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:	Prehospital and ICU settings

ASSESSMENT

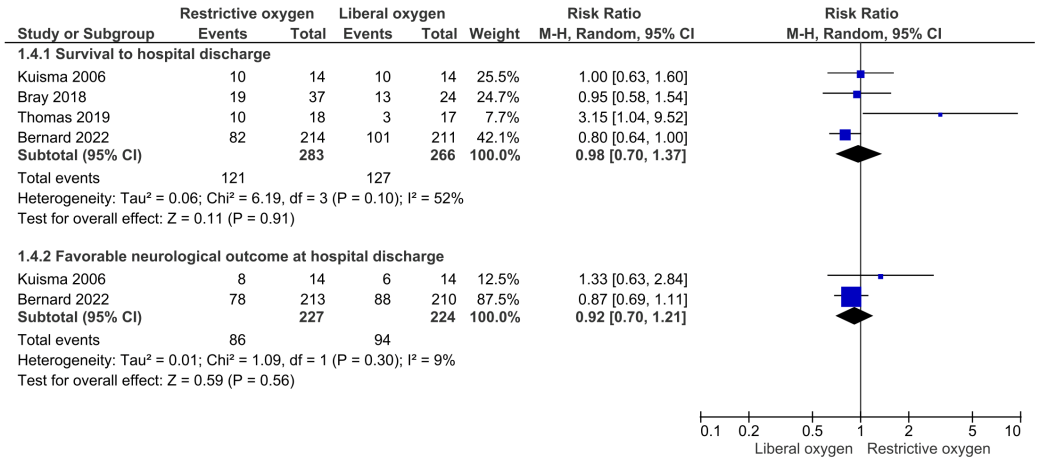
Problem
Is the problem a priority?

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.	

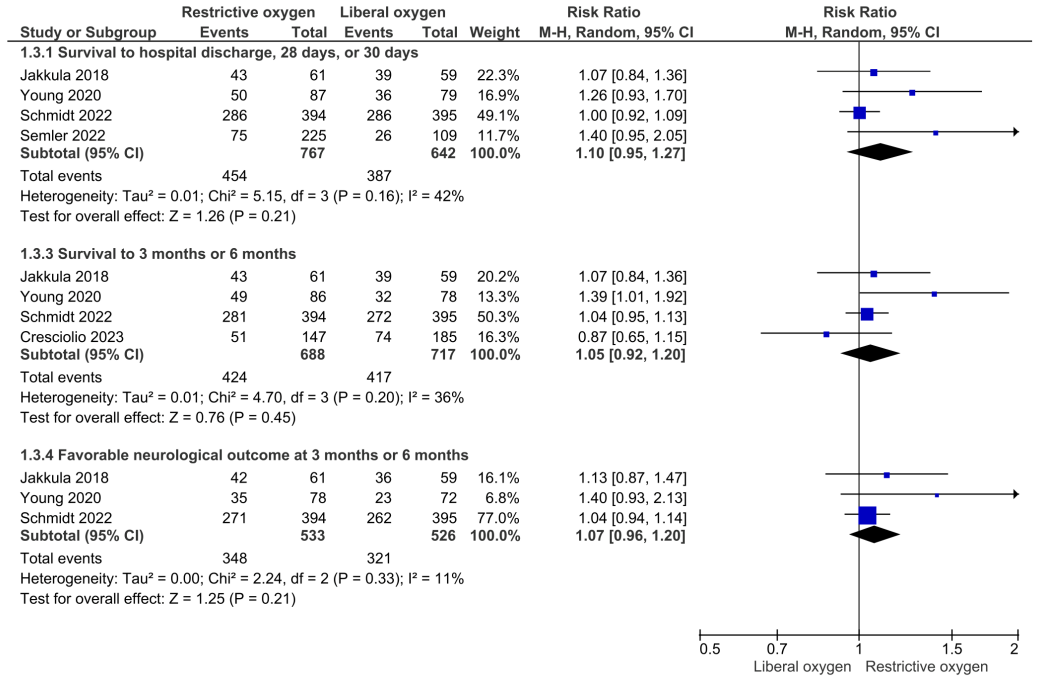
Desirable Effects
How substantial are the desirable anticipated effects?

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 prehospital 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 in-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 respectively, and found no significant evidence favoring either the higher or lower oxygen targets.	

Meta-analyses for oxygen targets in the prehospital 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 prehospital 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 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

[a] Included subgroup analyses of RCTs
[b] Confidence interval included both possible benefit and no harm

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

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 neurologic outcome and survival are generally accepted as critical outcomes. {Haywood 2018 e783}	

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 prehospital setting reported more desaturation of arterial blood in the lower oxygen target groups, and the largest trial in the prehospital 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 ● 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 ○ 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. {Sutherland 2019 1138}	

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 desaturation. 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**

	JUDGEMENT						
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

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 $PaO_2 \geq 300$ 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 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 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 and hyperoxemia becomes harmful
3. The optimal duration for specific oxygen strategies

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:	Prehospital and ICU settings

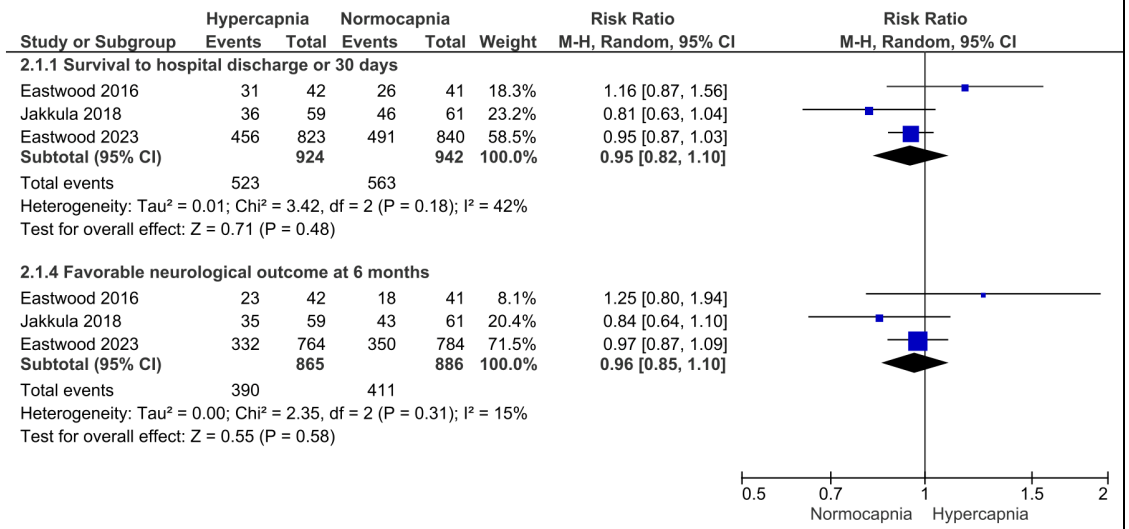
ASSESSMENT

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 when cerebral edema 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) {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.	



