organ transplant, i.e., lifelong dialysis or death from liver failure, a donation from a uDCD donor is probably still preferable.

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 the evidence was very low because: 1. All studies were observational 2. We found inconsistencies in the timing of the longest follow-up (from 7 days to 15 years) and the variables considered for adjustment. 3. There was indirectness: a. in some studies on organs retrieved from DBD donors, the timing of cardiac arrest and CPR was unclear (i.e., before vs. after death by neurological criteria), so we cannot completely exclude that in some patients, cardiac arrest and resuscitation may have followed, rather than preceded, death by neurological criteria (cardiac arrest in a brain-dead donor, Maastricht category IV). b. in some studies on organs retrieved from uDCD donors, the witnessed status of the original cardiac arrest was not specified. Therefore, we cannot exclude that in some patients, CPR was performed on a patient who would not be otherwise resuscitated (found dead and resuscitated solely for organ donation; Maastricht I donor).	

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	Organ shortage is an important problem worldwide. We assume that the community puts a high value on ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR. The results of our review's subgroup analysis showed that short- or middle-term outcomes of organs donated by uDCD donors could	

● Probably no important uncertainty or variability ○ No important uncertainty or variability	be worse than those of organs donated by DBDs. However, long-term outcomes were not significantly different, although this might be due to the smaller number of long-term survivors. In addition, the advantage of increasing the number of available organs for patients who need transplants may overcome the increased risk of short- and long-term failure of grafts from DCD donors.	

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	Our review showed no significant overall differences in graft survival or function between organs retrieved from donors with and without CPR. Therefore, patients who die after CPR can be considered suitable organ donors.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Organ donation results in a reduction of costs associated with morbidity of patients with end-stage organ failure. In a substudy of the PARAMEDIC2 trial, incorporating the indirect economic effects of transplanted organs substantially altered the cost-effectiveness of epinephrine administered to patients in cardiac arrest in favor of the drug [37]. In that study, the authors did not investigate what donor type (i.e., DBD or cDCD) contributed to the result.	

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	Because our review's overall certainty of evidence of effects is very low, the certainty of evidence regarding the required resources is also very low.	Given organ retrieval processes are already in place for donors who have not had CPR, the additional resources for donation after DBD or cDCD would be limited. Significant additional resource and ethical issues would need to be overcome to develop a uDCD program.

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	Donation after cardiac arrest results in similar rates of graft function or survival compared with donation in patients who did not have cardiac arrest. We conclude that the increased availability of organs from donors after cardiac arrest is cost-effective.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably	In some healthcare systems, as a result of organ shortage, some patients may consider traveling abroad to receive the organs they	

reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	need, which may result in considerable additional costs for those patients. Reducing organ shortage can result in increased equity and access to transplantation-	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention appears acceptable to the stakeholders. However, the practice of uDCD may raise ethical concerns in some countries or communities because of concern that patients with cardiac arrest are resuscitated for the sole purpose of organ donation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires an efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt. Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR. Implementing cDCD after CPR requires that all the necessary procedures to ascertain poor outcome with a high degree of certainty are conducted.	

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

	JUDGEMENT						
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 that all patients who have restoration of circulation after cardiopulmonary resuscitation and who subsequently progress to death be evaluated for organ donation (strong recommendation, low-certainty evidence).

Justification

The major concern with organ donation from patients who have undergone CPR is damage to their organs from ischemia and reperfusion injury. However, the suitability of organs for donation is based on criteria established by the transplantation team. This review suggests that, once these criteria are met, transplant organ outcomes are similar regardless of whether the organs come from donors who have had CPR or not before donation.

We have used the term 'restoration of circulation' to include patients who become potential organ donors after ECPR and are stabilized on VA-ECMO but do not have spontaneous circulation.

Despite the low-certainty evidence, the TF has made a strong recommendation. This is because the TF values ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR, given that a large number of studies show organ function and recipient outcomes are similar in CPR+ and CPR- groups.

Subgroup considerations

Nine of the 33 studies in this review compared the outcomes of kidneys and livers transplanted from patients who died after unsuccessful resuscitation (uncontrolled donors after cardiac death [uDCDs]; Maastricht category II) with those of organs transplanted from donors after death by neurological criteria (donors after brain death [DBDs]; eight studies [13, 14, 19-22, 25, 27] or from donors who die by cardiac criteria after life-sustaining treatment is suspended because of futility (controlled donors after cardiac death [cDCDs]: Maastricht category III; one study [17]). In these studies, the outcomes of organs transplanted from uDCDs at one month and one year were significantly worse than in the comparator group.

