A1. DOUBLE SEQUENTIAL DEFIBRILLATION_ALS 2003_ETD

QUESTION

Should Double Sequential Defibrillation vs. Standard defibrillation be used for Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm?

POPULATION:	Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm
INTERVENTION:	Double Sequential Defibrillation
COMPARISON:	Standard defibrillation
MAIN OUTCOMES:	Good Neurological Outcome at Discharge; Survival to Hospital Discharge; Survival to Hospital Admission; Return of Spontaneous Circulation; Termination of VF;
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	Survival from sudden cardiac arrest is low. Patients who present in an initial cardiac rhythm of ventricular fibrillation (VF) have a higher rate of good outcome. Approximately 20% of VF patients, however, will remain in VF (after 5 shocks) despite standard resuscitation interventions. Patients in refractory VF have significantly lower rates of survival than patients who respond to standard resuscitation treatments.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Earlier termination of VF, and restoration of spontaneous circulation is associated with better outcomes from cardiac arrest.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	It is not currently known if there are undesirable effects of double sequential defibrillation. Excess defibrillation energy may cause myocardial stunning and prevent return of organised rhythm post-defibrillation [Crampton 1980 167].	There are possibly undesirable effects associated with double dispatching multiple units in order to perform DSED. including clinical risk to other patients

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty around the evidence for DSED compared to standard defibrillation is very low. The results across studies are inconsistent and there is a large degree of potential confounding within each study. The case reports of DSD effectiveness are likely to represent no more than publication bias.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	There is little uncertainty around the value that people put on the main outcome of neurological survival and/or survival to hospital discharge.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There is no clear evidence for either intervention, but current evidence is more in favour of comparator group (standard defibrillation). The current quality of evidence is very-low and is at high risk of confounding.	

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	No research examined costs associated with the intervention.	There are most likely costs associated with double dispatching multiple units in order to perform DSED. The extent of the costs associated with this intervention will vary from service to service. Documented defibrillator damage may also result in increased service/repair costs.

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 research examined the resource requirements for the intervention	There are costs associated with the intervention as it requires multiple defibrillators to perform. The resource requirements to carry out the intervention will vary across EMS services.

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	Not known. 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	The intervention would be utilized equally across different subgroups of patients.	It is possible that in lower income communities it is not possible to perform DSED due to additional resource requirements.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Stakeholders are likely to accept the benefit vs risk. If effective, the benefit is high, while the relative risks would be low. The certainty around the level of evidence however is very low and there is no evidence that the intervention is beneficial in terms of our outcomes of interest (neurological outcome and survival to hospital discharge).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	There is no research examining the feasibility of this intervention. It is likely that the feasibility will be dependent on the setting that it is applied.	Feasibility will depend on dispatching procedures, availability of units with defibrillators and training of personnel.

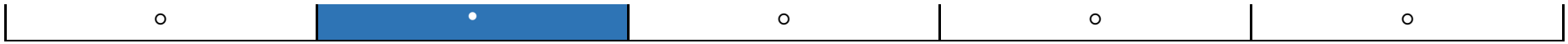
○ Probably yes ○ Yes ● Varies ○ Don't know		Feasibility may also depend on the setting, rural vs. urban vs. remote settings. May also depend on low vs high resource settings.

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

TYPE OF RECOMMENDATION

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



CONCLUSIONS

Recommendation

We suggest against routine use of a double sequential defibrillation strategy in comparison to standard defibrillation strategy for cardiac arrest with a shockable rhythm (weak recommendation, very low certainty of evidence).

Justification

The evidence available (very-low-quality evidence) suggests lower rates of survival and neurological outcome for patients treated with DSED.
There is no evidence suggesting deviation from standard of care.

Subgroup considerations

None

Implementation considerations

Implementation of DSED would require training to frontline staff as well as ensuring that there were defibrillators that were available to provide the intervention.

Monitoring and evaluation

It is important to monitor the intervention, not just to determine effectiveness but to track any adverse events such as harm to the patient, defibrillator damage, the increase in resource utilization etc.

Research priorities

1. High-quality study examining the effectiveness of DSED compared to standard defibrillation in terms of survival and neurological outcome at hospital discharge
2. What is the optimal timing of the intervention?
3. What is the optimal pad placement?

Reference

Crampton R. Accepted, controversial, and speculative aspects of ventricular defibrillation. Progress in Cardiovascular Diseases. Volume 23, Issue 3, 1980, 167-186.

A2. IV VERSUS IO_ALS 2046_ETD

QUESTION

POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest.
INTERVENTION:	Placement of an intraosseous (IO) cannula and drug administration through this IO during cardiac arrest.
COMPARISON:	Placement of an intravenous (IV) cannula and drug administration through this IV during cardiac arrest.
MAIN OUTCOMES:	Return of spontaneous circulation, survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome.

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. Certain drugs (epinephrine, amiodarone, lidocaine) are suggested/recommended during cardiac arrest in order to improve patient outcome. However, it can often be difficult to obtain intravascular access especially in the prehospital setting. Intraosseous (IO) access as an alternative to intravenous (IV) access is increasingly used during cardiac arrest. However, whether drugs are as effective when administered IO vs. IV is unknown.	A number of observational studies addressing this topic has been published within the last years..

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Use of IO access might result in faster drug delivery (Reades 2011 509) which could lead to improved outcomes. Furthermore, when IV access is not possible, IO access can facilitate drug administration. The survival to hospital discharge outcome is considered critical. Given that the effect of drugs during cardiac arrest on this outcome is likely small (Holmberg 2019 111; Ali 2018 63), any difference in critical outcomes between IO and IV drug administration is likely to be small. The findings from observational studies (see table below) do not indicate that there is any desirable effect of IO access.	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IV	Risk difference with IO
Return of spontaneous circulation	70419 (4 observational studies)	⨁◯◯◯ VERY LOW[a,b]	**OR 0.72** (0.68 to 0.76)	Study population	
				280 per 1.000	**61 fewer per 1.000** (71 fewer to 52 fewer)
Survival to hospital discharge	70419 (4 observational studies)	⨁◯◯◯ VERY LOW[a,b]	**OR 0.71** (0.63 to 0.79)	Study population	
				72 per 1.000	**20 fewer per 1.000** (25 fewer to 14 fewer)
Survival to hospital discharge with a favorable neurological outcome	68619 (3 observational studies)	⨁◯◯◯ VERY LOW[a,b]	**OR 0.60** (0.52 to 0.69)	Study population	
				50 per 1.000	**19 fewer per 1.000** (23 fewer to 15 fewer)

a. Assessed using the ROBINS-I tool. Table X. Overall rated as serious risk of bias due to confounding and selection bias.
b. Based on variations in effect size and I^2 statistics

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Use of IO access might result in decreased drug effectiveness due to a changed pharmacokinetic profile or misplaced IO lines. Complications could include bone injury and infection.
The survival to hospital discharge is considered critical. Given that the effect of drugs during cardiac arrest on this outcome is likely small/moderate (Holmberg 2019 111; Ali 2018 63), any difference in critical outcomes between IO and IV drug administration is likely to be small/moderate. It is therefore unlikely that the relatively strong association seen in observational studies (see table below) entirely reflects a causal effect. It is therefore likely that any anticipated undesirable effect is small to moderate.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IV	Risk difference with IO
Return of spontaneous circulation	70419 (4 observational studies)	⨁◯◯◯ VERY LOW[a,b]	**OR 0.72** (0.68 to 0.76)	Study population	
				280 per 1.000	**61 fewer per 1.000** (71 fewer to 52 fewer)
Survival to hospital discharge	70419 (4 observational studies)	⨁◯◯◯ VERY LOW[a,b]	**OR 0.71** (0.63 to 0.79)	Study population	
				72 per 1.000	**20 fewer per 1.000** (25 fewer to 14 fewer)

ADDITIONAL CONSIDERATIONS

Survival to hospital discharge with a favorable neurological outcome	68619 (3 observational studies)	⊕◯◯◯ VERY LOW[a,b]	**OR 0.60** (0.52 to 0.69)	Study population		
				50 per 1.000	**19 fewer per 1.000** (23 fewer to 15 fewer)	

a. Assessed using the ROBINS-I tool. Table X. Overall rated as serious risk of bias due to confounding and selection bias.
b. Based on variations in effect size and I^2 statistics

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty in the evidence from the observational studies is very low (see GRADE table). The subgroup results from ALPS and PARAMEDIC2 (Daya 2020 188; Nolan 2020) are not directly applicable to the GRADE process. However, given the nature of these analyses (secondary subgroup analysis) and the uncertainty in the estimates (i.e. non-significant interaction terms), the certainty in this evidence can also be considered very low.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Patients and providers are likely to value the included outcomes (Haywood 2018 e789).	Longer term outcomes and health-related quality of life was not addressed in the available studies

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 pooled results from the observational studies favor the comparison (IV). However, there is very low certainty in these results as noted above. The subgroup analyses from the two large trials (ALPS, PARAMEDIC2) are not definitive (Daya 2020 188; Nolan 2020). In both trials, the results demonstrated no statistically significant interactions between the route of access and study drugs on clinical outcomes. However, these two trials were underpowered to assess such interactions for any outcomes other than ROSC. As such, these results could be due to chance.	

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 that specifically compared resources including costs between the two interventions.	The costs will vary according to the setting, type, and availability of devices. Both IV and IO access require specific training and experience.

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 that specifically compared 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	We did not identify any studies that addressed cost-effectiveness.	

● 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	We did not identify any studies that addressed health equity.	IO access is not available in all locations especially in low-resource settings. A recommendation for IO access could therefore increase 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.	Both IO and IV access is likely acceptable to key stakeholders as both are currently being used in clinical practice.

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 a pre-specified outcome in this systematic review. In the only randomized trial on the topic, tibial IO access as compared to humeral IO or peripheral IV had a higher successful first attempt success (Reades 2011 509). Observational studies have had mixed results, but IO access appears to be feasible although there is some concern related to potential unrecognized misplacement. IO access was used in 20-30% of patients in two recent large trials (ALPS, PARAMEDIC2).	

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

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

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest IV access as compared to IO access as the first attempt for drug administration during adult cardiac arrest (weak recommendation, very low-certainty evidence).
If attempts at IV access are unsuccessful or IV access is not feasible, we suggest IO access as a route for drug administration during adult cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

Although the overall certainty in the evidence is very low, the current evidence suggests that outcomes might be better when drugs are administered intravenously as compared to intraosseously. The task force discussed the possibility of unaccounted for confounders in comparing patients for whom an IV could be obtained to those who required IO placement for access.
Current guidelines suggest that IO access should only be used if IV access is "difficult or impossible" (Soar 2015 110) or "not readily available" (Link 2015 S459). There is no new evidence to support a change to these guidelines.

Subgroup considerations

The included studies did not allow for meaningful analyses of specific subgroups. The IO site was often not documented or primarily tibial. As such, no statements can be made about difference between tibial and humeral (or other) IO access.

All studies were conducted in out-of-hospital cardiac arrest. Although most in-hospital cardiac arrest patients likely have pre-existing IV access, this is not universally the case. Although there might be differences in provider skills and patient characteristics between out-of-hospital and in-hospital cardiac arrest, we consider it unlikely that these would lead to substantial effect modification. As such, the above recommendations apply to both out-of-hospital and in-hospital cardiac arrest.

Implementation considerations

Since both IO and IV access are currently used in clinical practice, we see no substantial concerns related to implementation.

Monitoring and evaluation

Since both IO and IV access are currently used in clinical practice, we see no substantial concerns related to monitoring and evaluation.

Research priorities

The overall certainty in the evidence is very low. As such, there is clinical equipoise for additional trials related to IV vs. IO drug administration during cardiac arrest. These could include trials that directly compare IV to different sites of IO access (e.g. tibial, humeral).

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A3. Point of care echo_ALS 658_ETD

QUESTION

POPULATION:	Adults in any setting (in-hospital or out-of-hospital) in non-traumatic cardiac arrest
INTERVENTION:	A particular finding on point-of-care echocardiography during CPR
COMPARISON:	The absence of that finding or a different finding on point-of-care echocardiography during CPR
MAIN OUTCOMES:	ROSC, survival to hospital admission, survival to hospital discharge, survival to 180 days, good neurologic outcome at hospital discharge, good neurologic outcome at 180 days
SETTING:	1) In hospital cardiac arrest 2) Out of hospital cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Historically, physiologic monitoring and feedback to the clinician during cardiac arrest resuscitation remains relatively crude, primarily comprising ECG monitoring and manual pulse checks. Various modalities have since been tested to estimate hemodynamic, cerebral hemodynamic, gas exchange, and metabolic conditions during resuscitation, all in an attempt to provide insight into the likelihood of return of spontaneous circulation (ROSC) and subsequent neurologic recovery. Point-of-care echocardiography has become prevalent as a decision tool for termination of resuscitation, in that the absence of cardiac motion is associated with the absence of ROSC. A useful test to prognosticate clinical outcomes during cardiac arrest resuscitation is a very desirable clinical tool. Point-of-care echocardiography has become common in clinical practice without recognizing the potential pitfalls or potential for misinterpretation.	This topic was prioritized by the ALS Task Force based on the high prevalence of point-of-care echocardiography during cardiac arrest without recognizing the potential pitfalls for misinterpretation as an adjunct diagnostic and/or prognostic tool. Given the high penetration of point-of-care echocardiography during cardiac arrest into

		current clinical practice, a comprehensive and rigorous summary of its intra-arrest prognostic capabilities provides valuable information to both the resuscitation science community and bedside clinicians.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ● **Varies**
- ○ Don't know

RESEARCH EVIDENCE

The primary desirable effect is to prognosticate clinical outcomes with both classification accuracy and certainty during cardiac arrest resuscitation. This could either result in continuing resuscitation efforts in patients that could still survive or terminating resuscitation in patients who would ultimately prove refractory to resuscitation efforts.

	Outcome (+) (e.g. ROSC)	Outcome (-) (e.g. No ROSC)
Outcome (+) (e.g. organized motion present)	True Positive	False Positive
Outcome (-) (e.g. organized motion absent)	False Negative	True Negative

We found wide variability in both the point estimates and certainty around point estimates to prognosticate clinical outcomes.
Some sonographic findings had higher ranges of specificity (Sp) for clinical outcomes, but the certainty of this evidence is very low.
No sonographic finding had sufficient and/or consistent sensitivity (Sn) for any clinical outcome to be used a sole criterion to terminate resuscitative efforts, but the certainty of this evidence is very low.

US Findings	Outcome					
	ROSC	Survival Hospital Admission	Survival Hospital DC	Survival 180 days	Good Neuro Outcome Hospital DC	Good Neuro Outcome 180 days
Organized motion (unspecified timing)	Sn range 0.34 to 0.79	Sn range 0.39 to 1.00	Sn range 0.67 to 1.00	Sn 1.00 (95% CI 0.40-1.00)		
	Sp range 0.68 to 0.96	Sp range 0.91 to 0.91	Sp range 0.51 to 0.89	Sp 0.49 (95% CI 0.34-0.64)		

ADDITIONAL CONSIDERATIONS

When considering prognostic tests that influence the decision to continue or terminate resuscitation, it is helpful to consider the body of work on the Universal Termination of Resuscitation (TOR) guidelines. Universal TOR rules have approximately a 0.5% false positive rate (erroneously recommending termination in patients who would have otherwise survived). (Morrison 2006 478)
It is generally considered more acceptable to continue resuscitation efforts that prove futile than to erroneously terminate resuscitation in a patient who would have otherwise survived.

