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Review

# Opioid-associated cardiac arrest: A systematic review of intra-arrest naloxone and other opioid-specific advanced life-support therapies

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## Abstract

**Aim**: Cardiac arrest due to opioid toxicity is a leading cause of life-years lost in many countries. Since the pathophysiology of cardiac arrest from opioid toxicity is different than primary cardiac etiologies, we sought to identify opioid-specific resuscitative interventions demonstrating benefit.

**Methods**: We searched Medline, EMBASE, CENTRAL, and the Web of Science (September 2024) for randomized or observational studies examining the benefit of opioid-specific advanced life support-level therapies for cardiac arrest. The primary and secondary outcomes were favourable neurological outcomes and survival at 30-days or hospital discharge, respectively. Risk of Bias and Certainty of Evidence were assessed with the ROBINS-I tool and GRADE methodology, respectively.

**Results**: We reviewed 1051 studies; six observational studies met criteria for analysis. Five studies examined the association of naloxone and outcomes (three included undifferentiated cases, one included non-shockable initial rhythm cases, and two included cases with "drug overdose"): two reported that naloxone was associated with improved outcomes, and three did not detect an association. One additional study examined the association of bicarbonate and outcomes, reporting that bicarbonate was associated with decreased survival at hospital discharge. All studies were limited by serious risk of bias and indirectness, with the certainty of evidence judged to be very low. No studies exclusively examined opioid-related cases.

**Conclusions**: There is currently no evidence demonstrating benefit for any advanced life support interventions specific to treating cardiac arrest from opioid toxicity. Data examining naloxone for undifferentiated or "drug-related" cardiac arrest are heterogenous with high risk of bias and low certainty of evidence.

**Keywords**: Opioid toxicity, Cardiac arrest, Heart arrest, Advanced life support

## Introduction

Out-of-hospital cardiac arrest (OHCA) is common, affecting 140 individuals per 100,000 population in the United States (US) annually; however, despite ongoing research and quality improvement efforts, the proportion of emergency medical system (EMS)-treated OHCA who survive has remained relatively stable for more than a decade, at approximately 10%.[1,2] The incidence and mortality of OHCA occurring in the context of non-prescription drugs (also known as "illicit drugs") has increased and is implicated in 10% of OHCA in some jurisdictions.[3,4] Although the majority of OHCAs occurring in the context of non-prescription drugs involve multiple substances, opioids are the most common drug implicated.[4-6] A study from Washington state classified 10% of OHCAs over a 6-year period as "overdose-related", and reported that opioids were implicated in

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71% of these cases.[4] In British Columbia, Canada, approximately 90% of patients with non-prescription drug toxicity-related deaths tested positive for fentanyl.[7]

Opioids suppress the respiratory drive, leading to hypoxia and hypercapnia, progressive ischemia, and eventually cardiac arrest.[8] Naloxone, a potent antagonist of the μ-opioid receptor, is a highly effective reversal agent for opioid-induced respiratory depression. However, the benefit of opioid antagonist therapy is unclear after a patient with opioid poisoning has progressed to cardiac arrest, particularly when artificial respiration is provided.[8] There are few human studies that examine the benefit of naloxone or other opioid-specific treatments among OHCAs. One study examined 42 OHCAs who received naloxone, and reported that 42% had an improvement in the ECG rhythm at some time following naloxone administration.[9] Several rat cardiac arrest models have shown that naloxone may improve the probability of return of spontaneous circulation (ROSC) over standard resuscitation even in the absence of opioids,[10-12] one of which found that naloxone administration decreased the time to ROSC and neurological injury.[12]

Although the pathophysiology of opioid-associated OHCA is different from OHCA due to primary cardiac etiologies,[8] current resuscitation guidelines do not recommend utilizing opioid-specific therapies for patients in cardiac arrest.[13] The aim of this systematic review was to examine the published literature to identify any opioid-specific advanced life support (ALS)-level therapies demonstrating benefit. These data informed the International Liaison Committee on Resuscitation (ILCOR) consensus on science and treatment recommendations.

