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Naloxone and Clinical Outcomes in Suspected Opioid-Associated Out-of-Hospital Cardiac Arrests

Ralph C. Wang, MD, MAS; Jake Toy, DO, MS; Juan Carlos C. Montoy, MD, PhD; Juliana Tolles, MD, MHS; Paul F. Ehlers, MD, MS; J Joelle Donofrio-Odmann, DO; James J. Menegazzi, PhD; Marianne Gausche-Hill, MD; Robert M. Rodriguez, MD; David G. Dillon, MD, PhD; for the CAL-ROC Investigators

Abstract

IMPORTANCE Although US opioid overdose deaths have recently declined, mortality remains higher than before the COVID-19 pandemic, and the role of naloxone in opioid-associated out-of-hospital cardiac arrest (OA-OHCA) remains uncertain. The American Heart Association has identified a critical evidence gap regarding the role of naloxone in resuscitation care.

OBJECTIVE To assess the association between naloxone administered by emergency medical services (EMS) clinicians and outcomes in patients with suspected OA-OHCA.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study of adults (aged ≥18 years) with EMS-treated OHCA used data from the California Resuscitation Outcomes Consortium from January 1, 2021, to December 31, 2022. The primary cohort was patients with OA-OHCA, identified using the Naloxone Cardiac Arrest Decision Instrument (NACARDI) as age younger than 50 years and unwitnessed cardiac arrest. Additional analyses were conducted in patients with EMS-presumed drug-related OHCA and all patients with OHCA. Data were analyzed between November 2024 and July 2025.

EXPOSURE Naloxone administration during EMS resuscitation.

MAIN OUTCOMES AND MEASURES The primary outcome was survival to hospital discharge. Secondary outcomes were favorable neurologic outcome and return of spontaneous circulation (ROSC). Inverse probability weighted regression was used to estimate naloxone treatment effects as absolute risk differences (ARDs).

RESULTS Among 3811 patients meeting NACARDI criteria (median patient age, 37 years [IQR, 30-43 years]; 2792 [73.3%] male), 1251 (32.8%) received naloxone and 2560 (67.2%) did not. Survival to hospital discharge occurred in 101 patients (8.1%) who received naloxone vs 112 (4.4%) who did not. Favorable neurologic outcome occurred in 92 (7.4%) vs 84 (3.3%) and sustained ROSC in 177 (14.1%) vs 245 (9.6%), respectively. After adjustment for patient, OHCA incident, and agency-level factors, naloxone was associated with improved survival to hospital discharge (ARD, 2.75 percentage points [pp]; 95% CI, 1.25 to 4.26 pp), favorable neurologic outcome (ARD, 3.18 pp; 95% CI, 1.79 to 4.57 pp), and sustained ROSC (ARD, 3.27 pp; 95% CI, 1.11 to 5.43 pp). In sensitivity analyses of patients who received epinephrine, naloxone was not associated with improved survival to hospital discharge (adjusted ARD, 0.31 pp; 95% CI, −0.09 to 1.58 pp) or the other clinical outcomes.

CONCLUSIONS AND RELEVANCE In this cohort study, among patients with suspected OA-OHCA, EMS-administered naloxone was associated with improved survival and neurologic status and

(continued)

Key Points

Question Is naloxone administered by emergency medical services (EMS) clinicians associated with improved outcomes in patients with suspected opioid-associated out-of-hospital cardiac arrest (OA-OHCA)?

Findings In this cohort study of 3811 patients with suspected OA-OHCA, naloxone was associated with higher rates of survival to hospital discharge, return of spontaneous circulation, and favorable neurologic outcome. Risk differences were larger among patients who had EMS-presumed drug-related cardiac arrest and were attenuated among patients who received epinephrine.

Meaning The findings suggest naloxone administration during EMS resuscitation was associated with improved outcomes in patients with suspected OA-OHCA, supporting the need to assess effects of naloxone in opioid-associated cardiac arrest.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

sustained ROSC. These findings support the need for a randomized trial to assess the effects of naloxone in opioid-associated cardiac arrest.

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Introduction

Drug overdose deaths have increased over the past 2 decades in the US, peaking in 2023 at 114 664.[1] Although overdose deaths declined in 2024, mortality remains substantially higher than before the COVID-19 pandemic.[1-10] A corresponding increase in drug-related out-of-hospital cardiac arrests (OHCAs) has also been reported.[11-15] A decade ago, less than 3% of OHCAs were drug-related,[16-18] while recent studies have attributed up to 17% of OHCAs to drug overdose.[15,19,20]

Although naloxone has been clearly associated with reversal of the respiratory depression caused by opioid overdose,[21] its role in opioid-associated OHCA (OA-OHCA) remains unclear. American Heart Association guidelines suggest that it may be reasonable for emergency medical services (EMS) clinicians to administer naloxone in suspected or known OA-OHCA but caution that there is no evidence of benefit from clinical trials.[11,22,23] Current EMS practice is heterogeneous with regard to including naloxone use in OHCA protocols.[24] Our group previously identified an association between naloxone administration and survival to hospital discharge in a cohort of EMS-treated patients with OHCA in northern California.[25] In a systematic review,[26] the International Liaison Committee on Resuscitation found that EMS-administered naloxone in OHCA was associated with improved outcomes in 2 of 5 observational studies.[25-30] Given the inconsistent findings and limitations of the existing studies and the magnitude of the OA-OHCA public health problem, assessment of a larger dataset and more in-depth analytic approaches is warranted.

