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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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

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| ProblemIs 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 EffectsHow 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) 115; 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) 115, 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) 115; Scarpino 2019 (b) *in press*; Benarous 2019 20]In three studies [Lamartine 2016 153, 89 pts; Ruijter 2019 203, 469 pts; Scarpino 2019 (a) 115, 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; Ruiter 2019 203, 517 pts; Scarpino 2019 (b) *in press*, 240 pts] ***Sporadic, non-rhythmic/periodic discharges at 48-72h*** predicted poor neurological 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 [Ruiter 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). | The definition of epileptiform discharges was not consistent across studies.  |
| Undesirable EffectsHow 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 evidenceWhat 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). |
| ValuesIs 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 effectsDoes 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 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 requiredHow 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 epileptiform activity on EEG. However, specific equipment and skills are required for assessing it.  |  |
| Certainty of evidence of required resourcesWhat 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 effectivenessDoes 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.  |  |
| EquityWhat 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.  |  |
| AcceptabilityIs 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. |  |
| FeasibilityIs 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** |
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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 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**

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| Implementation considerations |

Use of 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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| 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. |