## Methods

### *Study design and registration*

This systematic review was commissioned by the ILCOR ALS Task Force. We performed a systematic review of the literature to address the clinical question: in adults and children experiencing cardiac arrest (in- or out-of-hospital) secondary to suspected opioid poisoning, do opioid-specific ALS-level therapies (e.g., naloxone, bicarbonate, or other drugs or ALS-level interventions), in comparison to standard advanced life support management,[14] yield improved outcomes at hospital discharge, at 30-days, or longer follow-up? Although naloxone is available in the US and Canada without a prescription and is being incorporated into general first aid training,[15] naloxone was included in this systematic review because medication administration during cardiac arrest is typically delivered via intravenous or intraosseous routes,[16,17] which are considered ALS interventions. The review was registered on October 12, 2024 at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024596637), and was performed using established processes of ILCOR using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework.[18,19]

### *Outcome measures*

Our primary outcome of interest was favourable neurological outcome at hospital discharge or 30-days, as defined by the study author. Secondary outcomes of interest included: survival to hospital discharge, 30-days, or post-discharge follow-up; favourable neurological outcome at post-discharge follow-up; ROSC; and any post-discharge quality of life metrics.

### *Inclusion criteria*

We included studies that: (1) were randomized controlled trials (RCT) or observational studies with a comparison group (e.g., non-randomized controlled trials, interrupted time series, before-and-after studies, cohort studies with an intervention and control group); (2) included cases suspected to be due to opioid toxicity or at high-risk of opioid-toxicity (at the individual or group level); (3) included cases undergoing active resuscitation (i.e., were pulseless); and, (4) evaluated a drug therapy or any other ALS-level therapy (including advanced airways or other procedures).[14] We excluded studies: (1) that did not evaluate any of the outcome measures of interest; (2) for which no English abstract was available; or, (3) that did not include human subjects. We did not exclude conference abstracts from our search.

### *Information sources*

To locate all relevant studies, we searched: Medline (Ovid), EMBASE (Ovid), Cochrane's Central Register of Controlled Trials (CENTRAL), and the Web of Science Core Collection, from inception to September 14, 2024 (search strategies are located in Supplementary Materials). To identify ongoing clinical trials, we searched the International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/) and the reference lists of relevant manuscripts.

### *Search strategy*

The search was developed iteratively by an information specialist (D. G.) with input from team members. Using highly relevant seed papers found in our early searching, team members worked with the information specialist to create a map of medical subject headings, keyword headings, and terms in titles and/or abstracts. Four search strategies were tested, and the search strategy was modified accordingly. The final search strategy was peer-reviewed by the ILCOR ALS Task Force members. Our search strategies were then adapted for trial registries and other information sources. We did not restrict our searches by date, types of publication, or language.

### *Data management*

The results of the database searches were deduplicated in Endnote, and loaded into Covidence for screening. For each included study, we abstracted data of: the study reference, the publication type (conference or full manuscript), setting, time period, study design, population, relevant subgroups (including any drug- or opioid-specific subgroups), exposure of interest, comparison group, outcome measures, analytical methods, and main and secondary results. We planned to use R and Review Manager to perform meta-analyses of the study data, if appropriate. The GRADEpro Guideline Development Tool was used to create Evidence Tables.[20]

### *Study selection process*

All titles and abstracts were independently screened by two reviewers (BG, BO, and/or EL) using Covidence. Disagreements were resolved via discussion between the reviewers, and a third reviewer if needed. Articles assessed by the title and abstract as clearly not eligible were excluded, and the remaining articles were reviewed, in full-text format, by two reviewers. Disagreements or unclear eligibility resulted in a full-text review by three reviewers (BC, BO, and EL), with a discussion to determine eligibility. We described the study selection process with a PRISMA diagram, showing the number of studies remaining after each stage of the selection process and reasons for exclusion of studies.

### Data synthesis

We planned to perform meta-analyses of the data if there were any randomized studies identified in our search that had similar methodology. We further planned subgroup analyses for the following subgroups: 1) out-hospital-cardiac arrest and in-hospital cardiac arrest, 2) shockable and non-shockable initial rhythm, 3) witnessed and unwitnessed cardiac arrest. We also planned to perform a sensitivity analysis for which data from conference abstracts were excluded. If only observational studies were identified, our plan was to perform a narrative synthesis of the data (with conference publications noted) including the reported results (with effect measures shown as published), and pool data if studies had homogenous methods. Given that no randomized studies were identified, we implemented the latter plan.

### Risk of bias in individual studies

Two investigators independently assessed the risk of bias for the included studies using the ROBINS-I tool for non-randomized studies.[21] Conflicts were resolved through discussion between reviewers, and consensus results were tabulated.

