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| Question |
| **Should Naloxone vs. No Naloxone 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:** | Naloxone |
| **Comparison:** | No Naloxone |
| **Main outcomes:** | Survival and Favourable Neurological Status at Hospital Discharge or later follow-up |
| **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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| ProblemIs 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 up to 10% of out-of-hospital cardiac arrests.1,2 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 EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | There have been no randomized controlled trials evaluating naloxone (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. Naloxone may confer benefit for opioid-associated cardiac arrest and improve survival and favourable neurological outcomes, however this is unknown. |
| Undesirable EffectsHow 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 naloxone (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. There is evidence from animal data showing worsening neurological outcomes among cases treated with opioid-reversal.3,4 Naloxone may also increase the risk of pulmonary edema.5 Finally, given the task-saturated nature of cardiac arrest resuscitations,6 the deployment of any additional interventions may interfere with or worsen the quality of standard resuscitation management. Naloxone may confer undesirable effects for opioid-associated cardiac arrest, however this is unknown. |
| 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 overall certainty of evidence is very low for all outcomes evaluated (including favourable neurological outcome, survival to hospital discharge, and return of spontaneous circulation). Existing data is highly limited due to high risk of bias and indirectness. |
| 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 | Previous data has shown that survival and neurological function are important outcomes after cardiac arrest. |
| 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 | 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.

| **Certainty assessment** | **Certainty** | **Importance** |
| --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |  |  |
| Survival to Hospital Discharge |
| 4 | non-randomised studies | very seriousa,b | seriousc | seriousd,e | not applicablej | none | ⨁◯◯◯Very lowa,b,c,d,e | CRITICAL |
| Return of Spontaneous Circulation |
| 3 | non-randomised studies | very seriousa,b | seriousf | seriouse,g | not applicablej | none | ⨁◯◯◯Very lowa,b,e,f,g | IMPORTANT |
| Favourable Neurological Status at Hospital Discharge |
| 3 | non-randomised studies | very seriousa,b | serioush | seriouse,i | not applicablej | none | ⨁◯◯◯Very lowa,b,e,h,i | CRITICAL |

