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| 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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

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| 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 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 ○ 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 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** | | | | | | |
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| **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

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| 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

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| 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 |   Using EEG-based predictors requires the availability of equipment, personnel, and skills. Use of consistent terminology and definitions is important for implementation of these predictors, in order to provide an objective evaluation, and limit interrater variability in EEG readings. |

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| 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. |