We conducted this cohort study using data from the California Resuscitation Outcomes Consortium (CAL-ROC), a network of 173 EMS agencies in California that serve a population of 24 million people and care for 19 000 OHCA cases per year.[31] Using CAL-ROC EMS data, we assessed the association between naloxone administration by EMS clinicians and survival in patients with suspected OA-OHCA.

Methods

Study Setting and Data Collection

We conducted a retrospective cohort study of patients with OHCA who were treated by EMS clinicians in the CAL-ROC network from January 1, 2021, to December 31, 2022, and data were analyzed between November 2024 and July 2025. CAL-ROC coordinates data collection on EMS-treated patients with OHCA across 4 clinical hubs in the University of California (UC) system: UC Davis, UC San Diego, UC San Francisco, and UC Los Angeles at Harbor-UCLA Medical Center. CAL-ROC includes data from participating EMS agencies that submit data to the Cardiac Arrest Registry to Enhance Survival (CARES), a prospective registry of OHCAs established by the Centers for Disease Control and Prevention.[31] Standardized Utstein definitions for reporting clinical variables and outcomes associated with cardiac arrest were used to ensure data uniformity.[32] Clinical and demographic data, including race and ethnicity, were collected from the prehospital or hospital electronic health records. Race and ethnicity data were included to characterize the study population and permit assessment of potential differences in presentation, treatment, and outcomes across demographic groups; categories were American Indian or Alaska Native, Asian, Black, Hispanic or Latino, Native Hawaiian or Pacific Islander, White, and other (not further subdivided in the available dataset) or unknown. This study was approved by the University of California, San Francisco institutional review board; informed consent was not applicable because CARES operates as a

deidentified public health surveillance and quality-improvement registry. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[33]

Participants

Patients included adults (aged ≥18 years) with nontraumatic OHCA with suspected OA-OHCA in whom resuscitation was attempted by EMS clinicians. We excluded patients who were younger than 18 years or older than 120 years, who had a cardiac arrest witnessed after EMS arrival, in whom the location of arrest was a hospital or long-term care facility, and/or who had traumatic arrest etiology. In addition, we predefined 3 cohorts of patients with suspected OA-OHCA (**Table 1** shows cohort definitions and rationale). The primary cohort was defined using the Naloxone Cardiac Arrest Decision Instrument (NACARDI), a validated tool designed to help EMS clinicians recognize OA-OHCA in the field.[34,35] In a recently published external validation study using medical examiner–adjudicated causes of death, the NACARDI criteria (age <50 years and unwitnessed cardiac arrest) demonstrated a sensitivity of 63.6%, specificity of 89.3%, positive predictive value of 51.7%, and negative predictive value of 93.2%.[34] A secondary cohort consisted of patients suspected by EMS clinicians to have drug-related OHCA,[36] and an additional secondary cohort consisted of all patients with OHCA.[36,37]

Outcomes and Exposure Variables

Our primary outcome was survival to hospital discharge. Our secondary outcomes were favorable neurologic outcome at hospital discharge (dichotomized as Cerebral Performance Category [CPC] score of 1-2 vs 3-5) and sustained return of spontaneous circulation (ROSC), defined as having a detectable pulse for at least 20 minutes or at the end of EMS care. The CPC scale ranges from 1 (good cerebral performance) to 5 (brain death), with scores of 1 or 2 representing favorable neurologic status. These outcomes are considered core outcomes for OHCA treatment effectiveness studies.[38]

Our exposure was EMS-administered naloxone during treatment of OHCA, identified using the EMS medication administration record. The comparator group ("no naloxone") included patients who did not receive EMS-administered naloxone. We collected covariates associated with the exposure and outcomes based on prior OA-OHCA literature: age, gender, initial cardiac rhythm, comorbidities, whether the OHCA was witnessed, location of cardiac arrest, bystander cardiopulmonary resuscitation (CPR), use of an automatic external defibrillator (AED), and EMS agency (to account for