### Certainty in cumulative evidence

We assessed the overall certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,[20] ranging from very low certainty of evidence to high certainty of evidence. We tabulated the assessment of overall risk of bias, inconsistency, indirectness, imprecision, and any other methodological issues using the GRADEpro GDT software.[20]

## Results

### Literature search

We identified 1051 studies from databases and registries, and after removal of duplicates, screened 896 unique studies, 817 of which were excluded based on title and abstract (Fig. 1). The remaining 79 were assessed in full-text, with six articles included in this review (four full-text manuscripts and two conference publications). Five studies reported the association of naloxone administration with outcomes, and one study reported the association of bicarbonate administration with outcomes. Given that no RCTs were identified and studies demonstrated substantial heterogeneity, results were not pooled.

### Naloxone literature identified

Dillon el. all performed a retrospective study of adult non-traumatic EMS-treated patients with OHCA (i.e. a group of undifferentiated OHCA), and compared cases treated with naloxone by EMS ($n$ = 1165) to those not treated with naloxone by EMS ($n$ = 8195).[22] The timing of naloxone administration was not known. Naloxone administration was associated with an increased probability of survival to hospital discharge and sustained ROSC. Investigators classified 8.7% of cases as "drug-related" (defined a cardiac arrest caused by a known or presumed overdose, as determined by treating EMS clinicians using available prehospital information). Although no subgroup analyses were performed on the "drug-related" cases, a secondary analysis of the full cohort incorporated an interaction term with naloxone administration and "drug-related OHCA" designation. Compared to the "non-drug related OHCA not treated with naloxone" category, both "non-drug related OHCA treated with naloxone" (adjusted odds ratio [AOR] 1.35, 95% confidence interval [CI] 1.04–1.77) and "drug-related OHCA treated with naloxone" (AOR 2.48, 95% CI 1.34–4.58) groups were associated with improved survival, but "drug-related OHCA not treated with naloxone" (AOR 0.91, 95% CI 0.54–1.53) was not. Confirmation of drug exposure was not reported.

Quinn et al. performed a retrospective study of adult EMS-treated non-traumatic OHCA in a region with a "high prevalence of opioid overdose". Individual cases suspected or confirmed to be related to opioid or other drug toxicity were not specifically identified. The authors created an Utstein/comorbidity-matched cohort (159 in each group) to compare those who were, and were not, treated with naloxone. The timing of naloxone administration was not known. Naloxone administration was not associated with survival to hospital discharge (AOR 1.01, 95% CI 0.46–2.21) or ROSC (AOR 0.43, 95% CI 0.16–1.20), compared with no naloxone administration.

Strong et al. (conference abstract) used the prospective non-traumatic OHCA registry (2018–2021 cases) in Oregon and included 218 adult OHCA due to presumed overdose (not specific to opioids).[23] Authors reported that naloxone administration (given prior to ROSC) was not associated with the odds of ROSC at emergency department arrival (AOR 1.43, 95% CI 0.64–3.20), survival at hospital discharge (AOR 1.99, 95% CI 0.39–10.30), or survival with favourable neurological outcome (AOR 1.99, 95% CI 0.34–11.55). In a subsequent study of cases from the same registry and time period, published in full manuscript form, Strong et al. included 1807 adult cases with initial non-shockable rhythms and examined the exposure of "early" naloxone administration, defied as naloxone provided by firefighters or police prior to vascular access attempts.[17] Patients who received naloxone after ROSC were excluded. Early naloxone administration was associated with an increased odds of ROSC (AOR 2.14, 95% CI 1.20–3.81), survival to discharge (AOR 4.41, 95% CI 1.78–10.97), and favourable neurologic outcomes (AOR 4.61, 95% CI 1.74–12.19), compared to no naloxone. A subgroup analysis of cases with substance use history or a presumed overdose cardiac arrest etiology found results consistent with the main analysis. Opioid or other drug exposure confirmation was not reported.

Love et al. (conference abstract) reported 164 adults with OHCA presenting to the emergency department with a history of overdose or substance use (not specific to opioids), and reported that favourable neurological outcomes were not more common among patients treated with naloxone than those without (26% vs 27%, respectively; unadjusted $p$ = 0.915).[24]

### Bicarbonate literature identified

Alqahtani et al. examined resuscitation outcomes for 1545 EMS-treated patients with OHCA due to suspected "drug overdose", defined as evidence of "deliberate or accidental overdose of prescribed medications, recreational drugs [sic], or ethanol", treated over an 18-year period.[25] The authors analyzed multiple factors associated with survival to hospital discharge, and reported that bicarbonate treatment (compared to no sodium bicarbonate treatment) was associated with a decreased odds of survival to hospital discharge (AOR 0.16, 95% CI 0.08–0.31). Drug exposure confirmation was not reported.

