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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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

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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 | **Burst-suppression**  Burst suppression was investigated in five observational studies [Sadaka 2015 292; Leao 2015 322; Zhou 2019 343; Westhall 2016 1482; Backman 2018 24].  In one study [Sadaka 2015 292, 58 pts] ***burst suppression within 24h*** predicted poor neurological outcome to hospital discharge with 100% specificity and 51.5% sensitivity (certainty of evidence very low).  In four studies [Leao 2015 322, 67 pts; Zhou 2019 343, 197 pts; Westhall 2016 1482, 103 pts; Backman 2018 24, 207 pts] ***burst suppression at 24-76h*** predicted poor neurological outcome at 6 months with specificity ranging from 91.7% to 100% and sensitivity ranging from 13.9% to 21.8% (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.  Synchronous BS  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).  Heterogeneous BS  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 ○ Low ○ Moderate ○ High ○ 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 |
| ○ 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 | 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 ○ 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 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 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** | | | | | | |
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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 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 |

Use of EEG-based predictors requires the availability of equipment, personnel, and skills. Use of consistent terminology and definitions is important for implementation of EEG-based 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 |
| 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. |