Table 1. Study Cohort Definitions

Study cohort	Cohort definition	Rationale for study cohort
Primary		
Met NACARDI criteria	Included if both NACARDI criteria were met: (1) age <50 y and (2) unwitnessed cardiac arrest[34]	NACARDI was developed using autopsy data, which assessed all consecutive sudden cardiac deaths prospectively, and was externally validated using cases adjudicated by a medical examiner; NACARDI test characteristics had sensitivity of 63.6% (95% CI, 54.4%-72.2%), specificity of 89.3% (95% CI, 86.7%-91.5%), PPV of 51.7% (95% CI, 43.4%-59.9%), and NPV of 93.2% (95% CI, 90.9%-95.0%)[34,35]
Secondary		
EMS-suspected drug-related OHCAs	Included any cardiac arrest caused by a presumed or known overdose of medication or drugs; EMS impressions were based on information from bystanders, the presence of drug paraphernalia, or a medical history suggesting an overdose[19]	In a study of 1654 patients with OHCA who underwent toxicologic assessment by a medical examiner, 150 were adjudicated as OA; the sensitivity of drug-related OHCA for OA-OHCA was 27% (95% CI, 20%-35%), specificity was 99% (95% CI, 98%-99%), PPV was 68% (95% CI, 56%-78%), and NPV was 93% (95% CI, 93%-94%)[36]
All OHCAs	Included any cardiac arrest in which EMS clinicians may have administered naloxone, as documented in the patient care record[37]	In a study of 1654 patients with OHCA who underwent toxicologic assessment by a medical examiner, 150 were adjudicated as OA; receipt of naloxone had sensitivity of 39% (95% CI, 31%-47%), specificity of 96% (95% CI, 95%-97%), PPV of 52% (95% CI, 44%-59%), and NPV of 94% (95% CI, 93%-94%)[36]

Abbreviations: EMS, emergency medical services; NACARDI, Naloxone Cardiac Arrest Decision Instrument; NPV, negative predictive value; OA, opioid associated; OHCA, out-of-hospital cardiac arrest; PPV, positive predictive value.

agency-level differences in naloxone use and OHCA survival).[25,26,28,29,39,40] All patients received standard advanced cardiovascular life support (ACLS) resuscitation ("usual care") according to local EMS protocols.

Statistical Analysis

We described patient characteristics stratified by naloxone administration; binary variables are presented as counts and percentages and continuous variables as means (SDs) or medians (IQRs). We report between-group differences as absolute risk differences (ARDs) and risk ratios (RRs) with 95% CIs. All hypothesis tests were 2-sided, and statistical significance was defined a priori as $P < .05$. All analyses were conducted in R, version 2023.12.0 (R Project for Statistical Computing).

To address bias associated with nonrandomized treatment assignments, we developed a propensity score for naloxone administration. We assessed the effectiveness of the propensity weighting by calculating standardized mean differences of covariates, with values below 0.1 (or 10%) indicating adequate balance (eFigure 2 in Supplement 1).

We estimated the treatment effect of naloxone using inverse probability weighted regression adjustment (IPWRA), which combines outcome modeling with treatment probability modeling to address confounding.[41] Inverse probability weights were derived from the treatment model to balance measured covariates between groups and were applied in weighted outcome models to estimate the average treatment effects (ATEs)—ARDs and RRs—for survival to hospital discharge, neurologic outcome, and ROSC.[25] We used IPWRA to estimate the ATEs of naloxone in the primary cohort and in the secondary cohort of patients with EMS-presumed drug-related OHCA. We used IPWRA to estimate the average treatment effect in the treated (ATT) of naloxone in the secondary cohort of all OHCAs, estimating the association between naloxone and the treatment outcomes among all patients who received the therapy.

In addition, we conducted an a priori–defined sensitivity analysis to mitigate the bias attributable to potential misclassification of patients with respiratory arrest and a difficult-to-palpate pulse as having OA-OHCA. As naloxone is beneficial in patients with respiratory arrest without concurrent cardiac arrest,[42] a misclassification of isolated respiratory arrest as cardiac arrest would be expected to result in a positive association between naloxone and survival. We restricted the cohort in this sensitivity analysis to patients meeting the NACARDI criteria who received ACLS care, including having received a dose of epinephrine, to exclude patients with respiratory arrest.

Results

Study Participants

We identified 38 408 medical records of patients treated for OHCA; 11 804 medical records were excluded based on age, arrest witnessed by EMS, occurrence in inpatient facilities, do-not-resuscitate status, or traumatic etiology. Of the 26 604 enrolled patients, 22 793 did not meet NACARDI criteria, resulting in a primary cohort of 3811 patients (**Figure**); secondary cohorts are described in eFigure 1 in Supplement 1. Of the 3811 patients in the primary cohort, 1018 (26.7%) were female, 2792 (73.3%) were male, and 1 (<0.1%) was nonbinary, with a median age of 37 years (IQR, 30-43 years) (**Table 2**). Ten patients (0.3%) were American Indian or Alaska Native; 123 (3.2%), Asian; 467 (12.3%), Black; 943 (24.7%), Hispanic or Latino; 26 (0.7%), Native Hawaiian or Other Pacific Islander; 968 (25.4%), White; 24 (0.6%), other race and ethnicity; and 1250 (32.8%) had unknown race and ethnicity. We found that 3139 patients (82.4%) had asystole, 400 (10.5%) had pulseless electrical activity, and 272 (7.1%) had a shockable rhythm. A total of 1184 (31.1%) were identified as having presumed drug-related OHCA by the treating EMS clinician.