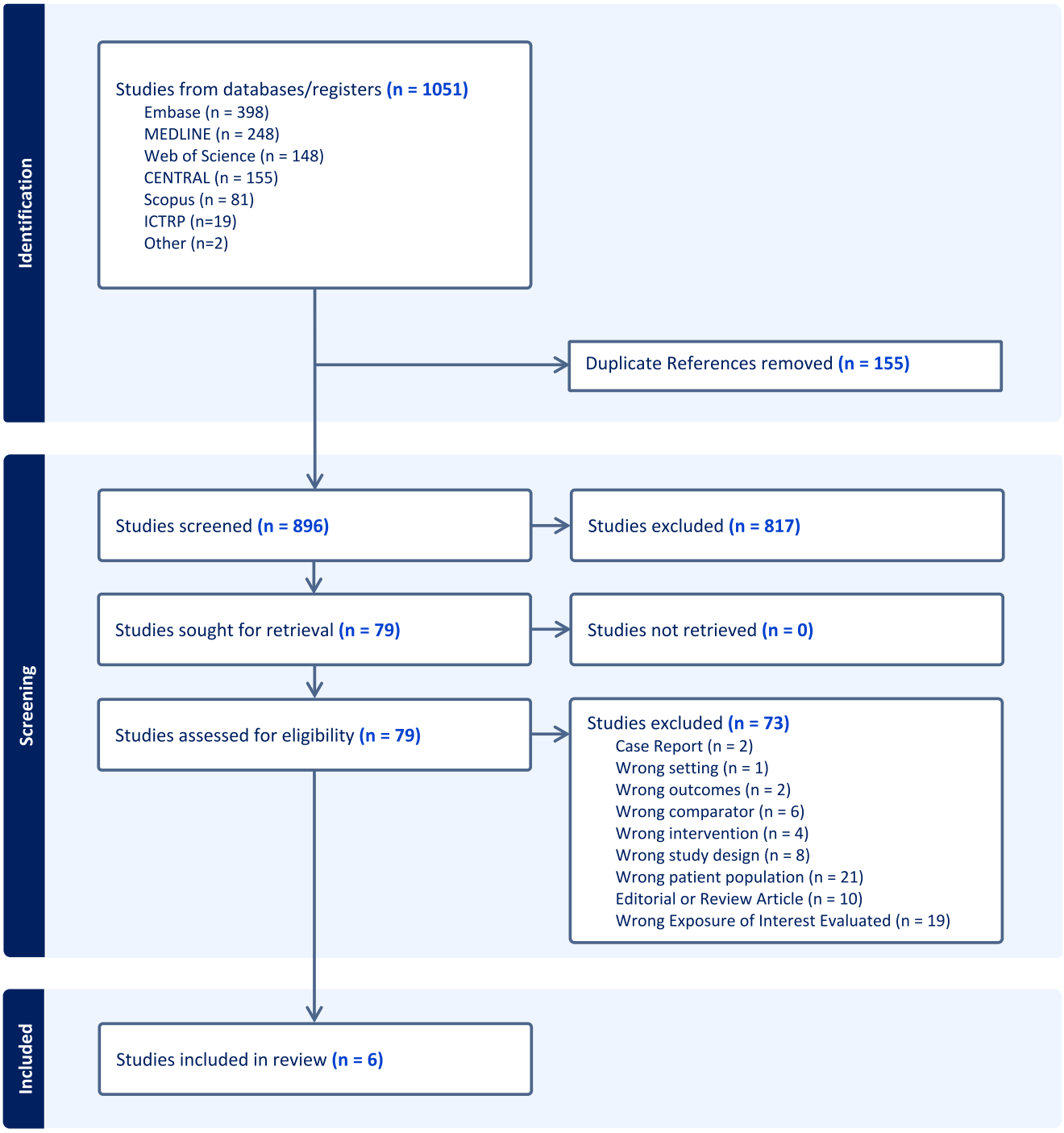


**Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram.**

### *Risk of bias in individual studies*

The Risk of Bias summary for individual included studies is shown in Fig. 2. All studies were judged to be of serious risk of bias due to confounding. Previous studies have shown that drug-related OHCA is associated with better outcomes compared to undifferentiated OHCA,[26,27] and that opioid-related OHCA is associated with better outcomes compared to other drug-related OHCA.[4] Drug-related cases are more likely to be treated with naloxone than undifferentiated OHCA,[22] and opioid-related OHCA are more likely to be treated with naloxone than other drug-related cases.[4] This creates a high risk of bias in studies including undifferentiated OHCAs, as treatment with naloxone may simply be a marker of opioid toxicity and its apparent superior prognosis, rather than providing any actual benefit. Current guidelines call for CPR administration for all patients who are unresponsive and not breathing normally unless a definite pulse is felt; this may lead some patients to be misclassified as having cardiac arrest when the patient is rather obtunded with respiratory arrest, in which case naloxone would be expected to be effective. Existing studies did not account for the specific timing of medication administration in analyses, and thus are limited by resuscitation time