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 ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Survival with favorable neurologic outcome and survival are generally accepted as critical outcomes. {Haywood 2018 e783}	

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 blood gas analysis is not available.	

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

QUESTION

Should a higher MAP target (>71 mmHg) vs. a lower MAP target (65-70 mmHg) be used for patients treated in the intensive care unit after cardiac arrest (out-of-hospital or in-hospital)?	
POPULATION:	Patients treated in the intensive care unit after cardiac arrest (out-of-hospital or in-hospital)
INTERVENTION:	A higher MAP target (>71 mmHg)
COMPARISON:	A lower MAP target (65-70 mmHg)
MAIN OUTCOMES:	180-day mortality; Good functional outcome at 180-days; ICU mortality; Severe arrhythmia or cardiac arrest in the ICU;
SETTING:	Any setting
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Most death in those admitted to an intensive care unit after cardiac arrest are due to circulatory failure, multiorgan failure or hypoxic brain injury. Monitoring and treatment of blood pressure is an integral part of management in the ICU for all types of patients. Vasopressors such as noradrenaline are very commonly used and provide the opportunity to increase the mean arterial blood pressure (MAP) easily. A higher MAP could improve cerebral and coronary blood flow and decrease the risk of ischaemia, but whether this influences patient outcome is unclear.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small	It would be very desirable if MAP augmentation could improve outcome in patients after cardiac arrest. The use of vasopressors to increase MAP is a very	

○ Moderate ○ Large ○ Varies ○ Don't know	common and simple intervention that is likely to be available in most settings. Using a higher MAP target would need minimal resources compared to current practice. The current evidence rules out larger relative treatment effects than 25%. If the baseline outcome rate is 50% this would equal a difference of 12.5% (a number needed to treat of 8). It is likely that a smaller treatment effect would also be considered desirable.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The use of vasopressors to target a higher MAP could have undesirable effects such as the onset of cardiac arrhythmias, worsening cardiac function due to an increase in cardiac oxygen consumption and recurrent cardiac arrest. Observational studies in cardiac arrest patients and general ICU patients suggest that an increase in vasopressor load may be associated with poor outcome. However, the results of this systematic review do not suggest that targeting a higher MAP results in more cardiac arrhythmias or recurrent cardiac arrests.	

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 level of evidence for targeting a MAP of higher than 65 mmHg compared to a higher target is judged to be moderate to low. There is some imprecision with regards to the true effect of the intervention. There is also some inconsistency between the effect seen in the included studies. There is also indirectness as mainly patients who have experienced an out-of-hospital cardiac arrest due to a cardiac cause have been included. No study thus far has included in-hospital cardiac arrest patients.	

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 will value the patient centered outcomes of good functional recovery and death very highly. There may be more variability with regards to the value of the secondary outcomes such as cardiac arrhythmias and recurrent 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	The point estimate favors the comparison (MAP > 65 mmHg) rather than a higher MAP (MAP>70 mmHg) but the differences are not significant and very small.	Given the lack of evidence for a higher MAP, the balance of effects probably favors using a similar threshold for MAP as is used for other critical illness states such as septic shock.

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	Thus far the effect of a higher MAP compared to a lower MAP is unclear. By not suggesting a higher MAP target, vasopressor requirements may be lower, which could lead to modest cost savings.	

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 study including a cost analysis was identified. There may also be some variability in the price of vasopressors between different countries. In some settings the use of noradrenaline may mandate the use of a central venous cannula and the insertion of such may increase costs. However, it is likely that targeting a lower MAP will result in the use of fewer central venous cannulas.	

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 assessing cost effectiveness were identified.	We assume that costs would not play any major role as the difference in cost would likely only be due to the different amount of vasopressor used and that is likely to be minimal.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Given the lack of evidence to support a benefit from targeting a higher MAP, we do not think the intervention would have any effect on equity. Vasopressors, while relatively inexpensive compared to other critical care interventions, are still limited in some lower-resource setting, so an intervention requiring more vasopressors without benefitting the patients could place financial stress on some settings and thus decrease equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	If the evidence showed a clear benefit from a higher MAP target, the intervention would probably be acceptable to stakeholders. There is however still uncertainty about the overall effect of a higher MAP on outcome after cardiac arrest. Therefore, it is difficult to assess the acceptability.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Using vasopressors to target a lower or higher MAP goal is likely to be feasible to implement worldwide.	

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

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

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

There is insufficient scientific evidence to recommend a specific blood pressure goal after cardiac arrest. Therefore, we suggest a mean arterial blood pressure of at least 60-65mmHg in patients after out-of-hospital (moderate to low certainty of evidence) and in-hospital cardiac arrest (low to very low certainty of evidence).

Justification

● The prior treatment recommendation read as follows: “We suggest haemodynamic goals (eg, mean arterial pressure, systolic blood pressure) be considered during postresuscitation care and as part of any bundle of postresuscitation interventions (weak recommendation, low-certainty evidence). There is insufficient evidence to recommend specific haemodynamic goals; such goals should be considered on an individual patient basis and are likely to be influenced by post-cardiac arrest status and preexisting comorbidities”. The four RCTs conducted since that recommendation was formulated provide significant new evidence but have not yet identified an optimal blood pressure strategy.