In uDCD studies, the donors' witnessed status was not always explicitly reported. Consequently, there was a chance that some donors were unrecoverable at the arrival of the treating team (found dead) and that resuscitation was started only with the aim of potential donation (Maastricht category I). Because of this inconsistency, the Task Force decided not to make any recommendation regarding uncontrolled organ donors.

Implementation considerations

Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt.

Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR.

Implementing cDCD after CPR requires that all the necessary procedures be conducted to ascertain a poor outcome with a high degree of certainty [38].

Monitoring and evaluation

Research priorities

- Future studies on DBDs who underwent CPR should clearly identify those who evolved towards death by neurological criteria after resuscitation, to avoid confusion with DBDs who had cardiac arrest before organ retrieval.
- Comparative studies are needed to investigate cDCD donation after CPR
- Future studies should investigate the utilization rate of donors who underwent CPR vs those who did not.
- There are no established criteria to identify the potential for donation in patients who die after CPR.

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Organ Donation After Cardiac Arrest (ALS 3600)

QUESTION

Organ Donation from Donors with Cardiac Arrest	
POPULATION:	Adults and children who are receiving solid organ transplantation in any setting

INTERVENTION:	Transplantation of an organ retrieved from a donor who, following cardiac arrest, received cardiopulmonary resuscitation (e.g., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation).
COMPARISON:	Transplantation of an oran retrieved from a donor who did not receive cardiopulmonary resuscitation.
MAIN OUTCOMES:	Primary outcome: graft function or recipient survival at the longest follow-up available. Secondary outcomes: graft function or recipient survival at 30 days and 1 year.
SETTING:	In-hospital or out-of-hospital cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is currently a mismatch between organ availability and demand worldwide. Only a minority of this demand can be met by donations from living donors, and only for some organs, such as kidneys. Therefore, the contribution from deceased donors is crucial. Patients who do not recover after cardiac arrest represent a potential source of organ donation. This can occur when patients die after initial successful resuscitation from cardiac arrest because of brain death (donors after death by neurological criteria, DBD) or following withdrawal of life-sustaining treatment (WLST) because of predicted poor outcome (controlled donors after cardiac death, cDCD)[1]. In other patients, cardiac death is pronounced at the end of an unsuccessful resuscitation attempt (uncontrolled donors after cardiac death uDCD). With organs from donors who have had cardiopulmonary resuscitation, there is concern that whole-body ischemia-reperfusion injury can result in significant extracerebral organ damage, making organs unsuitable for transplantation or at risk of worse outcomes and complications for the recipient. Given the important worldwide implications, we aim to assess whether organs retrieved from donors who died after sudden cardiac arrest and received cardiopulmonary resuscitation (i.e., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation) have comparable outcomes compared to organs retrieved from donors who did not suffer a cardiac arrest (i.e., living donors or DBD donors). This topic had previously been reviewed for the 2010[2]and 2015[3] ILCOR COSTR. However, a recent ILCOR nonsystematic review[1] showed that a considerable amount of evidence needing assessment has been accumulated since then, and a new systematic review is desirable.	

	The systematic review included evidence from studies conducted in adults or children. No date or language limits were imposed. The primary outcome measure was graft function or recipient survival at the longest available follow-up. The secondary outcome measures were graft function or recipient survival at 1 month and 1 year. Subgroup analyses were conducted based on the type or organ, outcome measure, and donor pathway (DBD or DCD). DCDs were further divided into uDCD (also classified as Maastricht category II donors) and cDCD (also classified as Maastricht category III) donors.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A total of 33 observational studies (25 retrospective and 8 prospective) were identified. Of these, 7 reported on heart donation, 14 on kidney donation, nine on liver donation, three on pancreas donation, one on lung donation, and one on intestine donation. Two studies reported more than one organ outcome. Twenty-six studies included adults, three included children, and four included a mix of adults and children. The risk of bias was assessed using the ROBINS-I tool. The outcomes of graft function or recipient survival at 30 days, 1 year, and the longest available follow-up are reported separately for each transplanted organ (heart, kidney, liver, lung, pancreas, intestine). The outcomes were compared in brain-dead donors (DBD) with prior cardiopulmonary resuscitation (CPR) vs. DBD without prior CPR in 22 studies, in donors from uncontrolled donation after circulatory death (uDCD) vs DBD without prior CPR in eight studies, in donors from uDCD vs donors from controlled donation after circulatory death (cDCD) without prior CPR in two studies, and in donors from cDCD with prior CPR vs DBDs. One study had two comparison groups (DBDs and cDCDs). **Heart** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,842 patients; six [4-9] enrolling 40,542 adults and one [10] enrolling 7300 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.27 [95% CI, 0.99 to 1.63]), in	Most of the evidence was on heart, liver and kidney transplantation. Limited evidence was available for lung, pancreas and intestine. Evidence for kidney and liver transplants showed worse 30-day and 1-year function or survival for grafts transplanted from uDCD donors compared to DBD donors who did not undergo CPR. However, we did not observe significant differences in organ function or survival at the longest available follow-up.

