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| Question |
| **Post Cardiac Arrest Seizure Prophylaxis and Treatment**  |
| **Population:** | Unresponsive adults (>18 years old) with sustained return of spontaneous circulation (ROSC) after cardiac arrest in any setting (in-hospital or out-of-hospital). |
| **Intervention:** | One strategy for seizure prophylaxis or treatment |
| **Comparison:** | Another strategy or no seizure prophylaxis or treatment |
| **Main outcomes:** | Survival to hospital discharge, 3 months or longer; survival with favorable neurologic outcome at hospital discharge, 3 months or longer. |
| **Setting:** | Any setting (in-hospital or out-of-hospital). |

# 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, both in the out-of-hospital and in-hospital setting, is relatively common and has a very high mortality, with hypoxic-ischemic brain injury as a common cause of death. Clinical convulsions (mainly myoclonus) and epileptiform activity in the EEG are common manifestations of post-cardiac arrest brain injury with substantial overlap and an approximate incidence of 20-30% (Seder 2015 965, Lybeck 2017, 146, Backman 2017 681, Beretta 2018 e2153). The prognosis for patients with clinical and electrographic seizures is usually poor but some patients recover and may ultimately have a good neurologic outcome (Backman 2017 681, Beretta 2018 e2153).  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | **Post-Cardiac Arrest Seizure Prophylaxis:** For the critical outcomes of survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year and survival at discharge, 30 days, 60 days, 180 days AND/OR 1 year, 2 prospective randomized clinical trials involving a total of 562 subjects provided very low-certainty evidence (downgraded for risk of bias, indirectness and imprecision)(BRCT Investigators 1986 397;Longstreth 2002 506) of no benefit from seizure prophylaxis.**Post-Cardiac Arrest Seizure Treatment:** For the critical outcomes of survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year and survival at discharge, 30 days, 60 days, 180 days AND/OR 1 year we identified no randomized controlled trials (RCTs) or non-randomized studies that addressed post-cardiac arrest seizure treatment. Indirect evidence from case series suggest that sedating agents such as propofol are effective in suppressing both clinical convulsions and epileptiform activity on EEG in this patient population (Thömke 2010 1392, Aica Rapun 2017 169, Kotroumanidis 2015 255). A recent retrospective study provides some evidence that conventional antiepileptic agents (specifically valproate and levetiracetam) also have an effect in suppressing epileptiform activity in the EEG (Solanki 2019 82). |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial○ Varies● Don't know | There is no direct evidence of undesirable effects of antiepileptic drug therapy in comatose post-cardiac arrest survivors. Treatment with sedatives and conventional antiepileptic drugs in high doses has the potential to cause delayed awakening, prolonged need for mechanical ventilation, and increased ICU days. Importantly, generalized myoclonus in combination with epileptiform discharges may be manifestations of Lance-Adams syndrome which is compatible with a good outcome (Elmer 2016 175, Aica-Rapun 2017 169 ). In such cases, overly aggressive sedation and treatment with high doses of conventional antiepileptic drugs may confound the clinical examination and lead to overly pessimistic prognostication. |  |
| 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 |  Seizure ProphylaxisThe certainty of evidence is very low because the 2 randomized clinical trials were designed to test the neuroprotective effects of agents that also had potential antiepileptic effects typically given as a single dose post-ROSC. These trials were not designed to optimize seizure prophylaxis and the methodology for measuring seizure incidence was poorly defined. . Also, it is typical for post-cardiac arrest patients to receive levels of sedation that potentially have antiepileptic effects during the first days after ROSC. The impact of this practice on incidence of post-cardiac arrest seizures and outcomes is currently unknown.Seizure TreatmentThe certainty of evidence is very low because no randomized controlled clinical trials have compared one strategy for seizure treatment to another strategy or placebo. Published case series lack control comparators and have highly variable inclusion criteria and outcomes.  | A large randomized trial is currently underway investigating the benefit of systematic antiepileptic drug therapy with the goal of suppressing all epileptiform activity on the EEG vs. standard treatment of clinical seizures only in post-cardiac arrest status epilepticus (TELSTAR trial, NCT02056236). |
| 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 | Survival with favorable neurologic outcome and survival are generally accepted as critical outcomes (Hayward COSCA). |  |
| 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 | **Seizure Prophylaxis**The balance of evidence favors no treatment. In making this recommendation, the task force acknowledged the lack of confidence in a treatment effect on the critical outcome of survival with good neurologic function treatment. The task force also considered that seizure prophylaxis in other forms of acute brain injuries is not associated with improved outcomes, and that most drugs have significant side effects.**Seizure Treatment**The balance of evidence favors treatment. In making this recommendation, we acknowledge very low confidence in the estimated treatment effect. However, ongoing seizures have the potential to worsen brain injury, and treatment of recurrent seizures and SE is the standard of care in other patient populations (Glauser 2016 48). | The main difference between post-cardiac arrest patients and patients with status epilepticus of other etiologies is the severity of the underlying brain injury, which is the main determinant of the prognosis.Task force discussed difficulty in diagnosing seizures in settings that do not routinely monitor EEG. |
| 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 | We did not identify any studies evaluating the cost of a sedating agents and conventional antiepileptic agents in post-cardiac arrest patients. Cost is variable depending on type and number of agents used. Continuous EEG monitoring is used to assess prognosis and to diagnose seizures and monitor response to therapy. It is labor intensive and likely to add significant cost to patient care. The net cost-effectiveness of this approach is controversial and may depend substantially on the organization (Crepeau 2014 785, Sondag 2017 111 ). There is also the potential cost of delayed neurologic prognostication and prolonged ICU care. |  |
| 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 have not identified studies evaluating the cost of sedating agents and conventional antiepileptic agents in this patient population. Two studies have reported the cost of continuous EEG-monitoring for cardiac arrest patients (Crepeau 214 785, Sondag 2017 111) |  |
| 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 post-cardiac arrest seizure prophylaxis or treatment.  |  |
| 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 | We identified no studies that addressed health equity. Disparities in the availability of AED therapy in various settings was not investigated. However, it is likely that the availability of specific agents will vary with setting and region. The availability of conventional and continuous EEG monitoring is likely to be limited in low resourced environments.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We identified no research that assessed acceptability, but these treatment recommendations do not include any substantial changes compared to 2015. |  |
| 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 by this review, but recommendations should be feasible in most settings given that this is not a significant change in recommendation.  |  |

