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| Question | |
| **S-100B protein 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:** | S-100B protein, 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 | S-100B protein was investigated in three observational studies [Jang 2019 e14496; Duez 2018 79; Stammet 2017 153].  In two studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts] ***S-100B protein with a cut-off ranging from 3.58 to 16.6 μg/L immediately after ROSC*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 2.8% to 26.9% (certainty of evidence from moderate to very low).  In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.193 to 2.59 μg/L at 24h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 10.1% to 77.6% (certainty of evidence from moderate to very low).  In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.159 to 3.67 μg/L at 48h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 5% to 77.6% (certainty of evidence from moderate to very low).  In three studies [Jang 2019 e14496, 97 pts; Duez 2018 79, 115 pts; Stammet 2017 153, 687 pts] ***S-100B protein with a cut-off ranging from 0.202 to 1.83 μg/L at 72h*** predicted poor neurological outcome from 3 to 6 months with 100% specificity and sensitivity ranging from 5% to 61.2% (certainty of evidence from moderate to very low). | Although specificity of S-100B protein is high, the variability of thresholds for 100% specificity is wide. In addition, the number of studies documenting S-100B protein as a predictor of poor outcome after cardiac arrest is low. |
| 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 S-100B protein 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 extracerebral sources of S-100B protein. |  |
| 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 S-100B protein is low because of the limitations of included studies, and the wide inconsistency of the thresholds for 100% specificity.  S-100B protein was not used as a criterion for WLST in any of the three included studies. However, in one of these studies, the treating team was not blinded to the results of S-100B protein measurement.  The major problems with S-100B protein are the very few studies assessing it as a predictor after cardiac arrest and the wide variability of thresholds. | Differently from other predictors, like those based on clinical examination, S-100B protein is not affected by sedation or paralysis, and it can be assessed blindly. In two of the three studies we included results of S-100B protein were concealed from the treating team.  An additional source of confounding is represented by extracerebral sources of S-100B protein (of particular relevance for post-CPR patients, musculoskeletal tissues). |
| 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 | Even if the specificity of S-100B protein is high, the variability of S-100B thresholds for 100% specificity is very high. The number of studies assessing S-100B is low. |  |
| 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 S-100B protein 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 S-100B protein 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. |  |

# 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 against using S-100B protein for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).** |
| Justification |
| Although the risk of self-fulfilling prophecy for S-100B protein is lower than that observed in other predictors, the evidence is limited by the low number of available studies and the wide variability of thresholds for 100% specificity across studies. This may also be due to the presence of extracerebral sources of S-100B protein and possibly to indirectness. In fact, S-100B protein does not originate from the neurons, but from the glial cells. |

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

Measurement of S-100B requires a specific equipment.

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| Monitoring and evaluation |
| None. |
| Research priorities |
| Large cohort studies are desirable to identify a consistent S-100B protein threshold for predicting poor neurological outcome after cardiac arrest. |