● While no specific mean arterial blood pressure strategy has been found to be beneficial in cardiac arrest trials, the task force thought it was important to provide more specific guidance than had been provided previously. The threshold of 65mmHg was agreed upon as it is the standard in other forms of critical illness and there is no evidence to deviate from that practice in post-arrest patients. Observational data (Bro Jeppesen 2015, Laurikkala 2015, McGuigan 2023) suggest that the lowest MAP not associated

with worse outcome after cardiac arrest is around 60-70 mmHg, and the Surviving Sepsis Guidelines recommend targeting a MAP of higher 65 mmHg in patients with septic shock (Rhodes 2017)

● We observed no statistically significant benefit from targeting a higher MAP for any critical outcome

● We observed no statistically significant harm, in relation to the occurrence of a new cardiac arrest or an arrhythmia resulting in haemodynamic compromise, from targeting a higher MAP

● All RCT studies conducted thus far have focused on patients with a likely cardiac cause of the arrest and a high likelihood of a favorable outcome

● Whether a higher MAP target, such as 80-100mmHg, may be beneficial for some patients has not been determined by trials to-date. The task force acknowledged that this is part of clinical practice at some cardiac arrest centers. The current treatment recommendation purposefully does not proscribe an upper limit for MAP targets as one is not clearly superior to the other.

Subgroup considerations

Sub-group analyses performed based on patient age (higher or lower than 65), presence of chronic hypertension as a comorbidity (based on the use of medication for chronic hypertension), non-shockable compared to shockable initial rhythm and the temperature target (33 or 36 degrees) did not show any significant subgroup effects. There was an interaction between treatment group in the sub-group of patients based on time to return of spontaneous circulation (ROSC). It appeared that in patients with a time to ROSC longer than 25 minutes targeting a higher MAP resulted in worse outcome.

Implementation considerations

It is likely that the implementation of a lower or higher MAP goal in cardiac arrest patient would be feasible in most settings. Different MAP goals are common in ICU patients, and we may assume that having different MAP goals in cardiac arrest patients would be feasible.

Monitoring and evaluation

All performed cardiac arrest studies have included fairly homogenous samples of patients. We do not know the effect or the safety profile of targeting a higher or lower MAP in other types of cardiac arrest patients.

Research priorities

All conducted studies have focused on patients with a probable cardiac cause of the cardiac arrest. There is limited evidence as to the optimal MAP in patients not meeting these criteria.

Data on MAP targets after in-hospital cardiac arrest are lacking.

Data on MAP targets in the pre-hospital setting are lacking.

The current evidence can exclude a relative positive or negative treatment effect of targeting a higher MAP of more than 25% but not lower. This difference may unrealistic and there may be a need for larger trials

Whether the effect of MAP on outcome could be different in certain sub-groups of patients, such as those with chronic hypertension, is currently unknown.

Targeting a higher blood pressure could be beneficial in patients with deranged autoregulation but to date there are limited data on how this could be done in the early hours of care in the ICU which would be needed for it to be used for individualization of the MAP target

There are limited data on whether increasing MAP influences cerebral or coronary blood flow

There are limited data on whether MAP as opposed to some other proxy for organ perfusion (lactate clearance, urinary output, capillary refill) is the optimal bed-side target

The optimal strategy to achieve a target MAP following cardiac arrest is uncertain. This may include use of intravenous fluids (fluid type and volume), specific vasopressors or combinations of vasopressors, and use of mechanical support.

QUESTION

Temperature control in adult cardiac arrest	
POPULATION:	**Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest**
INTERVENTION 1:	**Temperature control [Temperature control studies targeting hypothermia at 32-34 C included in the systematic review]**
COMPARISON 1:	**No Temperature control [Temperature control studies targeting normothermia or fever prevention included in the systematic review]**
INTERVENTION 2:	**Temperature control induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))**
COMPARISON 2:	**Temperature control induction after that specific time point**
INTERVENTION 3:	**Temperature control at a specific temperature (e.g. 33°C)**
COMPARISON 3:	**Temperature control at a different specific temperature (e.g. 36°C)**
INTERVENTION 4:	**Temperature control for a specific duration (e.g. 48 hours)**
COMPARISON 4:	**Temperature control at a different specific duration (e.g. 24 hours)**
INTERVENTION 5:	**Temperature control with a specific method (e.g. external)**
COMPARISON 5:	**Temperature control with a different specific method (e.g. internal)**
INTERVENTION 6:	**Temperature control with a specific rewarming rate**
COMPARISON 6:	**Temperature control with a different specific rewarming rate or no specific rewarming rate**
MAIN OUTCOMES:	**Any clinical outcome, including Survival to hospital discharge ; Favourable neurological outcome at hospital discharge or 30 days; Survival to 90 or 180 days; Favourable neurological outcome at 90 or 180 days**
SETTING:	ANY SETTING
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest mortality remains very high. Neurologic injury is the leading cause of death in those who obtain return of spontaneous circulation but do not survive to hospital discharge. Among those who do survive, neurologic injury is also common. Post-arrest temperature control has long been thought to be one of the only interventions that improves neurologic outcome, but recent trials have not replicated the benefits seen in earlier studies, making this an important question to address. This topic includes consideration of whether or not to control temperature, whether to start temperature control intra-arrest or before hospital arrival, whether there is an optimal temperature to use, how long to control temperature, what method to use for controlling temperature, and how to approach rewarming.	In 2022 ILCOR moved away from the term targeted temperature management and adopted terminology that includes hypothermic temperature control, normothermic temperature control, fever prevention temperature control, and no temperature control. .

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	While the earliest trials suggested a benefit from temperature control with hypothermia, this has not been replicated in more recent and larger trials. Although the exact intervention and comparison groups differ somewhat across trials and the certainty of evidence is low for most aspects of the temperature control topic (moderate certainty for avoiding pre-hospital cooling with cold IV fluids), it appears clear that if there are any desirable effects they are small, and have not been detectable in recent trials.	The TF discussed the fact that trials have largely not been able to get patients to the target hypothermic temperature faster than 4-8 hours after ROSC. Whether faster cooling after arrest would be beneficial is unknown.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● **Moderate** ● **Small** ○ Trivial ○ Varies ○ Don't know	Range of TF opinion <u>small to moderate</u> Task force members differed in their opinions on the TTM2 trial and whether the level of harm caused by 33 C v normothermia/fever prevention is significant or trivial given no difference in overall outcomes. Adverse events that were more common in the 33 C group included arrhythmia resulting in haemodynamic compromise, 24% v 16%. No difference in other complications - pneumonia, sepsis, bleeding, skin problems For pre-hospital cooling, more rearrest was noted with the used of cold IV fluids in the pre-hospital setting, with no counterbalancing benefit seen.	