	adults-only studies (OR 1.24 [95% CI, 0.93 to 1.64], and in children study (OR 1.41 [95% CI,1.19 to 1.68]). For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,854 patients; six [4-9] enrolling 40,554 adults and one [10] enrolling 7,300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.07 [95% CI, 0.97 to 1.18]), in adults-only studies (OR 1.06 [95% CI, 0.96 to 1.18], and in children study (OR 1.14 [95% CI, 0.85 to 1.53]). For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 6 studies (46,665 patients; five [4-8] enrolling 39,365 adults and one [10] enrolling 7300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.11 [95% CI, 0.96 to 1.28]), in adults-only studies (OR 1.11 [95% CI, 0.95 to 1.29], and in children study (OR 1.11 [95% CI, 0.70 to 1.74]). **Kidney** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low-certainty evidence (downgraded for inconsistency and indirectness) from 14 studies (17,839 patients; 12 studies [11-22] enrolling 4,459 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.96 [95% CI, 0.69 to 1.33]), in adults-only studies (OR 1.02 [95% CI, 0.69 to 1.49], and in mixed adults and children studies (OR 0,76 [95% CI, 0.27 to 2.17]). For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 10 studies (15,758 patients; 8 studies [11, 12, 14, 15, 18-21] enrolling 2,378 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.89 [95% CI, 0.55 to 1.46]), in adults-only studies (OR 0.99 [95% CI, 0.55 to 1.77]).and in mixed	

	adults and children studies (OR, 0.63 [95% CI, 0.14 to 2.73]). One [18] of these studies compared DBDs after ECPR with DBDs who did not receive ECPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 9 studies (3,279 patients), 8 studies [12, 13, 15, 16, 19-22] enrolling 2,994 adults and one study [23] enrolling 285 adults and children. These studies showed worse graft or recipient survival in organ recipients from donors who received CPR versus donors who did not (OR, 0.45 [95% CI, 0.25 to 0.81]). However, this was observed only when the comparison was made between uDCDs vs. DBDs, while it was not observed when it was made between uDCDs vs. cDCDs or DBDs after CPR vs. DBDs without CPR. **Liver** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness from 9 studies (3,739 patients; six [11, 25-29] enrolling 3,348 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.88 [95% CI, 0.68 to 1.15]), in adults-only studies (OR 0.81 [95% CI, 0.55 to 1.19], in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and in children studies (OR 0.95 [95% CI, 0.36 to 2.47]). However, in the subgroup analysis, we observed a worse outcome when comparing uDCDs to DBDs (OR 0.51 [95% CI, 0.32 to 0.83]), while this was not observed when comparing DBDs after CPR to DBDs without CPR. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 3 studies [11, 25, 27] in 469 adult patients, showing no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not (OR, 0.53 [95% CI, 0.27 to 1.02]). However, in the subgroup analysis, we observed a worse outcome when the comparison was made between uDCDs vs. DBDs (De carlis, Justo) (OR 0.42 [95% CI,	

	0.25 to 0.72]), while this was not observed when the comparison was made between DBDs after CPR vs. DBDs without CPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (3,610 patients; four [26-29] enrolling 3,219 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.84 [95% CI, 0.45 to 1.59]), in adults-only studies (OR 0.49 [95% CI, 0.18 to 1.30]), and in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and better in 1 pediatric study (OR 2.23 [95% CI, 1.07 to 4.67]). **Lung** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33] enrolling 236 adult patients, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 1.50 [95% CI, 0.77 to 2.90]). We found no studies reporting the critical outcome of **graft function or recipient survival at 1 year**. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33], which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 0.67 [95% CI, 0.38 to 1.19]). **Pancreas** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for indirectness) from 3 studies (14,043 patients; two [34, 35] enrolled 948 adults and one [24] enrolled 13,095 adults and children. The studies showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.83 to 1.23]), in adults-only studies (OR 1.03 [95% CI, 0.62 to 1.72], and in mixed	

