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| Question | |
| **Corneal reflex 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:** | Corneal reflex (CR), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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, and 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 | CR was investigated in fourteen observational studies [Choi 2017 70; Chung-Esaki 2018 99; Kim 2013 134; Ryoo 2015 2370; Sivaraju 2015 1264; Matthews 2018 66; Fatuzzo 2018 29; Dragancea 2015 164; Solari 2017 804; Kongpolprom 2018 509; Zhou 2019 343; Greer 2013 (a) 1546; Greer 2013 (b) 899; Kim 2018 57].  In three studies [Choi 2017 70, 115 pts; Kim 2013 134, 51 pts; Ryoo 2015 2370, 172 pts;] ***absent corneal reflex immediately after ROS*C** predicted poor neurological outcome at hospital discharge with specificity ranging from 25.8% to 50% and sensitivity ranging from 93.2% to 96.4% (very-low certainty of evidence).  In two studies [Sivaraju 2015 1264, 97 pts; Matthews 2018 66, 137 pts;] ***absent corneal reflex at ≤24h*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 58.6% to 65.7% and sensitivity ranging from 51% to 79.4% (very-low certainty of evidence).  In five studies [Fatuzzo 2018 29, 490 pts; Sivaraju 2015 1264, 83 pts; Kongpolprom 2018 509, 51 pts; Dragancea 2015 164, 33 pts; Solari 2017 804, 99 pts] ***absent corneal reflex at 36-72h*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 88.9% to 100% and sensitivity ranging from 33.3% to 67.3% (very-low certainty of evidence).  In four studies [Chung-Esaki 2018 99, 85 pts; Greer 2013 (a) 1546, 104 pts; Greer 2013 (b) 899, 80 pts; Matthews 2018 66, 137 pts] ***absent corneal reflex at 72h*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 94.3% to 100% and sensitivity ranging from 32.4% to 48.8% (very-low certainty of evidence).  In five studies [Dragancea 2015 164, 127 pts; Kim 2018 57, 173 pts; Matthews 2018 66, 137 pts; Kongpolprom 2018 509, 51 pts; Greer 2013 (a) 1546, 59 pts] ***absent corneal reflex at 72h-day 7*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 98.8% to 100% and sensitivity ranging from 23.1% to 64.1% (very-low 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 a bilaterally absent corneal reflex may suggest that poor neurological outcome is likely in a patient with an eventually good neurological recovery. Our evidence review shows that this is more likely to occur during the first 72h after ROSC. Interference from sedation and/or paralysis may partly explain this. WLST based uniquely on an absent corneal reflex is unlikely. None of the studies included in our systematic review used corneal reflex as a criterion for WLST. |  |
| 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 for corneal reflex is very low because of the risk of bias, especially self-fulfilling prophecy, and the potential pharmacological interference on index assessment. | CR is prone to confounding due to sedation and paralysis, especially during targeted temperature management (TTM).  Similarly to other predictors based on clinical examination, corneal reflex cannot be concealed from the treating team, which implies the risk of self-fulfilling prophecy. |
| 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 | Considering the high specificity of corneal reflex assessed at 72h or later after cardiac arrest, and the low likelihood that WLST is based only on corneal reflex, the balance of effects favors 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 | Costs for the assessment of corneal reflex are virtually nil. No study assessing savings from prognostication based on corneal reflex 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 corneal reflex. |  |
| 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 | Considering the negligible costs of corneal reflex, a problem of inequity is unlikely. |  |
| 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, 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. The assessment of corneal reflex does not require special skills or equipment. Nevertheless, the examiner needs to be familiar with the basics of clinical neurological examination. |  |

# 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 bilateral absence of corneal reflex at 72h or later after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).** |
| Justification |
| Low-certainty evidence suggests that prediction of poor neurological outcome using CR can be made with high specificity at 72h or later after cardiac arrest. This predictor is prone to confounding due to the effects of sedatives or muscle relaxants used for TTM or to facilitate ventilation. Only part of the included studies specifically excluded the presence of residual sedation or paralysis at the time CR was assessed. Lack of blinding is a major limitation of CR, however WLST based on CR only has not been documented in any of the studies included in our review and appears to be unlikely.  Despite its limitations, given the easiness of assessment and the minimal costs and required equipment, the balance between the costs and benefits favours benefits. Combining CR with other predictors is reasonable. |

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

CR is easy to implement. However, the examiner needs to be familiar with the basics of clinical neurological examination.

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| None. |
| Monitoring and evaluation |
| None. |

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| Research priorities |
| Absence of residual effects from sedatives or paralyzing agents needs to be specifically assessed in studies evaluating the accuracy of predictors based on clinical examination after cardiac arrest. |