|  |  |
| --- | --- |
| QUESTION | |
| **Full-montage EEG with continuous or nearly continuous background without discharges or seizures for prediction of good 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:** | Full-montage EEG assessed within five days after cardiac arrest. |
| **COMPARISON:** | *None.* |
| **MAIN OUTCOMES:** | Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 3 or 6 months after cardiac arrest |
| **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 good 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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:** | An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary.  The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022. |

# ASSESSMENT

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Trivial ● Small  ○ Moderate ○ Large ○ Varies ○ Don't know | Twelve studies (Admiraal, 2019; Backman 2018; Beretta, 2019; Carrai, 2016; Carrai, 2021; Duez, 2019; Hofmeijer, 2015; Rossetti, 2017; Scarpino, 2021; Sivaraju 2015; Sondag, 2017; Westhall, 2016) investigated the ability of a **benign EEG pattern** recorded **during the first five days after ROSC** to predict good outcome. The benign EEG pattern consisted of a **continuous or nearly continuous background without** superimposed **abundant/generalized periodic discharges or seizures**. In all 12 studies, the 2012 American Clinical Neurophysiology Society (ACNS) standardized terminology for use in critical care was adopted, or the pattern definitions were consistent with ACNS.  Twelve studies (Admiraal, 2019; Backman 2018; Beretta, 2019; Carrai, 2016; Carrai, 2021; Duez, 2019; Hofmeijer, 2015; Rossetti, 2017; Scarpino, 2021; Sivaraju 2015; Sondag, 2017; Westhall, 2016) investigated the ability of a **benign EEG pattern** recorded **during the first five days after ROSC** to predict good outcome. The benign EEG pattern consisted of a **continuous or nearly continuous background without abundant/generalized discharges or seizures**. In all 12 studies, the 2012 American Clinical Neurophysiology Society (ACNS) standardized terminology for use in critical care was adopted, or the pattern definitions were consistent with ACNS.  The criteria for both the superimposed discharges and the background varied slightly across studies.  In six studies (Admiraal, 2019; Backman, 2018; Duez, 2018; Hofmeijer, 2015; Sondag, 2017; Westhall, 2016), the definition of background was consistent (continuous or nearly continuous, normal voltage), with minor variations (see below), while criteria for superimposed discharges were different: four of these studies (Admiraal 2019; Backman 2018; Duez 2019; Westhall 2016) used the absence of abundant (> 50% of the record) periodic discharges or abundant spike-wave as a criterion (**definition A1a** in the systematic review), while two studies (Duez, 2019; Hofmeijer 2015; Sondag, 2019) used the absence of generalized periodic discharges as a criterion (**definition A1b** in the systematic review). One study (Duez, 2019) assessed the predictive value of both criteria.  Two of the four studies using definition A1a (Backman 2018; Westhall 2016) used an additional criterion (normal anteroposterior EEG gradient) to define a benign pattern. Two of these four studies (Westhall, 2016; Duez, 2019) also investigated a more restrictive definition by further adding reactivity.  Concerning background, besides the continuous or nearly continuous normal voltage, four studies (Carrai, 2016; Carrai, 2021; Rossetti 2017; Scarpino 2021) also included a low-voltage background among benign EEGs (**definition A2** in the systematic review). In one of these studies [Rossetti, 2017], reactivity was required to define EEG as favorable. Two studies (Beretta 2018); Sivaraju 2015), besides the continuous or nearly continuous normal voltage, alos included a discontinuous background (**definition A3** in the systematic review), provided that the voltage was normal [Sivaraju 2015] or that the background was reactive [Beretta 2018).  In the six studies using the A1a and A1b definitions (**continuous or nearly continuous, normal-voltage background without abundant/generalized periodic discharges or seizures**), sensitivity and specificity for good outcome prediction ranged from 51 to 63% and from 82% to 88% at 12h, respectively. At 24h, these were 39–78% and 67–100%. The highest specificities for good outcome (90-100%) were observed in studies using the most restrictive definition of benign EEG (A1a, reactive, normal gradient).  In studies assessing the EEG at multiple time points (Admiraal, 2019; Duez, 2019; Hofmeijer 2015) the specificities decreased, and the sensitivities increased over time.  In the four studies using the A2 definition [Carrai, 2021, 133; Carrai, 2016, 940; Scarpino 2021, 162; Rossetti, 2017, e674], at an early time window (<6 hours to 24 h after ROSC), specificities ranged between 87% to 98% and sensitivities ranged between 57% to 100% [Carrai, 2021, 133; Carrai 2016, 940; Scarpino, 2021, 162] At a later time window (48–72 h after ROSC) in two studies (Carrai 2016; Rossetti 2017) specificities were 83% and sensitivities 91% and 100%.  In one of the two studies [Beretta, 2019, 106374] using the A3 definition, the specificity to predict good outcome was 77% (sensitivity 77%) at 0-5 days from ROSC. In the other study [Sivaraju, 2015, 1264], the specificity for good outcome was 97% (sensitivity 72) within 72 hours after ROSC. This specificity decreased remarkably (84%) if the EEG record included discharges.  