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| Question |
| **Apparent diffusion coefficient (ADC) on brain magnetic resonance imaging (MRI) 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:** | Apparent diffusion coefficient (ADC) on brain magnetic resonance imaging (MRI), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 | ADC was investigated in three studies [Moon 2018 36; Kim 2013 1393; Hirsch 2019 *in press*].In one study [Moon 2018 36, 44 pts] mean ADC ≤726× 10−6 mm2/s at <48h predicted poor neurological outcome at 6 months with 100% specificity and 44% sensitivity (very-low certainty of evidence).In one study [Moon 2018 36, 66 pts] mean ADC ≤627× 10−6 mm2/s at 48h-7days predicted poor neurological outcome at 6 months with 100% specificity and 20.8% sensitivity (very-low certainty of evidence).In one study [Moon 2018 36, 44 pts] ADC volume proportion (400× 10−6 mm2/s) >2.5% at <48h predicted poor neurological outcome at 6 months with 100% specificity and 64% sensitivity (very-low certainty of evidence).In one study [Moon 2018 36, 66 pts] ADC volume proportion (400× 10−6 mm2/s) >1.66% at 48h-7days predicted poor neurological outcome at 6 months with 100% specificity and 79.2% sensitivity (very-low certainty of evidence).In one study [Kim 2013 1393, 51 pts] Maximum Cluster Size in different cerebral regions on CT ≤151.7× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 62.5% to 90% (very-low certainty of evidence).In one study [Kim 2013 1393, 51 pts] the Lowest Mean ADC in different cerebral regions on CT ≤555.7× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 50% to 72.5% (very-low certainty of evidence).In one study [Kim 2013 1393, 51 pts] the Lowest Minimum ADC in different cerebral regions on CT ≤466.8× 10−6 mm2/s at 46 (37-52)h predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 42.5% to 82.5% (very-low certainty of evidence).In one study [Hirsch 2019 *in press*, 51 pts] ≥10% of ADC<650× 10−6 mm2/s at 1-7 days predicted poor neurological outcome at 6 months with 100% specificity and 51.4% sensitivity (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 falsely pessimistic prediction based on ADC values above the threshold for 100% specificity may lead to treatment restrictions in patients destined to a good recovery. This risk is increased by the wide variability of ADC cut-offs for 100% specificity across studies.  | In none of the studies we included ADC was used 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 for DWI-MRI was very low because of the high risk of bias, especially self-fulfilling prophecy and selection bias. An additional source of confounding is represented by the different available methods and sites of measurement. | Differently from other predictors, like those based on clinical examination, imaging is not affected by sedation or paralysis, and it can be potentially assessed blindly. |
| 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 |
| ○ Favours the comparison○ Probably favours the comparison○ Does not favour either the intervention or the comparison● Probably favours the intervention○ Favours the intervention○ Varies○ Don't know | ADC has a potential for predicting poor outcome after cardiac arrest. In all three studies we included ADC predicted poor outcome with 100% specificity and high sensitivity. However, a high heterogeneity across studies in both the methods used to calculate ADC and the thresholds associated with 100% specificity was observed. |  |
| 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 | The costs of imaging assessment are higher when compared with those of clinical examination. In addition, measurement of ADC requires specific skills. No study assessing savings from prognostication based on imaging 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 imaging for prognostication after cardiac arrest.  |  |
| 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 | A problem of inequity is possible, since prognostic assessment using imaging requires resources and skills that may not be available anywhere anytime.  |  |
| 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 | Feasibility was not specifically addressed in any of the studies included in this review. MRI cannot be performed at the bedside, and it carries additional risks due to the magnetic field, which makes it incompatible with most standard monitoring equipment and with some implanted devices, such as pacemakers/defibrillators. In addition, MRI recording is a relatively long procedure. |  |

# 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 ADC on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).**  |
| Justification |
| Assessing apparent diffusion coefficient (ADC) has a potential for predicting poor neurological outcome after cardiac arrest with high sensitivity. There is a wide heterogeneity of measurement techniques (sites and calculation methods) for ADC across studies. The supporting evidence for ADC had very low certainty.  |

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| Subgroup considerations |
| None |
| Implementation considerations |

Prognostication based on imaging requires technology and skills that may not be universally available.

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| Monitoring and evaluation |
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| Research priorities |
| A consistent ADC threshold for predicting poor neurological outcome after cardiac arrest should be identified. A standardisation of the methods for ADC calculation is urgently needed.  |

 None |