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| QUESTION |
| **Neuron Specific Enolase (NSE) 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:** | Neuron specific enolase (NSE), assessed within 72 h after cardiac arrest. |
| **COMPARISON:** | *None.* |
| **MAIN OUTCOMES:** | Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at ICU discharge or at 6-12 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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. A systematic review was published in 2021 identified three studies that evaluated the use of NSE for prediction of good functional outcome and an updated search conducted in May 2022 identified one more study. |

# 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 majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on the high likelihood of severe hypoxic brain injury are the results of 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. Identifying patients with a likely good outcome based on prognostication results could facilitate the continuation of care in some unconscious patients.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Trivial● Small○Moderate○ Large○ Varies○ Don’t know | NSE was investigated in four observational studies [Zellner, 2013; Moseby-Knappe, 2021; Streitberg 2017, Wihersaari]. In two studies [Zellner, 2013; Moseby-Knappe, 2021] blood NSE values within the upper limit of the normal range (17–18 μg/L) at 24h predicted good neurological outcome at 6 months with specificities of 85% and 89%, respectively (sensitivities 46% and 26%, respectively). At 48h normal NSE values predicted good neurological outcome with specificities of 84% and 89% (corresponding sensitivities 58% and 41%). certainty of evidence low or moderateOne study [Moseby-Knappe, 2021] reported that normal NSE blood levels ( =<17 μg/L) at 72h predicted good neurological outcome at 6 months after cardiac arrest with specificity of 80% and sensitivity of 75%. certainty of evidence low or moderateIn one study [Streitberger, 2017] normal blood NSE levels (=< 17 μg/L ) at 72h predicted good neurological outcome at ICU discharge determined as CPC scores 1–3 with specificity of 87% and sensitivity of 33%. (certainty of evidence low or moderate)In one study [Wihersaari, 2022] normal NSE values (=< 17 μg/L ) at 48 hours predicted favorable functional outcome at 12 months with a specificity of 54% and sensitivity of 90%.  | All three studies determined the specificity for the normal upper limit of blood NSE levels. At 48h normal NSE blood level predicted good outcome with good specificities (84–89%) but only moderate sensitivity (41–58%).Patients dying from non-neurological causes may influence the neuronal biomarkes’ ability to predict good outcome |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Large○ Moderate○ Small● Trivial○Varies ○Don't know | False positive prediction occurring in patients having serum NSE levels below the upper limit of normal range (17 μg/L ) may lead to falsely optimistic prediction, inappropriate continuation of life sustaining therapy and falsely optimistic information provided for relatives in patients destined to poor recovery. This is possible with the reported cut-off of 17 μg/L for blood NSE given the specificity less than 90% to predict good outcome reported in all three studies.  | NSE has confounding sources (red blood cells;haemolysis, neuroendocrine tumours), however, this is more of a problem in poor outcome prediction. Method for NSE determination vary between laboratories and can influence levels measured in the clinical/experimental settings |
| 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 for NSE in predicting good outcome is very low. There is imprecision given the wide variation in the sensitivities and specificities of NSE less than the upper limit of normal for the prediction of good outcome. In addition, there is the problem of indirectness as most studies have included only patients included in interventional randomized controlled trials with strict inclusion criteria. There is a clear risk of bias based on the use of NSE in clinical practice to withdraw care in case of high levels, i.e. a 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 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.  |
| 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 | It is common to define CPC scores 1–2 as good neurological outcome after cardiac arrest. One found study [Streiberger, 2017] used CPC scores 1–3 as the definition for good neurological recovery. There is limited data available regarding if some people value a CPC 1-3 as the same way as a CPC 1-2. |  |
| 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 | NSE is recommended for the prediction of poor outcome in cardiac arrest patients Therefore the result will be available in many patients, and in case of a low level will favour prolonging care until other means of prognostication can be completed or the patient´s clinical status changes.  |  |
| 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 | The costs of biomarkers’ assessment are higher when compared with prognostication without biomarkers. No study assessing cost from prognostication based on NSE has been included in our review. | NSE is widely available in clinical laboratories |
| 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 costs of NSE for prognostication after cardiac arrest.  |  |
| 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 addressing cost-effectiveness. |  |
| 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 | A problem of inequity is possible, since assessment of biomarkers is a resource that cannot be universally available.  | However, NSE is rather widely available in clinical laboratories |
| AcceptabilityIs 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 as the use of NSE is already part of a multimodal approach to determine the prognosis after cardiac arrest.  |  |
| FeasibilityIs 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 already included as a means to identify patients with poor outcome as part of a multimodal approach. In addition, 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 normal NSE (<17 μg/L) within 72 hours after ROSC, in combination with other tests, for predicting favorable neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
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| Justification |
| Four studies including more than 1000 patients suggest that a normal NSE value at 48 hours has some accuracy to predict good functional outcome.  |
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| Subgroup considerations |
| The studies have included mainly patients with OHCA, a cardiac origin and those who have undergone TTM.  |
| Implementation considerations |

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| Monitoring and evaluation |
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| Research priorities |

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* Larger studies including heterogenous samples of cardiac arrest including those with a non-cardiac cause of the arrest and in-hospital cardiac arrest
* The use of NSE together with other recommended modalities for predicting good outcome

References:

Moseby-Knappe M, Mattsson-Carlgren N, Stammet P, Backman S, Blennow K, Dankiewicz J, Friberg H, Hassager C, Horn J, Kjaergaard J, Lilja G, Rylander C, Ullen S, Unden J, Westhall E, Wise MP, Zetterberg H, Nielsen N, Cronberg T (2021) Serum markers of brain injury can predict good neurological outcome after out-of-hospital cardiac arrest. Intensive Care Med 47:984–994

Zellner T, Gärtner R, Schopohl J, Angstwurm M NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest, Resuscitation 84. 1382–1386

Streitberger KJ, Leithner C, Wattenberg M, et al. Neuron-Specific Enolase Predicts Poor Outcome After Cardiac Arrest and Targeted Temperature Management: A Multicenter Study on 1,053 Patients

Wihersaari L, Reinikainen M, Furlan R, Mandelli A, Vaahersalo J, Kurola J, Tiainen M, Pettilä V, Bendel S, Varpula T, Latini R, Ristagno G, Skrifvars MB.Neurofilament light compared to neuron-specific enolase as a predictor of unfavourable outcome after out-of-hospital cardiac arrest. Resuscitation. 2022 May;174:1-8