Naloxone Administration by EMS Clinicians

Naloxone was administered in 1251 (32.8%) of the cases meeting NACARDI criteria (Table 1). The demographic and arrest characteristics of the patients treated with naloxone differed from the

nonexposed group; the naloxone group was younger, more likely to be male, and had fewer comorbidities. Patients with presumed drug-related OHCA and patients with pulseless electrical activity had higher odds of receiving naloxone (odds ratios after adjusting for individual variables were 5.45 [95% CI, 4.59-6.46] and 1.46 [95% CI, 1.14-1.87], respectively) (**Table 3**).

Naloxone Association With Survival, Neurologic Outcome, and ROSC

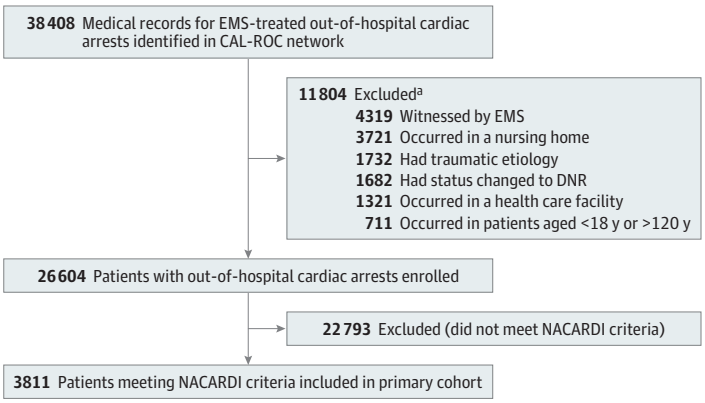
In the primary cohort, patients who received naloxone (n = 1251 [32.8%]) vs patients who did not receive naloxone (n = 2560 [67.2%]) had a higher probability of survival to hospital discharge (101 [8.1%] vs 112 [4.4%]), favorable neurologic outcome at discharge (92 [7.4%] vs 84 [3.3%]), and ROSC (177 [14.1%] vs 245 [9.6%]) (Table 2). The unadjusted ARD associated with naloxone administration was 3.70 percentage points (pp) (95% CI, 1.99-5.40 pp) for survival to hospital discharge, 4.07 pp (95% CI, 2.47-5.68 pp) for discharge with a favorable neurologic outcome, and 4.58 pp (95% CI, 2.34-6.82 pp) for ROSC (**Table 4**). After adjustment using IPWRA, the ATE of naloxone remained positive and statistically significant: ARD, 2.75 pp (95% CI, 1.25-4.26 pp) for survival to hospital discharge, 3.18 pp (95% CI, 1.79-4.57 pp) for discharge with a favorable neurologic outcome, and 3.27 pp (95% CI, 1.11-5.43 pp) for ROSC. RRs from both unadjusted and IPWRA models similarly demonstrated positive associations (Table 4).

In our analysis of the secondary cohort of patients with EMS-presumed drug-related OHCA, naloxone administration was associated with improved survival to hospital discharge (unadjusted ARD, 8.73 pp; 95% CI, 5.85-11.61 pp), favorable neurologic outcome (unadjusted ARD, 8.74 pp; 95% CI, 6.05-11.43 pp), and ROSC (unadjusted ARD, 9.90 pp; 95% CI, 6.43-13.37 pp) (Table 4). When estimated using IPWRA, the risk differences remained positive and statistically significant at 8.58 pp (95% CI, 5.27-11.89 pp) for survival to discharge, 9.00 pp (95% CI, 5.74-12.23 pp) for favorable neurologic outcome, and 8.81 (95% CI, 4.88-12.75 pp) for ROSC. RRs from both unadjusted and IPWRA models were similarly positive (Table 4).

In the analysis of the secondary cohort comprising all patients with OHCA, the unadjusted ARD was 3.32 pp (95% CI, 2.19-4.46 pp) for survival to discharge, 3.81 pp (95% CI, 2.74-4.89 pp) for favorable neurologic outcome, and 2.61 pp (95% CI, 1.17-4.06 pp) for ROSC (Table 4). The IPWRA ATE yielded similar findings, with ARDs of 2.89 pp (95% CI, 1.14-4.63 pp) for survival to discharge, 3.57 pp (95% CI, 1.79-5.36 pp) for favorable neurologic outcome, and 3.12 pp (95% CI, 0.97-5.28 pp) for ROSC. RRs again showed positive associations across both unadjusted and adjusted models (Table 4).