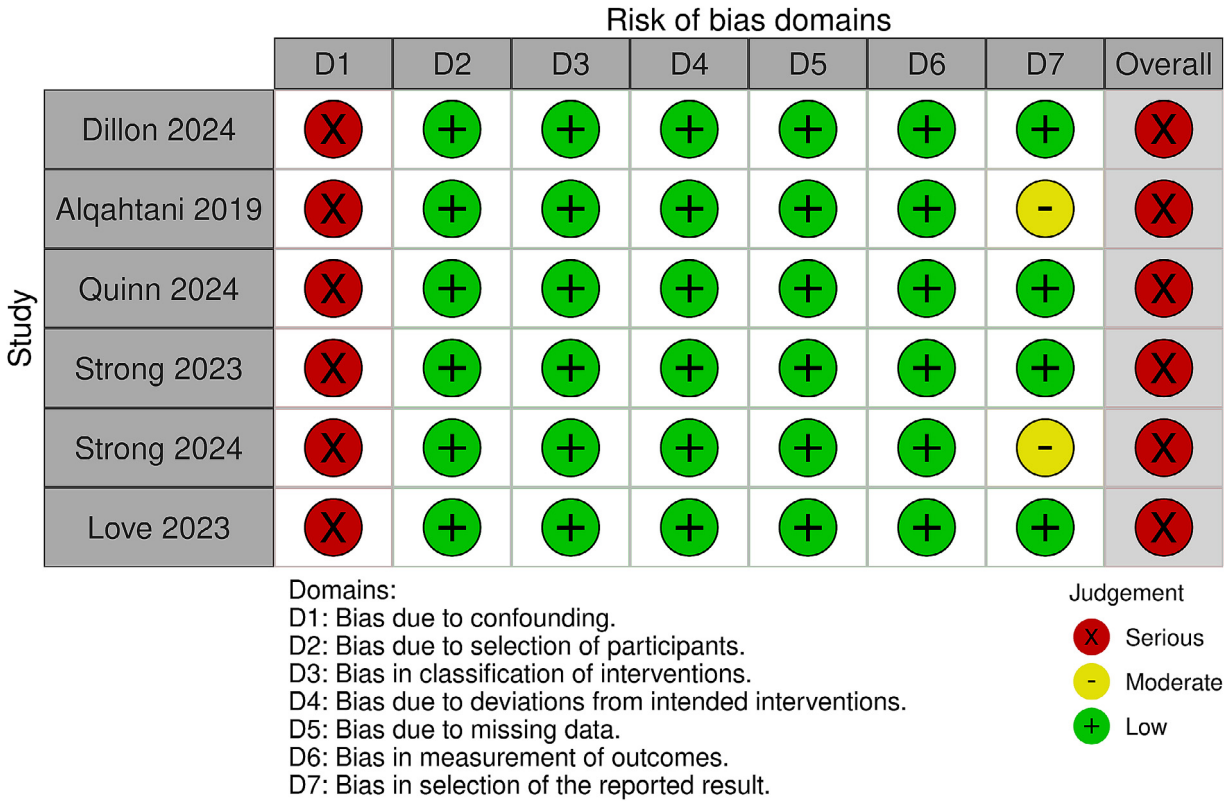


**Fig. 2 – Results of the "Risk Of Bias In Non-randomized Studies of Interventions" (ROBINS-I) Assessment.**

bias: events which occur later in the resuscitation will be associated with poor outcomes regardless of their effectiveness, given that longer durations of failed resuscitation are associated with worse outcomes.[28,29] No studies specifically examined confirmed or even suspected opioid-related OHCA, nor did any studies perform biochemical drug testing. Additional concerns were noted for two studies with regards to the selection of the reported result, given the change of study cohort and conclusions from the abstract[25] to the full-text manuscript,[17] and in another study for the number of analyses performed.[25]

### *Certainty in cumulative evidence*

GRADE Evidence Tables are available in Appendix B and C. For all outcomes the certainty of evidence was assessed at "very low", all downgraded for risk of bias (as described above) and indirectness. We assessed available evidence as indirect as there were no studies which actually examined the population of interest for this review, i.e., those with opioid-associated OHCA. Some studies included undifferentiated OHCAs,[16,17,22] and others included cases with suspected drug-overdose[25–27] (including prescription and non-prescription drugs, as well as ethanol). There were no studies which examined any outcomes (including survival, neurological outcomes, or quality-of-life metrics) beyond hospital discharge.