	adults and children studies (OR 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in children. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for indirectness) from one study [24] enrolling 13,095 adults and children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in adults only or in children. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for indirectness) from one study [35] enrolling 606 adults, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 0.60 [95% CI, 0.24 to 1.50]). We found no studies reporting this outcome in children. **Intestine** For the critical outcome of **graft function or recipient survival at the longest follow-up available**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [36] enrolling 67 adults. The study showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus those who did not in all studies (OR, 1.11 [95% CI, 0.21 to 5.88]). We found no studies reporting this outcome for the critical outcome of **graft function or recipient survival at 1 year** or for the critical outcome of **graft function or recipient survival at 30 days**.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We could not identify any remarkable undesirable effect for organ donation from DBDs. For organ donation from uDCD donors, there is potentially an increased risk of graft failure.	Given the alternatives of not having a solid organ transplant, i.e., lifelong dialysis or death from liver failure, a donation from a uDCD donor is probably still preferable.

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 the evidence was very low because: 4. All studies were observational 5. We found inconsistencies in the timing of the longest follow-up (from 7 days to 15 years) and the variables considered for adjustment. 6. There was indirectness: a. in some studies on organs retrieved from DBD donors, the timing of cardiac arrest and CPR was unclear (i.e., before vs. after death by neurological criteria), so we cannot completely exclude that in some patients, cardiac arrest and resuscitation may have followed, rather than preceded, death by neurological criteria (cardiac arrest in a brain-dead donor, Maastricht category IV). b. in some studies on organs retrieved from uDCD donors, the witnessed status of the original cardiac arrest was not specified. Therefore, we cannot exclude that in some patients, CPR was performed on a patient who would not be otherwise resuscitated (found dead and resuscitated solely for organ donation; Maastricht I donor).	

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	Organ shortage is an important problem worldwide. We assume that the community puts a high value on ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR. The results of our review's subgroup analysis showed that short- or middle-term outcomes of organs donated by uDCD donors could	

● Probably no important uncertainty or variability ○ No important uncertainty or variability	be worse than those of organs donated by DBDs. However, long-term outcomes were not significantly different, although this might be due to the smaller number of long-term survivors. In addition, the advantage of increasing the number of available organs for patients who need transplants may overcome the increased risk of short- and long-term failure of grafts from DCD donors.	

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	Our review showed no significant overall differences in graft survival or function between organs retrieved from donors with and without CPR. Therefore, patients who die after CPR can be considered suitable organ donors.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Organ donation results in a reduction of costs associated with morbidity of patients with end-stage organ failure. In a substudy of the PARAMEDIC2 trial, incorporating the indirect economic effects of transplanted organs substantially altered the cost-effectiveness of epinephrine administered to patients in cardiac arrest in favor of the drug [37]. In that study, the authors did not investigate what donor type (i.e., DBD or cDCD) contributed to the result.	

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	Because our review's overall certainty of evidence of effects is very low, the certainty of evidence regarding the required resources is also very low.	Given organ retrieval processes are already in place for donors who have not had CPR, the additional resources for donation after DBD or cDCD would be limited. Significant additional resource and ethical issues would need to be overcome to develop a uDCD program.

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	Donation after cardiac arrest results in similar rates of graft function or survival compared with donation in patients who did not have cardiac arrest. We conclude that the increased availability of organs from donors after cardiac arrest is cost-effective.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably	In some healthcare systems, as a result of organ shortage, some patients may consider traveling abroad to receive the organs they	

reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	need, which may result in considerable additional costs for those patients. Reducing organ shortage can result in increased equity and access to transplantation-	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention appears acceptable to the stakeholders. However, the practice of uDCD may raise ethical concerns in some countries or communities because of concern that patients with cardiac arrest are resuscitated for the sole purpose of organ donation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires an efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt. Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR. Implementing cDCD after CPR requires that all the necessary procedures to ascertain poor outcome with a high degree of certainty are conducted.	

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

	JUDGEMENT						
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 that all patients who have restoration of circulation after cardiopulmonary resuscitation and who subsequently progress to death be evaluated for organ donation (strong recommendation, low-certainty evidence).

Justification

The major concern with organ donation from patients who have undergone CPR is damage to their organs from ischemia and reperfusion injury. However, the suitability of organs for donation is based on criteria established by the transplantation team. This review suggests that, once these criteria are met, transplant organ outcomes are similar regardless of whether the organs come from donors who have had CPR or not before donation.