In a sensitivity analysis of patients meeting NACARDI criteria who received epinephrine, the unadjusted ARD associated with naloxone was −0.21 pp (95% CI, −1.52 to 1.10 pp) for survival to hospital discharge, 0.22 pp (95% CI, −0.92 to 1.36 pp) for discharge with a favorable neurologic outcome, and 0.47 pp (95% CI, −1.62 to 2.56 pp) for ROSC (Table 4). Using IPWRA, the ARD was 0.31

Figure. Inclusion Flow Diagram for Primary Cohort



The California Resuscitation Outcomes Consortium (CAL-ROC) is a statewide network of emergency medical services (EMS) systems in California that includes 173 EMS agencies. Naloxone Cardiac Arrest Decision Instrument (NACARDI) criteria included age younger than 50 years and sustaining an unwitnessed out-of-hospital cardiac arrest.[31,34] DNR indicates do not resuscitate.

[a] Some patients met more than 1 exclusion criterion.

Table 2. Demographic and Clinical Characteristics of the Primary Analysis Cohort, Stratified by Naloxone Administration

Characteristic	Patients, No. (%)			*P* value
	Overall (N = 3811)	No naloxone (n = 2560)	Naloxone (n = 1251)	
Age, median (IQR), y	37 (30-43)	39 (31-44)	34 (29-40)	<.001
Gender				
Female	1018 (26.7)	725 (28.3)	293 (23.4)	<.001
Male	2792 (73.3)	1835 (71.7)	957 (76.5)	
Nonbinary	1 (<0.1)	0	1 (<0.1)	
Race and ethnicity[a]				
American Indian or Alaska Native	10 (0.3)	7 (0.3)	3 (0.2)	NA
Asian	123 (3.2)	103 (4.0)	20 (1.6)	
Black	467 (12.3)	324 (12.7)	143 (11.4)	
Hispanic or Latino	943 (24.7)	663 (25.9)	280 (22.4)	
Native Hawaiian or Other Pacific Islander	26 (0.7)	22 (0.9)	4 (0.3)	
White	968 (25.4)	600 (23.4)	368 (29.4)	
Other	24 (0.6)	18 (0.7)	6 (0.5)	
Unknown	1250 (32.8)	823 (32.1)	427 (34.1)	
Reported medical comorbidities				
Yes	2073 (54.4)	1425 (55.7)	648 (51.8)	NA
No	578 (15.2)	372 (14.5)	206 (16.5)	
Unknown	1160 (30.4)	763 (29.8)	397 (31.7)	
Specific medical comorbidity				
Cancer	33 (0.9)	29 (1.1)	4 (0.3)	.01
Diabetes	162 (4.3)	133 (5.2)	29 (2.3)	<.001
Heart disease	144 (3.8)	116 (4.5)	28 (2.2)	<.001
Hyperlipidemia	34 (0.9)	30 (1.2)	4 (0.3)	.01
Hypertension	361 (9.5)	301 (11.8)	60 (4.8)	<.001
Kidney disease	37 (1.0)	32 (1.3)	5 (0.4)	.01
Respiratory disease	41 (1.1)	27 (1.1)	14 (1.1)	.86
Stroke	25 (0.7)	19 (0.7)	6 (0.5)	.35
None, unknown, or other[b]	1774 (46.5)	1182 (46.2)	592 (47.3)	.50
Location of cardiac arrest				
Home	2776 (72.8)	1950 (76.2)	826 (66.0)	<.001
Public	1035 (27.2)	610 (23.8)	425 (34.0)	
Bystander CPR	1278 (33.5)	866 (33.8)	412 (32.9)	.58
AED applied prior to EMS arrival				
Yes, with defibrillation	75 (2.0)	55 (2.1)	20 (1.6)	<.001
Yes, without defibrillation	377 (9.9)	217 (8.5)	160 (12.8)	
No	3359 (88.1)	2288 (89.4)	1071 (85.6)	
Presumed cause of cardiac arrest				
Drowning or submersion	47 (1.2)	42 (1.6)	5 (0.4)	NA
Drug overdose	1184 (31.1)	511 (20.0)	673 (53.8)	
Electrocution	6 (0.2)	6 (0.2)	0	
Exsanguination or hemorrhage	30 (0.8)	28 (1.1)	2 (0.2)	
Presumed cardiac etiology	2320 (60.9)	1789 (70.0)	531 (42.4)	
Respiratory or asphyxia	204 (5.4)	167 (6.5)	37 (3.0)	
Other[c]	20 (0.5)	17 (0.7)	3 (0.2)	
Initial rhythm				
Asystole or other unshockable rhythm	3139 (82.4)	2108 (82.3)	1031 (82.4)	.001
PEA	400 (10.5)	247 (9.6)	153 (12.2)	
Shockable rhythm	272 (7.1)	205 (8.0)	67 (5.4)	
Airway placed in field	1161 (30.5)	731 (28.6)	430 (34.4)	<.001
Epinephrine administered	3187 (83.6)	2041 (79.7)	1146 (91.6)	<.001
Sustained ROSC	422 (11.1)	245 (9.6)	177 (14.1)	<.001
Survival to hospital admission	492 (12.9)	285 (11.1)	207 (16.5)	<.001
Survival to hospital discharge	213 (5.6)	112 (4.4)	101 (8.1)	<.001
Discharged with favorable neurologic outcome[d]	176 (4.6)	84 (3.3)	92 (7.4)	<.001

Abbreviations: AED, automatic external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; NA, not applicable; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation.

