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| Question |
| **Highly malignant EEG patterns 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 highly malignant EEG patterns, 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 | Highly malignant EEG patterns were investigated in thirteen observational studies [Grippo 2017 641; Hofmeijer 2015 137; Admiraal 2019 17; Ruijter 2019 203; Scarpino 2019 (a) 115; Sivaraju 2015 1264; Duez 2019 145; Sondag 2017 111; Caporro 2019 146; Youn 2017 120; De Santis 2017 119; Backman 2018 24; Westhall 2016 1482].In nine studies [Grippo 2017 641, 78 pts; Hofmeijer 2015 137, 230 pts; Admiraal 2019 17, 141 pts; Scarpino 2019 (a) 115, 346 pts; Sivaraju 2015 1264, 89 pts; Duez 2019 145, 120 pts; Sondag 2017 111, 357 pts; Caporro 2019 146, 184 pts; Rujter 2019 203, 742 pts] ***highly malignant EEG within 36h*** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 90.6% to 100% and sensitivity ranging from 0.4% to 97% (certainty of evidence from moderate to low).In one study [De Santis 2017 119, 65 pts] ***highly malignant EEG (Suppression without or with GPEDs, burst suppression) at 0-48h*** predicted poor neurological outcome at 3 months with 93.3% specificity and 74.3% sensitivity (low certainty of evidence).In five studies [Duez 2019 145, 44 pts; Hofmeijer 2015 137, 187 pts; Ruijter 2019 203, 497 pts; Youn 2017 120, 240 pts; Grippo 2017 641, 76 pts] ***highly malignant EEG at 48-72h*** predicted poor neurological outcome at 6 months with specificity ranging from 95.5% to 100% and sensitivity ranging from 4% to 48.3% (certainty of evidence from moderate to low).In two studies [Backman 2018 24, 207 pts; Westhall 2016 1482, 103 pts] ***highly malignant EEG at the median time of 76-77h*** predicted poor neurological outcome at 6 months with specificity ranging from 98.5% to 100% and sensitivity ranging from 31.2% to 50% (moderate certainty of evidence).In one study [Ruijter 2019 203, 133 pts] ***highly malignant EEG at 96-120h*** predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 8.5% to 11.8% (certainty of evidence from low to very low). |  |
| 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 specificity of highly malignant EEG patterns was 100% in most studies and above 90% in all studies included in our review.  |  |
| 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 highly malignant EEG patterns varied from moderate to very low, because of the risk of self-fulfilling prophecy. Inconsistent definitions across studies of what represents a malignant EEG was also an issue. Definitions included a combination of unfavourable EEG patterns such as low-voltage, suppression, burst-suppression, burst-attenuation, and periodic discharges. In most studies the definitions of the individual EEG patterns was consistent with the American Clinical Neurophysiology Society (ACNS) standardised terminology (Hirsch LJ et al., J Clin Neurophysiol 2013;30: 1–27).ACNS terminology.  | Interference from sedation on EEG-based predictors cannot be excluded. The interpretation of EEG-based predictors is prone to interrater variability. |
| 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 highly malignant EEG patterns predicted poor outcome with 100% specificity in most of the studies we included. In all studies, specificity was above 90%. |  |
| 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 | Specific equipment and skills are required for neuroprognostication after cardiac arrest using EEG. |  |
| 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 assessing 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 | In one study (Sondag 2017 111) a cost-minimisation analysis of using highly malignant EEG patterns for deciding on treatment within 24 hours from ROSC in patients who are comatose after cardiac arrest was performed. The study showed that if treatment withdrawal was decided after24 hours based on an unfavourable EEG pattern, this would result in a cost reduction of €334 per patient. |  |
| 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 as a predictor. 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 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 highly malignant EEG patterns 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 |
| The presence of highly malignant EEG patterns predicted poor outcome with 100% specificity in most of the studies we included. In all studies, specificity was above 90%. However, the combination of patterns corresponding to a highly malignant EEG was not consistent in studies. Most of these patterns, such as burst-suppression or periodical discharges, showed a high specificity in studies where they were evaluated individually. In most studies, the definition of these patterns was consistent with the American Clinical Neurophysiology Society (ACNS) terminology. EEG is prone to interference from sedation and evaluating these patterns off sedation is prudent.  |
| 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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| Monitoring and evaluation |
| None  |
| Research priorities |
| Achieving a consensus definition of highly malignant EEG patterns in patients who are comatose after resuscitation from cardiac arrest is desirable.  |