Unspecified motion (initial echo)	Sn range 0.25 to 0.64	Sn range 0.11 to 0.92	Sn range 0.06 to 0.91		Sn 1.00 (95% CI 0.03-1.00)	
	Sp range 0.78 to 1.00	Sp range 0.55 to 0.85	Sp range 0.49 to 0.94		Sp 0.78 (95% CI 0.62-0.89)	
Unspecified motion (every echo)		Sn range 0.46 to 0.80				
		Sp range 0.92 to 1.00				
Unspecified motion (unspecified timing)	Sn range 0.62 to 1.00	Sn range 0.72 to 0.86	Sn 0.48 (95% CI 0.28-0.69)		Sn 1.0 (95% CI 0.03-1.00)	Sn 1.0 (95% CI 0.40-1.00)
	Sp range 0.33 to 0.98	Sp range 0.60 to 0.84	Sp 0.77 (95% CI 0.69-0.83)		Sp 0.86 (95% CI 0.75-0.93)	Sp 0.49 (95% CI 0.34-0.64)
Return of organized motion (subsequent echo)	Sn 0.67 (95% CI 0.22-0.96)		Sn 0.50 (95% CI 0.01-0.99)			
	Sp 1.00 (95% CI 0.77-1.00)		Sp 0.79 (95% CI 0.54-0.94)			
Visibly clotted intra-cardiac blood (20-30 min CPR)	Sn 0.00 (95% CI 0.00-0.46)		Sn 0.00 (95% CI 0.00-0.84)			
	Sp 0.21 (95% CI 0.05-0.51)		Sp 0.45 (95% CI 0.23-0.68)			
Sonographic evidence treatable pathology	Sn range 0.00 to 1.00	Sn range 0.03 to 0.04	Sn range 0.00 to 0.15			
	Sp range 0.84 to 0.94	Sp range 0.95 to 0.99	Sp range 0.89 to 0.98			

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ● **Varies** ○ Don't know	The primary undesirable effect is falsely interpreting sonographic findings or overestimating the prognostic strength of sonographic findings during the course of resuscitation. This could either result in continuing futile resuscitation efforts or prematurely terminating resuscitation in patients that could have otherwise survived. The additional time spent continuing otherwise futile resuscitation efforts is likely a small incremental burden of resource utilization. Whereas is it very undesirable to prematurely terminate resuscitation in patients that could have otherwise survived. We found wide variability in both the point estimates and certainty around point estimates to prognosticate clinical outcomes. See the associated Consensus on Science and Treatment Recommendation (CoSTR) document that delineates the assorted sensitivities, specificities, and odds ratios for each sonographic finding and clinical outcome. The prognostic implications of sonographic findings during cardiac arrest are at high risk of over-interpretation or providing false reassurance. A secondary undesirable effect is additional interruptions in otherwise continuous chest compressions (Huis In't Veld 2017 95, Clattenburg 2018 65).	When considering prognostic tests that influence the decision to continue or terminate resuscitation, it is helpful to consider the body of work on the Universal Termination of Resuscitation (TOR) guidelines. Universal TOR rules have approximately a 0.5% false positive rate (erroneously recommending termination in patients who would have otherwise survived). (Verbeek 2002 671) It is generally considered more acceptable to continue resuscitation efforts that prove futile than to erroneously terminate resuscitation in a patient who would have otherwise survived.

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 of the prognostic ability of point-of-care echocardiography during cardiac arrest was uniformly very low due to risk of bias, inconsistency, and imprecision.	

US Findings	Outcome					
	ROSC	Survival Hospital Admission	Survival Hospital DC	Survival 180 days	Good Neuro Outcome Hospital DC	Good Neuro Outcome 180 days
Organized motion (unspecified timing)	VERY LOW	VERY LOW	VERY LOW	VERY LOW		
Unspecified motion (initial echo)	VERY LOW	VERY LOW	VERY LOW		VERY LOW	

Unspecified motion (every echo)		VERY LOW					
Unspecified motion (unspecified timing)	VERY LOW	VERY LOW	VERY LOW		VERY LOW	VERY LOW	
Return of organized motion (subsequent echo)	VERY LOW		VERY LOW				
Visibly clotted intra-cardiac blood (20-30 min CPR)	VERY LOW		VERY LOW				
Sonographic evidence treatable pathology	VERY LOW	VERY LOW	VERY LOW				

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	None of the identified studies specifically address this question.	The COSCA (Core Outcome Set for Cardiac Arrest) project demonstrates that patients value longer term outcomes (Haywood 2018 147). The included studies did contain the clinical outcomes survival to 180 days and good neurologic outcome at 180 days. Health related quality of life outcomes were not addressed in the included studies.

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**	No sonographic finding had sufficiently or consistently high sensitivity to support its use as a sole criterion to terminate resuscitation. Some sonographic findings tended to have higher ranges of specificity than others for clinical outcomes. See Table above under “Desirable effects”. In this manner, point-of-care echocardiography might be useful to identify sonographic findings that support continuation of resuscitation. However, the presence or absence of any particular finding had insufficient sensitivity to use a sole criterion for termination of resuscitation. Thus, paradoxically, the presence of certain sonographic findings might encourage the continuation of resuscitative efforts, but absence of the same is not sufficient justification (in isolation) to cease resuscitative efforts. Furthermore, the lack of standardized uniform definitions of cardiac motion in the included studies, the wide variability in both point estimates and confidence intervals around point estimates, and the very low certainty of evidence render these data extremely difficult to interpret.	

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**	None of the identified studies specifically address this question.	Point-of-care echocardiography is available in most Emergency Departments. We expect additional fixed and/or recurring equipment costs to be low. Introducing point-of-care echocardiography to new inpatient or prehospital settings carries new fixed and recurring equipment costs. We expect the incremental cost of continuing resuscitation efforts in the same setting in which they have already been started is low. The cost to continue resuscitation efforts in a new setting (e.g. transitioning from prehospital to Emergency Department setting) is higher.

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**	None of the identified studies specifically address this question.	Unknown

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**	None of the identified studies specifically address this question.	Considerations of cost are noted above under "Resources required". The effectiveness of prognostication with point-of-care echocardiography during cardiac arrest is currently uncertain.

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**	None of the identified studies specifically address this question.	Due to fixed and recurring equipment costs, there may be global or regional discrepancies in the availability of point-of-care echocardiography during cardiac arrest.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● **Don't know**	None of the identified studies specifically address this question.	Point-of-care echocardiography is already commonly used in the Emergency Department to guide treatment decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance. Introducing point-of-care echocardiography to new inpatient or prehospital settings may generate new challenges to acceptability in those clinical settings.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● **Don't know**	None of the identified studies specifically address this question. A central component to operational feasibility of prognostication with point-of-care echocardiography is sufficient inter-rater reliability. Only two included studies (Flato 2015 1; Gaspari 2016 33) reported estimates of inter-rater reliability (Kappa 0.63 and 0.93, respectively). Other estimates report moderate inter-rater reliability (Krippendorff's α 0.47) (Hu 2018 193)	Point-of-care echocardiography is already commonly used in the Emergency Department to guide treatment decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the

		existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance. Introducing point-of-care echocardiography to new inpatient or prehospital settings may generate new challenges to feasibility in those clinical settings.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	**Small**	Moderate	Large		**Varies**	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		**Varies**	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	**Don't know**

	JUDGEMENT						
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 using point-of-care echocardiography for prognostication during in-hospital or out-of-hospital cardiac arrest (weak recommendation, very low certainty of evidence).

Justification

This topic was prioritized by the ALS Task Force based on the high prevalence of point-of-care echocardiography during cardiac arrest without recognizing the potential pitfalls for misinterpretation as an adjunct prognostic tool. Given the high penetration of point-of-care echocardiography during cardiac arrest into current clinical practice, a comprehensive and rigorous summary of its intra-arrest prognostic capabilities provides valuable information to both the resuscitation science community and bedside clinicians.
In making these recommendations, the ALS Task Force considered the following:

- There were inconsistent definitions and terminology around sonographic evidence of cardiac motion. This included wide variation in the classification of anatomy, type of motion, and timing of point-of-care echocardiogram. We strongly encourage the establishment of uniform definitions and terminology to describe sonographic findings of cardiac activity during cardiac arrest.

- Most of the identified studies suffer from high risk of bias related to prognostic factor measurement, outcome measurement, lack of adjustment for other prognostic factors, and confounding from self-fulfilling prophecy and unspecified timing of point-of-care echocardiography. Due to the risk of bias and heterogeneity between studies, no meta-analyses were performed. The evidence supporting use of point-of-care echocardiography as a prognostic tool during cardiac arrest is uniformly of very low certainty. Clinicians should interpret sonographic findings during cardiac arrest in light of these limitations. We strongly encourage subsequent investigations of point-of-care echocardiography during cardiac arrest to employ methodology that mitigates these risks of bias.

- Only included 2 studies (Flato 2015 1; Gaspari 2016 33) reported estimates of inter-rater reliability (Kappa 0.63 and 0.93). One additional study estimated moderate inter-rater reliability (Krippendorff's α 0.47) (Hu 2018 193). We strongly encourage subsequent investigations of point-of-care echocardiography during cardiac arrest to estimate inter-rater reliability.

- No sonographic finding had sufficient and/or consistent sensitivity for any clinical outcome to be used a sole criterion to terminate resuscitative efforts, but the certainty of this evidence is very low.

- Some sonographic findings had higher ranges of specificity for clinical outcomes, but the certainty of this evidence is very low.

- The impact of extracorporeal CPR (ECPR) on the prognostic accuracy of point-of-care echocardiography is uncertain.

- Point-of-care echocardiography may still have utility to diagnose treatable etiologies of cardiac arrest or to intermittently assess hemodynamic responses to resuscitative treatments. These applications are not within the scope of this particular PICOST question. We do caution against over-interpreting the finding of right ventricular dilation in isolation as a diagnostic indicator of massive pulmonary embolism. Right ventricular dilation begins a few minutes after onset of cardiac arrest as blood shifts from the systemic circulation to the right heart along its pressure gradient. (Querellou 2009 769, Blanco 2016 15) Right ventricular dilation was uniformly observed in a porcine model of cardiac arrest across etiologies of hypovolemia, hyperkalemia, and primary arrhythmia. (Aagaard 2017 e963)

- Clinicians should be cautious about introducing additional interruptions in chest compressions with a transthoracic approach to point-of-care echocardiography during cardiac arrest. (Huis In't Veld 2017 95, Clattenburg 2018 65).

- Point-of-care echocardiography is subject to availability of equipment and skilled operators.

Subgroup considerations

We identified the following *a priori* subgroups: witnessed vs. unwitnessed collapse, shockable vs. non-shockable initial cardiac rhythm, and in-hospital vs. out-of-hospital cardiac arrest. However, risk of bias and other confounding precluded the ability to pool data or conduct meaningful analyses of these subgroups.

Implementation considerations

Until such time as uniform definitions and terminology to describe sonographic findings of cardiac activity during cardiac arrest are established, subsequent investigations employ methodology that mitigates the inherent risks of bias and confounding, and subsequent investigations characterize inter-rater reliability, we suggest against using point-of-care echocardiography for prognostication during in-hospital or out-of-hospital cardiac arrest.
Otherwise, point-of-care echocardiography is already commonly used in the Emergency Department to guide treatment decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance.
Introducing point-of-care echocardiography to new inpatient or prehospital settings may generate new implementation challenges.

Monitoring and evaluation

Until such time as uniform definitions and terminology to describe sonographic findings of cardiac activity during cardiac arrest are established, subsequent investigations employ methodology that mitigates the inherent risks of bias and confounding, and subsequent investigations characterize inter-rater reliability, we suggest against using point-of-care echocardiography for prognostication during in-hospital or out-of-hospital cardiac arrest.
Otherwise, we encourage the use of robust quality assurance programs with expert oversight to ensure both valid and reliable interpretation of sonographic findings.

Research priorities

There is no standardized or uniform definition of cardiac motion visualized on point-of-care echocardiography during cardiac arrest.
There are very few prognostic factor studies of point-of-care echocardiography during cardiac arrest performed with methodology that minimizes risk of bias.
The inter-rater reliability of point-of-care echocardiography during cardiac arrest is uncertain.
There were no studies identified that provided data on resource requirement, cost-effectiveness, equity, acceptability, or feasibility.

A4. Pulmary Embolism_ALS 435_ETD

QUESTION

POPULATION:	Among adults who are in cardiac arrest due to PE or suspected PE in any setting (P),
INTERVENTION:	does any specific alteration in treatment algorithm (eg, fibrinolytics, or any other) (I),
COMPARISON:	compared with standard care (according to 2015 treatment algorithm) (C),
MAIN OUTCOMES:	Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, ROSC (O)
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	Pulmonary Embolism is a (possibly) reversible cause of cardiac arrest and represents 2-7% of all causes of OHCA {Javaudin 20191167} {Böttiger 2008 2651}. Overall mortality is high, and chances for ROSC and survival can be significantly higher when the embolus is removed from the pulmonary artery. Thus, treatment options for cardiac arrest secondary to pulmonary embolism include administration of fibrinolytics, surgical embolectomy, and percutaneous mechanical thrombectomy.	eCPR is a relatively new therapy concept for CA caused by PE, and this was not included in the systematic review for 2015.. At the moment, this is only available for certain patients in certain designated centres.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Fibrinolysis, surgical embolectomy, and percutaneous mechanical thrombectomy can lead to higher rates of ROSC and finally survival (treatment option for a reversible cause of cardiac arrest, ERC 2015). New evidence since 2015:	French study is registry data of patients with OHCA who were transported to hospital and had diagnosis of PE

	In a large observational trial, survival at 24 hours was comparable (66% in the thrombolysis group and 63% in the control group, p = .76). {Javaudin 2019 1167} Survival at 30 days was significantly better in fibrinolysis group 9/58 (16%) vs. 12/188 (6%) ; (p=0.005; adjusted log-rank test). {Javaudin 2019 1167} Survival with good neurological outcome (CPC 1-2) on day 30 was not significantly better in the thrombolysis group: six (10%) vs nine (5%) in the control group (adjusted relative risk, 1.97; 95% CI, 0.70-5.56). {Javaudin 2019 1167} A small observational study showed that ROSC was comparable in both groups (tPA 9/19 = 47.4% vs control 11/23 =47.8%, p=0.98) {Yousuf 2016 190} and also. survival to discharge was comparable (2/19 =10.5% vs 2/23 =8.7%; p=1.00) {Yousuf 2016 190} NO new results were identified for surgical embolectomy, and for percutaneous mechanical thrombectomy.	Absolute numbers for 24h survival were not provided

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	In the most recent studies, death from hemorrhage did not occur more often in thrombolysis group than in the control group (6% vs 5%; P = .73) {Javaudin 2019 1167}, and major bleeding complications were not more frequent (5.3% tPA vs. 4.3% control; p=1.00) {Yousuf 2016 190}. The results from TROICA study – which is the largest study with thrombolysis during cardiac arrest – suggest that there is a certain risk for bleeding in the thrombolysis group (any intracranial hemorrhage 2.7 vs 0.4 %, RR 6.95 (1.59–30.41), p=0.006), but major bleeding complications did not occur more often in thrombolysis group (symptomatic intracranial hemorrhage 0.8% vs 0%, RR 8.93 (0.48– 165.45), p=0.13; major non-intracranial hemorrhage 7.7% vs 6.4; RR 1.21 (0.77–1.88), p=0.48; Ischemic stroke 0.8% vs. 0.6%; RR 1.32 (0.30–5.88), p=1.00). {Böttiger 2008 2651}.	Patients die from PE cardiac arrest rather from the treatment. If fibrinolysis used in patient without PE, there is a risk of bleeding

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	Very low. Only one RCT. Small observational studies with high risk of bias.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● **No important uncertainty or variability**	No	

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 presented results probably favors the intervention when PE is highly suspected.	Given the high mortality from cardiac arrest from PE, a small benefit would be of value

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 studies addressing the costs. For fibrinolysis, the costs must be considered as moderate.	Optimal strategy (dose, drug choice) for use of fibrinolysis is uncertain

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 comparing costs between the 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**	There is no research evidence on the impact on health equity.	