[a] Race and ethnicity were collected during the prehospital or hospital phase of care and assigned as reported by the patient, family, or health care practitioner. "Other" was not further subdivided in the dataset.

[b] The dataset specifies "other" as medical conditions not included in the named categories but that may affect patient survival.

[c] Includes trauma, poisoning or intoxication, or another cause that was known and documented but did not fit one of the categories listed in the dataset.

[d] Defined as a Cerebral Performance Category score of 1 or 2 vs 3 to 5 on a scale from 1 (good cerebral performance) to 5 (brain death), with scores of 1 or 2 representing favorable neurologic status.

pp (95% CI, −0.09 to 1.58 pp) for survival to discharge, 0.84 pp (95% CI, −0.18 to 1.86 pp) for discharge with a favorable neurologic outcome, and 0.97 pp (95% CI, −1.44 to 3.38 pp) for ROSC.

Discussion

In this large cohort of EMS-treated patients with OHCA with suspected OA-OHCA, EMS administration of naloxone was associated with improved clinical outcomes for patients meeting NACARDI criteria, including increased rates of survival to hospital discharge, survival with favorable neurologic outcome, and ROSC. The observed association with improved outcomes was substantial, with ARDs estimated to be 3 to 4 pp. A similarly positive association was found in the cohort with EMS-presumed drug-related OHCA, which represents a subgroup that is likely to have true OA-OHCA, with ARDs for improved outcomes of 8 to 9 pp. This positive association was also observed among patients treated with naloxone among all OHCAs. The similarity between the ARD in the all-OHCA cohort and the cohort meeting NACARDI criteria likely reflects that naloxone administration in the all-OHCA cohort was concentrated among patients with EMS-presumed drug-related etiology, effectively enriching the treated group for opioid-associated arrest.

The findings from the sensitivity analysis restricted to patients meeting NACARDI criteria who received epinephrine warrant careful interpretation. This restriction was intended to reduce inclusion of patients in opioid-induced respiratory arrest with difficult-to-palpate pulses who may have been misclassified as having cardiac arrest. In this subgroup, naloxone was not associated with sustained ROSC, survival to hospital discharge, or favorable neurologic outcome. One possible explanation is that restriction to patients who received epinephrine reduced inclusion of individuals with

Table 3. Odds of Receiving Naloxone by Patient and Clinical Characteristics

Characteristic	AOR (95% CI)[a]
Intercept	0.34 (0.26-0.43)
Age quantile, y	
18-30	1 [Reference]
31-37	1.03 (0.84-1.27)
38-43	0.77 (0.62-0.95)
44-49	0.56 (0.45-0.70)
Male gender	1.08 (0.91-1.29)
Medical history suggesting prior overdose	
Yes	1 [Reference]
No	1.01 (0.81-1.26)
Unknown	0.94 (0.78-1.13)
Public location	1.58 (1.32-1.89)
Presumed drug overdose	5.45 (4.59-6.46)
Bystander CPR	1.04 (0.88-1.23)
AED applied prior to EMS arrival[b]	1.03 (0.81-1.31)
Initial rhythm	
Asystole	1 [Reference]
PEA	1.46 (1.14-1.87)
Shockable	0.96 (0.70-1.32)

Abbreviations: AED, automatic external defibrillator; AOR, adjusted odds ratio; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; PEA, pulseless electrical activity.

[a] We fit a generalized linear model with a binomial distribution and logit link function to model the binary outcome of naloxone administration. We accounted for site-level differences through including each of the 19 centers as a fixed effect. When fitting a mixed-effects model with center included as a random effect, the results were unchanged.

