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| QUESTION | |
| **Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI) for prediction of good 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:** | Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI), assessed within eight days after cardiac arrest. |
| **COMPARISON:** | *None.* |
| **MAIN OUTCOMES:** | Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1–2 at 6 months after cardiac arrest. |
| **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 good 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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:** | An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest was necessary.  The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022. |

# 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 | Neurologic injury is the most common cause of death in patients with post-cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Trivial  ● Small  ○ Moderate ○ Large ○ Varies ○ Don’t know | DWI was investigated in five observational studies [Park, 2020; Oh, 2019; Jang, 2019; Mlynash, 2010, Wouters, 2021]  Park JS, In YN, You YH, et al. (2020) Ultra-early neurologic outcome prediction of out-of-hospital cardiac arrest survivors using combined diffusion-weighted imaging find- ings and quantitative analysis of apparent diffusion coefficient. Resuscitation 148:39–48  Oh SH, Park KN, Choi SP, et al. (2019) Beyond dichotomy: patterns and amplitudes of SSEPs and neurological outcomes after cardiac arrest. Crit Care 23:224  Jang J, Oh SH, Nam Y, et al. BS (2019) Prognostic value of phase information of 2D T2\*-weighted gradient echo brain imaging in cardiac arrest survivors: A preliminary study. Resuscitation 140:142–149  Mlynash M, Campbell DM, Leproust EM, et al. (2010) Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. Stroke 41:1665–1672  Wouters A, et al., Added Value of Quantitative Apparent Diffusion Coefficient Values for Neuroprognostication After Cardiac Arrest, Neurology, 2021. 96(21): p. e2611.  In one study [Oh, 2019] on MRI immediately after rewarming, **absence of restricted diffusion** on DWI predicted good outcome with specificity of **95% (sensitivity 72%),** and the **presence of a single area of restricted diffusion** predicted good outcome with **92% specificity (sensitivity 94%)**.  In one study [Park, 2020], **the absence of restricted diffusion** was assessed at 3.1 h and 77.6 h after ROSC. Earlier MRI assessment predicted good outcome at six months with **specificity of 60% (sensitivity 100%)** and later MRI assessment with **specificity of 93% (sensitivity 100%)**. In another study [Jang 2020], the MRI was assessed around 70 hours (74.5 h) after ROSC. In that study, **absence of DWI lesions** predicted good outcome at six months **with specificity of 93% (sensitivity 92%).**  In one study (Jang, 2019, 142) on 39 patients, the **absence of restricted diffusion** on MRI at 77.6 (75.9–80) h after ROSC predicted good outcome at 6 months with **93.3 [68.1–99.8] specificity** and **100 [86.7–100] sensitivity** (very-low certainty of evidence).  One study [Milnash, 2010] assessed **the absence of DWI or fluid-attenuated inversion recovery (FLAIR) lesions** within 8 days from ROSC at cortex, deep grey nuclei, and cerebellum and pons. Accuracy for predicting good outcome at six months was **specificity** **80%, sensitivity 79%** for **absence of lesions in the cortex, specificity 87%, sensitivity 50%,** for **absence of lesions in the deep grey nuclei,** and **specificity 20%, sensitivity 100%** for **absence of lesions in** **the brainstem and cerebellum.**  One study [Wouters, 2021] determined the predictive accuracy for good outcome at six months of **average apparent diffusion coefficient (ADC)** value and **percentage of brain voxels with an ADC value <450 x 10-6 mm2/s**. The thresholds for average ADC and percentages of ADC< 450 x 10-6 mm2 were determined according to 100% sensitivity to predict good outcome. **The average ADC value** to predict good outcome **with 100% sensitivity was >931 x 10-6 mm2/s (specificity 38%).** The threshold of **<6.5% of brain voxels with an ADC value <450 x 10-6 mm2/s predicted good outcome with 100% sensitivity and 26% specificity.**  The certainty of evidence was very low for all studies. | Acute PCABI is characterised by cytotoxic oedema, cellular swelling, and restriction of water diffusion in affected brain areas which appears as a hyperintensity on DWI with corresponding low apparent diffusion coefficient (ADC).  The absence of DWI changes is a potentially valuable predictor of good clinical  The development of brain oedema after CA is time-dependent, and the extent of changes may not be evident before 3–7 days after CA .The only study we included that assessed MRI serially showed that the accuracy of MRI was higher at 77.6h vs 3.1h after ROSC.  The spatial distribution of brain injury is also of relevance, due to the selective vulnerability of specific brain areas to post CA brain injury. