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| Question |
| **Should presence of pupillary light reflex (PLR) vs. absence be used for predicting good neurological outcomes in children after cardiac arrest?** |
| **Population:** | Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause. |
| **Intervention:** | Pupillary light reflex (PLR) present within 10 days after cardiac arrest. |
| **Comparison:** | Non-reactive pupillary response |
| **Main outcomes:** | Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2. |
| **Study DESIGN** | Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.  |
| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022. |

# 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 uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | The predictive ability of presence of pupil reactivity to classify good neurological outcome was evaluated in 8 studies [Abend 2012 32, Anton-Martin 2020 607, Brooks 2018 324, Ducharme-Crevier 2017 452, Fink 2014 664, Topjian 2021 282, Nishisaki 2007 10, Lin 2020 534], in 402 patients, within 1 hour, 6-12 h, 24h, and 72 h post-resuscitation. Most studies had a sensitivity greater than 82% at all assessment time points with the exception of Lin 2020 (50%) and Anton-Martin 2020 (40%) and corresponding FPR ranged from 3.2% to 67%. Within 12 hours of ROC the FPR was less than 33% in 3 out of 4 studies reporting this time period [Anton-Martin 2020 607, Brooks 2018 324, Lin 2020 534]. FPR increased (38-68%) at 24-72 hours and corresponding sensitivity for predicting good neurological outcome was 100% at 48-72 hrs following ROC [Abend 2012 32, Fink 2014 664]. No studies evaluated automated pupillometer monitoring devices.  |  |
| 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 of a good outcome and continued treatment based on pupillary reactivity may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes pupil reactivity (e.g. medication).  |  |
| 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 pupil light reflect is very low because of the risk of bias, especially self-fulfilling prophecy. |  |
| 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 | Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological outcome. |  |
| 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 sensitivity of pupillary light reflex and lower false positive rate in the first 12 hours, the balance of effects favours use of pupillary light reflex as a predictor of good neurological outcome in the early time period after ROC. |  |
| 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. However, 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 assessing cost 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 key requirement is a light source. 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 within 12 hours after ROSC for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very low certainty of evidence).**  |
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| Justification |
| For pupillary light reflex, limited evidence suggests that the specificity for prediction of good neurological outcome is similar across all assessment time points (<1 hour to 72hours or later) after cardiac arrest, although the FPR ranges from 3.2-67%.This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions (e.g., targeted temperature management) or to facilitate ventilation. No studies reported any assessment of counfounding influence of medication. No studies included blinding of test results from treating clinician and only one study had blinded outcome assessment.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 ease of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.  |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| Pupillary light reflect is an easy clinical assessment; however, the examiner requires knowledge of basic neurological examination. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| The examination of the impact of residual medication on pupillary light reflex assessment in infants and children is needed. No studies evaluated automated pupillometer monitoring devices, research is needed to assess cost and benefits of the use of pupillometry compared to pupillary light reflex assessment. |

# References Summary