[b] With or without defibrillation.

respiratory arrest misclassified as having OHCA.[11] However, this is unlikely to have affected our results, as 82.4% of patients who did not receive epinephrine were documented as being in asystole, consistent with established cardiac arrest. Second, naloxone may exert benefit in OA-OHCA when administered early, so excluding shorter resuscitations may have preferentially removed patients most likely to respond—consistent with prior observational work when naloxone was administered early in nonshockable OHCA.[28]

Third, restricting to patients who received epinephrine may have selected for longer or more refractory arrests, introducing resuscitation-time bias. While ACLS guidelines recommend epinephrine as soon as feasible after identification of nonshockable rhythms,[23] in practice this is often delayed.[43] Because longer arrest duration is associated with worse outcomes,[43,44] restricting the analysis to patients who received epinephrine may have preferentially selected individuals with longer resuscitations. In addition, the timing and decision to administer epinephrine may reflect differences in resuscitation timing, team performance, airway management, and overall resuscitation intensity that are not fully captured in these data. In the absence of reliable time stamps for medication administration and ROSC, we were unable to account for arrest duration and treatment timing, raising the possibility of resuscitation-time bias.[44] Importantly, because naloxone may be administered either earlier or later in the course of resuscitation, the net direction of any time-related

Table 4. Treatment Outcomes of Naloxone in Patients With Suspected Opioid-Associated OHCA

Average treatment effect	Treatment outcome		
	Survival to hospital discharge	Neurologically intact survival[a]	ROSC
Primary cohort (met NACARDI criteria)[b]			
Unadjusted			
ARD (95% CI), pp	3.70 (1.99 to 5.40)	4.07 (2.47 to 5.68)	4.58 (2.34 to 6.82)
RR (95% CI)	1.85 (1.42 to 2.39)	2.24 (1.68 to 2.99)	1.48 (1.23 to 1.77)
IPWR adjusted[c]			
ARD (95% CI), pp	2.75 (1.25 to 4.26)	3.18 (1.79 to 4.57)	3.27 (1.11 to 5.43)
RR (95% CI)	1.68 (1.29 to 2.19)	2.10 (1.56 to 2.81)	1.36 (1.13 to 1.63)
Secondary cohorts			
Presumed drug-related OHCA			
Unadjusted			
ARD (95% CI), pp	8.73 (5.85 to 11.61)	8.74 (6.05 to 11.43)	9.90 (6.43 to 13.37)
RR (95% CI)	2.11 (1.61 to 2.76)	2.39 (1.77 to 3.24)	1.71 (1.40 to 2.10)
IPWR adjusted[c]			
ARD (95% CI), pp	8.58 (5.27 to 11.89)	9.00 (5.74 to 12.23)	8.81 (4.88 to 12.75)
RR (95% CI)	2.05 (1.57 to 2.68)	2.39 (1.78 to 3.22)	1.60 (1.32 to 1.95)
All OHCAs			
Unadjusted			
ATT ARD (95% CI), pp[d]	3.32 (2.19 to 4.46)	3.81 (2.74 to 4.89)	2.61 (1.17 to 4.06)
RR (95% CI)	1.48 (1.32 to 1.66)	1.71 (1.51 to 1.94)	1.17 (1.08 to 1.27)
IPWR adjusted[c]			
ATT ARD (95% CI), pp[d]	2.89 (1.14 to 4.63)	3.57 (1.79 to 5.36)	3.12 (0.97 to 5.28)
RR (95% CI)	1.44 (1.22 to 1.69)	1.63 (1.36 to 1.95)	1.25 (1.11 to 1.40)
Sensitivity cohort (met NACARDI criteria and received epinephrine)[e]			
Unadjusted			
ARD (95% CI), pp	−0.21 (−1.52 to 1.10)	0.22 (−0.92 to 1.36)	0.47 (−1.62 to 2.56)
RR (95% CI)	0.94 (0.64 to 1.38)	1.09 (0.70 to 1.71)	1.05 (0.84 to 1.32)
IPWR adjusted[c]			
ARD (95% CI), pp	0.31 (−0.09 to 1.58)	0.84 (−0.18 to 1.86)	0.97 (−1.44 to 3.38)
RR (95% CI)	1.13 (0.78 to 1.64)	1.56 (1.01 to 2.42)[f]	1.11 (0.89 to 1.39)

Abbreviations: ARD, absolute risk difference; ATT, average treatment effect in the treated; IPWR, inverse probability weighted regression; NACARDI, Naloxone Cardiac Arrest Decision Instrument; OHCA, out-of-hospital cardiac arrest; pp, percentage points; RR, risk ratio.

[a] Neurologically intact survival was defined as a Cerebral Performance Category score of 1 or 2 vs 3 to 5 on a scale from 1 (good cerebral performance) to 5 (brain death), with scores of 1 or 2 representing favorable neurologic status.

[b] NACARDI criteria included age less than 50 years and sustaining an unwitnessed out-of-hospital cardiac arrest.[31,34]

[c] Adjusted for patient age, sex, initial cardiac rhythm, and comorbidities; whether the OHCA was witnessed; location of OHCA; bystander cardiopulmonary resuscitation; use of an automatic external defibrillator; and emergency medical services agency (to account for agency-level differences in naloxone use and OHCA survival).

[d] Estimated among all patients who received the therapy.

[e] Patients without documented administration of epinephrine were excluded from this sensitivity analysis.

[f] We consider this result to be nonsignificant. The difference in statistical significance between the average treatment effect and the RR for neurologically intact survival is likely attributable to minor differences in how the SE was estimated.

bias cannot be determined from these data. These results underscore the challenges of evaluating time-dependent intra-arrest therapies in observational data and highlight the need for randomized evaluation.

