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| Question |
| **Pupillary light 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:** | Pupillary light reflex (PLR), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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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| 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 | A bilaterally absent standard pupillary light reflex was investigated in twenty-four observational studies [Choi 2017 70; Chung-Esaki 2018 99; Kim 2013 57; Ryoo 2015 2370; Javaudin 2018 8; Sivaraju 2015 1264; Scarpino 2019 *in press*; Dhakal 2016 116; Matthews 2018 66; Oddo 2018 2102; Fatuzzo 2018 29; Tsetsou 2018 104; Dragancea 2015 164; Solari 2017 804; Rossetti 2017 e674; Hofmeijer 2015 137; Kongpolprom 2018 509; Roger 2015 231; Zhou 2019 343; Greer 2013 (a) 1546; Greer 2013 (b) 899; Ruijter 2015 1845; Kim 2018 33; Lee 2017 1628]. In four studies [Choi 2017 70, 115 pts; Kim 2013 57, 51 pts; Ryoo 2015 2370, 172 pts; Javaudin 2018 8, 10151 pts] ***absent standard pupillary light reflex immediately after ROS*C** predicted poor neurologic outcome at hospital discharge or 1 month with specificity ranging from 47.6% to 75.9% and sensitivity ranging from 65.5% to 86.7% (very-low certainty of evidence).In five studies [Sivaraju 2015 1264, 97 pts; Scarpino 2019 *in press*, 336 pts; Dhakal 2016 116, 99 pts; Matthews 2018 66, 392 pts; Oddo 2018 2102, 137 pts] ***absent standard pupillary light reflex at ≤24h*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 80% to 92.3% and sensitivity ranging from 26.5% to 63.2 % (very-low certainty of evidence).In three studies [Fatuzzo 2018 29, 490 pts; Dragancea 2015 164, 36 pts; Solari 2017 804, 99 pts] ***absent standard pupillary light reflex at 36-72h*** predicted poor neurologic outcome from 3 months to 12 months with specificity ranging from 95.8% to 100% and sensitivity ranging from 36.5% to 48.4% (very-low certainty of evidence).In five studies [Oddo 2018 2102, 279 pts; Hofmeijer 2015 137, 272 pts; Sivaraju 2015 1264, 83 pts; Kongolprom 2018 509, 51 pts; Roger 2015 231, 61 pts] ***absent standard pupillary light reflex 48-72h*** predicted poor neurologic outcome from hospital discharge to 6 months with specificity ranging from 89.7% to 100% and sensitivity ranging from 17.8% to 58.2% (very-low certainty of evidence). In eight studies [Dhakal 2016 116, 98 pts; Greer 2013 (a) 1546, 104 pts; Greer 2013 (b) 899, 80 pts; Chung-Esaki 2018 99, 90 pts; Ruijter 2015 1845, 47 pts; Matthews 2018 66, 137 pts] ***absent standard pupillary light reflex at 72h*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 93.6% to 100% and sensitivity ranging from 10.8% to 29.2% (very-low certainty of evidence).In seven studies [Dragancea 2015 164, 78 pts; Kim 2018 33, 192 pts; Lee 2017 1628, 53 pts; Zhou 2019 343, 189 pts; Matthews 2018 66, 137 pts; Kongolprom 2018 509, 51 pts; Greer 2013 (a) 1546, 59 pts] ***absent standard pupillary light reflex from 72h to day 7*** predicted poor neurologic outcome from hospital discharge to 12 months with specificity ranging from 92.3% to 100% and sensitivity ranging from 17.9% to 63.1% (very-low certainty of evidence). |  |
| Undesirable EffectsHow 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 pupillary reflex may suggest a likely poor neurological outcome in a patient destined to a good recovery. Our evidence review shows that this is more likely to occur during the first 36h after ROSC, which may partly be explained with Interference from sedation. However, none of the studies included in our systematic review used pupillary reflex 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 from pupillary reflex is very low because of the risk of bias, especially self-fulfilling prophecy, and the risk of pharmacological interference on index assessment.  | Similarly to other predictors based on clinical examination, pupillary reflex cannot be concealed from the treating team, which implies the risk of self-fulfilling prophecy.Pupillary reflex is prone to confounding due to sedation.The characteristics of the light stimulus eliciting the pupillary reflex are not standardized. |
| 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%, 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 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 | Considering the high specificity of pupillary light reflex when evaluated at 72h or later, the balance of effects favors the predictor. |  |
| 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 | Costs for the assessment of pupillary reflex are negligible. On the other side, no study assessing savings from prognostication based on pupillary reflex has been included in our review |  |
| 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 pupillary light reflex.  |  |
| 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 | Considering the negligible costs of pupillary light reflex, 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 study assessing 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 | Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of pupillary light reflex does not require special skills. The only equipment needed is a light source. 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 pupillary light reflex at 72h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).**  |
| Justification |
| For standard pupillary light reflex, limited evidence suggests that the highest specificity for prediction of poor neurological outcome is achieved at 72h or later after cardiac arrest. This may be partly due to confounding from the effect of sedatives used for TTM or to facilitate ventilation. Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review.Despite its limitations, given the easiness of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.  |

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

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

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| Monitoring and evaluation |
| None. |

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| Research priorities |
| Absence of residual effects from sedatives needs to be specifically assessed in studies evaluating the accuracy of predictors based on clinical examination after cardiac arrest. The interrater agreement for the assessment of standard pupillary light reflex in patients resuscitated from cardiac arrest deserves investigation.  |