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| Question |
| **Should Vasopressin and Corticosteroids vs. usual care without vasopressin and corticosteroids be used for Adults in IHCA?** |
| **Population:** | Adults in IHCA |
| **Intervention:** | Vasopressin and Corticosteroids  |
| **Comparison:** | usual care without vasopressin and corticosteroids  |
| **Main outcomes:** | Return of spontaneous circulation ; Survival to hospital discharge; Survival to Hospital Discharge with Good Neurological Outcome; Health Related Quality of Life; Health Related Quality of Life; |
| **Setting:** | In-Hospital Cardiac Arrest |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** |  |

# 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 | Across the world, sudden cardiac arrest is an important cause of premature death and morbidity. Survival rates are low. Optimising outcomes from cardiac arrest is a key international priority. |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate● Large○ Varies○ Don't know | The anticipated effects are very substantial if the intervention improves ROSC and even more so if it improves survival with good neurological outcome.The effect of the intervention on return of spontaneous circulation is substantial (relative effect- odds ratio 2.09, 95% CI 1.54 to 2.09; absolute effect 181 more per 1,000, 95% CI 108 more to 250 more). The evidence is categorised as low certainty. Even at the lower end of the 95% confidence interval, this would still represent a substantial benefit. This improvement in return of spontaneous circulation does not translate in to a benefit in survival or survival with good neurological outcome across the three eligible studies. As such, there is uncertainty as to whether the intervention improves these longer-term outcomes that are considered important by patients.  |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial○ Varies● Don't know | There was no evidence that the intervention might cause direct harm. However, an intervention that improves ROSC but not overall survival might be viewed as undesirable, depending on cultural norms. There are potential side-effects that may be associated with use of vasopressin and steroids (e.g. infection, hyperglycaemia, peripheral ischaemia). However, these effects are likely to be considered acceptable by patients and clinicians if the outcome improves patient outcomes, such as survival.  |  |
| 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 | Overall, evidence certainty was categorised as low or very low to reflect indirectness and imprecision.  |  |
| 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 | The current evidence shows that the interventions improves rates of return of spontaneous circulation, but this does not translate in to improvements in survival. For some, any intervention that improves ROSC may be viewed as valuable. Obtaining ROSC is an essential step in the pathway to overall survival, but even in patients that do not survive, it might be viewed as providing an opportunity for organ donation or for the patient's relatives to spend time with them while they are alive. The consequences of this include increased burden on the healthcare system (particularly ICU beds). This might be a particular challenge in systems where there is limited ICU capacity. It is also known that post-arrest/ ICU interventions may be painful or distressing for the patient, even if they appear to be adequately sedated. The balance of these values likely varies across cultures.  |  |
| 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 | The balance between desirable and undesirable effects likely depends on a value judgement, based on the importance of obtaining ROSC where this does not translate in to an effect on overall survival.  |  |
| 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 | There are no studies directly addressing this.Corticosteroids are relatively cheap and readily available across most systems. In some systems they may only be available in powder form , requiring reconstitution before use, which might have an effect on how rapidly they can be available for use. Vasopressin is relatively expensive. For integration in to resuscitation care, some systems may require that vasopressin be made available in pre-filled syringes which would further increase its costs. Vasopressin also ideally requires refrigeration until use, potentially creating additional costs and complexity in availability.Aside from drugs and refrigeration costs, there are likely to be no other significant costs.  |  |
| 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 identified no relevant studies.  |  |
| 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 that addressed the cost effectiveness of the addition of vasopressin and corticosteroids to standard care during cardiac arrest. An increase in ROSC without associated increase in improved functional recovery would likely increase healthcare costs through increased demand on ICU beds.  |  |
| 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 availability of vasopressin and corticosteroids across all health settings is unknown, particularly in low and middle-income countries.  | Though steroids are cheap and readily available, it is unclear if Vasopressin is readily available in all countries and all environments outside of ICUs. Potentially this might have a negative effect on health equity. |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | PATIENTS:The combination of corticosteroids and vasopressin is likely to be acceptable to patients if it improves outcomes that are important to patients. The combination of corticosteroids and vasopressin is likely to be acceptable to patients if it improves outcomes that are important to patients. CLINICIANS:Current resuscitation guidelines prioritise the development of straightforward treatment processes that be easily implemented in care. The addition of vasopressin and corticosteroids to standard resuscitation treatment would add a degree of complexity to current care.This is particularly the case for systems where corticosteroids are only available in powder form & require reconstitution prior to administration. For in-hospital settings in such systems, higher numbers of clinical personnel mean that it is likely that the team would be able to safely reconstitute drugs. However, the added complexity may be a barrier to implementation in some settings. Vasopressin ideally requires refrigeration prior to use , though in some circumstances this may not be essential.  |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | Key challenges to implementation include:- In some systems corticosteroids need to be reconstituted prior to administration, - Ideally vasopressin in recommended to be stored in a refrigeratorThese issues might add complexity to resuscitation care. Whilst likely feasible in the hospital setting, implementation in the out-of-hospital setting may be more challenging in some systems.  |  |

# 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 against the use of the combination of vasopressin and corticosteroids in addition to usual care for adult in-hospital cardiac arrest, due to low confidence in effect estimates for critical outcomes. (weak recommendation, low to moderate-certainty evidence) |
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| Justification |
| **Overall justification**For in-hospital cardiac arrest, there is moderate evidence that vasopressin and corticosteroids given during cardiac arrest, increase ROSC. However, this does not appear to translate into improvement in survival +/or survival with good neurological outcome.**Detailed justification***Balance of effects*For IHCA, there appears to be moderate evidence that the addition of vasopressin and corticosteroids to usual care improves ROSC. However, this does not seem to translate into a meaningful increase in survival +/or survival with good neurological outcome, therefore the overall value of the intervention is unclear.  |

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| Subgroup considerations |
| Prespecified subgroup analyses were conducted according to age , witnessed status, the initial rhythm (shockable or not), time from cardiac arrest to administration of trial drug and cause of cardiac arrest. There was no effect measure modification for any of these outcomes.  |

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| Implementation considerations |
| Corticosteroids are generally cheap and readily available, but in some systems come in a powdered from which requires reconstitution - this may be challenging in cardiac arrest settings.Vasopressin is less readily available and is ideally kept in a fridge, which may add complexity to its widespread use. |

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| Monitoring and evaluation |
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| Research priorities |
| There is need for a large randomised control trial to compare outcomes between cardiac arrest victims in hospital treated with standard care, and those treated with vasopressin and corticosteroids in addition to standard care. Post-ROSC treatment should also be standardised between groups, ideally with the addition of hydrocortisone to those with post-ROSC hypotension, as this was used in the Mentzelopoulos studies.  |