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 of evidence was low for most treatment recommendations, and moderate for pre-hospital cooling with intravenous fluids. Some statements were created as good practice statements since the task force thought there was not enough evidence available to provide a degree of certainty. Although there are many clinical trials of temperature management, the specific areas of duration of temperature control, rewarming rate and whether temperature control devices should include feedback systems based on continuous temperature monitoring do not have sufficient trial data to support a treatment recommendation with 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	Survival and survival with favorable neurologic outcome are generally accepted as critical.	

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 task force generally supported fever prevention, given the lack of evidence for using more hypothermic temperatures in the available trials. The task force agreed that whether certain subpopulations of cardiac arrest patients (such as those with a non-cardiac cause of cardiac arrest or in-hospital cardiac arrest) may benefit from targeting hypothermia at 32-34 C, a more rapid induction of hypothermia, or a longer duration of temperature prevention and sedation remains unknown. This EtD includes several aspects of temperature control, and the balance of effects varies across these PICOS. The balance favors fever prevention (comparison) over hypothermic temperature control, and favors not using cold IV fluids for pre-hospital cooling. The balance of effects is unclear in other comparisons, which is why in some cases the task force generated good practice statements in place of treatment recommendations.	In 2015 we wrote an additional statement: Whether certain subpopulations of cardiac arrest patients may benefit from lower (32 C–34 C) or higher (36 C) temperatures remains unknown, and further research may help elucidate this.

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	In settings where temperature control with a device is already used, these recommendations will not require additional resources. Some settings likely do not have resources to use temperature control devices. The evolution of temperature control recommendations over the past several years is likely leading to a slight decrease in resources required overall, as not all patients will need a device for fever prevention, although 46% in the normothermia group in TTM2 did require a device.	

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 have not identified recent studies on this issue	Post resuscitation care and temperature control at any temperature target does require significant critical care resources to optimise outcome and costs will vary across settings. Fewer patients require active cooling when normothermia or fever control targeted.

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 do a specific cost effectiveness analysis. We identified one modelling study in the review conducted for 2022 (of which this review is an update). Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes. 2009;2(5):421-428.	No current cost effectiveness data.

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 - probably varies	Post resuscitation care and TTM at any temperature target does require significant resources to optimise outcome

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No formal studies identified that looked at acceptability of hypothermia but both fever prevention and hypothermic temperature control are used widely already.	The points below were noted when this review was updated for 2022, and remain true. Within ALS TF and different settings/regions there is considerable variation as to the acceptance of either intervention at 32-34 v normothermia Animal data of early/immediate post ROSC cooling show a consistent and strong protective effect across animal species and models. Reasons have been put forward as to why the largest and most recent RCTs have not managed to replicate animal data - cooling too late, too slow, wrong dose duration, wrong patient population. Some observational evidence or concerns that using 'normothermia' targets or switch from 32-34 to 36 C has been associated with worse outcomes. Most recent large observational study from UK does not suggest this and raises the issue that ICU risk models and risk adjustment cannot differentiate between

		therapeutic and pathological temperature changes when looking at observational data. Nolan JP, et al. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021 May;162:304-311.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Both intervention (hypothermia) and normothermia/fever prevention are feasible in most settings that care for post cardiac arrest patients and already use TTM.	TF considered that post resuscitation care is resource intensive, and temperature control is feasible in most settings that provide this care. Yes - in high resource settings. Hypothermia more challenging in low resource settings

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	**Moderate**	High			No included studies

	JUDGEMENT						
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 actively preventing fever by targeting a temperature ≤37.5°C for those patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low certainty evidence).

Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32-34°C remains uncertain.

Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).

We recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate certainty evidence).

We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).

When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).

We suggest active prevention of fever for 36–72 hours in post-cardiac arrest patients who remain comatose (good practice statement).

Justification

- This topic was prioritized by the ALS Task Force due to the emergence of additional trial data since the prior review in 2022.

Defining Post-Cardiac Arrest Temperature Management Strategies

- The term TTM on its own is not helpful and it is preferable to use the terms active temperature control, hypothermia, normothermia, or fever prevention. To provide additional clarity for interpreting future clinical trials, systematic reviews and CoSTRs we propose the following terms are used:
    - Hypothermic TTM (H-TTM) = active temperature control with the target temperature below the normal range.
    - Normothermic TTM = active temperature control with the target temperature in the normal range.
    - Fever prevention TTM (FP-TTM) = monitoring temperature and actively preventing and treating temperature above the normal range
    - No TTM = no protocolised active temperature control strategy.

Hypothermia v normothermia or prevention of fever

- The majority of the Task Force favored fever prevention for comatose patients following ROSC as opposed to hypothermia, based on the systematic review and because this intervention requires fewer resources and had fewer side effects than hypothermia treatment.
- The Task Force noted that in the TTM2 trial (Dankiewicz 2021 2283), pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature were used to maintain a temperature of $\leq$ 37.5 C (99.5 F) in the normothermia/fever prevention group. If the temperature was > 37.7 C (99.9 F) a cooling

device was used and set at a target temperature of ≤ 37.5 C (99.5 F). 95% of patients in the hypothermia group and 46% in the fever prevention group received temperature control with a device.

- We chose prevention of fever as opposed to normothermia in the treatment recommendation.
- The Task Force acknowledged that the systematic review found no difference in overall outcomes between patients treated with hypothermia and normothermia or fever prevention.