The overall certainty of the evidence for the use of the separate EEG modalities included was very low. Most studies had a moderate risk of bias, due to lack of blinding that may have caused a self-fulfilling prophecy. Imprecision was also an issue, due to the small sample size and the heterogeneity in timing of assessment and – partly – in definitions, which prevented pooling.  Admiraal MM, van Rootselaar AF, Hofmeijer J, et al. (2019) Electro- encephalographic reactivity as predictor of neurological outcome in postanoxic coma: a multicenter prospective cohort study. Ann Neurol 86:17–27.  Backman S, Cronberg T, Friberg H, et al. (2018) Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the target temperature management trial. Resuscitation 131:24–28  Beretta S, Coppo A, Bianchi E, et al. (2019) Neurological outcome of postanoxic refractory status epilepticus after aggressive treatment. Epilepsy Behav E&B 101:106374  Carrai R, Spalletti M, Scarpino M, et al. (2021) Are neurophysiologic tests reliable, ultra-early prognostic indices after cardiac arrest? Neurophysiol Clin (Clinical neurophysiology) 51:133–144  Carrai R, Grippo A, Scarpino M, et al. (2016) Time- dependent and independent neurophysiological indicators of prognosis in post-anoxic coma subjects treated by therapeutic hypothermia. Minerva Anestesiol 82:940–949  Duez CHV, Johnsen B, Ebbesen MQ, Kvaloy MB, Grejs AM, Jeppesen AN, Soreide E, Nielsen JF, Kirkegaard H (2019) Post resuscitation prognostica- tion by EEG in 24 vs 48h of targeted temperature management. Resusci- tation 135:145–152  Hofmeijer J, Beernink TM, Bosch FH, et al., (2015) Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 85:137–143  Rossetti AO, Tovar Quiroga DF, Juan E, et al. (2017) Electroencephalography pre- dicts poor and good outcomes after cardiac arrest: a two-center study. Crit Care Med 45:e674–e682  Scarpino M, Lolli F, Lanzo G, et al. (2021) SSEP amplitude accurately predicts both good and poor neurological outcome early after cardiac arrest; a post-hoc analysis of the ProNeCA multicentre study. Resuscitation 163:162–171  Sivaraju A, Gilmore EJ, Wira CR, et al. (2015) Prognostication of post-cardiac arrescoma: early clinical and electroencephalographic predictors of outcome.Intensive Care Med 41:1264–1272  Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, et al. (2017) Early EEG for outcome predic- tion of postanoxic coma: prospective cohort study with cost-minimiza- tion analysis. Crit Care 21:111  Westhall E, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, et al. (2016) Standardized EEG inter- pretation accurately predicts prognosis after cardiac arrest. Neurology 86:1482–1490 | One reason for higher specificity for good outcome prediction in the most restrictive definitions of favorable EEG could be the inclusion of EEG reactivity.  This was observed across different populations [Admiraal, 2019, 17; Duez, 2019], different subpopulations of the same study cohort [Backmann, 2018; Westhall, 2016], and in the same dataset when EEG reactivity was not considered [Westhall, 2016]. However, the assessment of EEG reactivity was not standardized in the studies. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Large ○ Moderate  ○ Small ○ Trivial ○ Varies  ● Don't know | None known. | A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to the delivery of futile care. |
| 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 of evidence for EEG with continuous or nearly continuous background pattern without abundant/generalized periodic discharges or seizures is very low because of bias (mainly due to lack of blinding) and imprecision. Although all studies adopted the ACNS terminology, there were some inconsistencies in the definition of periodic discharges. | The EEG background is affected by sedation and systemic organ dysfunction. How this may affect the ability of EEG to predict good neurological outcome is uncertain. |
| 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 | All prognostic studies defined good outcome as CPC 1–2 or mRS 0-3. | Additional outcomes about neurocognitive status and quality of life were not assessed. |
| 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 | Evidence from twelve studies shows that a continuous or nearly continuous EEG background with a normal voltage without abundant/generalized periodic discharges or seizures within 72h from ROSC predicts good neurological outcome after cardiac arrest with a specificity >80% and a sensitivity >50% in most studies. | The severity of periodic discharges (generalized vs abundant) is not measured consistently across studies.  Sedation might suppress some favorable EEG features, thus reducing the ability of EEG to predict good outcome. However, this remains to be investigated. |
| 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 EEG costs. However, specific equipment and skills are required for assessing 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 identify any studies specifically assessing costs of EEGs. |  |
| 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 EEGs. |  |
| 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 specific equipment and skills needed to assess EEGs are not available everywhere. 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 the 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 | A survey (Friberg, 2015, 158) published in 2015 showed that EEG is the most widely used predictor of neurological outcome after cardiac arrest. However, that survey was conducted in high-income countries. The availability of the equipment and skills required to use EEG for assessing post-cardiac arrest brain injury may be lower in other countries and communities. | Using a standard (ACNS) definition for the EEG patterns is important for their implementation. Most studies used the 2012 ACNS terminology but none used the 2021 ACNS terminology. |