Acceptability

Is the intervention acceptable to keystakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes**	Currently part of guidelines	

○ 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	Fibrinolysis is already implemented; Surgical embolectomy and percutaneous mechanical thrombectomy are available at specialized centres only (no new studies identified).	eCPR was not part of this question as has been addressed in CoSTR 2019

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

	JUDGEMENT						
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 administering fibrinolytic drugs for cardiac arrest when PE is the suspected cause of cardiac arrest (weak recommendation, very low certainty ofevidence).**
- **We suggest the use of fibrinolytic drugs or surgical embolectomy or percutaneous mechanical thrombectomy for cardiac arrest when PE is the known cause of cardiac arrest (weak recommendation, very low certainty of evidence).**

Justification

We updated our systematic review from the 2015 guidelines, and we found no new evidence to change the existing recommendations.

Although the overall certainty in the evidence is very low, the current evidence suggests administering fibrinolytic drugs for cardiac arrest when PE is the suspected cause of cardiac arrest. There is no new evidence to support a change to these guidelines.

Newer case series and cohort studies report that eCPR – alone or in combination with one or more of the standard therapies fibrinolysis, surgical embolectomy and/or percutaneous mechanical thrombectomy – may be an effective therapy for CA caused by PE. There is not enough evidence to make a recommendation at the time being. Further studies are required to evaluate this therapy for CA due to PE.

For the role of eCPR on patients with cardiac arrest due to pulmonary embolism, we refer to the ILCOR CoSTR 2019: 'We suggest that ECPR may be considered as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings in which it can be implemented (weak recommendation, very low certainty of evidence).'[2019 ILCOR CoSTR] {Soar 2019 145}{ Soar 2019 e826}

Subgroup considerations

Subgroups comparing different drugs for fibrinolysis exist, but there is not enough evidence to support either of the drugs Implementation considerations

Since fibrinolytic drugs are already in use in most systems, we see no substantial concerns related to implementation of this. The option for eCPR depends on the availability in hospital. Diagnosis of PE in cardiac arrest not straight forward.

The optimal dosing regimen is unknown.

Monitoring and evaluation

Since fibrinolysis is an implemented therapy, we see no substantial concern regarding this therapy.

Research priorities

The overall certainty in the evidence is very low.

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A5. O2 after ROSC_ALS 448_ETD

QUESTION

Oxygenation strategy after return of spontaneous circulation (ROSC) in adults with cardiac arrest	
POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest from any aetiology who have attained ROSC
INTERVENTION:	A specific oxygenation strategy
COMPARISON:	An alternative oxygenation strategy or no specific oxygenation strategy
MAIN OUTCOMES:	Survival to hospital discharge, 3 months, or longer; survival to hospital discharge, 3 months, or longer with favorable neurologic outcome.
SETTING:	Pre-hospital and ICU settings

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest, both in and out-of hospital, is relatively common and has a very high mortality. Previously, both hypoxemia and hyperoxia have been reported to be associated with worse outcome in patients who are post-cardiac arrest. Hypoxemia may worsen ischemic brain injury and injury to other organs, while hyperoxia may lead to increased oxidative stress and organ damage after reperfusion. Several new studies, both observational and randomized trials, have been published since this topic was last updated in 2015. There are three ongoing randomized trials investigating different oxygenation strategies (NCT03138005, NCT03653325, NCT03141099), demonstrating that this continues to be a topic of high interest.	The ongoing trials are scheduled to complete enrollments in 2020-2021.

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 hyperoxia on survival and neurologic outcome is very mixed, with many inconsistencies across studies in both methodology and results. Randomized trials done to date are very small and the observational studies are all at serious or critical risk of bias. Within these limitations, studies have reported a mix of positive and negative results, leaving true uncertainty. Randomized trials and observational studies have generally found either no effect or a possible benefit from normoxia compared to hyperoxia. Trials done in a hospital/ICU setting are more suggestive of benefit from normoxia than trials done in the pre-hospital setting, but the pre-hospital trials are limited by very small sample size. A recent randomized trial {Mackle 2019 } that was an ICU intervention and included a subgroup of post-arrest patients (larger than any of the RCTs done previously) found a benefit in the conservative (lower) oxygen group. Although the certainty of this finding is limited by the fact that it was a subgroup analysis, it does support the possibility of a true benefit from conservative oxygen therapy in post-cardiac arrest patients. We divided the available trial data into interventions carried out in the pre-hospital setting and those carried out in the intensive care unit, as below. PRE-HOSPITAL INTERVENTION	Ongoing trials as noted

№ of studies	Study design	Lower % oxygen pre-hospital	higher % oxygen pre-hospital	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Survival to Discharge, O_2 in pre-hospital setting - Kuisma, Bray							
2	randomised trials	29/51 (56.9%)	23/38 (60.5%)	**RR 0.97** (0.68 to 1.37)	**18 fewer per 1,000** (from 194 fewer to 224 more)	⨁⨁◯◯ LOW	CRITICAL
Survival to Discharge, O_2 in pre-hospital setting -Thomas (cluster randomized by paramedic)							
1	randomised trial	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	CRITICAL
Favorable neurological outcome (OPC < 3) at discharge - Kuisma							
1	randomised trial	8/14 (57.1%)	6/14 (42.9%)	**RR 1.33** (0.63 to 2.84)	**141 more per 1,000** (from 159 fewer to 789 more)	⨁⨁◯◯ LOW	CRITICAL
Discharge to home-Young							
1	randomised trial	2/8 (25.0%)	4/9 (44.4%)	**RR 0.56** (0.14 to 2.29)	**196 fewer per 1,000** (from 382 fewer to 573 more)	⨁◯◯◯ VERY LOW	CRITICAL

ICU INTERVENTION

№ of studies	Study design	lower % oxygen	higher % oxygen	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Survival to discharge -Young							
1	randomised trial	4/8 (50.0%)	4/9 (44.4%)	**RR 1.13** (0.41 to 3.08)	**58 more per 1,000** (from 262 fewer to 924 more)	⨁◯◯◯ VERY LOW	CRITICAL
Survival to discharge - Jakkula							
1	randomised trial	43/61 (70.5%)	39/59 (66.1%)	**RR 1.07** (0.84 to 1.36)	**46 more per 1,000** (from 106 fewer to 238 more)	⨁⨁⨁◯ MODERATE	CRITICAL
3 month survival - ICU-ROX							

1	randomised trial	49/86 (57.0%)	32/78 (41.0%)	**RR 1.39** (1.01 to 1.92)	**160 more per 1,000** (from 4 more to 377 more)	⨁⨁◯◯ LOW	CRITICAL

Discharge to home -Young

1	randomised trial	2/8 (25.0%)	4/9 (44.4%)	**RR 0.56** (0.14 to 2.29)	**196 fewer per 1,000** (from 382 fewer to 573 more)	⨁◯◯◯ VERY LOW	CRITICAL

CPC 1-2 at 6 months - Jakkula

1	randomised trial	42/61 (68.9%)	36/59 (61.0%)	**RR 1.13** (0.87 to 1.47)	**79 more per 1,000** (from 79 fewer to 287 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Favorable GOSE at 6 months - ICU-ROX

1	randomised trial	35/78 (44.9%)	23/72 (31.9%)	**RR 1.40** (0.93 to 2.13)	**128 more per 1,000** (from 22 fewer to 361 more)	⨁◯◯◯ VERY LOW	CRITICAL

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. The undesirable effects of hyperoxia on neurologic outcome are very uncertain due to inconsistency in study results, but a small negative effect on neurologic outcome and survival is possible based on limited existing evidence (see evidence tables above).	

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 (see tables above).	

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 effects2018

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.	

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/lower oxygen saturation. 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 (see Equity section).

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 2015.	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 oxygen saturations may be hard to obtain reliably. Some pre-hospital systems utilize transport ventilators that do not have the capacity to adjust the fraction of inspired oxygen, which may also limit feasibility in the pre-hospital setting. There may be significant limitations to feasibility for many aspects of post-arrest care in resource-poor settings, but this is not specific to oxygen titration.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**

	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

Recommendations

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

Justification

In making the recommendation to avoid hypoxemia, the task force acknowledges that the evidence is of very low certainty. The task force 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 hyperoxia is based on low to moderate certainty evidence that showed either harm or no benefit from hyperoxia. In light of the possible benefit and lack of evidence for harm, the task force suggests targeting normoxia and avoiding hyperoxia. The task force acknowledges that the primary randomized trial evidence suggesting benefit from avoiding hyperoxia is from a subgroup analysis only, and more trials (three currently recruiting) will be helpful. It is also important to consider that the trials generally compare a strategy of more conservative (lower) oxygen administration strategy to a higher oxygen administration strategy. The "higher" arm varies across trials from being usual care (as determined by clinical teams) to a defined intervention of 100% oxygen. Observational studies, which compare oxygen levels rather than strategies, generally defined the hyperoxia group as those with $PaO_2 \geq 300$mmHg, a level above what many would consider usual care. The trials enrolling currently will shed much-needed light on this question.
The task force felt that titration of oxygen should not be attempted until oxygen levels (peripheral oxygen saturation or partial pressure of oxygen in arterial blood) could be measured reliably. This is most likely to be an important consideration in the pre-hospital setting where arterial blood gas analysis is rarely available and peripheral oxygen saturation may be difficult to obtain. Some of the randomized trials done in the pre-hospital setting, although very small, reported more desaturation in the lower oxygen group, which reinforces the task force suggestion to administer 100% oxygen until reliable measurement of oxygen level is possible. This is likely to be more important in the pre-hospital setting.

Subgroup considerations

The studies available have included both IHCA and OHCA, 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 2015, 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 very limited. As noted above there are three trials ongoing which are likely to clarify this question.

1. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S, Freebairn R, King V, Linke N, Litton E, McArthur C, McGuinness S, Panwar R, Young P and Group I-RIatAaNZICSCT. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med*. 2019.
2. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong ME, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD and Collaborators C. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. *Circulation*. 2018;137:e783-e801.
3. Sutherland T, Moriau V, Niyonzima JM, Mueller A, Kabeja L, Twagirumugabe T, Rosenberg N, Umuhire OF, Talmor DS and Riviello ED. The "Just Right" Amount of Oxygen. Improving Oxygen Use in a Rwandan Emergency Department. *Ann Am Thorac Soc*. 2019;16:1138-1142.

A6. CO2 after ROSC_ALS 571_ETD

QUESTION

Carbon dioxide targets after return of spontaneous circulation (ROSC) in adults with cardiac arrest	
POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest from any aetiology who have attained ROSC
INTERVENTION:	A strategy targeting hypo- or hypercapnia
COMPARISON:	A strategy targeting normocapnia
MAIN OUTCOMES:	Survival to hospital discharge, 3 months or longer; survival with favorable neurologic outcome at hospital discharge, 3 months or longer.
SETTING:	Post-ROSC patients in the hospital setting

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 neurologic injury as a common cause of death. 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 present is not known.	A large randomized trial is currently underway investigating different CO_2 targets in the first 24 hours of ICU admission in post-arrest patients (TAME trial, NCT03114033).

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The available evidence on the effects of both hypercapnia and hypocapnia is inconsistent, with the randomized trials done to-date showing no effect. One RCT compared moderate hypercapnia as a target to normocapnia {Eastwood 2016}, while the other compared high-normal CO_2 as a target with low-normal CO_2.{Jakkula 2018} Neither trial was powered to clinical outcomes, and both failed to demonstrate a difference in their primary or secondary outcomes. Inconsistency was noted as point estimates were opposite in direction. Given the variability in results across the two trials and observational studies, the effect is likely to be small, if any. However, the trials thus far are small. There are some data on the effect of carbon dioxide values on cerebral perfusion but the clinical significance of this is unknown.	Ongoing trial as noted

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ventilation strategy targeting PaCO2 50-55mmHg	ventilation strategy targeting PaCO2 35-45mmHg	Relative (95% CI)	Absolute (95% CI)		
Survival to discharge-Eastwood												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	31/42 (73.8%)	26/41 (63.4%)	**RR 1.16** (0.87 to 1.56)	**101 more per 1,000** (from 82 fewer to 355 more)	⨁⨁◯◯ LOW	CRITICAL
Discharge to home-Eastwood												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	23/42 (54.8%)	18/41 (43.9%)	**RR 1.25** (0.80 to 1.94)	**110 more per 1,000** (from 88 fewer to 413 more)	⨁⨁◯◯ LOW	CRITICAL
Favorable neurologic outcome (GOSE score) at 6 months												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	23/39 (59.0%)	18/39 (46.2%)	**RR 1.28** (0.83 to 1.96)	**129 more per 1,000** (from 78 fewer to 443 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ventilation strategy targeting PaCO2 5.9-6.0kPa	ventilation strategy targeting PaCO2 4.5-4.7kPa	Relative (95% CI)	Absolute (95% CI)		
Survival to 30 days-Jakkula												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	36/59 (61.0%)	46/61 (75.4%)	**RR 0.81** (0.63 to 1.05)	**143 fewer per 1,000** (from 279 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL
Favorable neurologic outcome (CPC 1-2) at 6 months												

1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	35/59 (59.3%)	43/61 (70.5%)	**RR 0.84** (0.64 to 1.10)	**113 fewer per 1,000** (from 254 fewer to 70 more)	⊕⊕◯◯ LOW	CRITICAL

a. Results opposite in direction from similar trial
b. Small sample size and confidence interval includes 1

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, with the small randomized trials done to-date failing to show any effect (see tables above). Given the variability in results the effect, if any, is likely to be small. However, the trials thus far are small. There are some preclinical data on the effect of carbon dioxide values on cerebral perfusion but the clinical significance of this is unknown.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ●Low ○ Moderate ○ High ○ No included studies	The certainty of evidence from randomized trials is low because the trials are small and the results are inconsistent. The strsategies used in the two trials also differs, with one comparing moderate hypercapnia to normocapnia and one comparing high-normal CO_2 to low-normal CO_2.	

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.	

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, 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 (see Equity).	

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	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, 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 2015.	

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

There is insufficient evidence to suggest for or against targeting mild hypercapnia compared with normocapnia in adults with ROSC after cardiac arrest.
We suggest against routinely targeting hypocapnia in adults with ROSC after cardiac arrest (weak recommendation, low-certainty evidence).

Justification

Evidence from existing randomized trials and observational studies is very inconsistent. Both randomized trials failed to show an effect of different CO_2 targets (mild to moderate hypercapnia compared to normocapnia in one trial and high-normal $PaCO_2$ compared to low-normal $PaCO_2$ in the other). Observational studies were evenly distributed in showing benefit, harm or no effect associated with hypercapnia. Hypocapnia results were also inconsistent, although no studies found an association with benefit. In light of the lack of evidence for benefit, and lack of consistent evidence for harm from CO_2 levels higher than normal, the task force did not think there was sufficient evidence to suggest for or against targeting mild hypercapnia compared to normocapnia. An ongoing trial investigating this comparison may bring clarity to this issue. For hypocapnia, very limited evidence suggests either no benefit or harm, supporting the task force's suggestion against routinely targeting hypocapnia. As with all critically ill patients, there may be specific scenarios in which a patient's CO_2 level may need to be higher or lower than normal to accommodate or compensate for other illness (e.g. severe lung injury or metabolic acidosis).

Subgroup considerations

Although the task force discussed whether patients with baseline chronic lung disease and chronic CO_2 retention might respond differently to different CO_2 targets, no evidence addressing this subgroup was found. The task force agreed it would be reasonable to adjust $PaCO_2$ targets in patients with known chronic CO_2 retention, but this is expert opinion only as no evidence was identified on this topic.