- Several members of the Task Force were keen to leave open the option to use hypothermia (33°C). The discussions included:
    - No trials have shown that normothermia is better than hypothermia.
    - Among non-shockable cardiac arrest patients, the Hyperion trial (Lascarrou 2019 2327) showed better survival with favorable functional outcome in the hypothermia group (although 90-day survival was not significantly different and the Fragility Index was only 1).
    - Although our systematic review did not find evidence favoring TTM with hypothermia in multiple subgroups, there remained a view that some populations of cardiac arrest patient could potentially benefit from hypothermia treatment at 32-34 C. Specifically, the largest TTM studies (TTM1 and TTM2) have mainly included cardiac arrests with a primary cardiac cause and this may not reflect the total population of post cardiac arrest patients treated (Chen 2018 33).
    - There was a suggestion that we should only advocate fever prevention for those with a primary cardiac arrest in the main treatment recommendation – our systematic review did not find any evidence supporting targeting hypothermia in patients with a cardiac arrest due to other causes.
    - Concerns were raised that the TTM2 trial cooling rates were too slow and that the time to target temperature was outside the therapeutic window. In animal studies rapid induction of hypothermia after ROSC is required for a beneficial effect (Arrich 2021 47). The time to target temperature in TTM-2 is consistent with virtually all other human observational studies and RCTs including those where there was no delay caused by the need for consent/randomization (see ETD). Of the RCTs included, only the Bernard study (Bernard 2002 557) had a rapid time (2 hours after ROSC) to achieve target temperature (33.5 C). It remains possible that there is a therapeutic window within which hypothermia is effective that has not been rigorously tested in randomized clinical trials.
    - There was a unanimous desire to leave open the opportunity for further research on post-cardiac arrest hypothermia, not least because animal models have shown consistent and convincing evidence of benefit.
    - Finally, there are concerns that poor implementation of temperature control may lead to patient harm - for example the publication of the TTM trial in 2013 (Nielsen 2013 2197) may have led to some clinicians abandoning temperature control after cardiac arrest which in turn was associated with worse outcomes (Bray 2017 39, Salter 2018 1722, Nolan 2021 304). Whether this was caused by abandoning the use of temperature control is uncertain.
- In our meta-analysis we decided to use a random effects model a priori (as opposed to fixed effects). The point estimates of the random-effects meta-analysis favors hypothermia. However, the random effects model assigns a relatively higher weight to smaller studies; thus, the smaller and older less methodologically robust studies published in 2002 (Bernard 2002 557, HACA 2002 549) had a greater influence on the point estimate than would be expected based on the trial sizes.
- We chose the term 'comatose' instead of 'unresponsive' to define the population of patients who do not wake up after ROSC. Another option considered was 'unconscious' – in the TTM2 trial this was defined as not being able to obey verbal commands and no verbal response to pain after sustained ROSC. The Task Force acknowledges that patients are unconscious and sedated after ROSC for a number of reasons in addition to a hypoxic ischemic brain injury including the need for airway protection with a tracheal tube, lung injury, and to facilitate interventions.
- We have made no comments on sedation use or its duration but noted that in the TTM2 trial, patients in the normothermia/fever prevention arm were sedated for 40 hours to ensure a similar duration of sedation to the hypothermia arm.
- Although there was no direct evidence in our systematic review, the Task Force made a good practice statement supporting the avoidance of active warming of patients who have passively become mildly hypothermia (e.g. 32-36) immediately after ROSC there was concern that this may be a harmful intervention. The Task Force noted that in the TTM2 trial, patients in the normothermia/fever prevention arm with an initial temperature above 33 C were not actively warmed. The Task Force noted that

in the Hyperion trial (Lascarrou 2019 2327), patients allocated to normothermia whose temperature was below 36.5 C at randomization were warmed at 0.25 - 0.5 C/hour and then maintained at 36.5 - 37.5 C.

- There was discussion about the definitions of normothermia and fever. Among a diverse cohort of 35,488 hospital patients the 99% range for normal temperature was 35.3-37.7°C, and 95% range was 35.7 to 37.3 C (Obermeyer 2017 j5468). Whether these ranges can be generalized to the adult post cardiac arrest patient population is uncertain.

Alternate temperature comparisons

- In addition, in our systematic review and meta-analysis we looked at comparisons between 33 v 36 C (Nielsen 2013 2197), 32 v 34 C (Lopez-de-Sa 2018 1807, Lopez-de-Sa 2012 2826), 33 v 34 C (Lopez-de-Sa 2018 1807) and 33 v 32 C (Lopez-de-Sa 2018 1807). There was no difference between control and intervention groups for all these comparisons and the certainty of evidence was low for all comparisons.
- The comparison between 33 v 36 C (Nielsen 2013 2197) was included in a sensitivity analysis of 33 C v normothermia/fever prevention, as 36 C falls within the normothermia temperature range – this did not change the point estimates in favor of either group.

Research priorities

- There are no RCTs of no TTM versus fever prevention TTM.
- There are few RCTs of TTM after eCPR.
- There are no large RCTs of TTM after in-hospital cardiac arrest.
- Is there a therapeutic window within which hypothermic TTM (H-TTM) is effective in the clinical setting?
- If a therapeutic window exists, are there clinically feasible cooling strategies that can rapidly achieve therapeutic target temperatures within the therapeutic window?
- Is the clinical effectiveness of hypothermia dependent on providing the appropriate dose (target temperature and duration) based on the severity of brain injury?
- Are there unidentified subsets of post-cardiac arrest patient who would benefit from H-TTM as currently practiced?
- Is TTM using a cooling device with feedback more effective than TTM without a feedback controlled cooling device?

QUESTION

Should one pharmacological strategy for seizure treatment vs. another pharmacological strategy or no seizure treatment be used for patients with ROSC after cardiac arrest?	
POPULATION:	patients with ROSC after cardiac arrest
INTERVENTION:	one pharmacological strategy for seizure treatment
COMPARISON:	another pharmacological strategy or no seizure treatment
MAIN OUTCOMES:	Good neurological outcome; Survival ;
SETTING:	In-hospital or out-of-hospital
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

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 has a very high mortality, with hypoxic-ischemic brain injury as a common cause of death. Clinical convulsions, including myoclonus, and epileptiform activity in the EEG are common manifestations of post-cardiac arrest brain injury with substantial overlap and an approximate incidence of 20-30% (Seder 2015 965, Lybeck 2017, 146, Backman 2017 681, Beretta 2018 e2153). The prognosis for patients with clinical and electrographic seizures is usually poor but some patients recover and may ultimately have a good neurologic outcome (Backman 2017 681, Beretta 2018 e2153).	