## Discussion

This systematic review did not identify evidence to support modifications to standard ALS resuscitation care that would specifically improve outcomes in suspected opioid-related cardiac arrest. Several studies were identified that examined cases of undifferentiated cardiac arrest, cardiac arrest due to non-shockable rhythms, or "drug-related" cases, which reported mixed results. Given the state of the evidence, further research is needed to provide higher certainty evidence to inform the optimal management of this common condition.

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),[10-12] however other data suggests opioid-reversal may worsen cerebral injury.[30,31] While it is unlikely that naloxone provides harm to cardiac arrest patients, there may be opportunity cost to adding additional interventions to cardiac arrest resuscitations that have no evidence supporting their use. Cardiac arrest resuscitations are time-sensitive task-saturated endeavors[14] with multiple competing priorities, and additional steps in the resuscitation may delay or impair the effectiveness of other interventions that are of known benefit.

Unfortunately, morbidity and mortality from opioid toxicity is too common, with 81,083 deaths in the US attributed to opioid toxicity in 2023.[32] Opioid poisoning may account for up to 10% of OHCA cases in some regions,[8,33] supporting the importance of further research in this area. The studies found in this review demonstrate how current cardiac arrest registry data are not well suited for examining the question of opioid-related cardiac arrest, given the concerns of bias by indication and resuscitation-time bias, misclassification bias around the ascertainment of cardiac vs. respiratory arrest,

and the unstructured manner in which drug and opioid toxicity is suspected in everyday prehospital practice. Current international guidelines recommend registries identify cases with "drug overdose", defined as "evidence that the cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational [sic] drugs, or ethanol."[34] In addition to relying on unstructured clinical judgement, this category would occur a wide array of substances, for example, from an accidental supratherapeutic ingestion of a beta-blocker in an 85-year-old, to a toxic-level injection of fentanyl in a 24-year-old. One can assume it would be difficult to find a signal between naloxone and outcomes among "drug overdose" cases if many of the cases are not opioid-related.

Despite these limitations, recent studies have made substantial gains in moving the field forward,[16,17,22,23] and provide a strong rationale for further study. Further observational studies are unlikely to answer the important clinical question of whether naloxone improves outcome in OHCA due to opioid poisoning when added to standard resuscitation care including chest compressions with ventilations. A randomized clinical trial is likely necessary to answer the question, and a careful evaluation of the available evidence shows that equipoise exists. Death from opioid poisoning remains at epidemic levels; a rigorously-designed randomized clinical trial of naloxone administration for OHCA from suspected opioid poisoning is both necessary and ethical.

Our systematic review is limited by the intrinsic limitations of the included studies. Further, it is possible we missed eligible studies in our review process.

## Conclusion

This systematic review identified no evidence to support modifications to standard ALS resuscitation specific to treating cardiac arrest from opioid toxicity. Available studies examining naloxone for undifferentiated or "drug related" cardiac arrest are heterogenous, with high risk of bias and low certainty of evidence. Because of the large impact on individuals and society and the inherent limitations of observational studies, a clinical trial is warranted to assess whether naloxone or other therapies provide benefit to patients with OHCA due to opioid toxicity.

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## CRediT authorship contribution statement

**Brian Grunau:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Brian J. O'Neil:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Dean Giustini:** Writing – review & editing, Methodology, Investigation, Data curation. **Ian R. Drennan:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Eric J. Lavonas:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix 1

Non-author Task Force Member Collaborators: Markus Skrifvars, Katherine Berg, Ari Moskowitz, Asger Granfeldt, Carolyn Zelop, Helen Pocock, Karen Hirsch, Keith Couper, Mathias Holmberg, Nikolaos Nikolaou, Rakesh Garg, Shannon Fernando, Shinichiro Ohshimo, Sonia D'Arrigo, Tommaso Scquizzato, Yew Woon Chia, Sandroni Claudio, Peter J. Kudenchuk, Jasmeet Soar, Jerry Nolan, Charles Deakin, and Robert Neumar.

## Appendix A. Supplementary material

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