Implementation considerations

The prior treatment recommendation (2015) was a suggestion to maintain normocapnia. The updated treatment recommendation supports this approach, while allowing that we do not currently know if an approach targeting mild hypercapnia is beneficial, harmful, or equal in comparison to targeting normocapnia. The task force discussed the possible complication of acidemia from hypercapnia. The presence or absence of metabolic acidosis is generally something that needs to be considered when choosing a ventilation strategy and $PaCO_2$ target, and metabolic acidosis is common in post-arrest patients. The $PaCO_2$ targets or ranges also differed somewhat between studies. The Eastwood et al trial used a target of 50-55mmHg for the hypercapnia group while the Jakkula trial used 5.8-6kPa (equivalent to 43-45mmHg) for the higher target, and they used 35-45mmHg and 4.5-4.7kPa (equivalent to 33-35mmHg) for the lower target. For this reason, the task force chose not to pool the trials, and not to define specific numeric targets as no optimal target or range has been made clear. Additionally, opinions vary on whether arterial blood gas analysis in patients receiving targeted temperature management should be adjusted for temperature. Once again trials differed in their approach, with the Eastwood trial using the alpha-stat method (values measured at a temperature of 37) while the Jakkula trial adjusted values to reflect the patient's actual temperature at time of measurement. Approaches to blood gas interpretation regarding temperature also varied across the observational studies. These variations in methodology and in definitions of target ranges prohibit the task force from being able to recommend specific numbers or a specific method for blood gas analysis for systems implementing these recommendations.

Monitoring and evaluation

Research priorities

As the current evidence is inconsistent, primarily from observational studies and from only small RCTs, a large RCT to address the utility of this intervention will be useful, and is recruiting currently.

A7. Post ROSC antibiotics_ALS 2000_ETD

QUESTION

Should Early/ prophylactic antibiotics vs. Delayed/ clinically-driven administration be used for Adult patients following return of spontaneous circulation from cardiac arrest?	
POPULATION:	Adult patients following return of spontaneous circulation from cardiac arrest
INTERVENTION:	Early/ prophylactic antibiotics
COMPARISON:	Delayed/ clinically-driven administration
MAIN OUTCOMES:	Survival with good neurological outcome- last recorded time point (up to day 30)- randomised controlled trials; Survival with good neurological outcome- last recorded time point (up to day 30)- observational studies; Survival- last recorded timepoint (up to 30-days)- randomised controlled trials; Survival- last recorded timepoint (up to day 30)- observational studies; Pneumonia- randomised controlled trials; Pneumonia- observational studies; Critical care length of stay- randomised controlled trials; Critical care length of stay- observational studies; Duration of mechanical ventilation- randomised controlled trials; Duration of mechanical ventilation- observational studies; Antibiotic duration- randomised controlled trials; Antibiotic duration- observational studies;
SETTING:	Any setting (in-hospital and 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	Infective complications are common in patients admitted to intensive care units. Such complications are associated with increased length of stay. In patients admitted following cardiac arrest, pneumonia has been reported in 50-60% of patients. In part, this reflects the risk of aspiration during the cardiac arrest events. In this patient group, a key challenge is early and accurate identification of infection. Standard criteria for identifying infection are affected by patient treatment (i.e. targetted temperature management) and pathophysiology following cardiac arrest (i.e. systemic inflammatory response as part of the post-cardiac arrest syndrome). The decision to treat infection is further complicated by the need for prudent antibiotic prescribing in all health settings driven by the international challenge of antibiotic resistance. However, in patients that die on the intensive care unit following cardiac	

	arrest, caus e of death is typically attributed to multi-organ failure or neurological failure, rather than an infective complication.	

Desirable Effects

How substantial are the desirable anticipated effects ?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Our meta-analyses of observational studies and randomised controlled trials did not find any statistically significant evidence of harm in relation to the intervention for any important or critical outcome. We did not include any outcomes that specifically address potential complications of antibiotic use, such as gastrointestinal effects or development of resistant organisms. An additional issue is the potential for antibiotics to lead to the generation of anti-biotic resistant organisms at a population level.	

Undesirable Effects

How substantial are the undesirable anticipated effects ?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Our meta-analyses of observational studies and randomised controlled trials did not find any statistically significant evidence of harm in relation to the intervention for any important or critical outcome. We did not include any outcomes that specifically address potential complications of antibiotic use, such as gastrointestinal effects or development of resistant organisms. An additional issue is the potential for antibiotics to lead to the generation of anti-biotic resistant organisms at a population level.	

Certainty of evidence

What is the overall certainty of the evidence of effects ?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ● Low ○ Moderate ○ High ○ No included studies	Across all outcomes, evidence certainty was recorded as low or very low.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	There is possible important uncertainty in how clinicians value the outcome of incidence of pneumonia. Some may take the view that the purpose of prophylactic antibiotics is to to reduce infective complications, such that the incidence of pneumonia is the most important outcome even if this does not translate in to improved survival or reduced critical care length of stay. Others may take the view that the expressed international need for prudent use of antibiotics and the potential side-effects of antibiotics means that antibiotic prophylaxis should not be used unless it is shown to have an effect on key clinical outcomes.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There is important uncertainty as to benefit of the intervention. Our review did not explicitly examine harms of the intervention. There may be different clinical approaches regarding antibiotic use in patients with evidence of gastric aspiration. These patients were excluded from randomised controlled trials, and management of this patient was not addressed in any observational study. There is a need for further research in this area.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies	At an individual level, the intervention is likely to be acceptable to clinicians and patients. Antibiotics do have adverse effects including allergic reaction, gastrointestinal effects and increased individual antibiotic resistance. The financial cos t of antibiotics is likely acceptable. At a societal level, antimicrobial resistance is identified by the World Health	

○ Don't know	Organisation as a key global health concern. The clinically appropriate use of antibiotics is a key factor in limiting the development of antimicrobial resistance.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Antibiotics are commonly used drugs. The intervention is feasible to implement.	

SUMMARY OF JUDGEMENTS

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

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest against the use of prophylactic antibiotics in patients following return of spontaneous circulation.

Justification

In our review of the evidence, we found that the use of prophylactic antibiotics did not affect key clinical outcomes, although we acknowledge the overall low certainty of evidence. Furthermore, we note international concerns regarding antimicrobial resistance and the need for prudent use of antibiotics.

We note the results of a recent high-quality randomised controlled trial which reported a reduced incidence of pneumonia in patients treated with prophylactic antibiotics. However, this study not detect any difference in other key outcomes such as critical care length of stay, although we acknowledge that the study was not powered to detect such a difference.

Subgroup considerations

N/A

Implementation considerations

This recommendation explicitly refers to the use of prophylactic antibiotics.
Randomised controlled trials excluded patients with presumed infection at baseline. Cardiac arrest patients with clinical evidence of infection should continue to be treated in line with current hospital guidelines.

Monitoring and evaluation

N/A

Research priorities

- Randomised controlled trials powered to reliably evaluate the effect of antibiotic prophylaxis on outcomes such as critical care length of stay or duration of invasive mechanical ventilation.
- Development of guidelines to inform the decision to prescribe antibiotics following cardiac arrest, particularly where there is gastric aspiration.

A8. Seizure_Treatment & Prophylaxis post ROSC_ALS 431 & 868_ETD

QUESTION

Post Cardiac Arrest Seizure Prophylaxis and Treatment	
POPULATION:	Unresponsive adults (≥18 years old) with sustained return of spontaneous circulation (ROSC) after cardiac arrest in any setting (in-hospital or out-of-hospital).
INTERVENTION:	One strategy for seizure prophylaxis or treatment
COMPARISON:	Another strategy or no seizure prophylaxis or treatment
MAIN OUTCOMES:	Survival to hospital discharge, 3 months or longer; survival with favorable neurologic outcome at hospital discharge, 3 months or longer.
SETTING:	Any setting (in-hospital or out-of-hospital).

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 (mainly 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	**Post-Cardiac Arrest Seizure Prophylaxis:** For the critical outcomes of survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year and survival at discharge, 30 days, 60 days, 180 days AND/OR 1 year, 2 prospective randomized clinical trials	

○ Large ○ Varies ● Don't know	involving a total of 562 subjects provided very low-certainty evidence (downgraded for risk of bias, indirectness and imprecision)(BRCT Investigators 1986 397;Longstreth 2002 506) of no benefit from seizure prophylaxis. **Post-Cardiac Arrest Seizure Treatment:** For the critical outcomes of survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year and survival at discharge, 30 days, 60 days, 180 days AND/OR 1 year we identified no randomized controlled trials (RCTs) or non-randomized studies that addressed post-cardiac arrest seizure treatment. Indirect evidence from case series suggest that sedating agents such as propofol are effective in suppressing both clinical convulsions and epileptiform activity on EEG in this patient population (Thömke 2010 1392, Aica Rapun 2017 169, Kotroumanidis 2015 255). A recent retrospective study provides some evidence that conventional antiepileptic agents (specifically valproate and levetiracetam) also have an effect in suppressing epileptiform activity in the EEG (Solanki 2019 82).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	There is no direct evidence of undesirable effects of antiepileptic drug therapy in comatose post-cardiac arrest survivors. Treatment with sedatives and conventional antiepileptic drugs in high doses has the potential to cause delayed awakening, prolonged need for mechanical ventilation, and increased ICU days. Importantly, generalized myoclonus in combination with epileptiform discharges may be manifestations of Lance-Adams syndrome which is compatible with a good outcome (Elmer 2016 175, Aica-Rapun 2017 169). In such cases, overly aggressive sedation and treatment with high doses of conventional antiepileptic drugs may confound the clinical examination and lead to overly pessimistic prognostication.	

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	Seizure Prophylaxis The certainty of evidence is very low because the 2 randomized clinical trials were designed to test the neuroprotective effects of agents that also had potential antiepileptic effects typically given as a single dose post-ROSC. These trials were not designed to optimize seizure prophylaxis and the methodology for measuring seizure incidence was poorly defined. . Also, it is typical for post-cardiac arrest patients to receive levels of sedation that potentially have antiepileptic effects during the first days after ROSC. The impact of this practice on incidence of post-cardiac arrest seizures and outcomes is currently unknown. Seizure Treatment The certainty of evidence is very low because no randomized controlled clinical trials have compared one strategy for seizure treatment to another strategy or placebo. Published case series lack control comparators and have highly variable inclusion criteria and outcomes.	A large randomized trial is currently underway investigating the benefit of systematic antiepileptic drug therapy with the goal of suppressing all epileptiform activity on the EEG vs. standard treatment of clinical seizures only in post-cardiac arrest status epilepticus (TELSTAR trial, NCT02056236).

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	Survival with favorable neurologic outcome and survival are generally accepted as critical outcomes (Hayward COSCA).	

○ No important uncertainty or variability		

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○Probably favors the comparison ○ Does not favor either the intervention or the comparison ○Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	**Seizure Prophylaxis** The balance of evidence favors no treatment. In making this recommendation, the task force acknowledged the lack of confidence in a treatment effect on the critical outcome of survival with good neurologic function treatment. The task force also considered that seizure prophylaxis in other forms of acute brain injuries is not associated with improved outcomes, and that most drugs have significant side effects. **Seizure Treatment** The balance of evidence favors treatment. In making this recommendation, we acknowledge very low confidence in the estimated treatment effect. However, ongoing seizures have the potential to worsen brain injury, and treatment of recurrent seizures and SE is the standard of care in other patient populations (Glauser 2016 48).	The main difference between post-cardiac arrest patients and patients with status epilepticus of other etiologies is the severity of the underlying brain injury, which is the main determinant of the prognosis. Task force discussed difficulty in diagnosing seizures in settings that do not routinely monitor EEG.

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 antiepileptic agents 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 prophylaxis or 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 AED 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	We identified no research that assessed acceptability, but these treatment recommendations do not include any substantial changes compared to 2015.	

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

Feasibility

Is the intervention feasible to implement?

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

	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

Recommendations

We suggest against seizure prophylaxis in adult comatose cardiac arrest survivors. (weak recommendation, very low certainty of evidence)
We suggest treatment of seizures in adult comatose cardiac arrest survivors. (weak recommendation, very low certainty of evidence)

Justification

Post-Cardiac Arrest Seizure Prophylaxis
In making this recommendation, the task force acknowledged the lack of confidence in a treatment effect on the critical outcome of survival with good neurologic function. The task force also considered that seizure prophylaxis in other forms of acute brain injuries is not associated with improved outcomes, and that most drugs have significant side effects.
Post-Cardiac Arrest Seizure Treatment
In making this recommendation, we acknowledge very low confidence in the estimated treatment effect. However, ongoing seizures have the potential to worsen brain injury, and treatment of recurrent seizures and SE is the standard of care in other patient populations(Glauser 2016 48)..

Subgroup considerations

Subgroups of patients with either potentially favorable or poor prognosis have been identified in several retrospective studies. A continuous EEG-background preceding the start of status epilepticus, reactive background and later start of status epilepticus are factors associated with a potentially favorable outcome. Conversely, early onset of status epilepticus in the EEG (<24 hours), a preceding burst-suppression pattern, lack of EEG-background and EEG-background reactivity are EEG-features associated with a poor prognosis (Rossetti 2009 744, Backman 2017 128, Elmer 2016 175). In addition, reliable prognosticators of poor outcome other than EEG may identify patients who are not likely to benefit from prolonged treatment (Dragancea 2015 173, Beretta 2018 e2153).

Implementation considerations

Indirect evidence from case series suggests that sedatives such as propofol are effective in suppressing both clinical convulsions and epileptiform activity on EEG in these patients (Thömke 2010 1392, Aica Rapun 2017 169, Kotroumanidis 2015 255). A recent retrospective study provides some evidence that conventional antiepileptic drugs (specifically valproate and levetiracetam) also have an effect in suppressing epileptiform activity in the EEG (Solanki 2019 82). In a recent comparison of valproate, levetiracetam and fosphenytoin for convulsive status epilepticus, the three drugs were equally effective but fosphenytoin caused more episodes of hypotension and need for intubation (Kapur 2019 2103).These results suggest that valproate and levetiracetam may be reasonable first line drugs in post-cardiac arrest seizure management.

Monitoring and evaluation

Since the recommendations are unchanged, we do not foresee issue in monitoring or evaluating implementation

Research priorities

- There is no high certainty evidence for the effect of antiepileptic drugs on the outcome of post-cardiac arrest patients with seizures
- There are no RCTs specifically designed to evaluate the impact of post-cardiac arrest seizure prophylaxis on the incidence of seizures and neurologic outcome.
- There are inadequate data regarding the timing, duration, dosing, and choice of antiepileptic drugs for seizure prophylaxis in comatose post–cardiac arrest patients.
- The utility of continuous EEG versus intermittent EEG monitoring in the diagnosis and treatment of seizures in comatose post–cardiac arrest patients remains controversial due to resource utilization and lack of evidence for improved outcomes.
- The threshold for treating epileptiform activity other than convulsive seizures (eg, generalized epileptiform discharges) is poorly defined
- Standardized terminology for classification of epileptiform activity in the EEG of comatose post–cardiac arrest patients is increasingly used. There remains a need to develop consensus on the definition of post cardiac arrest status epilepticus
- The value of using volatile anesthetics to treat refractory status epilepticus on post-cardiac arrest patients is currently unknown.

