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| Question |
| **High amplitude of the N20 wave of somatosensory evoked potenials (SSEPs) 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:** | A N20 wave voltage of median nerve somatosensory evoked potentials (SSEP), assessed within 96 h 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 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 was necessary.The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022. |

# 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 | Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The vast majority 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 EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | SSEPs were investigated in five observational studies [Endisch, 2015; Oh,2019; Glimmerween, 2020; Scarpino, 2021; Benghanem 2022]The amplitude was calculated in microvolts (μV) as the difference between the voltage of the N20 negative wave and the voltage of the following positive P25 wave **(N20–P25**), but in one study [Endisch,2015] the baseline-N20 amplitude was occasionally used if it was larger than the N20–P25 difference. One study [Benghanem, 2022] reported both N20–P25 and **N20–baseline** amplitudes. The largest amplitude of the two sides was used, except in one study [Glimmerween, 2020], where the smallest amplitude was used.In one study (Oh, 2019) an amplitude threshold >2.31 µV at 48-72h after ROSC predicted good outcome at six months with **97% specificity** and **53% sensitivity**.In one study [Benghanem, 2022], an amplitude threshold **>3.2 μV** measured at a median of 3[2-4] days after ROSC predicted good outcome at six monthswith **93% specificity** and **29% sensitivity**).In one study [Glimmerveen 2020] an amplitude threshold **>3.6 μV** (smallest of the two sides) at 48-72h after ROSCpredicted good outcome at six months with **96% specificity and 32% sensitivity**.In one study [Scarpino, 2021], an amplitude threshold > **4 μV at 12 h, 24 h, and 72 h** after ROSC predicted good outcome at six months with **specificities between 86 and 91%,** **with 48–51% sensitivity**.In one study [Endisch, 2015] an N20 amplitude threshold **>4.2 μV** at 24–96h predicted good outcome at ICU discharge with **92% specificity** and **28%** **sensitivity.**In three studies [Endisch, 2015; Scarpino, 2021; Oh, 2019] higher amplitude thresholds above 5 μV and up to 10 μV were investigated. Specificities ranged from **93% and 100%**, while **sensitivities** ranged from **6% to 37%.**In one study [Benghanem, 2022], an **N20-baseline amplitude >2 μV** predicted good outcome at six months with **73% specificity (39% sensitivity)** while an **N20 baseline amplitude >2.7 μV** predicted a good outcome at six months with **87% specificity and 28% sensitivity**.The risk of bias was moderate in four studies, and high in one study. | A universally recognised normal range for N20-P25 amplitude has not been established. SSEP recording methods need standardisation. The N20 amplitude is affected by recording parameters, such as the electrode position or montage and how the amplitude is calculated. While most studies measured the N20 amplitude as the difference between the N20 and the P25 peak, two studies calculated it as the N20-baseline difference in some or all patients. This variability may partly explain the variability of the SSEP thresholds.Limited evidence ([Glimmerveen 2020, Scarpino, 2022) suggests that the amplitude of the N20 SSEP wave evolves over time after ROSC.In all but one study (Glimmerveen 2020) the largest amplitude of the two sides was used. |
| Undesirable EffectsHow 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 therapeutic obstinacy. |
| 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 SSEP is very low, mainly because of lack of blinding, inconsistent voltage thresholds across studies, and serious imprecision.  | While the absence of the N20 SSEPs wave is probably not influenced by sedation and temperature, the effects of these confounders on the N20Amp are less known. |
| 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 | All studies defined good outcome as CPC 1–2. | There may be interindividual variations on how good neurological outcome is perceived. |
| 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 evidence shows that a high N20Amp predicts good neurological outcome after cardiac arrest with high specificity. In all but one study included in our review, an N20 amplitude threshold >4.0 µV yielded a specificity above 90%. However, the thresholds varied widely across studies. The methods to calculate the N20 amplitude were inconsistent. |  |
| 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 SSEP costs. However, specific equipment and skills are required for assessing SSEPs.  |  |
| 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 the costs of SSEPs.  |  |
| 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 related to this question. |  |
| 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 | We did not identify any studies related to this question. However, the specific equipment and skills needed to assess SSEPs are not available everywhere. 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 did not identify any studies related to this question. However, acceptability of SSEPs is likely. |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We did not identify any studies related to this question. | SSEPs have been used for decades and are implemented in many hospitals worldwide. However, the equipment and skills required for their assessment may represent an obstacle for their implementation. The lack of consensus about the N20Amp to use for predicting good neurological outcome may represent an issue. |

# 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 against using the amplitude of the N20 SSEP wave to predict good neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).** |
| Justification |
| Although very-low-certainty evidence suggests that a high N20 amplitude predicts good neurological outcome after cardiac arrest with high specificity, the amplitude threshold for this prediction varied widely across studies. The methods to calculate the N20 amplitude were inconsistent. There is observational evidence that sedative agents, especially Midazolam, decrease the N20 amplitude. Finally, the optimal timing for predicting good outcome using SSEP amplitude has not been established yet. In making their recommendation, the task force members also considered evidence from additional studies, not included in the 2021 review, showing an overlap in the distribution of the highest N20 wave amplitude values in patients with poor and good outcome. |
| Subgroup considerations |
| None |
| Implementation considerations |

Implementing SSEPs requires appropriate equipment and skills that may not be available anywhere, anytime. The assessment of the N20 amplitude for prognostication has only recently been introduced in clinical practice, and it is less established than the assessment of the simple presence or absence of the N20 SSEP wave.

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| Monitoring and evaluation |
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| Research priorities |
| The methods to calculate the N20 SSEP amplitude need to be standardized.The interrater variability in the assessment of the N20 SSEP amplitude must be investigatedThe optimal N20 SSEP amplitude for predicting good outcome needs to be establishedThe effects of sedation on the N20 SSEP amplitude must be investigated.There is still limited evidence on the correlation between time after ROSC and the N20 SSEP amplitude.There is still limited evidence on the added value of the combination of a high N20 SSEP wave amplitude with other predictors of good neurological outcome |