# 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 a continuous or nearly continuous normal voltage EEG background without abundant/generalised periodic discharges or seizures within 72h from ROSC to predict good outcome in patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).**  **There is insufficient evidence to recommend for or against using a low voltage or a discontinuous EEG background on days 0-5 from ROSC to predict good neurological outcome after cardiac arrest (weak recommendation, very low-certainty evidence).**  **We suggest that the American Clinical Electrophysiology Society (ACNS) terminology be used to classify the EEG patterns used for prognostication (good practice statement).** |
| Justification |
| In making their recommendation in favor of a continuous or nearly continuous, normal-voltage EEG background without abundant/generalized periodic discharges or seizures as a predictor of good neurological outcome in patients who are comatose after cardiac arrest, the TF members considered the consistency of the evidence (12 studies, mostly with >80% specificity and >50% sensitivity) and the consistency of the definition, made using an ACNS or ACNS-compatible terminology.  The background definition was consistent in six of these studies. Although the criteria for periodic discharges varied slightly within this subgroup, this did not affect the prediction accuracy.  Evidence from the remaining six studies confirmed the ability of a continuous or nearly continuous, normal-voltage EEG background without seizures or discharges to predict good neurological outcome. These studies also included a low-voltage or discontinuous EEG background among the ‘benign’ EEG patterns. These patterns are farther from normal than a continuous or nearly continuous background, and their accuracy could not be assessed separately. The ILCOR TF considered the evidence supporting these patterns insufficient for recommending their use. |
| Subgroup considerations |
| None. |
| Implementation considerations |

|  |
| --- |
| Monitoring and evaluation |
|  |
| Research priorities |

The effects of sedation and systemic organ dysfunction on the predictive value of the EEG background should be investigated.

The value of low-voltage background and discontinuous reactive/normal voltage background fro predicting good outcome should be investigated

The value of EEG reactivity for predicting good outcome deserves further investigation using standardized stimulation and assessment.

It is not clear which aspect of periodic discharges (ie distribution, morphology, prevalence, etc.) has greatest importance in affecting the prognosis of a favorable EEG pattern.

The value of dominant EEG rhythms (e.g. theta) in prognostication after cardiac arrest deserves investigation.

The predictive value of favorable EEG patterns defined according the 2021 ACNS definitions deserves investigation, albeit the differences vs the 2012 definitions regarding the features used for predicting a good outcome are minimal.