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A9. PLR_ETD

QUESTION

Pupillary light reflex for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management
INTERVENTION:	Pupillary light reflex (PLR), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A bilaterally absent standard pupillary light reflex was investigated in seventeen observational studies [Choi 2017 70; Chung-Esaki 2018 99; Ryoo 2015 2370; Javaudin 2018 8; Scarpino 2019 in press; Dhakal 2016 116; Matthews 2018 66; Oddo 2018 2102; Fatuzzo 2018 29; Dragancea 2015 164; Hofmeijer 2015 137; Kongpolprom 2018 509; Roger 2015 231; Zhou 2019 343; Greer 2013 1546; Kim 2018 33; Lee 2017 1628]. In three studies [Choi 2017 70, 115 pts; Ryoo 2015 2370, 172 pts; Javaudin 2018 8, 10151 pts] **absent standard pupillary light reflex immediately after ROSC** predicted poor neurologic outcome at hospital discharge or 1 month with specificity ranging from 68.8% to 75.9% and sensitivity ranging from 65.5% to 77.1% (very-low certainty of evidence). In four studies [Scarpino 2019 in press, 336 pts; Dhakal 2016 116, 99 pts; Matthews 2018 66, 392 pts; Oddo 2018 2102, 137 pts] **absent standard pupillary light reflex at ≤24h** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 80% to 92.3% and sensitivity ranging from 26.5% to 51.8 % (very-low certainty of evidence). In two studies [Fatuzzo 2018 29, 490 pts; Dragancea 2015 164, 36 pts] **absent standard pupillary light reflex at 36-72h** predicted poor neurologic outcome from 3 months to 6 months with specificity ranging from 96.9% to 100% and sensitivity ranging from 36.5% to 48.4% (very-low certainty of evidence). In four studies [Oddo 2018 2102, 279 pts; Hofmeijer 2015 137, 272 pts; Kongolprom 2018 509, 51 pts; Roger 2015 231, 61 pts] **absent standard pupillary light reflex 48-72h** predicted poor neurologic outcome from hospital discharge to 6 months with specificity ranging from 89.7% to 100% and sensitivity ranging from 17.4% to 51.4% (certainty of evidence from low to very-low). In six studies [Dhakal 2016 116, 98 pts; Greer 2013 1546, 104 pts; Chung-Esaki 2018 99, 90 pts; Matthews 2018 66, 137 pts, Oddo 2018 2102, 206 pts; Zhou 2019 343, 206 pts] **absent standard pupillary light reflex at 72h** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 93.6% to 100% and sensitivity ranging from 18% to 29.2% (very-low certainty of evidence). In seven studies [Dragancea 2015 164, 78 pts; Kim 2018 33, 192 pts; Lee 2017 1628, 53 pts; Zhou 2019 343, 189 pts; Matthews 2018 66, 137 pts; Kongolprom 2018 509, 51 pts; Greer 2013 1546, 59 pts] **absent standard pupillary light reflex from 72h to day 7** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 92.3% to 100% and sensitivity ranging from 17.9% to 63.1% (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

O Large O Moderate O Small ● Trivial O Varies O Don't know	A false positive prediction based on a bilaterally absent pupillary reflex may suggest a likely poor neurological outcome in a patient destined to a good recovery. Our evidence review shows that this is more likely to occur during the first 36h after ROSC, which may partly be explained with Interference from sedation. However, none of the studies included in our systematic review used pupillary reflex in isolation as a criterion for WLST.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low O Low O Moderate O High O No included studies	The certainty of evidence from pupillary reflex is very low because of the risk of bias, especially self-fulfilling prophecy, and the risk of pharmacological interference on index assessment.	Similarly to other predictors based on clinical examination, pupillary reflex cannot be concealed from the treating team, which implies the risk of self-fulfilling prophecy. Pupillary reflex is prone to confounding due to sedation. The characteristics of the light stimulus eliciting the pupillary reflex are not standardized.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

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	Considering the high specificity of pupillary light reflex when evaluated at 72h or later, the balance of effects favors the predictor.	

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	Costs for the assessment of pupillary reflex are negligible. On the other side, no study assessing savings from prognostication based on pupillary reflex has been included in our review	

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 assessing costs of pupillary light reflex.	

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	We did not identify any studies addressing cost-effectiveness.	

○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Considering the negligible costs of pupillary light reflex, a problem of inequity is unlikely.	

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 study assessing acceptability, but acceptability is likely.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of pupillary light reflex does not require special skills. The only equipment needed is a light source. Nevertheless, the examiner needs to be familiar with the basics of clinical neurological examination.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using pupillary light reflex at 72h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

For standard pupillary light reflex, limited evidence suggests that the highest specificity for prediction of poor neurological outcome is achieved at 72h or later after cardiac arrest. This may be partly due to confounding from the effect of sedatives used for TTM or to facilitate ventilation. Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review.
Despite its limitations, given the easiness of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

None.

Research priorities

Absence of residual effects from sedatives needs to be specifically assessed in studies evaluating the accuracy of predictors based on clinical examination after cardiac arrest.

The interrater agreement for the assessment of standard pupillary light reflex in patients resuscitated from cardiac arrest deserves investigation.

A10. Pupillometry_ETD

QUESTION

Automated pupillary reflex (pupillometry) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Pupillary reflex, automatically assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, and the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Automated assessment of pupillary reflex to light (PLR) has been made by measuring two variables: 1) The percentage of reduction in pupillary size, reported as qPLR 2) The neurological pupil index (NPi), based on several variables, such as pupillary size, percentage of constriction, constriction velocity and latency. **AUTOMATED PUPILLOMETRY: qPLR** Quantitative pupillary light reflex was investigated in three observational studies [Oddo 2018 2102; Heimburger 2016 88; Solari 2017 804]. In three studies [Oddo 2018 2102, 434 pts; Heimburger 2016 88, 82 pts; Solari 2017 804, 101 pts] **qPLR from 0% to 13% at 24h** predicted poor neurological outcome from 3 months to 12 months with specificity ranging from 77.8% to 98.9% and sensitivity ranging from 17% to 66% (certainty of evidence from moderate to very low). In three studies [Oddo 2018 2102, 356 pts; Heimburger 2016 88, 82 pts; Solari 2017 804, 101 pts] **qPLR from 0% to 13% at 48h** predicted poor neurological outcome from 3 months to 12 months with specificity ranging from 95.7% to 100% and sensitivity ranging from 18.1% to 58.5% (certainty of evidence from low to very low). In one study [Oddo 2018 2102, 234 pts] **qPLR=0% at 72h** predicted poor neurological outcome at 3 months with 100% specificity and 4.9% sensitivity (moderate certainty of evidence). **AUTOMATED PUPILLOMETRY: NPi** NPi was investigated in three observational studies [Riker 2019 in press; Obling 2019 in press; Oddo 2018 2102]. In three studies [Riker 2019 in press, 52 pts; Obling 2019 in press, 127 pts; Oddo 2018 2102, 450 pts] **NPi from 0 to 2.40 within 24h** predicted poor neurological outcome from hospital discharge to 3 months with 100% specificity and sensitivity ranging from 22% to 43.9% (certainty of evidence from moderate to very low). In one study [Oddo 2018 2102, 361 pts] **NPi≤2 at 48h** predicted poor neurological outcome at 3 months with 100% specificity and 18.8% sensitivity (moderate certainty of evidence). In one study [Oddo 2018 2102, 271 pts] **NPi≤2 at 72h** predicted poor neurological outcome at 3 months with 100% specificity and 16.9% sensitivity (moderate certainty of evidence).	Differently from standard pupillary light reflex, in quantitative pupillometry the reflex is assessed in standard and reproducible conditions. Calculation of NPi is based on a proprietary algorithm. Results of qPLR suggest that prediction is more accurate if assessment is performed at 72h from cardiac arrest. However, this is based on only one study.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large O Moderate O Small ● Trivial O Varies O Don't know	As for every other predictor of poor outcome, a false positive result of quantitative pupillometry may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. Differently from standard pupillary light reflex, NPi showed a consistent 0% false positive rate at all time points in a single multicenter study. However, this needs to be confirmed in further studies. None of the studies included in our systematic review used pupillometry in isolation as a criterion for WLST.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Very low ● Low O Moderate O High O No included studies	The certainty of evidence about pupillometry is low. In some of the studies we included, the results of pupillometry were conceived to the treating team. However, results of standard PLR - that are inevitably correlated to those of pupillometry – cannot be concealed. The thresholds for 100% specificity for both qPLR and NPi are inconsistent.	An additional source of confounding is represented by the different available devices and methods of measurement.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	Considering the high specificity and the reproducibility of quantitative pupillometry, the balance of effects favors the predictor.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large costs O Moderate costs O Negligible costs and savings O Moderate savings O Large savings ● Varies O Don't know	Quantitative pupillometry requires a specific equipment, with relevant costs. These costs may vary according to the model of pupillometer and possibly across different countries. The technology allowing portable pupillometry is at its beginning and costs may decrease in the future.	

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Very low O Low O Moderate O High ● No included studies	We did not identify any studies specifically assessing costs of pupillometry.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison	We did not identify any studies addressing cost-effectiveness of pupillometry.	

○ 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	The costs of pupillometry are higher than those of standard pupillary light reflex. This may represent a problem in terms of equity, if pupillometry will consistently demonstrate to be superior to standard pupillary light reflex for prognostication after cardiac arrest.	

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 acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the technique of pupillometry is easy and it does not require special skills. In addition, the standardized evaluation achieved by quantitative pupillometry minimizes the risk of disagreement between assessors.	

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 using quantitative pupillometry at 72h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).

Justification

Limited evidence suggests that pupillometry using NPi achieves 100% specificity for prediction of poor neurological outcome as early as 24h after cardiac arrest. The choice of 72h for this recommendation has been made based on a parallel evidence regarding s-PLR, on the lower likelihood of persisting effects from sedation at that time point, and on the fact that specificity of a qPLR seems to increase from 24h to 72h. However, the number of available studies is still low and no consistent qPLR or NPi threshold for 100% poor outcome has been identified.
Although in some of the studies the treating team was blinded to results of pupillometry, a correlation with standard PLR, which cannot be blinded, is likely. WLST based on results of pupillometry has not been documented in any of the studies included in our review.
Because of its high specificity and the standardized assessment parameters, the balance between the costs and benefits favours benefits.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

Research priorities

The number of studies documenting pupillometry for predicting poor outcome after cardiac arrest is still low. A consistent threshold for 100% specificity has not been identified neither for qPLR nor for NPi.

A11. Corneal reflex_ETD

QUESTION

Corneal reflex for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Corneal reflex (CR), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, and the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	CR was investigated in eleven observational studies [Choi 2017 70; Chung-Esaki 2018 99; Ryoo 2015 2370; Sivaraju 2015 1264; Matthews 2018 66; Fatuzzo 2018 29; Dragancea 2015 164; Kongpolprom 2018 509; Zhou 2019 343; Greer 2013 1546; Kim 2018 57]. In two studies [Choi 2017 70, 115 pts; Ryoo 2015 2370, 172 pts;] **absent corneal reflex immediately after ROSC** predicted poor neurological outcome at hospital discharge with specificity ranging from 25.8% to 50% and sensitivity ranging from 93.2% to 96.4% (very-low certainty of evidence). In two studies [Sivaraju 2015 1264, 97 pts; Matthews 2018 66, 137 pts;] **absent corneal reflex at ≤24h** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 58.6% to 65.7% and sensitivity ranging from 51% to 79.4% (very-low certainty of evidence). In four studies [Fatuzzo 2018 29, 490 pts; Sivaraju 2015 1264, 83 pts; Kongpolprom 2018 509, 51 pts; Dragancea 2015 164, 33 pts] **absent corneal reflex at 36-72h** predicted poor neurologic outcome from hospital discharge to 6 months with specificity ranging from 88.9% to 100% and sensitivity ranging from 33.3% to 67.3% (very-low certainty of evidence). In three studies [Chung-Esaki 2018 99, 85 pts; Greer 2013 1546, 104 pts; Matthews 2018 66, 137 pts] **absent corneal reflex at 72h** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 94.3% to 100% and sensitivity ranging from 32.4% to 48.8% (very-low certainty of evidence). In five studies [Dragancea 2015 164, 127 pts; Kim 2018 57, 173 pts; Matthews 2018 66, 137 pts; Kongpolprom 2018 509, 51 pts; Greer 2013 1546, 59 pts] **absent corneal reflex at 72h-day 7** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 98.8% to 100% and sensitivity ranging from 23.1% to 64.1% (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○Varies ○Don't know	A false positive prediction based on a bilaterally absent corneal reflex may suggest that poor neurological outcome is likely in a patient with an eventually good neurological recovery. Our evidence review shows that this is more likely to occur during the first 72h after ROSC. Interference from sedation and/or paralysis may partly explain this. WLST based uniquely on an absent corneal reflex is unlikely. None of the studies included in our systematic review used corneal reflex as a criterion for WLST.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low O Low O Moderate O High O No included studies	The certainty of evidence for corneal reflex is very low because of the risk of bias, especially self-fulfilling prophecy, and the potential pharmacological interference on index assessment.	CR is prone to confounding due to sedation and paralysis, especially during targeted temperature management (TTM). Similarly to other predictors based on clinical examination, corneal reflex cannot be concealed from the treating team, which implies the risk of self-fulfilling prophecy.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	Considering the high specificity of corneal reflex assessed at 72h or later after cardiac arrest, and the low likelihood that WLST is based only on corneal reflex, the balance of effects favors the predictor.	

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	Costs for the assessment of corneal reflex are virtually nil. No study assessing savings from prognostication based on corneal reflex has been included in our review.	

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 assessing costs of corneal reflex.	

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	Considering the negligible costs of corneal reflex, a problem of inequity is unlikely.	

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 acceptability is likely.	

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 in any of the studies included in this review. The assessment of corneal reflex does not require special skills or equipment. Nevertheless, the examiner needs to be familiar with the basics of clinical neurological examination.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using bilateral absence of corneal reflex at 72h or later after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

Low-certainty evidence suggests that prediction of poor neurological outcome using CR can be made with high specificity at 72h or later after cardiac arrest. This predictor is prone to confounding due to the effects of sedatives or muscle relaxants used for TTM or to facilitate ventilation. Only part of the included studies specifically excluded the presence of residual sedation or paralysis at the time CR was assessed. Lack of blinding is a major limitation of CR, however WLST based on CR only has not been documented in any of the studies included in our review and appears to be unlikely.
Despite its limitations, given the easiness of assessment and the minimal costs and required equipment, the balance between the costs and benefits favours benefits.
Combining CR with other predictors is reasonable.

Subgroup considerations

None.

Implementation considerations

None.

Monitoring and evaluation

None.

Research priorities

Absence of residual effects from sedatives or paralyzing agents needs to be specifically assessed in studies evaluating the accuracy of predictors based on clinical examination after cardiac arrest.

A12. Myoclonus-Status Myoclonus_ETD

QUESTION

Myoclonus and status myoclonus for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Myoclonus or status myoclonus, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards. In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, and the topic needs an update.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Myoclonus** Myoclonus was investigated in sixstudies [Sadaka 2015 292; Fatuzzo 2018 29; Kongpolprom 2018 509; Sivaraju 2015 1264; Lybeck 2017 146; Reynolds 2018 249]. In six studies [Sadaka 2015 292, 58 pts; Fatuzzo 2018 29, 493 pts; Kongpolprom 2018 509, 51 pts; Sivaraju 2015 1264, 100 pts; Lybeck 2017 146, 933 pts; Reynolds 2018 249, 583] **presence of myoclonus within 96h** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 77.8% to 97.4% and sensitivity ranging from 18.2% to 36.1% (very-low certainty of evidence). Definitions of myoclonus were provided in only two of these six studies [Sadaka 2015 292; Lybeck 2017 146]. These definitions differed among studies. **Status myoclonus** Status myoclonus was investigated in two studies [Ruknuddeen 2015 304, 121 pts; Zhou 2019 343, 226 pts]. In these two studies, **presence of status myoclonus within 72h** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 97.0% to 100% and sensitivity ranging from 30.6% to 49.1% (very-low certainty of evidence). Status myoclonus was not defined in Zhou, 2019. In Ruknuddeen 2015 304, status myoclonus was defined as “spontaneous or sound-sensitive, repetitive, irregular brief jerks in both face and limb present most of the day within 24 h post-CA”. This definition was derived from Wijdicks 1994 239.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○Don't know	As for every other predictor of poor outcome, a false positive result of myoclonus may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. None of the studies included in our systematic review used myoclonus in isolation as a criterion for WLST.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low O Low O Moderate O High O No included studies	The certainty of evidence about myoclonus is very low. In particular, the definition of myoclonus was not provided in all studies, and when it was, it was inconsistent across studies.	Like other clinical predictors, myoclonus cannot be assessed blindly, so that there is a risk of self-fulfilling prophecy. There is a potential of confounding with Lance-Adams syndrome, a benign form of post-anoxic myoclonus that can occur early after arrest.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	The available evidence shows that presence of myoclonus was associated with poor outcome after cardiac arrest. In most studies, specificity was higher than 90% but the 95% confidence intervals were wide. The specificity of status myoclonus was higher than that of myoclonus, but only two studies were included. Definitions were inconsistent for both myoclonus and status myoclonus.	