# 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 against seizure prophylaxis in adult comatose cardiac arrest survivors. (weak recommendation, very low certainty of evidence)We suggest treatment of seizures in adult comatose cardiac arrest survivors. (weak recommendation, very low certainty of evidence) |

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| Justification |
| Post-Cardiac Arrest Seizure ProphylaxisIn making this recommendation, the task force acknowledged the lack of confidence in a treatment effect on the critical outcome of survival with good neurologic function. The task force also considered that seizure prophylaxis in other forms of acute brain injuries is not associated with improved outcomes, and that most drugs have significant side effects.Post-Cardiac Arrest Seizure TreatmentIn making this recommendation, we acknowledge very low confidence in the estimated treatment effect. However, ongoing seizures have the potential to worsen brain injury, and treatment of recurrent seizures and SE is the standard of care in other patient populations(Glauser 2016 48)..  |

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| Subgroup considerations |
| Subgroups of patients with either potentially favorable or poor prognosis have been identified in several retrospective studies. A continuous EEG-background preceding the start of status epilepticus, reactive background and later start of status epilepticus are factors associated with a potentially favorable outcome. Conversely, early onset of status epilepticus in the EEG (<24 hours), a preceding burst-suppression pattern, lack of EEG-background and EEG-background reactivity are EEG-features associated with a poor prognosis (Rossetti 2009 744, Backman 2017 128, Elmer 2016 175). In addition, reliable prognosticators of poor outcome other than EEG may identify patients who are not likely to benefit from prolonged treatment (Dragancea 2015 173, Beretta 2018 e2153). |

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| Implementation considerations |
| Indirect evidence from case series suggests that sedatives such as propofol are effective in suppressing both clinical convulsions and epileptiform activity on EEG in these patients (Thömke 2010 1392, Aica Rapun 2017 169, Kotroumanidis 2015 255). A recent retrospective study provides some evidence that conventional antiepileptic drugs (specifically valproate and levetiracetam) also have an effect in suppressing epileptiform activity in the EEG (Solanki 2019 82). In a recent comparison of valproate, levetiracetam and fosphenytoin for convulsive status epilepticus, the three drugs were equally effective but fosphenytoin caused more episodes of hypotension and need for intubation (Kapur 2019 2103).These results suggest that valproate and levetiracetam may be reasonable first line drugs in post-cardiac arrest seizure management.  |

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| Monitoring and evaluation |
| Since the recommendations are unchanged, we do not foresee issue in monitoring or evaluating implementation |

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| Research priorities |
| * There is no high certainty evidence for the effect of antiepileptic drugs on the outcome of post-cardiac arrest patients with seizures
* There are no RCTs specifically designed to evaluate the impact of post-cardiac arrest seizure prophylaxis on the incidence of seizures and neurologic outcome.
* There are inadequate data regarding the timing, duration, dosing, and choice of antiepileptic drugs for seizure prophylaxis in comatose post–cardiac arrest patients.
* The utility of continuous EEG versus intermittent EEG monitoring in the diagnosis and treatment of seizures in comatose post–cardiac arrest patients remains controversial due to resource utilization and lack of evidence for improved outcomes.
* The threshold for treating epileptiform activity other than convulsive seizures (eg, generalized epileptiform discharges) is poorly defined
* Standardized terminology for classification of epileptiform activity in the EEG of comatose post–cardiac arrest patients is increasingly used. There remains a need to develop consensus on the definition of post cardiac arrest status epilepticus
* The value of using volatile anesthetics to treat refractory status epilepticus on post-cardiac arrest patients is currently unknown.
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