We have used the term 'restoration of circulation' to include patients who become potential organ donors after ECPR and are stabilized on VA-ECMO but do not have spontaneous circulation.

Despite the low-certainty evidence, the TF has made a strong recommendation. This is because the TF values ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR, given that a large number of studies show organ function and recipient outcomes are similar in CPR+ and CPR- groups.

Subgroup considerations

Nine of the 33 studies in this review compared the outcomes of kidneys and livers transplanted from patients who died after unsuccessful resuscitation (uncontrolled donors after cardiac death [uDCDs]; Maastricht category II) with those of organs transplanted from donors after death by neurological criteria (donors after brain death [DBDs]; eight studies [13, 14, 19-22, 25, 27] or from donors who die by cardiac criteria after life-sustaining treatment is suspended because of futility (controlled donors after cardiac death [cDCDs]: Maastricht category III; one study [17]). In these studies, the outcomes of organs transplanted from uDCDs at one month and one year were significantly worse than in the comparator group.

In uDCD studies, the donors' witnessed status was not always explicitly reported. Consequently, there was a chance that some donors were unrecoverable at the arrival of the treating team (found dead) and that resuscitation was started only with the aim of potential donation (Maastricht category I). Because of this inconsistency, the Task Force decided not to make any recommendation regarding uncontrolled organ donors.

Implementation considerations

Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt.

Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR.

Implementing cDCD after CPR requires that all the necessary procedures be conducted to ascertain a poor outcome with a high degree of certainty [38].

Monitoring and evaluation

Research priorities

- Future studies on DBDs who underwent CPR should clearly identify those who evolved towards death by neurological criteria after resuscitation, to avoid confusion with DBDs who had cardiac arrest before organ retrieval.
- Comparative studies are needed to investigate cDCD donation after CPR
- Future studies should investigate the utilization rate of donors who underwent CPR vs those who did not.
- There are no established criteria to identify the potential for donation in patients who die after CPR.

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Organ Donation After Cardiac Arrest (ALS 3600)

QUESTION

Organ Donation from Donors with Cardiac Arrest	
POPULATION:	Adults and children who are receiving solid organ transplantation in any setting

INTERVENTION:	Transplantation of an organ retrieved from a donor who, following cardiac arrest, received cardiopulmonary resuscitation (e.g., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation).
COMPARISON:	Transplantation of an oran retrieved from a donor who did not receive cardiopulmonary resuscitation.
MAIN OUTCOMES:	Primary outcome: graft function or recipient survival at the longest follow-up available. Secondary outcomes: graft function or recipient survival at 30 days and 1 year.
SETTING:	In-hospital or out-of-hospital cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is currently a mismatch between organ availability and demand worldwide. Only a minority of this demand can be met by donations from living donors, and only for some organs, such as kidneys. Therefore, the contribution from deceased donors is crucial. Patients who do not recover after cardiac arrest represent a potential source of organ donation. This can occur when patients die after initial successful resuscitation from cardiac arrest because of brain death (donors after death by neurological criteria, DBD) or following withdrawal of life-sustaining treatment (WLST) because of predicted poor outcome (controlled donors after cardiac death, cDCD)[1]. In other patients, cardiac death is pronounced at the end of an unsuccessful resuscitation attempt (uncontrolled donors after cardiac death uDCD). With organs from donors who have had cardiopulmonary resuscitation, there is concern that whole-body ischemia-reperfusion injury can result in significant extracerebral organ damage, making organs unsuitable for transplantation or at risk of worse outcomes and complications for the recipient. Given the important worldwide implications, we aim to assess whether organs retrieved from donors who died after sudden cardiac arrest and received cardiopulmonary resuscitation (i.e., donation after initial successful cardiopulmonary resuscitation or after unsuccessful cardiopulmonary resuscitation) have comparable outcomes compared to organs retrieved from donors who did not suffer a cardiac arrest (i.e., living donors or DBD donors). This topic had previously been reviewed for the 2010[2]and 2015[3] ILCOR COSTR. However, a recent ILCOR nonsystematic review[1] showed that a considerable amount of evidence needing assessment has been accumulated since then, and a new systematic review is desirable.	

