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| Question |
| **Automated pupillary reflex (pupillometry) 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 reflex, automatically 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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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| 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 | Automated assessment of pupillary reflex to light (PLR) has been made by measuring two variables:1. The percentage of reduction in pupillary size, reported as qPLR
2. The neurological pupil index (NPi), based on several variables, such as pupillary size, percentage of constriction, constriction velocity and latency.

**AUTOMATED PUPILLOMETRY: qPLR**Quantitative pupillary light reflex was investigated in three observational studies [Oddo 2018 2102; Heimburger 2016 88; Solari 2017 804]. In three studies [Oddo 2018 2102, 434 pts; Heimburger 2016 88, 82 pts; Solari 2017 804, 101 pts] ***qPLR from 0% to 13% at 24h*** predicted poor neurological outcome from 3 months to 12 months with specificity ranging from 77.8% to 98.9% and sensitivity ranging from 17% to 66% (certainty of evidence from moderate to very low). In three studies [Oddo 2018 2102, 356 pts; Heimburger 2016 88, 82 pts; Solari 2017 804, 101 pts] ***qPLR from 0% to 13% at 48h*** predicted poor neurological outcome from 3 months to 12 months with specificity ranging from 95.7% to 100% and sensitivity ranging from 18.1% to 58.5% (certainty of evidence from low to very low). In one study [Oddo 2018 2102, 234 pts] ***qPLR=0% at 72h*** predicted poor neurological outcome at 3 months with 100% specificity and 4.9% sensitivity (moderate certainty of evidence).**AUTOMATED PUPILLOMETRY: NPi**NPi was investigated in three observational studies [Riker 2019 *in press*; Obling 2019 *in press*; Oddo 2018 2102]. In three studies [Riker 2019 *in press*, 52 pts; Obling 2019 *in press*, 127 pts; Oddo 2018 2102, 450 pts] ***NPi from 0 to 2.40 within 24h*** predicted poor neurological outcome from hospital discharge to 3 months with 100% specificity and sensitivity ranging from 22% to 43.9% (certainty of evidence from low to very low). In one study [Oddo 2018 2102, 361 pts] ***NPi≤2 at 48h*** predicted poor neurological outcome at 3 months with 100% specificity and 18.8% sensitivity (moderate certainty of evidence).In one study [Oddo 2018 2102, 271 pts] ***NPi≤2 at 72h*** predicted poor neurological outcome at 3 months with 100% specificity and 16.9% sensitivity (moderate certainty of evidence). | Differently from standard pupillary light reflex, in quantitative pupillometry the reflex is assessed in standard and reproducible conditions.Calculation of NPi is based on a proprietary algorithm.Results of qPLR suggest that prediction is more accurate if assessment is performed at 72h from cardiac arrest. However, this is based on only one study. |
| 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 quantitative pupillometry may suggest that poor neurological outcome is likely in patients with an eventually good neurological recovery. Differently from standard pupillary light reflex, NPi showed a consistent 0% false positive rate at all time points in a single multicenter study. However, this needs to be confirmed in further studies. None of the studies included in our systematic review used pupillometry 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 pupillometry is low. In some of the studies we included, the results of pupillometry were conceived to the treating team. However, results of standard PLR - that are inevitably correlated to those of pupillometry – cannot be concealed. The thresholds for 100% specificity for both qPLR and NPi are inconsistent.  | An additional source of confounding is represented by the different available devices and methods of measurement. |
| 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 | Considering the high specificity and the reproducibility of quantitative pupillometry, 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 | Quantitative pupillometry requires a specific equipment, with relevant costs. These costs may vary according to the model of pupillometer and possibly across different countries. The technology allowing portable pupillometry is at its beginning and costs may decrease in the future.  |  |
| 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 pupillometry.  |  |
| 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 pupillometry.  |  |
| 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 | The costs of pupillometry are higher than those of standard pupillary light reflex. This may represent a problem in terms of equity, if pupillometry will consistently demonstrate to be superior to standard pupillary light reflex for prognostication after cardiac arrest.  |  |
| 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 | Although feasibility was not specifically addressed in any of the studies included in this review, the technique of pupillometry is easy and it does not require special skills. In addition, the standardized evaluation achieved by quantitative pupillometry minimizes the risk of disagreement between assessors.  |  |

# 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 quantitative pupillometry at 72h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).** |
| Justification |
| Limited evidence suggests that pupillometry using NPi achieves 100% specificity for prediction of poor neurological outcome as early as 24h after cardiac arrest. The choice of 72h for this recommendation has been made based on a parallel evidence regarding s-PLR, on the lower likelihood of persisting effects from sedation at that time point, and on the fact that specificity of a qPLR seems to increase from 24h to 72h. However, the number of available studies is still low and no consistent qPLR or NPi threshold for 100% poor outcome has been identified. Although in some of the studies the treating team was blinded to results of pupillometry, a correlation with standard PLR, which cannot be blinded, is likely. WLST based on results of pupillometry has not been documented in any of the studies included in our review. Because of its high specificity and the standardized assessment parameters, the balance between the costs and benefits favours benefits.  |

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

Automated pupillometry allows a quantitative and standardised evaluation of pupillary reflex to light, therefore minimising the risk of interobserver variability. However, it requires a specific equipment, with relevant costs.

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| Monitoring and evaluation |
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| Research priorities |
| The number of studies documenting pupillometry for predicting poor outcome after cardiac arrest is still low. A consistent threshold for 100% specificity has not been identified neither for qPLR nor for NPi.  |