The positive associations we found were consistent with and improved upon those from prior studies. The previously cited International Liaison Committee on Resuscitation systematic review noted improved outcomes with EMS-administered naloxone in 2 of 5 observational studies.[26] Strong et al[28] found an association between early naloxone use (prior to EMS vascular access) and survival in patients with nonshockable OHCA, which is consistent with our results. This study also confirms our group's prior work in northern California, with the additional benefit of broader geographic and demographic diversity and methods more focused on patients with suspected OA-OHCA as opposed to the general population with OHCA.[25] Overall, this study contributes stronger evidence than our group's previous study by restricting the analysis to patients with suspected OA-OHCA and addressing potential biases in a larger, more diverse population.

Limitations

This study has several limitations that deserve consideration. First, as a retrospective analysis, residual confounding remains possible despite adjustment. We were unable to measure CPR quality, timing of medication administration, or total duration of resuscitation. Naloxone administration may be a marker of resuscitation quality or earlier intervention rather than exerting an independent treatment effect. In addition, patients receiving naloxone were more likely to receive epinephrine, which is associated with improved outcomes when administered early.[28] If naloxone use correlates with differences in CPR quality or medication timing, the observed association may partially reflect resuscitation care rather than an effect of the drug. Because the dataset lacks reliable time stamps for naloxone administration, we could not determine whether naloxone was given early or late in the arrest course or assess the direction of time-related bias.

Second, although the NACARDI tool enriches for patients with suspected OA-OHCA, its test characteristics are imperfect, and misclassification remains possible. Some non–opioid-related arrests may have been included, likely biasing results toward no association. Conversely, cardiac arrest in the prehospital setting is a clinical diagnosis and pulses may be difficult to palpate, and some patients classified as OHCA may have been in opioid-induced respiratory arrest rather than established cardiac arrest. In such cases, early naloxone may restore ventilation and prevent progression to sustained arrest, complicating interpretation.

Third, attenuation of associations in the epinephrine-restricted cohort suggests that resuscitation processes may partly explain the findings. Restricting to patients who received epinephrine may better confirm pulseless arrest but may also select for longer or more refractory resuscitations. Fourth, airway management practices varied across EMS agencies, and we could not determine whether airway interventions occurred before or after naloxone administration. Adjusting for airway placement without reliable time sequencing could have distorted the association. Fifth, naloxone administration by bystanders and adverse events potentially attributable to naloxone were not captured. Sixth, because data were drawn exclusively from California EMS systems, results may not generalize to other regions.

Conclusions

In this cohort study, EMS administration of naloxone in patients with suspected OA-OHCA was associated with increased survival to hospital discharge, favorable neurologic outcomes, and ROSC. Our findings support a potential benefit of EMS-administered naloxone in OA-OHCA, particularly in patients with EMS-presumed drug overdose. However, the interpretation of contradictory findings is challenging and highlights the limitations inherent in retrospective data. These results reinforce the need for a randomized study to determine the effect of naloxone on suspected OA-OHCA.

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Corresponding Author: Ralph C. Wang, MD, MAS, Department of Emergency Medicine, University of California San Francisco, 521 Parnassus Ave, San Francisco, CA 94143 (ralph.wang@ucsf.edu).

Author Affiliations: Department of Emergency Medicine, University of California, San Francisco (Wang, Montoy, Ehlers); Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California (Toy, Tolles); The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California (Toy, Tolles, Gausche-Hill); Los Angeles County Emergency Medical Services Agency, Santa Fe Springs, California (Toy); David Geffen School of Medicine at UCLA, Los Angeles, California (Tolles, Gausche-Hill); California Poison Control System, San Francisco Division, San Francisco, California (Ehlers); Department of Pediatrics, University of California, San Diego (Donofrio-Odmann); Rady Children's Hospital, San Diego, California (Donofrio-Odmann); Department of Emergency Medicine, University of California, San Diego (Donofrio-Odmann); Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Menegazzi); Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California (Gausche-Hill); Department of Medicine, University of California, Riverside School of Medicine (Rodriguez); Department of Emergency Medicine, University of California, Davis, Sacramento (Dillon).

Author Contributions: Dr Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wang, Toy, Montoy, Gausche-Hill, Rodriguez, Dillon.

Acquisition, analysis, or interpretation of data: Wang, Toy, Montoy, Tolles, Ehlers, Donofrio-Odmann, Menegazzi, Rodriguez, Dillon.

Drafting of the manuscript: Wang, Toy, Ehlers, Menegazzi, Rodriguez, Dillon.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Wang, Toy, Tolles, Menegazzi, Dillon.

Administrative, technical, or material support: Ehlers, Donofrio-Odmann, Gausche-Hill.

Supervision: Wang, Ehlers, Rodriguez, Dillon.

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