Desirable Effects

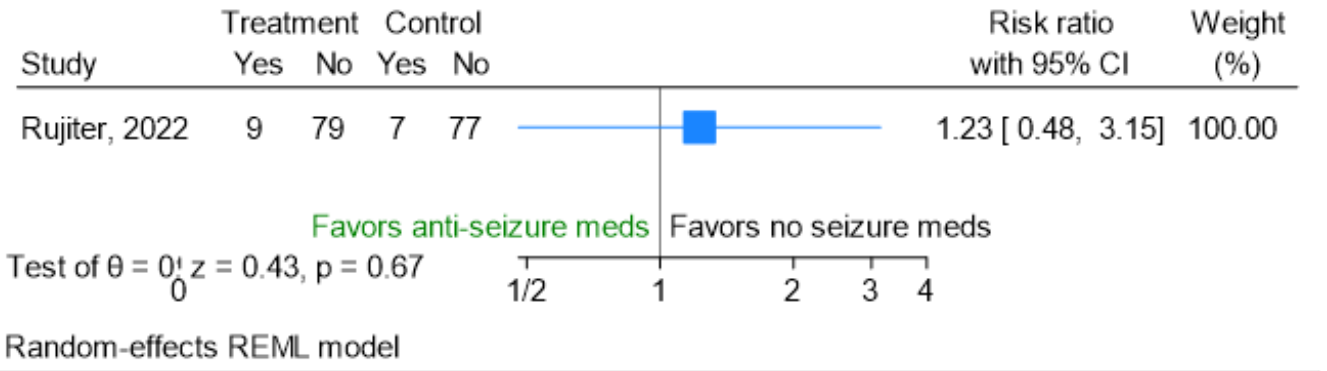
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large	For the critical outcomes of survival with favourable neurological outcome (CPC Score or 1 or 2), or survival at discharge/ 30 days or longer, we identified no RCTs or nonrandomized studies that addressed the effect on outcomes of treatment of clinical seizures post-cardiac arrest, compared with no seizure treatment.	Since the last SR on the topic (2020), no new studies were identified regarding the treatment of

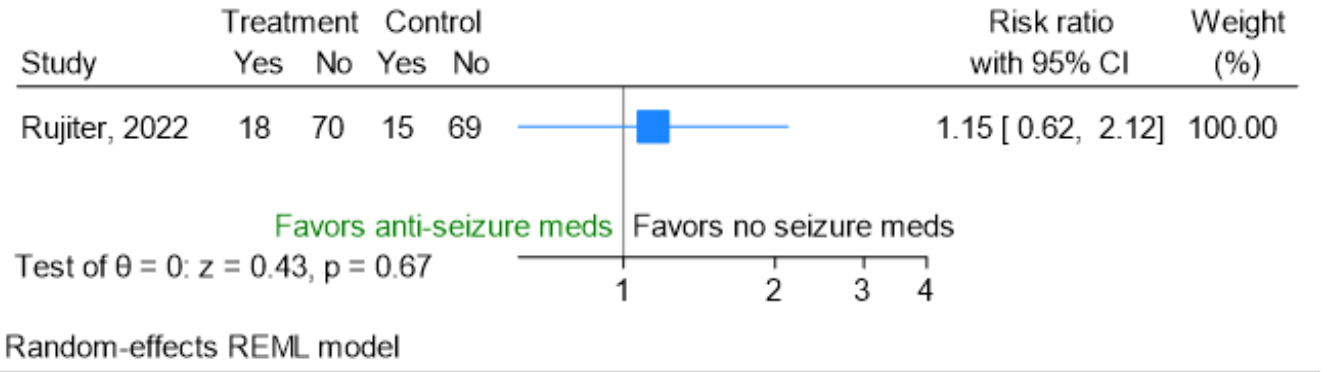
○ Varies ○ Don't know	For the critical outcome of survival with favourable neurological outcome at 3 months (CPC score 1 or 2), we identified one RCT {Ruijter 2022, 724) involving 172 patients, that addressed the effect of treatment of rhythmic and periodic EEG patterns in comatose patients post-cardiac arrest, compared with no treatment. This provides low-certainty evidence (downgraded two levels for very serious imprecision) for no significant difference for the intervention (administration of anti-seizure medications for generalized- periodic discharges) compared with standard care (RR 1.23 [95% CI 0.48 to 3.15; or 19 more survivors per 1000 patients, [95% CI from 43 fewer to 179 more]). Table 1:	seizures, but there was a new RCT addressing the effect of treatment of rhythmic & periodic EEG patterns post cardiac arrest. Therefore, decision was made to develop a treatment recommendation based on EEG patterns, and make a Good Practice Statement around treating clinical +/or EEG seizures.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with another pharmacological strategy or no seizure treatment	Risk difference with one pharmacological strategy for seizure treatment
Good neurological outcome assessed with: CPC Score 1 or 2 follow-up: 3 months	172 (1 RCT)	⨁⨁◯◯ Low[a]	**RR 1.23** (0.48 to 3.15)	Study population	
				83 per 1,000	**19 more per 1,000** (43 fewer to 179 more)
Survival follow-up: 3 months	172 (1 RCT)	⨁⨁◯◯ Low[a]	**RR 1.15** (0.62 to 2.12)	Study population	
				179 per 1,000	**27 more per 1,000** (68 fewer to 200 more)

a. Downgraded as 95% Confidence Interval for Risk Difference is very wide (RR < 0.50 or > 2.00) and includes both appreciable benefit and appreciable harm.



For the critical outcome of survival at 3 months post cardiac arrest, we identified low certainty of evidence from 1 RCT (Ruijter 2022) for little effect of anti-seizure medications compared with no seizure treatment : RR 1.15 (95% CI 0.62-2.12); or 27 more survivors per 1000 patients (95% CI from 68 fewer to 200 more) for improved outcome (see Table 1 above).



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 direct evidence of undesirable effects of antiseizure medications in comatose post-cardiac arrest survivors. Treatment with sedatives and conventional antiseizure medications in high doses has the potential to delay awakening, prolong the need for mechanical ventilation, and increase critical care days. The task force also discussed the potential cost of delayed neurological prognostication and prolonged ICU care associated with active treatment of seizures because of the need to continue sedation.	

