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| Question | |
| **Neuron Specific Enolase (NSE) 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:** | Neuron specific enolase (NSE), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 were 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 | NSE was investigated in thirteen observational studies [Dhakal 2016 116; Lee 2013 1387; Chung-Esaki 2018 99; Vondrakova 2017 172; Duez 2018 79; Kim 2018 33; Stammet 2015 2104; Zellner 2013 1382; Tsetsou 2018 104; Helwig 2017 68; Moseby-Knappe 2017 89; Zhou 2019 343; Rossetti 2017 e674].  In thirteen studies [Dhakal 2016 116, 78 pts; Lee 2013 1387, 224 pts; Chung-Esaki 2018 99, 72 pts; Vondrakova 2017 172, 153 pts; Duez 2018 79, 115 pts; Kim 2018 33, 125 pts; Stammet 2015 2104, 686 pts; Zellner 2013 1382, 110 pts; Tsetsou 2018 104, 61 pts; Helwig 2017 68, 100 pts; Moseby-Knappe 2017 89, 276 pts; Zhou 2019 343, 34 pts; Rossetti 2017 e674, 329 pts] ***NSE with a cut-off ranging from 33 to 120 μg/L within 72h*** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 75% to 100% and sensitivity ranging from 7.8% to 83.6% (certainty of evidence from moderate to very low).  In one study [Vondrakova 2017 172, 153 pts] ***NSE with a cut-off of 50.2 μg/L at day 4*** predicted poor neurological outcome at 1 month with 100% specificity and 42.1% sensitivity (moderate certainty of evidence). |  |
| 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 prediction based on NSE levels above the cut-off chosen for predicting poor neurological outcome may lead to treatment restrictions in patients destined to a good recovery. This is likely to occur given the variability of cut-offs for 100% specificity across studies, and the potential for confounding from haemolysis or other extracerebral sources of NSE. |  |
| 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 from NSE is very low because of the risk of bias, especially self-fulfilling prophecy. | Differently from other predictors, like those based on clinical examination, NSE is not affected by sedation or paralysis, and it can be assessed blindly. However, in most of the studies we evaluated, results of NSE measurement were not concealed from the treating team.  An additional source of confounding is represented by the different available methods of measurement. |
| 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 | Neurologic 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%, and that 59% of them 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 | Considering the high specificity of NSE, the balance of effects favours the predictor. |  |
| 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 | The costs of biomarkers’ assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on NSE has been included in our review. |  |
| 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 NSE for prognostication after cardiac arrest. |  |
| 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. |  |
| 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 | A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available. |  |
| 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 study assessing acceptability, but 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. Assessment of biomarkers requires resources that may not be universally available. However, NSE is routinely measured in many hospitals and clinics as a tumour biomarker. The most important caution required during withdrawing and managing the blood sample is avoiding haemolysis. |  |

# 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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| Recommendation |
| **We suggest using neuron specific enolase within 72h after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).** |
| Justification |
| Limited evidence suggests that high levels of neuron specific enolase (NSE) predict poor neurological outcome with 100% specificity at 24-72h after cardiac arrest. There is a wide variability of thresholds for 100% specificity across studies. Lack of blinding was a limitation in most of included studies, even if WLST based only on NSE was not documented. |

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| Subgroup considerations |
| None. |
| Implementation considerations |

Measurement of NSE levels requires a specific equipment. NSE levels may vary across different methods o measurement.

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| Monitoring and evaluation |
| |  | | --- | | Research priorities | | Large cohort studies are desirable to identify a consistent NSE threshold for predicting poor neurological outcome after cardiac arrest.  There is very little evidence concerning the predictive value of NSE measured later than 72h after ROSC. | |