	The systematic review included evidence from studies conducted in adults or children. No date or language limits were imposed. The primary outcome measure was graft function or recipient survival at the longest available follow-up. The secondary outcome measures were graft function or recipient survival at 1 month and 1 year. Subgroup analyses were conducted based on the type or organ, outcome measure, and donor pathway (DBD or DCD). DCDs were further divided into uDCD (also classified as Maastricht category II donors) and cDCD (also classified as Maastricht category III) donors.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A total of 33 observational studies (25 retrospective and 8 prospective) were identified. Of these, 7 reported on heart donation, 14 on kidney donation, nine on liver donation, three on pancreas donation, one on lung donation, and one on intestine donation. Two studies reported more than one organ outcome. Twenty-six studies included adults, three included children, and four included a mix of adults and children. The risk of bias was assessed using the ROBINS-I tool. The outcomes of graft function or recipient survival at 30 days, 1 year, and the longest available follow-up are reported separately for each transplanted organ (heart, kidney, liver, lung, pancreas, intestine). The outcomes were compared in brain-dead donors (DBD) with prior cardiopulmonary resuscitation (CPR) vs. DBD without prior CPR in 22 studies, in donors from uncontrolled donation after circulatory death (uDCD) vs DBD without prior CPR in eight studies, in donors from uDCD vs donors from controlled donation after circulatory death (cDCD) without prior CPR in two studies, and in donors from cDCD with prior CPR vs DBDs. One study had two comparison groups (DBDs and cDCDs). **Heart** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,842 patients; six [4-9] enrolling 40,542 adults and one [10] enrolling 7300 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.27 [95% CI, 0.99 to 1.63]), in	Most of the evidence was on heart, liver and kidney transplantation. Limited evidence was available for lung, pancreas and intestine. Evidence for kidney and liver transplants showed worse 30-day and 1-year function or survival for grafts transplanted from uDCD donors compared to DBD donors who did not undergo CPR. However, we did not observe significant differences in organ function or survival at the longest available follow-up.

	adults-only studies (OR 1.24 [95% CI, 0.93 to 1.64], and in children study (OR 1.41 [95% CI,1.19 to 1.68]). For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (47,854 patients; six [4-9] enrolling 40,554 adults and one [10] enrolling 7,300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 1.07 [95% CI, 0.97 to 1.18]), in adults-only studies (OR 1.06 [95% CI, 0.96 to 1.18], and in children study (OR 1.14 [95% CI, 0.85 to 1.53]). For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 6 studies (46,665 patients; five [4-8] enrolling 39,365 adults and one [10] enrolling 7300 children) which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.11 [95% CI, 0.96 to 1.28]), in adults-only studies (OR 1.11 [95% CI, 0.95 to 1.29], and in children study (OR 1.11 [95% CI, 0.70 to 1.74]). **Kidney** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low-certainty evidence (downgraded for inconsistency and indirectness) from 14 studies (17,839 patients; 12 studies [11-22] enrolling 4,459 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.96 [95% CI, 0.69 to 1.33]), in adults-only studies (OR 1.02 [95% CI, 0.69 to 1.49], and in mixed adults and children studies (OR 0,76 [95% CI, 0.27 to 2.17]). For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 10 studies (15,758 patients; 8 studies [11, 12, 14, 15, 18-21] enrolling 2,378 adults and 2 studies [23, 24] enrolling 13,380 adults and children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR 0.89 [95% CI, 0.55 to 1.46]), in adults-only studies (OR 0.99 [95% CI, 0.55 to 1.77]).and in mixed	

	adults and children studies (OR, 0.63 [95% CI, 0.14 to 2.73]). One [18] of these studies compared DBDs after ECPR with DBDs who did not receive ECPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 9 studies (3,279 patients), 8 studies [12, 13, 15, 16, 19-22] enrolling 2,994 adults and one study [23] enrolling 285 adults and children. These studies showed worse graft or recipient survival in organ recipients from donors who received CPR versus donors who did not (OR, 0.45 [95% CI, 0.25 to 0.81]). However, this was observed only when the comparison was made between uDCDs vs. DBDs, while it was not observed when it was made between uDCDs vs. cDCDs or DBDs after CPR vs. DBDs without CPR. **Liver** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness from 9 studies (3,739 patients; six [11, 25-29] enrolling 3,348 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.88 [95% CI, 0.68 to 1.15]), in adults-only studies (OR 0.81 [95% CI, 0.55 to 1.19], in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and in children studies (OR 0.95 [95% CI, 0.36 to 2.47]). However, in the subgroup analysis, we observed a worse outcome when comparing uDCDs to DBDs (OR 0.51 [95% CI, 0.32 to 0.83]), while this was not observed when comparing DBDs after CPR to DBDs without CPR. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 3 studies [11, 25, 27] in 469 adult patients, showing no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not (OR, 0.53 [95% CI, 0.27 to 1.02]). However, in the subgroup analysis, we observed a worse outcome when the comparison was made between uDCDs vs. DBDs (De carlis, Justo) (OR 0.42 [95% CI,	