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 was no direct evidence for the treatment of seizures post cardiac arrest. The evidence for the treatment of rhythmic and periodic EEG patterns was of low-certainty (downgraded two levels for very serious imprecision).	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or	Survival with favorable neurologic outcome and 3 month survival are generally accepted as a critical outcomes (Hayward COSCA).	

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 TELSTAR study suggests that there is little improvement in outcome with treatment compared with no treatment, of rhythmic and periodic EEG discharges in patients who are post- cardiac arrest.	Detectinng seizures post cardiac arrest can be difficult unless the patient has cEEG monitoring. This is not available at many centres and is complicated, requiring availability of experts to interpret the recordings. Intermittent EEG recording has been shown to detect less episodes of seizure-like activity than cEEG - but if Rx of abnormal EEG activity doesnt alter patient outcome, there is less reason to do it, suggesting time and resources invested in cEEG monitoring maynot be worthwhile.

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 sedating agents and conventional anti-seizure medication in post-cardiac arrest patients. Cost is variable depending on type and number of agents used. Continuous EEG monitoring is used to assess prognosis and to diagnose seizures and monitor response to therapy. It is labor intensive and likely to add significant cost to patient care. The net cost-effectiveness of this approach is controversial and may depend substantially on the organization (Crepeau 2014 785, Sondag 2017 111). There is also the potential cost of delayed neurologic prognostication and prolonged ICU care.	

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 have not identified studies evaluating the cost of sedating agents and conventional antiepileptic agents in this patient population. Two studies have reported the cost of continuous EEG-monitoring for cardiac arrest patients (Crepeau 214 785, Sondag 2017 111)	

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 of post-cardiac arrest seizure treatment.	

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 identified no studies that addressed health equity. Disparities in the availability of ASM (anti-seizure medication) therapy in various settings was not investigated. However, it is likely that the availability of specific agents will vary with setting and region. The availability of conventional and continuous EEG monitoring is likely to be limited in low resourced environments.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We identified no 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 recommendations 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	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**

	JUDGEMENT						
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 use of prophylactic anti-seizure medication in adults post-cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest treatment of clinically apparent and electrographic (EEG) seizures in adults post-cardiac arrest (Good practice statement).

We suggest treatment of rhythmic and periodic EEG patterns that are on the ictal-interictal continuum in comatose adults post- cardiac arrest (weak recommendation, low-certainty evidence).

Justification

Prophylactic Anti-Seizure Medication

The task force decision to suggest against the use of prophylactic anti-seizure medication post- cardiac arrest was primarily based on the absence of direct evidence that prophylactic anti-seizure medication prevents seizures or improves important outcomes in adult comatose cardiac arrest survivors. However, the task force did recognize the very low certainty of the evidence from RCTs. The task force also considered that the administration of prophylactic anti-seizure medication in other forms of acute brain injury is not associated with improved outcomes, and that most prophylactic anti-seizure medications can have significant side effects. Finally, the task force acknowledged that most comatose cardiac arrest survivors routinely receive sedatives such as propofol or benzodiazepines that are known to have antiseizure effects. However, the task force identified no controlled studies that examined whether different sedation strategies or choices of sedation drugs had an impact on the incidence of post-cardiac arrest seizures.

Seizure Treatment

In 2021, The American Clinical Neurophysiology Society (ACNS) published updated criteria for electrographic seizures, electrographic status epilepticus, and the ictal-interictal continuum. The ictal-intercital continuum describes an EEG pattern that “does not qualify as an electrographic seizure or electrographic status epilepticus, but there is a reasonable chance that it may be contributing to impaired alertness, causing other clinical symptoms, and/or contributing to neuronal injury.”

In practice, seizures may be classified as clinical, electrographic, or electroclinical.

These distinctions rely on EEG monitoring and correlating EEG patterns with clinical manifestations and thus require the skilled interpretation of video EEG. The ictal-interictal continuum describes an EEG pattern that “does not qualify as an electrographic seizure or electrographic status epilepticus, but there is a reasonable chance that it may be contributing to impaired alertness, causing other clinical symptoms, and/or contributing to neuronal injury.”Untreated clinical seizure activity is thought to potentially cause additional brain injury, and thus treatment of clinical seizures is recommended despite the lack of high-certainty evidence. Rhythmic and period EEG patterns and other activities that do not meet criteria for electrographic seizures are of unclear significance in patients who are comatose after cardiac arrest. It is not clear if they represent a marker of an injured brain or if they are an abnormal pattern whose treatment may improve outcomes. Given the pathophysiologic concerns that electrographic seizures and discharges on the Ictal-Interictal Continuum may cause secondary brain injury, treatment of such waveforms (including electrographic status epilepticus) is suggested. The TELSTAR trial randomized 172 subjects to protocolized tiered treatment targeting suppression of electroencephalographic rhythmic or periodic patterns in adults with GCS<8 after cardiac arrest. However, the majority (~80%) of the EEG patterns treated were not electrographic seizures nor findings that met criteria for the IIC but were generalized period discharges of 0.5 – 2.5Hz without evolution. Whether such rhythmic or periodic EEG patterns deserve treatment is unknown. Of note however, though the numbers involved in the post-hoc subgroup analysis of TELSTAR were too small to be anything other than exploratory, they were suggestive of a beneficial effect for the treatment of electrographic seizures, but not for treatment of periodic discharges.

Indirect evidence from case series suggests that sedatives such as propofol are effective in suppressing both clinical and electrographic seizures in these patients. A retrospective study provides some evidence that conventional antiseizure medications (specifically valproate and levetiracetam) also have an effect in suppressing epileptiform activity in the EEG.

There is no direct evidence of undesirable effects of antiseizure medications in comatose post-cardiac arrest survivors. Treatment with sedatives and conventional antiseizure medications in high doses has the potential to delay awakening, prolong the need for mechanical ventilation, and increase critical care days. The task force also discussed the potential cost of delayed neurological prognostication and prolonged ICU care associated with active treatment of seizures because of the need to continue sedation.

The relative benefit of continuous EEG compared with intermittent EEG monitoring was not specifically reviewed. Continuous EEG monitoring is labour intensive and likely to add significant cost to patient care. The cost-effectiveness of this approach is controversial and may depend substantially on the setting. The Continuous EEG Randomized Trial in Adults (CERTA) study evaluated continuous vs intermittent EEG in critically ill adults with impaired consciousness, and approximately one third of the subjects had been resuscitated from cardiac arrest. No difference was found in outcome (6 month mortality) though the continuous EEG group had increased seizure detection and more frequent changes to antiseizure medications. Additional studies are needed in post-cardiac arrest patients.

