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| Question | |
| **Should Bicarbonate vs. No Bicarbonate be used for adults and children with cardiac arrest secondary to suspected opioid poisoning ?** | |
| **Population:** | Adults and children with cardiac arrest secondary to suspected opioid poisoning |
| **Intervention:** | Bicarbonate |
| **Comparison:** | No Bicarbonate |
| **Main outcomes:** | Return of Spontaneous Circulation, Survival to Hospital Discharge or 30-days, Survival to Hospital Discharge or 30-days with Favourable Neurological Status, Long Term Survival, Long Term Survival with Favourable Neurological Status |
| **Setting:** | In-hospital or out-of-hospital |
| **Perspective:** |  |
| **Background:** | Opioid toxicity is a common cause of cardiac arrest. |
| **Conflict of interests:** | None |

# 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 | Opioid toxicity is a major cause of death, and is responsible for approximately 10% of out-of-hospital cardiac arrests. The pathophysiology of opioid-associated cardiac arrest is systematically different from cardiac arrests due to primary cardiac etiologies, and thus may benefit from different interventions. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | There are no randomized controlled trials evaluating bicarbonate (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. Evidence is limited to a single observational study, in which the association of bicarbonate administration with outcomes was evaluated with a large list of other factors.1 Bicarbonate was found to be associated with a decreased odds of survival to hospital discharge. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | There have been no randomized controlled trials evaluating bicarbonate (vs. placebo) for opioid-associated cardiac arrest to inform questions of benefit or harm. The existing literature is limited to observational data, with substantial risk of bias. |  |
| 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 overall certainty of evidence is very low for the single outcome evaluated in the single observational study, due to indirectness and high risk of bias. |  |
| 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 | Previous data have shown that survival is an important outcome after cardiac arrest. |  |
| Balance of effects Does 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 | Currently available data examining the use of naloxone for cardiac arrest resuscitations are of very low certainty, and thus the balance between desirable and undesirable effects is unclear. The single available study is highly confounded by resuscitation time bias.   | **Certainty assessment** | | | | | | | **Certainty** | **Importance** | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |  |  | | Survival to Hospital Discharge | | | | | | | | | | | 1 | non-randomised studies | very seriousa | not serious | seriousb,c | not applicabled | none | ⨁◯◯◯ Very lowa,b,c | CRITICAL |   **CI:** confidence interval Explanations a. The time of the medication administration was not accounted for in the analysis. Given that longer durations of resuscitation are associated with worse outcomes, medications given later in the resuscitation will be associated with worse outcomes, even if the drug confers no material benefit (resuscitation time bias).  b. The study was not limited to opioid-associated OHCA, but rather included a broader population adult EMS-treated OHCA precipitated by "suspected drug overdose"  c. The single study identified was limited to adults in the out-of-hospital setting. Therefore, Indirectness is very serious when considering resuscitation of children and/or resuscitation from in-hospital cardiac arrest.”  d. Given the heterogeneity of the study populations and designs, data was not pooled and a pooled estimate was not calculated. Thus, imprecision is not applicable. |  |
| 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 no evidence to suggest that bicarbonate would not be acceptable to stakeholders. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Bicarbonate is readily available to advanced life support resuscitation teams, and may be provided via the intravenous routes. |  |

# 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** | Trivial | Small | Moderate | Large |  | 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 |
| **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 |
| *During advanced life support for cardiac arrest due to opioid poisoning, there is insufficient evidence to recommend any additional opioid-specific therapies (e.g., naloxone), beyond standard resuscitation care.* |
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| Justification |
| * We identified a single observational study in our systematic review, which was limited by serious risk of bias and indirectness. * Indirectness: There were no studies which actually examined the population of interest for this recommendation, i.e., those with opioid-associated OHCA. The single study identified included cases with “suspected drug overdose”, including all cases with evidence of deliberate or accidental overdose of any prescribed or non-prescribed drugs, or ethanol. In addition, there were no studies examining in-hospital cardiac arrest or pediatrics cases, and thus for these populations the evidence is very indirect. * Bias: Bicarbonate is a medication typically provided after initial resuscitative interventions have failed, and thus may be a marker of poor prognosis. The single study identified did not account for the specific timing of bicarbonate administration in analyses, and thus resuscitation time bias is a large limitation.2 * The single study reported that bicarbonate was associated with a decreased odds of survival to hospital discharge. We found no other evidence to support use of bicarbonate in opioid-associated OHCA resuscitation. |

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| Subgroup considerations |
| * Subgroups will be important to evaluate in future randomized controlled trials, however evidence to consider effectiveness in various subgroups is not currently available. |

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| Implementation considerations |
| * Further higher quality evidence is required prior to implementation plans. |

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| Monitoring and evaluation |
| * Further higher quality evidence is required prior to developing plans for monitoring and evaluation. |

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| Research priorities |
| * Further research to identify the optimal treatment for opioid-associated cardiac arrest is warranted, given the high incidence of this condition. Research should include in and out-of-hospital cardiac arrest, and adult and pediatric populations. |

References Summary

1. Alqahtani S, Nehme Z, Williams B, Bernard S, Smith K. Long-term trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose. *Resuscitation*. 2019;144:17-24. doi:10.1016/j.resuscitation.2019.08.036.

2. Andersen LW, Grossestreuer A V, Donnino MW. “Resuscitation time bias”-A unique challenge for observational cardiac arrest research. *Resuscitation*. 2018;125:79-82. doi:10.1016/j.resuscitation.2018.02.006.

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