	0.25 to 0.72]), while this was not observed when the comparison was made between DBDs after CPR vs. DBDs without CPR. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from 7 studies (3,610 patients; four [26-29] enrolling 3,219 adults, two [30, 31] enrolling 261 adults and children, and one [32] enrolling 130 children), which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus donors who did not receive cardiopulmonary resuscitation in all studies (OR 0.84 [95% CI, 0.45 to 1.59]), in adults-only studies (OR 0.49 [95% CI, 0.18 to 1.30]), and in mixed adults and children studies (OR 1.15 [95% CI, 0.30 to 4.43]), and better in 1 pediatric study (OR 2.23 [95% CI, 1.07 to 4.67]). **Lung** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33] enrolling 236 adult patients, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 1.50 [95% CI, 0.77 to 2.90]). We found no studies reporting the critical outcome of **graft function or recipient survival at 1 year**. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [33], which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR (OR, 0.67 [95% CI, 0.38 to 1.19]). **Pancreas** For the critical outcome of **graft function or recipient survival at the longest available follow-up**, we identified very low certainty of evidence (downgraded for indirectness) from 3 studies (14,043 patients; two [34, 35] enrolled 948 adults and one [24] enrolled 13,095 adults and children. The studies showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.83 to 1.23]), in adults-only studies (OR 1.03 [95% CI, 0.62 to 1.72], and in mixed	

	adults and children studies (OR 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in children. For the critical outcome of **graft function or recipient survival at 1 year**, we identified very low certainty of evidence (downgraded for indirectness) from one study [24] enrolling 13,095 adults and children, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 1.01 [95% CI, 0.81 to 1.25]). We found no studies reporting this outcome in adults only or in children. For the critical outcome of **graft function or recipient survival at 30 days**, we identified very low certainty of evidence (downgraded for indirectness) from one study [35] enrolling 606 adults, which showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received CPR versus donors who did not receive CPR in all studies (OR, 0.60 [95% CI, 0.24 to 1.50]). We found no studies reporting this outcome in children. **Intestine** For the critical outcome of **graft function or recipient survival at the longest follow-up available**, we identified very low certainty of evidence (downgraded for inconsistency and indirectness) from one study [36] enrolling 67 adults. The study showed no statistically significant difference in graft or recipient survival in organ recipients from donors who received cardiopulmonary resuscitation versus those who did not in all studies (OR, 1.11 [95% CI, 0.21 to 5.88]). We found no studies reporting this outcome for the critical outcome of **graft function or recipient survival at 1 year** or for the critical outcome of **graft function or recipient survival at 30 days**.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We could not identify any remarkable undesirable effect for organ donation from DBDs. For organ donation from uDCD donors, there is potentially an increased risk of graft failure.	Given the alternatives of not having a solid organ transplant, i.e., lifelong dialysis or death from liver failure, a donation from a uDCD donor is probably still preferable.

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 the evidence was very low because: 7. All studies were observational 8. We found inconsistencies in the timing of the longest follow-up (from 7 days to 15 years) and the variables considered for adjustment. 9. There was indirectness: a. in some studies on organs retrieved from DBD donors, the timing of cardiac arrest and CPR was unclear (i.e., before vs. after death by neurological criteria), so we cannot completely exclude that in some patients, cardiac arrest and resuscitation may have followed, rather than preceded, death by neurological criteria (cardiac arrest in a brain-dead donor, Maastricht category IV). b. in some studies on organs retrieved from uDCD donors, the witnessed status of the original cardiac arrest was not specified. Therefore, we cannot exclude that in some patients, CPR was performed on a patient who would not be otherwise resuscitated (found dead and resuscitated solely for organ donation; Maastricht I donor).	

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	Organ shortage is an important problem worldwide. We assume that the community puts a high value on ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR. The results of our review's subgroup analysis showed that short- or middle-term outcomes of organs donated by uDCD donors could	

● Probably no important uncertainty or variability ○ No important uncertainty or variability	be worse than those of organs donated by DBDs. However, long-term outcomes were not significantly different, although this might be due to the smaller number of long-term survivors. In addition, the advantage of increasing the number of available organs for patients who need transplants may overcome the increased risk of short- and long-term failure of grafts from DCD donors.	

