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| Question |
| **Myoclonus and status myoclonus 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:** | Myoclonus or status myoclonus, 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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:** | 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.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, and the topic needs an update. |

# 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 | 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 EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | **Myoclonus**Myoclonus was investigated in eight studies [Sadaka 2015 292; Fatuzzo 2018 29; Rossetti 2017 e674; Kongpolprom 2018 509; Sivaraju 2015 1264; Dhakar 2018 114; Lybeck 2017 146; Reynolds 2018 249]. In eight studies [Sadaka 2015 292, 58 pts; Fatuzzo 2018 29, 493 pts; Rossetti 2017 e674, 367 pts; Kongpolprom 2018 509, 51 pts; Sivaraju 2015 1264, 100 pts; Dhakar 2018 114, 59 pts; Lybeck 2017 146, 933 pts; Reynolds 2018 249, 583] ***presence of myoclonus within 96h*** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 77.8% to 97.8% and sensitivity ranging from 18.2% to 39.6% (very-low certainty of evidence). Definitions of myoclonus were provided in only three of these eight studies [Sadaka 2015 292; Dhakar 2018 114; Lybeck 2017 146]. These definitions differed among studies. Status myoclonusStatus myoclonus was investigated in two studies [Ruknuddeen 2015 304, 121 pts; Zhou 2019 343, 226 pts]. In these two studies, **presence of status myoclonus within 72h** predicted poor neurological outcome from hospital discharge to 6 months with specificity ranging from 97.0% to 100% and sensitivity ranging from 30.6% to 49.1% (very-low certainty of evidence).Status myoclonus was not defined in Zhou, 2019. In Ruknuddeen 2015 304, status myoclonus was defined as “spontaneous or sound-sensitive, repetitive, irregular brief jerks in both face and limb present most of the day within 24 h post-CA”. This definition was derived from Wijdicks 1994 239. |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small● Trivial○ Varies ○Don't know | As for every other predictor of poor outcome, a false positive result of myoclonus may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. None of the studies included in our systematic review used myoclonus in isolation as a criterion for WLST. |  |
| 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 myoclonus is very low. In particular, the definition of myoclonus was not provided in all studies, and when it was, it was inconsistent across studies.  | Like other clinical predictors, myoclonus cannot be assessed blindly, so that there is a risk of self-fulfilling prophecy. There is a potential of confounding with Lance-Adams syndrome, a benign form of post-anoxic myoclonus that can occur early after arrest.  |
| 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 | 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%. 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 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 available evidence shows that presence of myoclonus was associated with poor outcome after cardiac arrest. In most studies, specificity was higher than 90% but the 95% confidence intervals were wide. The specificity of status myoclonus was higher than that of myoclonus, but only two studies were included. Definitions were inconsistent for both myoclonus and status myoclonus.  |  |
| 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 | No specific resources are required for assessing myoclonus per se. However, post-anoxic myoclonus is often associated with epileptiform activity on EEG, so that when assessing myoclonus recoding a simultaneous EEG appears to be reasonable.  |  |
| 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 myoclonus |  |
| 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 of myoclonus.  |  |
| 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 | Considering the negligible costs of assessing myoclonus, a problem of inequity is unlikely. |  |
| 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 research that assessed acceptability, but acceptability is likely. |  |
| 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. The assessment of myoclonus does not require any special equipment. However, the examiner needs to be familiar with the basics of clinical neurological examination and be aware of the potential of confusing a malignant myoclonus with Lance-Adams Syndrome. EEG may provide additional information about the presence of epileptiform activity during myoclonic jerks. This may suggest that myoclonus as a prognostic index should be better evaluated in contexts where EEG analysis is 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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| Recommendations |
| **We suggest using presence of myoclonus or status myoclonus within 96h after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We also suggest recording EEG in presence of myoclonic jerks in order to detect an associated epileptiform activity.** |
| Justification |
| Although the definitions of both myoclonus and status myoclonus are absent or inconsistent in most studies, the presence of myoclonus is associated with poor outcome in patients who are comatose after resuscitation from cardiac arrest and it may be useful within the context of a multimodal prognostic assessment. Myoclonus and status myoclonus are inconsistently associated with epileptiform activity on EEG. |
| Subgroup considerations |
| None. |
| Implementation considerations |

 None.

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| Monitoring and evaluation |
| None. |
| Research priorities |
| Achieving a uniform and consensus-based definition of both myoclonus and status myoclonus is necessary. The role of EEG as an additional tool to investigate the nature and the prognostic significance of myoclonus deserves investigation.  |