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	No specific resources are required for assessing myoclonus per se. However, post-anoxic myoclonus is often associated with epileptiform activity on EEG, so that when assessing myoclonus recoding a simultaneous EEG appears to be reasonable.	

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 assessing costs of myoclonus	

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 myoclonus.	

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	Considering the negligible costs of assessing myoclonus, a problem of inequity is unlikely.	

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 acceptability is likely.	

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 in any of the studies included in this review. The assessment of myoclonus does not require any special equipment. However, the examiner needs to be familiar with the basics of clinical neurological examination and be aware of the potential of confusing a malignant myoclonus with Lance-Adams Syndrome. EEG may provide additional information about the presence of epileptiform activity during myoclonic jerks. This may suggest that myoclonus as a prognostic index should be better evaluated in contexts where EEG analysis is available.	

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 using presence of myoclonus or status myoclonus within 96h after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We also suggest recording EEG in presence of myoclonic jerks in order to detect an associated epileptiform activity.

Justification

Although the definitions of both myoclonus and status myoclonus are absent or inconsistent in most studies, the presence of myoclonus is associated with poor outcome in patients who are comatose after resuscitation from cardiac arrest and it may be useful within the context of a multimodal prognostic assessment.
Myoclonus and status myoclonus are inconsistently associated with epileptiform activity on EEG.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

None.

Research priorities

Achieving a uniform and consensus-based definition of both myoclonus and status myoclonus is necessary. The role of EEG as an additional tool to investigate the nature and the prognostic significance of myoclonus deserves investigation.

A13. SSEPs ETD

QUESTION

Absent N20 wave of somatosensory evoked potentials (SSEPs) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	A bilaterally absent N20 wave of somatosensory evoked potentials (SSEP), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form will be excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	SSEPs were investigated in fourteen observational studies [Grippo 2017 641; Scarpino 2019 (a) 104755; Choi 2017 70; Maciel 2017 469; Dhakal 2016 116; Fatuzzo 2018 29; Leao 2015 322; De Santis 2017 119; Kim 2018 (a) 33; Ruijter 2019 203; Oddo 2018 2102; Dragancea 2015 (a) 164; Kim 2018 (b) e545; Scarpino 2019 (b) in press]. In four studies [Grippo 2017 641, 78 pts; Choi 2017 70, 80 pts; Maciel 2017 469, 41 pts; Scarpino 2019 (b) in press, 218 pts] a bilaterally absent N20 SSEPs wave within 24h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 33.3% to 57.7% (very-low certainty of evidence). In one study [Scarpino 2019 (a) 104755, 346 pts] an absent N20 wave on one side and an absent or low-voltage N20 wave on the other side within 24h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and sensitivity 49.6% (very low certainty of evidence) In twelve studies [Dhakal 2016 116, 35 pts; Fatuzzo 2018 29, 457 pts; Leao 2015 322, 67 pts; De Santis 2017 119, 65 pts; Kim 2018 (a) 33, 127 pts; Ruijter 2019 203, 850 pts; Grippo 2017 641, 76 pts;; Oddo 2018 2102, 188 pts; Scarpino 2019 (b) in press, 240 pts; Choi 2017 70, 81 pts; Dragancea 2015 (a) 164, 201 pts; Kim 2018 (b) e545, 116 pts] a bilaterally absent SSEPs N20 wave at 24-96h predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 50% to 100% and sensitivity ranging from 18.2% to 69.1% (very-low certainty of evidence).	In two studies the specificity of a bilaterally absent N20 wave for prediction of poor neurological outcome was well below 100% (Dhakal 2016, 75[34.9-96.8]%; Leao, 2015, 50 [21.1-78.9]%;). For all these studies the certainty of evidence was very low. Evidence supporting the use of an only monolaterally absent N20 SSEP wave combined with a low-voltage N20 on the opposite side was limited to one multicentre study [Scarpino 2019(a)]. In that study, no threshold for defining low voltage of the N20 wave was specified.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result of SSEPs may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of SSEPs was 0% with high precision in almost all studies included in our review. However, SSEPs are considered to be very accurate predictors of poor outcome and as such were often used, in combination with other predictors, for decisions regarding WLST. In three studies from the same group of investigators [Grippo, 2017; Scarpino 2019 (a); Scarpino 2019 (b)] WLST was not performed. However, the treating team was not blinded to the results of SSEPs. In two studies the specificity of a bilaterally absent N20 wave for prediction of poor neurological outcome was well below 100% [Dhakal 2016, 75%; Leao, 2015, 50%]. The presence of survivors with false positive prediction in these studies demonstrates that WLST was not performed based only on SSEP results.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low O Low O Moderate O High O No included studies	The certainty of evidence about SSEP is very low, mainly because the risk of self-fulfilling prophecy.	Strengths of SSEPs include lack of interference from sedation and temperature, and high precision.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	In the vast majority of included studies, a bilaterally absent N20 SSEP wave predicts poor neurological outcome with high specificity and precision. As for other predictors, however, a risk of self-fulfilling prophecy cannot be excluded.	

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 include any specific studies assessing SSEP costs. However, specific equipment and skills are required for assessing SSEPs.	

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 assessing costs of SSEPs.	

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 SSEPs.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	The specific equipment and skills needed to assess SSEPs are not available everywhere. This can create a problem in terms of equity.	

○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of SSEPs. However, acceptability is likely.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	SSEPs have been used for decades and are implemented in many hospitals worldwide. However, the equipment and skills required for their assessment may represent an obstacle for their implementation. Some of the false positives reported in the studies on SSEPs we included may have been due to implementation issues (i.e., unreadable tracings due to artifacts, rather than "true" absence of N20 wave). This has been already documented in literature (Bowes et al, 2012).	

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

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

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendations

We suggest using a bilaterally absent N20 SSEP wave in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

Almost all studies we included showed that a bilaterally absent N20 SSEP wave predicted poor neurological outcome with very high specificity and precision. SSEPs are often used for decisions on WLST, which may create a self-fulfilling prophecy. However, the presence of survivors with false positive results indicates that WLST based on SSEP results only is not standard practice. In addition, a 100% specificity for a bilaterally absent SSEP was documented in three studies where WLST was not performed. These three studies were led by the same group Two of these studies were conducted on multiple centres.
In making this recommendation, the task force also considered that SSEP have a low risk of confounding from TTM or sedation and a large size of effect (high precision).
In order to limit the risk of self-fulfilling prophecy, combining SSEP with other indices of poor neurological outcome is prudent.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

None.

Research priorities

Further studies are needed to evaluate the added value of assessing SSEPs in combination with other predictors of poor neurological outcome after cardiac arrest.
The accuracy of a unilaterally absent SSEP wave combined with a low-voltage contralateral SSEP wave deserves further investigation.

A14. Unreactive EEG ETD

QUESTION

Lack of EEG background reactivity on electroencephalogram (EEG) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Lack of EEG background reactivity, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form will be excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Unreactive EEG was investigated in ten observational studies [Grippo 2017 641; Admiraal 2019 17; Alvarez 2015 128; Duez 2019 145; Fatuzzo 2018 29; Liu 2016 8273716; Westhall 2016 1482; Amorim 2016 121; Sivaraju 2015 1264; Benarous 2019 20]. In nine studies [Grippo 2017 641, 78 pts; Admiraal 2019 17, 149 pts; Alvarez 2015 128, 18 pts; Duez 2019 145, 120 pts; Fatuzzo 2018 29, 434 pts; Liu 2016 8273716, 12 pts; Amorim 2016 121, 373 pts; Sivaraju 2015 1264, 89 pts; Benarous 2019 20, 48 pts] unreactive EEG within 72h predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 41.7% to 100% and sensitivity ranging from 50% to 97.1% (certainty of evidence from low to very low). Specificity was below 90% in most of these studies, and it reached 100% in only in two of them. In one study [Westhall 2016 1482, 87 pts] unreactive EEG at a median of 77h (IQR 53-102) predicted poor neurological outcome at 6 months with 70% specificity and 88.1% sensitivity (very-low certainty of evidence).	The American Clinical Neurophysiology Society (ACNS) has established a standardised definition for EEG reactivity (Hirsch LJ et al., J Clin Neurophysiol 2013;30: 1–27).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result of EEG may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of an unreactive EEG background was more than 10% in most studies included in our review.	

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 about EEG reactivity was very low, because of the risk of self-fulfilling prophecy, very low precision, and inconsistency. In all studies we included, the treating team was aware of the results of the index test under assessment. Background reactivity was not defined in two studies. In the remaining studies, definition was mostly based on a change in amplitude or frequency, with inconsistent exclusion of muscular artefacts or stimulus-induced rhythmic, periodic, or ictal discharges. The type of stimulus used to induce background EEG reactivity varied across studies, the most commonly being auditory stimulus. In four studies, the type of stimulus was not described.	Like other EEG-based predictors, background reactivity may be prone to interference from sedative agents. The interpretation of EEG-based predictors is prone to interrater variability.

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	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

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	An absent EEG background reactivity was associated with poor neurological outcome in studies we included. However, the specificity of this sign was low in many of these studies, with low precision. In addition, the definitions of both background reactivity and the type of stimulus used were inconsistent across studies.	

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 include any specific studies assessing costs of EEG reactivity. However, specific equipment and skills are required for assessing it.	

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 assessing costs of EEG reactivity.	

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 EEG reactivity.	

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	According to a review published in 2015 (Friberg 2015 158) , EEG was the most commonly used tool for prognostication after cardiac arrest. However, the specific equipment and skills needed to assess EEG may not be available everywhere anytime. This can create a problem in terms of equity.	

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 of EEG. However, acceptability is likely.	

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 in any of the studies included in this review. Using background EEG reactivity for prognostication requires a specific equipment for recording EEG and the ability to interpret the tracing.	The lack of standardisation of the stimulus used to induce EEG reactivity may impair its practical implementation.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	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 against EEG background reactivity alone to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

In almost all studies we included the specificity of unreactive EEG background for predicting poor outcome, and its precision were low. In addition, both definitions and stimuli to induce EEG reactivity were inconsistent across studies.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

Research priorities

It is desirable that future studies will adopt a standard definition of background EEG reactivity. An international consensus statement on EEG reactivity testing (e.g. stimulus protocol) has been proposed (Admiraal 2018 36).

A15. Epileptiform discharges ETD

QUESTION

Epileptiform discharges on electroencephalogram (EEG) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Epileptiform discharges on EEG, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form will be excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Two main types of epileptiform discharges were described: rhythmic/periodic and non-rhythmic/periodic. **RHYTHMIC/ PERIODIC DISCHARGES** Rhythmic/periodic discharges were investigated in nine observational studies [Lamartine 2016 153; Scarpino 2019 (a) 104755; Scarpino 2019 (b) in press; Rossetti 2017 e674; Fatuzzo 2018 29; Westhall 2016 1482; Backman 2018 24; Benarous 2019 20; Beretta 2019 in press]. In two studies [Lamartine 2016 153, 89 pts; Scarpino 2019 (a) 104755, 218] Rhythmic/periodic discharges within 24h predicted poor neurological outcome from 3 months to 6 months with 100% specificity and sensitivity ranging from 2.4% to 7.9% (certainty of evidence from moderate to very low). In four studies [Lamartine 2016 153, 80 pts; Scarpino 2019 (b) in press, 346 pts; Rossetti 2017 e674, 175; Fatuzzo 2018 29, 200 pts] Rhythmic/periodic discharges within 48h predicted poor neurological outcome from 3 months to 6 months with specificity ranging from 97.2% to 100% and sensitivity ranging from 8.1% to 42.9% (certainty of evidence from moderate to very low). In three studies [Benarous 2019 20, 48 pts; Rossetti 2017 e674, 173 pts; Scarpino 2019 (b) in press, 240 pts] Rhythmic/periodic discharges at 48-72h predicted poor neurological outcome from 1 month to 6 months with specificity ranging from 66.7% to 96.1% and sensitivity ranging from 11.4% to 50.8% (certainty of evidence from low to very low). In two studies [Westhall 2016 1482, 103 pts; Backman 2018 24, 207 pts] Rhythmic/periodic discharges at the median time of 76-77h predicted poor neurological outcome at 6 months with specificity ranging from 97% to 100% and sensitivity ranging from 5% to 40% (certainty of evidence from low to very low). In one study [Beretta 2019 in press, 166 pts] Rhythmic/periodic discharges within 5 days predicted poor neurological outcome at 6 months with 100% specificity and 15.7% sensitivity (moderate certainty of evidence). **SPORADIC, NON-RHYTHMIC/PERIODIC DISCHARGES** Sporadic, non-rhythmic/periodic discharges were investigated in five observational studies [Lamartine 2016 153; Ruijter 2019 203; Scarpino 2019 (a) 104755; Scarpino 2019 (b) in press; Benarous 2019 20] In three studies [Lamartine 2016 153, 89 pts; Ruijter 2019 203, 469 pts; Scarpino 2019 (a) 104755, 218 pts;] Sporadic, non-rhythmic/periodic discharges within 24h predicted poor neurological outcome from 3 months to 6 months with specificity ranging from 84.6% to 100% and sensitivity ranging from 0.5% to 7.9% (certainty of evidence from moderate to very low). In three studies [Lamartine 2016 153, 80 pts; Ruijter 2019 203, 742 pts; Scarpino 2019 (b) in press, 346 pts] Sporadic, non-rhythmic/periodic discharges within 48h predicted poor neurological outcome from 3 months to 6 months with specificity ranging from 95.8% to 99.5% and sensitivity ranging from 0.4% to 13.3% (certainty of evidence from moderate to very low). In three studies [Benarous 2019 20, 48 pts; Ruijter 2019 203, 517 pts; Scarpino 2019 (b) in press, 240 pts] Sporadic, non-rhythmic/periodic discharges at 48-72h predicted poor neurological	The definition of epileptiform discharges was not consistent across studies.

	outcome from 1 month to 6 months with specificity ranging from 88.9% to 97.3% and sensitivity ranging from 0.6% to 38.5% (certainty of evidence from low to very low). In one study [Ruijter 2019 203, 133 pts] Sporadic, non-rhythmic/periodic discharges at 96-120h predicted poor neurological outcome at 6 months with specificity ranging from 66.7% to 82.1% and sensitivity ranging from 17.6% to 21.3% (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	A false positive result of EEG may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of both rhythmic/periodic discharges and on EEG was 0% in most of the studies included in our review. Sporadic, non-rhythmic/periodic discharges had lower specificity.	

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 about epileptiform discharges or was low or very low in most studies, because of the risk of self-fulfilling prophecy, low precision, and inconsistent definitions. The specificity of sporadic epileptiform discharges was lower than that of periodic/rhythmic discharges. In studies we included the treating team was not blinded to the results of the index test, with a consequent risk of self-fulfilling prophecy.	Like other EEG-based predictors, epileptiform activity may be prone to interference from sedative agents. However, postanoxic seizures are often resistant to treatment. The interpretation of EEG-based predictors is prone to interrater variability. The American Clinical Neurophysiology Society (ACNS) has established a standardised terminology for EEG discharges (Hirsch LJ et al., J Clin Neurophysiol 2013;30: 1–27).

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	The presence of periodic/epileptiform discharges on EEG predicted poor outcome with 100% specificity in most studies. Specificity was lower for sporadic epileptiform discharges and the balance of effects appears less favourable.	Along with the presence of epileptiform activity, the EEG background activity can also be important in prognostic assessment.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large costs O Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies ● Don't know	We did not include any specific studies assessing costs of epileptiform activity on EEG. However, specific equipment and skills are required for assessing it.	

