|  |  |
| --- | --- |
| Question | |
| **Absent N20 wave of somatosensory evoked potenials (SSEPs) 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:** | A bilaterally absent N20 wave of somatosensory evoked potentials (SSEP), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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

|  |  |  |
| --- | --- | --- |
| 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 | SSEPs were investigated in twenty observational studies [Grippo 2017 641; Scarpino 2019 (a) 115; Choi 2017 70; Maciel 2017 469; Dhakal 2016 116; Fatuzzo 2018 29; Leao 2015 322; Noirhomme 2014 6; Rossetti 2017 e674; De Santis 2017 119; Kim 2018 (a) 33; Ruijter 2019 203; Ruijter 2018 1534; Oddo 2018 2102; Sondag 2017 111; Hofmeijer 2015 137; Admiraal 2019 17; Dragancea 2015 (a) 164; Kim 2018 (b) e545; Scarpino 2019 (b) *in press*].  In four studies [Grippo 2017 641, 78 pts; Choi 2017 70, 80 pts; Maciel 2017 469, 41 pts; Scarpino 2019 (b) *in press*, 218 pts] ***a bilaterally absent N20 SSEPs wave within 24h from ROSC*** predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 33.3% to 57.7% (very-low certainty of evidence).  In one study [Scarpino 2019 (a) 115, 346 pts] ***an absent N20 wave on one side and an absent or low-voltage N20 wave on the other side within 24h from ROSC*** predicted poor neurological outcome at 6 months with 100% specificity and sensitivity 49.6% (very low certainty of evidence)  In eighteen studies [Dhakal 2016 116, 35 pts; Fatuzzo 2018 29, 457 pts; Leao 2015 322, 67 pts; Noirhomme 2014 6, 44 pts; Rossetti 2017 e674, 260 pts; De Santis 2017 119, 65 pts; Kim 2018 (a) 33, 127 pts; Ruijter 2019 203, 850 pts; Grippo 2017 641, 76 pts; Ruijter 2018 1534, 559 pts; Oddo 2018 2102, 188 pts; Sondag 2017 111, 178 pts; Hofmeijer 2015 137, 139 pts; Admiraal 2019 17, 38 pts; Scarpino 2019 (b) *in press*, 240 pts; Choi 2017 70, 81 pts; Dragancea 2015 (a) 164, 201 pts; Kim 2018 (b) e545, 116 pts] ***a bilaterally absent SSEPs N20 wave at 24-96h*** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 50% to 100% and sensitivity ranging from 18.2% to 69.1% (very-low certainty of evidence). | In three studies the specificity of a bilaterally absent N20 wave for prediction of poor neurological outcome was well below 100% (Dhakal 2016, 75[34.9-96.8]%; Leao, 2015, 50 [21.1-78.9]%; Sondag 2017, 82[66.5-92.5]%). For all these studies the certainty of evidence was very low.  Evidence supporting the use of an only monolaterally absent N20 SSEP wave combined with a low-voltage N20 on the opposite side was limited to one multicentre study [Scarpino 2019(a)]. In that study, no threshold for defining low voltage of the N20 wave was specified. |
| 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 SSEPs may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. The false positive rate of SSEPs was 0% with high precision in almost all studies included in our review. However, SSEPs are considered to be very accurate predictors of poor outcome and as such were often used, in combination with other predictors, for decisions regarding WLST. In three studies from the same group of investigators [Grippo, 2017; Scarpino 2019 (a); Scarpino 2019 (b)] WLST was not performed. However, the treating team was not blinded to the results of SSEPs.  In three studies the specificity of a bilaterally absent N20 wave for prediction of poor neurological outcome was well below 100% [Dhakal 2016, 75%; Leao, 2015, 50%; Sondag 2017, 82%]. The presence of survivors with false positive prediction in these studies demonstrates that WLST was not performed based only on SSEP results. |  |
| 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 certainty of evidence about SSEP is very low, mainly because the risk of self-fulfilling prophecy. | Strengths of SSEPs include lack of interference from sedation and temperature, and high precision. |
| 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 the vast majority of included studies, a bilaterally absent N20 SSEP wave predicts poor neurological outcome with high specificity and precision. 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 studies assessing SSEP costs. However, specific equipment and skills are required for assessing SSEPs. |  |
| 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 SSEPs. |  |
| 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 SSEPs. |  |
| 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 SSEPs 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 acceptability of SSEPs. 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 | 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.  Some of the false positives reported in the studies on SSEPs we included may have been due to implementation issues (i.e., unreadable tracings due to artifacts, rather than “true” absence of N20 wave). This has been already documented in literature (Bowes et al, 2012). |  |

# 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 bilaterally absent N20 SSEP wave in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).** |
| Justification |
| Almost all studies we included showed that a bilaterally absent N20 SSEP wave predicted poor neurological outcome with very high specificity and precision. SSEPs are often used for decisions on WLST, which may create a self-fulfilling prophecy. However, the presence of survivors with false positive results indicates that WLST based on SSEP results only is not standard practice. In addition, a 100% specificity for a bilaterally absent SSEP was documented in three studies where WLST was not performed. These three studies were led by the same group Two of these studies were conducted on multiple centres.  In making this recommendation, the task force also considered that SSEP have a low risk of confounding from TTM or sedation and a large size of effect (high precision).  In order to limit the risk of self-fulfilling prophecy, combining SSEP with other indices of poor neurological outcome is prudent. |
| Subgroup considerations |
| None. |
| Implementation considerations |

|  |
| --- |
| Monitoring and evaluation |
| None. |
| Research priorities |
| Further studies are needed to evaluate the added value of assessing SSEPs in combination with other predictors of poor neurological outcome after cardiac arrest.  The accuracy of a unilaterally absent SSEP wave combined with a low-voltage contralateral SSEP wave deserves further investigation. |