**CI:** confidence intervalExplanationsa. Given that study cases were not limited to those with opioid-associated cardiac arrest, there is substantial bias introduced by indication bias: it is likely that prehospital providers administered naloxone among OHCAs with evidence of opioid toxicity. Previous data has shown that OHCAs secondary to opioid toxicity have better outcomes than those with undifferentiated OHCA, and also those with non-opioid drug toxicity. Thus, results of the association of naloxone and outcomes may be simply be demonstrating an association of opioid-related OHCA and outcomes, as the drug was likely given to these selected individuals.b. The time of the medication administration was not accounted for in the analysis. Given that longer durations of attempted 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).c. Two reported that naloxone is associated with an improved odds of survival to hospital discharge, while two did not detect an association.d. No studies examining survival specifically included cases of suspected opioid-associated cardiac arrest. Dillon included adult EMS-treated OHCA (with a subgroup of drug-related OHCA), Quinn included adult EMS-treated OHCA, Strong 2023 included adult OHCA due to presumed overdose, and Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms.e. All identified studies were 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.”f. Two studies report that naloxone is associated with an improved odds of ROSC, while one did not detect an association.g. No studies examining ROSC specifically included cases of suspected opioid-associated cardiac arrest. Dillon included adult EMS-treated OHCA (with a subgroup of drug-related OHCA), Quinn included adult EMS-treated OHCA, and Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms.h. One study reported that naloxone is associated with an improved odds of favourable neurological outcome at hospital discharge, while two studies did not detect an association.i. No studies examining favourable neurological outcomes specifically included cases of suspected opioid-associated cardiac arrest. Strong 2023 included adult OHCA due to presumed overdose, Strong 2024 included adult EMS-unwitnessed OHCA with initial non-shockable rhythms, Love included adult EMS-treated OHCAs with a documented history or exam consistent with overdose, family report of overdose, or if the patient had a known history of substance use j. 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. |
| Resources required |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | Naloxone is widely available to teams performing cardiac arrest resuscitations. As such, implementing naloxone within resuscitations would result in only the cost of the drugs consumed. The cost of a single dose of naloxone is typically up to $60 USD. |
| 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 | Costs for naloxone involve only the cost of the drug itself, data for which may vary by region but is available. No additional training would be required, nor additional resources to add this drug to prehospital formularies.  |
| 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 | The overall certainty of evidence is very low, with existing data at high risk of bias and indirectness. The evidence is not sufficient to warrant changing the current standard of care to incorporate this drug into medical cardiac arrest management recommendations. Thus, given there is a cost of the drug, we believe it likely favours the comparison (i.e. no naloxone). |
| 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 clinical question of whether naloxone should be administered to those with opioid-associated cardiac arrest does often involve individuals from vulnerable populations. However, we do not believe equity would be increased or reduced. Equity would be enhanced, however, with resources allocated to creating high-quality evidence to assess the effectiveness of naloxone treatment among those with opioid-associated cardiac arrest. |
| AcceptabilityIs 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 naloxone would not be acceptable to stakeholders. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | Naloxone may be provided via intranasal, intramuscular, subcutaneous, intravenous, or intraosseous routes. Naloxone administration is feasible to implement, similarly to other pharmacological resuscitative interventions. |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **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 |
| **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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 |
| * Our aim was to evaluate the evidence of advanced treatments (e.g., intravascular naloxone) that may confer benefit for those with opioid toxicity and *confirmed* cardiac arrest. This recommendation is directed at providers of ALS,6 including clinicians with expertise with ascertaining pulselessness. However, if it is there is uncertainty regarding whether a patient is indeed in cardiac arrest vs. respiratory depression/apnea, implementing recommended treatments for respiratory depression/apnea (e.g. naloxone) is warranted
* This recommendation is not intended to inform the provision care by individuals without training to ascertain pulselessness. For these rescuers, when attending to patients with opioid toxicity it may be difficult or impossible to distinguish between an obtunded patient with respiratory depression/apnea vs. a patient in true cardiac arrest. In these scenarios, please refer to the ILCOR CoSTR “Resuscitation care for suspected opioid-associated emergencies (BLS #811)”.7
* Opioids suppress the respiratory drive, leading to hypoxia, and subsequent cardiac arrest. Naloxone is an effective reversal agent for opioid-induced respiratory depression, however its effectiveness in cardiac arrest is unclear, particularly when artificial respiration is provided.8 Animal models have shown that naloxone may improve the probability of ROSC over standard resuscitation (even in the absence of opioids),9–11 however other data suggests opioid-reversal may worsen cerebral injury.3,4
* We identified several observational studies in our systematic review, however which were 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. Some studies included undifferentiated OHCAs,12–14 and others included cases with suspected drug-overdose15–17 (including a wide array of prescription and non-prescription drugs, as well as 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: Previous studies have shown that drug-related OHCA is associated with improved outcomes compared to undifferentiated OHCA18,19, and that opioid-related OHCA is associated with improved outcomes compared to other drug-related OHCAs20. Drug-related cases are more likely to be treated with naloxone than undifferentiated OHCA,12 and opioid-related OHCA are more likely to be treated with naloxone than other drug-related cases.20 Thus, treatment with naloxone may simply be a marker of opioid toxicity and its apparent superior prognosis, rather than providing any actual benefit. In addition, existing studies did not account for the specific timing of naloxone administration in analyses, and thus are limited by resuscitation time bias.21
* We acknowledged that cardiac arrest resuscitations are task-saturated endeavors with multiple competing priorities.6 We did not believe that the very low certainty evidence regarding the benefit of any opioid-specific ALS intervention was sufficient to recommend incorporating into ALS algorithms, given the risk of interfering with other evidence-based interventions. Given the uncertain state of the evidence, there is also a possible risk of harm.
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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 |
| * High certainty evidence is required prior to implementation plans.
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| Monitoring and evaluation |
| * High certainty evidence is required prior to developing plans for monitoring and evaluation.
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| Research priorities |
| * There were no randomized controlled trials that evaluated naloxone, in comparison to placebo, for suspected opioid-associated cardiac arrest. Given the equipoise and high incidence of cases, an RCT is urgently needed to answer this question
* There was no evidence available for in-hospital cardiac arrest or pediatric cardiac arrest

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