Subgroup considerations

Post-hoc subgroup analysis of TELSTAR patients were too small to be anything other than exploratory. However, they were suggestive of a beneficial effect for the treatment of electrographic seizures, but not for treatment of periodic discharges.

Implementation considerations

The Task Force acknowledges the challenge of seizure diagnosis and the important role of confirmatory electroencephalographic (EEG) in addition to clinical signs of seizure to increase certainty of diagnosis. EEG confirmation remains the gold-standard approach for seizure diagnosis; however, EEG may not be available in many clinical settings as it requires significant resources, including neuro-physiology equipment, training and expertise. Continuous EEG monitoring is labour intensive and likely to add significant cost to patient care. The cost-effectiveness of this approach is controversial and may depend on the setting. The relative benefit of continuous EEG compared with intermittent EEG monitoring was not reviewed.

Monitoring and evaluation

EEG and cEEG monitoring requirement to identify seizures to treat versus clinical seizure only.

Research priorities

There are inadequate data about the timing, duration, dosing, and choice of antiseizure medications for seizure prophylaxis in comatose post-cardiac arrest patients.

The utility and cost-effectiveness of continuous EEG versus intermittent EEG monitoring in the diagnosis and treatment of seizures in comatose post- cardiac arrest patients is unknown.

There is no high-certainty evidence of a positive effect of anti-seizure medications on the outcome of post-cardiac arrest patients with either clinical seizures or rhythmic and periodic EEG patterns.

The threshold for treating rhythmic and period EEG activity is poorly defined.

QUESTION

POPULATION:	Adult (≥ 18 years) patients with cardiac arrest in any setting (out-of-hospital or in-hospital)
INTERVENTION:	Extracorporeal cardiopulmonary resuscitation (ECPR) including extracorporeal membrane oxygenation or cardiopulmonary bypass during cardiac arrest
COMPARISON:	Manual or mechanical cardiopulmonary resuscitation (CPR)
OUTCOMES:	Any clinical outcome
SETTING:	Any setting

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival for refractory cardiac arrest is low.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Based on the evidence (primarily RCTs), there is a potential for large benefit in highly selected patients.	The Task Force discussed the potential that ECPR could provide societal benefit by allowing initial survivors who subsequently meet criteria for brain death or withdrawal of life-sustaining treatment to be considered potential organ donors.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know		The risk of harm with the provision of ECPR likely depends on the scenario in which the intervention is applied. The risk of harm would be minimal or negligible if ECPR is provided in a patient who has already received prolonged advanced life support management and where no other treatment options are available. Conversely, if ECPR is provided early in the course of the cardiac arrest, then the risk of harm would include the possibility that ROSC and survival could have occurred without requiring ECPR since ECPR is known to have complications including but not limited to hemorrhage and death. Moreover, transportation to facilitate ECPR might reduce CPR quality. From a resource-allocation standpoint, the risks in applying ECPR to a non-selected population may be the provision of life support to patients who will inevitably not survive (e.g., elderly patient with comorbidities). The Task Force discussed the potential that ECPR could disadvantage individuals if ECPR increases probability of survival without good neurological recovery.
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	Low for out-of-hospital cardiac arrest. Very low for in-hospital cardiac arrest.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		The importance of neurologically 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 ○ Varies ○ Don't know	See systematic review and CoSTR.	Results of trials differ, and the task force discussed that this is likely due to both differences in trial design (including selection criteria and timing of randomization) and differences in delivery of the intervention.
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		The provision of ECPR followed by the management of patients with ongoing veno-arterial ECMO is resource intensive. This intervention is currently unavailable for most OHCA settings and only available in select emergency departments and in-hospital settings.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies		
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 has been no comprehensive cost-effectiveness analysis based on effectiveness data from RCTs.	
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 relevant studies have been identified; however logic would dictate that resource poor areas may not have local centers capable of providing this intervention.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes		This is not formally known, but the acceptability of this intervention to key stakeholders would likely depend on their available resources.

○ 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		Some are already poised to provide ECPR, but most centers and hospitals would require substantial additional resources and training to be capable of performing it.

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**

	JUDGEMENT						
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 extracorporeal cardiopulmonary resuscitation (ECPR) may be considered as a rescue therapy for selected adults with out-of-hospital cardiac arrest when conventional cardiopulmonary resuscitation is failing to restore spontaneous circulation, in settings where this can be implemented (weak recommendation, low certainty of evidence).

We suggest extracorporeal cardiopulmonary resuscitation (ECPR) may be considered as a rescue therapy for selected adults with in-hospital cardiac arrest when conventional cardiopulmonary resuscitation is failing to restore spontaneous circulation, in settings where this can be implemented (weak recommendation, very low certainty of evidence).

Justification

In making these recommendations, the task force acknowledges that results of the few available trials are inconsistent. However, in balance the evidence suggests that for some patients with refractory arrest, ECPR may be beneficial. More work is needed to determine the optimal patient selection, timing, and method for providing ECPR.

Subgroup considerations

There is no direct evidence for in-hospital cardiac arrest. The trials that have suggested benefit from ECPR have focused on those with an initial shockable rhythm.

Implementation considerations

ECPR is resource-intensive and the ability to implement it will vary significantly across different healthcare systems.

Monitoring and evaluation

Research priorities

- There are few, and no large, randomized trials of ECPR vs standard care
- The optimal patient population who may benefit from ECPR
- The optimal time to initiate ECPR in cases of refractory cardiac arrest
- Whether ECPR for out-of-hospital cardiac arrest should be initiated in the pre-hospital or in-hospital setting
- The optimal techniques for providing safe and timely ECPR
- The optimal post-cardiac arrest care strategy for patients resuscitated using ECPR

- Whether there are population-specific differences in performing ECPR for in-hospital cardiac arrest and out-of-hospital cardiac arrest
- Whether there are differences in quality of life between survivors of ECPR and standard CPR
- The cost-effectiveness of ECPR