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Large ○ Moderate ● Small  ○ Trivial  ○ Varies  ○ Don't know | Brain imaging is usually not available at the bedside. Patients after cardiac arrest are often hemodynamically unstable, and intra-hospital transport may carry additional risk. | A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to therapeutic obstinacy. |
| 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 the evidence for DWI-MRI is very low because of the lack of blinding and the lack of established criteria of DWI or ADC thresholds to define a ‘positive’ MRI. An additional issue is selection bias. All DWI-MRI studies investigating good outcome prediction were small retrospective studies.  Apparent diffusion coefficient (ADC) allows a quantification of the diffusion changes on brain MRI. However, the evidence is limited to one study, and no ADC threshold for prediction of good neurological outcome has been established. | Unlike other predictors, such as those based on clinical examination, imaging is not affected by sedation or paralysis and can potentially be assessed blindly.  The interpretation of quantitative imaging results is operator dependent. However, as far as poor outcome prediction is concerned, at least one study showed that expert neuroradiologists' visual assessment of brain CT provided an accurate prediction. Similarly, we feel that an expert neuroradiologist should be able to detect the absence of pathological findings on MRI.  Variations in the measurement methods (e.g., location of the region of interest) and differences in MRI scanners and scanning protocols might exist. Standardisation and normalisation of imaging techniques are of value. |
| 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 | A good outcome was defined as CPC 1-2 in all but one study (Mlynash, 2010, 1665), in which good outcome was defined as CPC 1-3. | There may be interindividual variations in how good neurological outcome is perceived. |
| Balance of effects Does 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 | The absence of restricted diffusion on MRI is associated with good outcome after cardiac arrest.  In two studies [Park, 2020; Jang 2020] the absence of restricted diffusion in DWI-MRI assessed at around three days after CA predicted good outcome with high sensitivity and specificity (92-100% and 93%, respectively). |  |
| 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 | No study assessing costs or savings related to prognostication based on imaging has been included in our review. However, the costs of MRI are higher when compared with those of clinical examination. |  |
| 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 imaging for prognostication after cardiac arrest. |  |
| 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 | We did not find any studies addressing this question. | A problem of inequity is possible, since prognostic assessment using imaging implies resources and skills that cannot be available anywhere anytime. |
| 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 study assessing 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. | MRI cannot be performed at the bedside, which is a major limitation, 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.  An MRI is available in most hospitals in high-income countries, but the skills to assess the severity of HIBI on brain MRI may not be universally available. |

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 the absence of diffusion restriction on cortical MRI between 72h and 7 days after ROSC, in combination with other tests, for predicting good neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).**  **We suggest against using ADC on brain MRI to predict good neurological outcome in patients who are comatose after cardiac arrest (weak recommendation, very-low certainty of evidence).** |
| Justification |
| Evidence from five studies consistently suggests that the absence of visible cytotoxic oedema, assessed as the absence of cortical DWI changes on brain MRI, predicts good neurological outcome with high specificity at 72h or later after cardiac arrest.  Apparent diffusion coefficient (ADC) allows quantifying diffusion changes on brain MRI. However, the evidence is limited to one study, and no ADC threshold for prediction of good neurological outcome has been established. |

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| Subgroup considerations |
| None |
| Implementation considerations |

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| Monitoring and evaluation |
| |  | | --- | | Research priorities | | The criteria for defining a normal MRI after cardiac arrest must be standardized.  The spatial distribution of DWI MRI changes due to HIBI varies widely. The best area of the brain to be assessed for predicting good outcome after cardiac arrest is currently unknown. | |  | |