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 assessing costs of epileptiform activity on EEG.	

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 epileptiform activity on EEG.	

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	According to a review published in 2015 (Friberg et al, Resuscitation 2015; 90:158-62), EEG was the most commonly used tool for prognostication after cardiac arrest. However, the specific equipment and skills needed to assess EEG may not be available everywhere anytime. This can create a problem in terms of equity.	

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 of EEG. However, acceptability is likely.	

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 in any of the studies included in this review. Evaluating epileptiform discharges on EEG for prognostication purposes requires a specific equipment for recording EEG and the ability to interpret the tracing.	

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 using the presence of epileptiform activity or on EEG to predict poor outcome in adult patients who are comatose after cardiac arrest.

Justification

In most of the studies we included the specificity of rhythmic/periodic epileptiform activity for predicting poor outcome was 100%. Specificity was lower for sporadic epileptiform discharges.

Subgroup considerations

None

Implementation considerations

Research priorities

It is desirable that future studies will adopt a standard definition of epileptiform discharges.
The specific predictive value of the different epileptiform subtypes, their prevalence, and their combination with background EEG deserves further investigation.

A16. Seizures ETD_Revised

QUESTION

Occurrence of Seizures for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Occurrence of seizures, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form will be excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Seizures were investigated in five observational studies [Lamartine 2016 153, 89 pts; Sadaka 2015 292, 58 pts; Benarous 2019 20, 48 pts; Westhall 2016 1482, 103 pts; Amorim 2016 121, 373 pts]. In these studies ***seizures on EEG within 120h*** predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 0.6% to 26.8% (certainty of evidence from moderate to very low).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	A false positive result of EEG may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of ACNS-defined seizures on EEG was 0% in all studies included in our review.	

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 about seizures was very low, because of the risk of self-fulfilling prophecy and a very low precision in most studies.	Interference from sedation is likely when evaluating seizures as a predictor, since usually sedative agents are administered to suppress them. Differently from other EEG-based predictors, seizures are not induced by sedative agents. Seizures were evaluated early after cardiac arrest in the studies we included. The latest evaluation was made at a median of 77 (IQR 53-102)h.

		The interpretation of EEG-based predictors is prone to interrater variability. The American Clinical Neurophysiology Society (ACNS) has established a standardised terminology for unequivocal seizures (Hirsch 2013 1).

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	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

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 presence of ACNS-defined seizures on EEG predicted poor outcome with 100% specificity in all studies we included.	

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 include any specific studies assessing costs of assessing seizures on EEG for neuroprognostication. However, specific equipment and skills are required.	

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify any studies specifically assessing costs of assessing seizures.	

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 seizures detection after cardiac arrest.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	According to a review published in 2015 (Friberg et al, Resuscitation 2015; 90:158-62) , EEG was the most commonly used tool for prognostication after cardiac arrest. However, the specific equipment and skills needed to assess EEG may not be available everywhere anytime. This can create a problem in terms of equity.	

○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of seizures as a predictor. However, acceptability is likely.	

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 in any of the studies included in this review. Evaluating seizures on EEG for prognostication purposes requires a specific equipment for recording EEG and the ability to interpret the tracing.	

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

	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

Recommendations

We suggest using seizures on EEG to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

In all studies we included the specificity of ACNS-defined seizures on EEG for predicting poor outcome was 100%. This specificity was consistent along the first 72h after ROSC.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

None

Research priorities

Even if 100% specificity was consistent across all studies we included, only one study assessed the accuracy of seizures at multiple time points. In addition, precision was low or very low in most studies. Further studies are needed to confirm the predictive value of seizures for poor outcome after cardiac arrest at all time points.

A17. Burst-suppression ETD

QUESTION

Burst suppression on electroencephalogram (EEG) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Burst-suppression on EEG, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form will be excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Burst-suppression** Burst suppression was investigated in six observational studies [Alvarez 2015 128; Sadaka 2015 292; Leao 2015 322; Zhou 2019 343; Westhall 2016 1482; Backman 2018 24]. In two study [Alvarez 2015 128, 18 pts; Sadaka 2015 292, 58 pts] burst suppression within 24h predicted poor neurological outcome to hospital discharge with specificity ranging from 50% to 100% and sensitivity ranging from 50% to 51.5% (certainty of evidence very low). In five studies [Alvarez 2015 128, 18 pts; Leao 2015 322, 67 pts; Zhou 2019 343, 197 pts; Westhall 2016 1482, 103 pts; Backman 2018 24, 207 pts] burst suppression at 24-120h predicted poor neurological outcome from hospital discharge to6 months with specificity ranging from 91.7% to 100% and sensitivity ranging from 13.9% to 55.6% (certainty of evidence from low to very low). Definitions of burst-suppression varied: in two studies (Westhall 2016 1482, Backman 2018 24) the ACNS (American Clinical Neurophysiology Society) definition was used. In one study a non-ACNS definition was used, while in other two studies no specific definition was used. <u>Synchronous BS</u> In one study [Ruijter, 2019 203, 742 pts] a synchronous BS at 6-96h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 1.1% to 31.7% (certainty of evidence from moderate to low). <u>Heterogeneous BS</u> In one study [Ruijter 2019 203, 742 pts] heterogeneous BS at 6-120h predicted poor neurological outcome at 6 months with specificity ranging from 90.7% to 100% and sensitivity ranging from 1.1% to 16.2% (certainty of evidence from moderate to very low).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	A false positive result of EEG may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of burst-suppression varied across studies and burst-suppression subtypes, but in most cases it was below 10%.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low O Low O Moderate O High O No included studies	In all studies we included BS predicted poor outcome with very high specificity. However, In all the studies we included, the treating team was not blinded to the presence of BS, and in most of these studies, BS was included among the criteria for WLST. Only part of the studies we included adopted a standardized definition of BS. Like other EEG-based predictors, burst-suppression may be prone to interference from sedative agents.	The synchronous subtype of burst suppression can be 100% predictive as early as few hours after ROSC. However, it has been described in only one of the studies included in this review.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ● Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability	Neurological outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%. In addition, 59% of respondents felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison ● Probably favors the intervention O Favors the intervention O Varies O Don't know	In all included studies, presence of burst-suppression predicted poor neurological outcome with a specificity above 90%. As for other predictors, however, a risk of self-fulfilling prophecy cannot be excluded.	

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 include any specific study assessing the costs of prognosticating using burst suppression. However, specific equipment and skills are required for recording and analyzing EEG.	

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 include any specific studies assessing the costs of prognosticating using burst suppression.	

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 include any specific studies assessing costs-effectiveness of prognosticating using burst suppression.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	According to a review published in 2015 (Friberg et al, Resuscitation 2015; 90:158-62) , EEG was the most commonly used tool for prognostication after cardiac arrest. However, the equipment and skills needed to assess EEG may not be available everywhere anytime. This can create a problem in terms of equity.	

○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of burst-suppression. However, acceptability is likely.	

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 in any of the studies included in this review. Using burst-suppression for prognostication requires a specific equipment for recording EEG and the ability to interpret the tracing.	

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

Recommendations

We suggest using burst-suppression on EEG to predict poor outcome in adult patients who are comatose and who are off sedation after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

All studies we included showed that the presence of burst-suppression on EEG predicted poor neurological outcome with a specificity above 90%, and in most of the studies specificity was 100%. Due to the potential interference of sedative agents on EEG, evaluating burst-suppression as a predictor off sedation appears as the most prudent strategy.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

None.

Research priorities

It is desirable that future studies will adopt a standard definition of burst suppression, such as the one included in the American Clinical Neurophysiology Society's (ACNS) Standardized Critical Care EEG Terminology (Hirsch 2013 1).

The accuracy of synchronous burst-suppression (identical/highly epileptiform bursts) deserves further investigation.

A18. NSE ETD

QUESTION

Neuron Specific Enolase (NSE) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Neuron specific enolase (NSE), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	NSE was investigated in twelve observational studies [Dhakal 2016 116; Lee 2013 1387; Chung-Esaki 2018 99; Vondrakova 2017 172; Duez 2018 79; Kim 2018 33; Stammet 2015 2104; Zellner 2013 1382; Tsetsou 2018 104; Helwig 2017 68; Zhou 2019 343; Rossetti 2017 e674]. In twelve studies [Dhakal 2016 116, 78 pts; Lee 2013 1387, 224 pts; Chung-Esaki 2018 99, 72 pts; Vondrakova 2017 172, 153 pts; Duez 2018 79, 115 pts; Kim 2018 33, 125 pts; Stammet 2015 2104, 686 pts; Zellner 2013 1382, 110 pts; Tsetsou 2018 104, 61 pts; Helwig 2017 68, 100 pts; 276 pts; Zhou 2019 343, 34 pts; Rossetti 2017 e674, 329 pts] ***NSE with a cut-off ranging from 33 to 120 µg/L within 72h*** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 75% to 100% and sensitivity ranging from 7.8% to 83.6% (certainty of evidence from moderate to very low). In one study [Vondrakova 2017 172, 153 pts] ***NSE with a cut-off of 50.2 µg/L at day 4*** predicted poor neurological outcome at 1 month with 100% specificity and 42.1% sensitivity (moderate certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	A false positive prediction based on NSE levels above the cut-off chosen for predicting poor neurological outcome may lead to treatment restrictions in patients destined to a good recovery. This is likely to occur given the variability of cut-offs for 100% specificity across studies, and the potential for confounding from haemolysis or other extracerebral sources of NSE.	

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 NSE is very low because of the risk of bias, especially self-fulfilling prophecy.	Differently from other predictors, like those based on clinical examination, NSE is not affected by sedation or paralysis, and it can be assessed blindly. However, in most of the studies we evaluated, results of NSE

		measurement were not concealed from the treating team. An additional source of confounding is represented by the different available methods of measurement.

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

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	Considering the high specificity of NSE, the balance of effects favours the predictor.	

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 costs of biomarkers' assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on NSE has been included in our review.	

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 assessing costs of NSE for prognostication after cardiac arrest.	

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	A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. Assessment of biomarkers requires resources that may not be universally available. However, NSE is routinely measured in many hospitals and clinics as a tumour biomarker. The most important caution required during withdrawing and managing the blood sample is avoiding haemolysis.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	**Trivial**		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using neuron specific enolase within 72h after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

Limited evidence suggests that high levels of neuron specific enolase (NSE) predict poor neurological outcome with 100% specificity at 24-72h after cardiac arrest. There is a wide variability of thresholds for 100% specificity across studies. Lack of blinding was a limitation in most of included studies, even if WLST based only on NSE was not documented.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

Research priorities

Large cohort studies are desirable to identify a consistent NSE threshold for predicting poor neurological outcome after cardiac arrest.

There is very little evidence concerning the predictive value of NSE measured later than 72h after ROSC.

A19. S-100B ETD

QUESTION

S-100B protein for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	S-100B protein, assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
●Trivial O Small OModerate O Large O Varies O Don't know	S-100B protein was investigated in three observational studies [Jang 2019 e14496; Duez 2018 79; Stammet 2017 153]. In two studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts] ***S-100B protein with a cut-off ranging from 3.58 to 16.6 µg/L immediately after ROSC*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 2.8% to 26.9% (certainty of evidence from moderate to very low). In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.193 to 2.59 µg/L at 24h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 10.1% to 77.6% (certainty of evidence from moderate to very low). In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.159 to 3.67 µg/L at 48h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 5% to 77.6% (certainty of evidence from moderate to very low). In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.202 to 1.83 µg/L at 72h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 5% to 61.2% (certainty of evidence from moderate to very low).	Although specificity of S-100B protein is high, the variability of thresholds for 100% specificity is wide. In addition, the number of studies documenting S-100B protein as a predictor of poor outcome after cardiac arrest is low.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
O Large O Moderate O Small ● Trivial O Varies O Don't know	A false positive prediction based on S-100B protein levels above the cut-off chosen for predicting poor neurological outcome may lead to treatment restrictions in patients destined to a good recovery. This is likely to occur given the variability of cut-offs for 100% specificity across studies, and the potential for confounding from extracerebral sources of S-100B protein.	

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 S-100B protein is low because of the limitations of included studies, and the wide inconsistency of the thresholds for 100% specificity. In none of the three included studies S-100B protein was used as a criterion for WLST. However, in one of these studies, the treating team was not blinded to the results of S-100B protein measurement. The major problems with S-100B protein are the very limited number of studies assessing it as a predictor after cardiac arrest and the wide variability of thresholds.	Differently from other predictors, like those based on clinical examination, S-100B protein is not affected by sedation or paralysis, and it can be assessed blindly. In two of the three studies we included results of S-100B protein were concealed from the treating team. An additional source of confounding is represented by extracerebral sources of S-100B protein (of particular relevance for post-CPR patients, musculoskeletal tissues).

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

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	Even if the specificity of S-100B protein is high, the variability of S-100B thresholds for 100% specificity is very high. The number of studies assessing S-100B is low.	

○ Favors the intervention ○ Varies ○ Don't know		

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 costs of biomarkers' assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on S-100B protein has been included in our review.	

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 assessing costs of S-100B protein for prognostication after cardiac arrest.	

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	A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. Assessment of biomarkers requires resources that may not be universally available.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	**Trivial**		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest against using S-100B protein for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).

Justification

Although the risk of self-fulfilling prophecy for S-100B protein is lower than that observed in other predictors, the evidence is limited by the low number of available studies and the wide variability of thresholds for 100% specificity across studies. This may also be due to the presence of extracerebral sources of S-100B protein and possibly to indirectness. In fact, S-100B protein does not originate from the neurons, but from the glial cells.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

None.

Research priorities

Large cohort studies are desirable to identify a consistent S-100B protein threshold for predicting poor neurological outcome after cardiac arrest.

A20. Other biomarkers ETD

QUESTION

GFAP, serum tau protein, and NFL for prediction of poor neurological outcome in adults with cardiac arrest	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Blood levels of biomarkers (GFAP, serum tau protein, NFL), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial O Small O Moderate O Large O Varies O Don't know	**Glial fibrillary acid protein (GFAP)** In one study [Helwig 2017 68, 100 pts] ***GFAP with a cut-off of 0.08 µg/L at 48±12h*** predicted poor neurological outcome at 1 month with 100% specificity and 21.3% sensitivity (low certainty of evidence). **Serum Tau Protein** In one study [Mattsson 2017 665, 667 pts] ***serum tau protein with a cut-off ranging from 72.7 to 874.5 ng/L at 24-72h*** predicted poor neurological outcome at 6 months with 100% specificity and a sensitivity ranging from 4% to 42% (very low certainty of evidence). **Serum Neurofilament Light Chain (NFL)** I In one study [Moseby-Knappe 2019 64, 717 pts] ***Serum Neurofilament Light Chain with a cut-off ranging from 1539 to 12317 pg/mL at 24-72h*** predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 53.1% to 65% (moderate certainty of evidence). In one study [Rana 2013 1322, 61 pts] ***Serum Neurofilament Light Chain with a cut-off ranging from 252 to 405 pg/mL from day 1 to day 7*** predicted poor neurological outcome (CPC 4-5) at 6 months with 100% specificity and sensitivity ranging from 55.6% to 94.4% (very low certainty of evidence).	Among the three biomarkers we included here, NFL showed the highest sensitivity with 100% specificity.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large O Moderate O Small ● Trivial OVaries ODon't know	A false positive prediction occurring in patients having serum levels of a given biomarker above the cut-off identified as the one for predicting poor neurological outcome with 100% specificity may lead to treatment restrictions in patients destined to a good recovery. This is not likely to occur with the biomarkers included in this list, since their investigation is still in the explorative phase and none of them has been adopted as a criterion for WLST.	None of these biomarkers are currently widely available for clinical use.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low O Low O Moderate O High O No included studies	The certainty of evidence for GFAP, serum tau protein, and NFL is very low because of the very limited number of studies.	Differently from other predictors, like those based on clinical examination, biomarkers are not affected by sedation or paralysis, and can be assessed blindly. A specific advantage of NFL is the fact of originating only

		in neurons. Both its sensitivity and specificity are high. However, the range of thresholds for 100% specificity is wide.