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	Our review showed no significant overall differences in graft survival or function between organs retrieved from donors with and without CPR. Therefore, patients who die after CPR can be considered suitable organ donors.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Organ donation results in a reduction of costs associated with morbidity of patients with end-stage organ failure. In a substudy of the PARAMEDIC2 trial, incorporating the indirect economic effects of transplanted organs substantially altered the cost-effectiveness of epinephrine administered to patients in cardiac arrest in favor of the drug [37]. In that study, the authors did not investigate what donor type (i.e., DBD or cDCD) contributed to the result.	

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	Because our review's overall certainty of evidence of effects is very low, the certainty of evidence regarding the required resources is also very low.	Given organ retrieval processes are already in place for donors who have not had CPR, the additional resources for donation after DBD or cDCD would be limited. Significant additional resource and ethical issues would need to be overcome to develop a uDCD program.

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	Donation after cardiac arrest results in similar rates of graft function or survival compared with donation in patients who did not have cardiac arrest. We conclude that the increased availability of organs from donors after cardiac arrest is cost-effective.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably	In some healthcare systems, as a result of organ shortage, some patients may consider traveling abroad to receive the organs they	

reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	need, which may result in considerable additional costs for those patients. Reducing organ shortage can result in increased equity and access to transplantation-	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention appears acceptable to the stakeholders. However, the practice of uDCD may raise ethical concerns in some countries or communities because of concern that patients with cardiac arrest are resuscitated for the sole purpose of organ donation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires an efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt. Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR. Implementing cDCD after CPR requires that all the necessary procedures to ascertain poor outcome with a high degree of certainty are conducted.	

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

	JUDGEMENT						
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 that all patients who have restoration of circulation after cardiopulmonary resuscitation and who subsequently progress to death be evaluated for organ donation (strong recommendation, low-certainty evidence).

Justification

The major concern with organ donation from patients who have undergone CPR is damage to their organs from ischemia and reperfusion injury. However, the suitability of organs for donation is based on criteria established by the transplantation team. This review suggests that, once these criteria are met, transplant organ outcomes are similar regardless of whether the organs come from donors who have had CPR or not before donation.

We have used the term 'restoration of circulation' to include patients who become potential organ donors after ECPR and are stabilized on VA-ECMO but do not have spontaneous circulation.

Despite the low-certainty evidence, the TF has made a strong recommendation. This is because the TF values ensuring that those waiting for a donated organ can benefit from organs donated by those who die after CPR, given that a large number of studies show organ function and recipient outcomes are similar in CPR+ and CPR- groups.

Subgroup considerations

Nine of the 33 studies in this review compared the outcomes of kidneys and livers transplanted from patients who died after unsuccessful resuscitation (uncontrolled donors after cardiac death [uDCDs]; Maastricht category II) with those of organs transplanted from donors after death by neurological criteria (donors after brain death [DBDs]; eight studies [13, 14, 19-22, 25, 27] or from donors who die by cardiac criteria after life-sustaining treatment is suspended because of futility (controlled donors after cardiac death [cDCDs]: Maastricht category III; one study [17]). In these studies, the outcomes of organs transplanted from uDCDs at one month and one year were significantly worse than in the comparator group.

In uDCD studies, the donors' witnessed status was not always explicitly reported. Consequently, there was a chance that some donors were unrecoverable at the arrival of the treating team (found dead) and that resuscitation was started only with the aim of potential donation (Maastricht category I). Because of this inconsistency, the Task Force decided not to make any recommendation regarding uncontrolled organ donors.

Implementation considerations

Donation of organs after CPR probably does not require special resources in healthcare systems where organ donation is already implemented. However, the implementation of uDCD requires efficient organization to ensure that the process of consent, diagnosis and organ retrieval is implemented rapidly after an unsuccessful resuscitation attempt.

Donations from DBDs after CPR require that healthcare professionals are aware of the possibility that patients with acute hypoxic-ischemic brain injury (HIBI) evolve to brain death 2-3 days after CPR.

Implementing cDCD after CPR requires that all the necessary procedures be conducted to ascertain a poor outcome with a high degree of certainty [38].

Monitoring and evaluation

Research priorities

- Future studies on DBDs who underwent CPR should clearly identify those who evolved towards death by neurological criteria after resuscitation, to avoid confusion with DBDs who had cardiac arrest before organ retrieval.
- Comparative studies are needed to investigate cDCD donation after CPR
- Future studies should investigate the utilization rate of donors who underwent CPR vs those who did not.
- There are no established criteria to identify the potential for donation in patients who die after CPR.

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