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ● Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Considering the little evidence supporting their use, the balance of effects suggests against using these biomarkers, or not favouring either option. Outside the context of studies, these biomarkers are not currently widely available and there are too few studies to support their use.	

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 costs of biomarkers' assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on GFAP, serum tau protein, or NFL has been included in our review.	

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 assessing costs of GFAP, serum tau protein, or NFL for prognostication after cardiac arrest.	

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 these biomarkers.	

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	A problem of inequity is possible, since assessment of biomarkers implies resources that could not be universally available.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. Assessment of biomarkers requires resources that may not be universally available. More specifically, GFAP, serum tau protein, and NFL have been assessed in highly specialised centres for research purposes and are not routinely available for clinical use in most hospitals.	

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

	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

We suggest against using serum levels of GFAP, serum tau protein, or NFL for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

Although these biomarkers, and in particular NFL, appear to be promising for prognostication after cardiac arrest, supporting evidence is limited to very few studies. Consistent thresholds for 100% specificity need to be identified before any of these biomarkers can be recommended for prognostication in the clinical setting.
These biomarker tests are not widely available. The methods used for measuring these biomarkers need to be more widely available, standardised, and studied.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

These tests are currently not widely available.

Research priorities

Further studies on GFAP, serum tau protein, and NFL are needed to confirm their predictive value after cardiac arrest, to assess their reproducibility, and to identify consistent thresholds for 100% specificity.

A21. GWR ETD_Revised

QUESTION

Grey matter/white matter ratio (GWR) on brain computed tomography (CT) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Grey matter/white matter ratio (GWR) on brain computed tomography (CT)), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Grey matter to white matter ratio (GWR) is the ratio between the densities (measured in Hounsfield units) of the grey matter and the white matter on brain CT. In the normal brain, the grey matter has a higher density than the white matter. Occurrence of brain oedema reduces GWR. The sites and methods for GWR calculation, and the GWR thresholds were inconsistent across studies. **GWR-AVERAGE (GWR-AVG)** GWR-AVG was investigated in seven observational studies [Jeon 2017 118; Kim 2013(a) 57; Kim 2014 1121; Kim 2018 33; Lee 2017 1628; Wang 2018 599; Youn 2017 120]. In four studies [Jeon 2017 118, 39 pts; Kim 2013 (a) 57, 51 pts; Kim 2014 1121, 91 pts; Kim 2018 33, 174 pts] GWR-AVG ≤1.23 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 13.3% to 83.8% (certainty of evidence from low to very-low). In one study [Lee 2017 1628, 67 pts] GWR-AVG ≤1.13 at 124.5±59.9 min from ROSC predicted poor neurological outcome at 1 month with 85% specificity and 29.8% sensitivity (very-low certainty of evidence). In one study [Youn 2017 120, 240 pts] GWR-AVG ≤1.077 within 24h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 15.6% sensitivity (very-low certainty of evidence). In one study [Wang 2018 599, 58 pts] GWR-AVG ≤1.14 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 38.1% sensitivity (very-low certainty of evidence). **GWR-Basal Ganglia (GWR-BG)** GWR-BG was investigated in four observational studies [Kim 2013 (a) 57; Scarpino 2018 114; Scarpino 2019104755; Wang 2018 599]. In one study [Kim 2013 (a) 57, 51 pts] GWR-BG ≤1.12 within 1h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.3% sensitivity (very-low certainty of evidence). In two studies [Scarpino 2018 114, 183 pts; Scarpino 2019 104755, 346 pts] GWR-BG ≤1.21 within 24h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 41.8% to 42.1% (certainty of evidence from moderate to very low). In one study [Wang 2018 599, 58 pts] GWR-BG ≤1.12 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.6% sensitivity (very-low certainty of evidence). **GWR Putamen/Corpus Callosum (P/CC)** GWR-P/CC was investigated in three observational studies [Lee 2013 1387; Lee 2018 37; Jeon 2017, 21].	

	In two studies [Lee 2013 1387, 186 pts; Jeon 2017 21, 39 pts] GWR-P/CC ≤1.17 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 31.3% to 52.9% (very-low certainty of evidence). In one study [Lee 2018 37, 258 pts] GWR-P/CC ≤0.91 within 24h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and 1.7% sensitivity (very-low certainty of evidence). **GWR-Simplified (GWR-SI: Putamen/Posterior limb of internal capsule).** GWR-SI was investigated in one observational study [Wang 2018 599]. In one study [Wang 2018 599, 58 pts] GWR-SI ≤1.1 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 28.6% sensitivity (very-low certainty of evidence). **GWR Caudate Nucleus/Posterior limb of internal capsule (CN/PIC)** GWR-CN/PIC was investigated in two observational studies [Lee 2013, 186 pts; Jeon 2017, 39 pts]. In two studies [Lee 2013 1387, 186 pts; Jeon 2017 21, 39 pts] GWR-CN/PIC ≤1.15 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 19.8% to 40.6% (very-low certainty of evidence). **GWR cerebrum** GWR-cerebrum was investigated in two observational studies [Kim 2013 (a) 57; Wang 2018 1599]. In one study [Kim 2013 (a) 57, 51 pts] GWR-cerebrum ≤1.12 within 1h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 20% sensitivity (very-low certainty of evidence). In one study [Wang 2018 599, 58 pts] GWR-cerebrum ≤1.09 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.6% sensitivity (very-low certainty of evidence). **GWR Thalamus/Corpus Callosum (GWR-T/CC)** GWR-T/CC was investigated in one observational study [Jeon 2017 118, 39 pts]. In this study GWR-T/CC ≤1.13 at median time of 90 (IQR 52–150) min predicted poor neurological outcome at 6 months with 100% specificity and 50% sensitivity (very-low certainty of evidence). **GWR Caudate nucleus /Corpus callosum (GWR-CN/CC)** GWR-CN/CC was investigated in one observational study [Jeon 2017 118, 39 pts]. In this study GWR-CN/CC ≤1.15 at median time of 90 (IQR 52–150) min predicted poor neurological outcome at 6 months with 100% specificity and 46.9% sensitivity (very-low certainty of evidence). **GWR in cardiac vs. non-cardiac etiology** In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-AVR ≤1.13 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-AVR ≤1.22 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.3% sensitivity (very-low certainty of evidence). In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-BG ≤1.11 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-BG ≤1.17 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 26.2% sensitivity (very-low certainty of evidence).	

	In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-P/CC ≤1.107 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 5.6% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-P/CC ≤1.2 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 43.4% sensitivity (very-low certainty of evidence). In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts;] GWR-SI ≤1.06 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 3.5% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-SI ≤1.12 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 9.7% sensitivity (very-low certainty of evidence). In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-CN/PIC ≤1.094 at 50 (26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-CN/PIC ≤1.138 at 67 (29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 20% sensitivity (very-low certainty of evidence). In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-cerebrum ≤1.15 at 50 (26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 4.2% sensitivity (very-low certainty of evidence). In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-cerebrum ≤1.2 at 67 (29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 11% sensitivity (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large O Moderate O Small ● Trivial O Varies O Don't know	A false positive prediction based on GWR levels above the cut-off chosen for predicting poor neurological outcome may lead to treatment restrictions in patients destined to a good recovery. An additional risk is represented by the wide variability of cut-offs for 100% specificity across studies.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low O Low	The certainty of evidence for GWR is very low because of the risk of bias, especially self-fulfilling prophecy and selection bias. In some studies, brain CT was performed in about half of the potentially	Differently from other predictors, like those based on clinical examination, imaging is

○ Moderate ○ High ○ No included studies	includible patients, because brain CT was not performed within the expected time window, or results of brain CT were discarded because of poor image quality or artefacts. A source of confounding for GWR is represented by the different available methods and sites of measurement.	not affected by sedation or paralysis, and it can be potentially assessed blindly. There is no consensus on what are the normal levels for GWR.

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	GWR has a potential for predicting poor outcome after cardiac arrest and several studies identified thresholds for predicting poor outcome with 100% specificity. However, there was a high heterogeneity in both the methods used to calculate GWR across studies and the thresholds associated with 100% specificity.	

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 costs of imaging assessment are higher when compared with those of clinical examination. In addition, measurement of GWR requires additional calculations and skills. No study assessing savings from prognostication based on imaging has been included in our review.	

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 assessing costs of imaging for prognostication after cardiac arrest.	

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	A problem of inequity is possible, since prognostic assessment using imaging implies resources and skills that may not be universally available.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. Imaging studies used for neuroprognostication after cardiac arrest cannot be performed at the bedside, and require transportation in a Radiology Department, with additional clinical and safety risks.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	**Small**	**Trivial**		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using grey matter/white matter (GWR) ratio on brain CT for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence). However, no GWR threshold for 100% specificity can be recommended.

Justification

A severe brain oedema in patients who are unconscious after cardiac arrest predicts poor outcome with high specificity. GWR allows a quantitative evaluation of brain oedema. However, there is a wide heterogeneity of measurement techniques (sites and calculation methods) for GWR. This may partly explain the wide variability of thresholds for 100% specificity across the studies we included. The evidence supporting GWR has very low certainty.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

None

Research priorities

A consistent GWR threshold for predicting poor neurological outcome after cardiac arrest should be identified.

A standardisation of the methods for GWR calculation is urgently needed.

The optimal timing for prognostication using brain CT after cardiac arrest is still unknown. Studies assessing serial brain CT after cardiac arrest are desirable.

A22. DWI ETD_Revised

QUESTION

Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O No O Probably no O Probably yes ● Yes	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

O Varies O Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Trivial ● Small O Moderate O Large O Varies O Don't know	DWI was investigated in five observational studies [Greer 2013 899; Jang 2019 142; Jeon 2017 118; Kim 2018 33; Ryoo 2015 2370]. In one study [Jeon 2017 118, 39 pts] high signal intensity on DWI-MRI within 6h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and 81.3% sensitivity (very-low certainty of evidence). In four studies [Greer 2013 899, 80 pts; Jang 2019 142, 39 pts, Kim 2018 33, 133 pts; Ryoo 2015 2370, 172 pts] positive findings on DWI-MRI within 5 days predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 55.7% to 100% and sensitivity ranging from 26.9% to 92.6% (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large O Moderate O Small ● Trivial O Varies O Don't know	A falsely pessimistic prediction based on DWI may lead to treatment restrictions in patients destined to a good recovery. This risk is increased by the imprecise definition of what represents a "positive" finding on DWI MRI.	In none of the studies we included DWI was used as a criterion for WLST.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low O Low O Moderate O High O No included studies	The certainty of evidence for DWI-MRI is very low because of the risk of bias, especially self-fulfilling prophecy. In all the studies we included the treating team was aware of the results of the index test. An additional issue is selection bias. The imprecise definition of what represents a "positive" finding on DWI MRI is another major concern.	Differently from other predictors, like those based on clinical examination, imaging is not affected by sedation or paralysis, and it can be potentially assessed blindly.

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	DWI has a potential for predicting poor outcome after cardiac arrest, even if in most studiesit did not achieve 100% specificity.	

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 costs of imaging assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on imaging has been included in our review.	

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 assessing costs of imaging for prognostication after cardiac arrest.	

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	A problem of inequity is possible, since prognostic assessment using imaging implies resources and skills that cannot be available anywhere anytime.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. MRI cannot be performed at the bedside, which is a major limitation, and it carries additional risks due to the magnetic field, which makes it incompatible with most standard monitoring equipment and with some implanted devices, such as pacemakers/defibrillators. In addition, MRI recording is a relatively long procedure.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	**Trivial**		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using DWI on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

Assessing DWI has a potential for predicting poor neurological outcome after cardiac arrest. The definition of what a positive DWI MRI after cardiac arrest was inconsistent or even absent in the studies we included. The supporting evidence had very low certainty.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

None

Research priorities

The criteria for defining a positive DWI MRI after cardiac arrest need to be standardised.

A23. ADC ETD_Revised

QUESTION

Apparent diffusion coefficient (ADC) on brain magnetic resonance imaging (MRI) for prediction of poor neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Apparent diffusion coefficient (ADC) on brain magnetic resonance imaging (MRI), assessed within one week after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update. The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	ADC was investigated in two studies [Moon 2018 36; Kim 2013 (b) 1393]. In one study [Moon 2018 36, 44 pts] mean ADC ≤726× 10−6 mm2/s at <48h predicted poor neurological outcome at 6 months with 100% specificity and 44% sensitivity (very-low certainty of evidence). In one study [Moon 2018 36, 66 pts] mean ADC ≤627× 10−6 mm2/s at 48h-7days predicted poor neurological outcome at 6 months with 100% specificity and 20.8% sensitivity (very-low certainty of evidence). In one study [Moon 2018 36, 44 pts] ADC volume proportion (400× 10−6 mm2/s) >2.5% at <48h predicted poor neurological outcome at 6 months with 100% specificity and 64% sensitivity (very-low certainty of evidence). In one study [Moon 2018 36, 66 pts] ADC volume proportion (400× 10−6 mm2/s) >1.66% at 48h-7days predicted poor neurological outcome at 6 months with 100% specificity and 79.2% sensitivity (very-low certainty of evidence). In one study [Kim 2013 (b) 1393, 51 pts] Maximum Cluster Size in different cerebral regions on CT ≤151.7× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 62.5% to 90% (very-low certainty of evidence). In one study [Kim 2013 (b) 1393, 51 pts] the Lowest Mean ADC in different cerebral regions on CT ≤555.7× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 50% to 72.5% (very-low certainty of evidence). In one study [1393, 51 pts] the Lowest Minimum ADC in different cerebral regions on CT ≤466.8× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 42.5% to 82.5% (very-low certainty of evidence).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A falsely pessimistic prediction based on ADC values above the threshold for 100% specificity may lead to treatment restrictions in patients destined to a good recovery. This risk is increased by the wide variability of ADC cut-offs for 100% specificity across studies.	In none of the studies we included ADC was used as a criterion for WLST.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence for DWI-MRI was very low because of the high risk of bias, especially self-fulfilling prophecy and selection bias. An additional source of confounding is represented by the different available methods and sites of measurement.	Differently from other predictors, like those based on clinical examination, imaging is not affected by sedation or paralysis, and it can be potentially assessed blindly.

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	Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead. We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	ADC has a potential for predicting poor outcome after cardiac arrest. In all three studies we included ADC predicted poor outcome with 100% specificity and high sensitivity. However, a high heterogeneity across studies in both the methods used to calculate ADC and the thresholds associated with 100% specificity was observed.	

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 costs of imaging assessment are higher when compared with those of clinical examination. In addition, measurement of ADC requires specific skills. No study assessing savings from prognostication based on imaging has been included in our review.	

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 assessing costs of imaging for prognostication after cardiac arrest.	

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	We did not identify any studies addressing cost-effectiveness.	

○ 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	A problem of inequity is possible, since prognostic assessment using imaging requires resources and skills that may not be available anywhere anytime.	

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 study assessing acceptability, but acceptability is likely.	

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 in any of the studies included in this review. MRI cannot be performed at the bedside, and it carries additional risks due to the magnetic field, which makes it incompatible with most standard monitoring equipment and with some implanted devices, such as pacemakers/defibrillators. In addition, MRI recording is a relatively long procedure.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	**Trivial**		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

We suggest using ADC on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

Assessing apparent diffusion coefficient (ADC) has a potential for predicting poor neurological outcome after cardiac arrest with high sensitivity. There is a wide heterogeneity of measurement techniques (sites and calculation methods) for ADC across studies. The supporting evidence for ADC had very low certainty.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

None

Research priorities

A consistent ADC threshold for predicting poor neurological outcome after cardiac arrest should be identified.

A standardisation of the methods for ADC calculation is urgently needed.