Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Original paper

A retrospective 'target trial emulation' comparing amiodarone and lidocaine for adult out-of-hospital cardiac arrest resuscitation

Tanner Smida[a,*], *Remle Crowe*[b], *Bradley S. Price*[c], *James Scheidler*[d], *P.S. Martin*[d], *Michael Shukis*[d], *James Bardes*[d]

Abstract

Objective: The administration of amiodarone or lidocaine is recommended during the resuscitation of out-of-hospital cardiac arrest (OHCA) patients presenting with defibrillation-refractory or recurrent ventricular fibrillation or ventricular tachycardia. Our objective was to use 'target trial emulation' methodology to compare the outcomes of patients who received amiodarone or lidocaine during resuscitation.

Methods: Adult, non-traumatic OHCA patients in the ESO Data Collaborative 2018–2023 datasets who experienced OHCA prior to EMS arrival, presented with a shockable rhythm, and received amiodarone or lidocaine during resuscitation were evaluated for inclusion. We used propensity score matching (PSM) to investigate the association between antiarrhythmic and outcomes. Return of spontaneous circulation (ROSC) was the primary outcome. Secondary outcomes included the number of post-drug defibrillations and survival to hospital discharge.

Results: After application of exclusion criteria, 23,263 patients from 1,707 EMS agencies were eligible for analysis. Prior to PSM, 6,010/20,284 (29.6%) of the patients who received amiodarone and 1,071/2,979 (35.9%) of the patients who received lidocaine achieved prehospital ROSC. Following PSM, lidocaine administration was associated with greater odds of prehospital ROSC (36.0 vs. 30.4%; aOR: 1.29 [1.16, 1.44], n = 2,976 matched pairs). Lidocaine administration was also associated with fewer post-drug defibrillations (median: 2 [0–4] vs. 2 [0–6], mean: 3.3 vs. 3.9, $p < 0.01$, n = 2,976 pairs), and greater odds of survival to discharge (35.1 vs. 25.7%; OR: 1.54 [1.19, 2.00], n = 538 pairs).

Conclusion: Our 'target trial emulation' suggested that lidocaine was associated with greater odds of prehospital ROSC in comparison to amiodarone when administered during resuscitation from shock refractory or recurrent VF/VT.

Keywords: Amiodarone, Lidocaine, Antiarrhythmic, Shockable, Ventricular fibrillation, Ventricular tachycardia, Refractory, Recurrent, Medication, Intravenous, Intraosseous

Introduction

Out-of-hospital cardiac arrest (OHCA) patients who present with an initial electrocardiogram (ECG) rhythm of ventricular fibrillation or ventricular tachycardia (VF/VT) comprise approximately 17.5% of the EMS-treated OHCA patients in the United States, which translates to approximately 50,000 patients per year.[1] Despite the favorable prognosis of VF/VT in comparison to other ECG rhythms, approximately half of these patients do not achieve sustained ROSC and only 29% survive to hospital discharge, which underscores the need to improve the delivery of resuscitation to this patient population.

An important subgroup of shockable OHCA patients experience VF/VT that is recurrent or refractory to defibrillation attempts. Several studies have suggested that 20 to 63% of patients presenting with a shockable rhythm will require more than three defibrillation attempts during resuscitation.[2–5] For this population, the administration of amiodarone or lidocaine is recommended by international guidelines.[6,7] Both of these medications have been shown to improve return of spontaneous circulation (ROSC) and survival to hospital admission in comparison to placebo in randomized controlled trials.[8,9] However, these trials have not conclusively established that either medication significantly improves survival to hospital discharge or survival with a favorable neurological outcome.

* Corresponding author at: 64 Medical Center Drive, Morgantown, WV 26506, United States.
E-mail address: tts00004@mix.wvu.edu (T. Smida).

https://doi.org/10.1016/j.resuscitation.2025.110515
Received 5 December 2024; Received in Revised form 15 January 2025; Accepted 16 January 2025

The largest prehospital randomized controlled trial comparing amiodarone and lidocaine to placebo for shock-refractory OHCA found that the group of patients who received lidocaine had a greater prevalence of ROSC at emergency department arrival in comparison to patients who received amiodarone, although this difference did not achieve statistical significance at an alpha of 0.05.[8] Observational studies in both adult[10] and pediatric in-hospital cardiac arrest (IHCA) cohorts[11] have suggested a similar association between lidocaine and increased odds of achieving ROSC.

As a result of these previous studies, we aimed to use a nationwide prehospital dataset to explore the relationship between the antiarrhythmic agent administered during resuscitation and the primary outcome of prehospital ROSC. As secondary aims, we assessed the association between antiarrhythmic agent and outcomes including the number of post-antiarrhythmic defibrillations, survival to hospital discharge, prehospital post-ROSC bradycardia, post-ROSC hypotension, and post-ROSC transcutaneous pacing.

Methods

Data source

We used the ESO Data Collaborative 2018–2023 annual datasets to perform this retrospective cohort study. These datasets are comprised of prehospital electronic health records (EHRs) completed by EMS clinicians from >2,000 EMS agencies across the United States during or subsequent to patient care.[12] A subset of EMS agencies consent to having deidentified data collected for research purposes from these EHRs. Each encounter included in the dataset has associated data describing patient demographics, exam findings, vital signs, and interventions – including the timing, route, and dose of medications - aligned with the National EMS Information System standard.[13] Approximately 20% of transported patients have linked hospital outcome data via a bi-directional health data exchange. Data from EHRs are automatically included in annual datasets without a need for any manual data abstraction. Use of these deidentified datasets was approved by an institutional review board (protocol 2202524583).

To minimize the influence of common sources of bias in observational data, we adhered to 'target trial emulation' methodology, which is a framework intended to minimize common sources of bias in observational research.[14,15] Supplemental Table 1 describes the 'target trial' and our corresponding attempt at emulation.

Eligibility criteria

We assessed all adult (18–80 years of age) non-traumatic OHCA patients with an initially shockable ECG rhythm and administration of lidocaine or amiodarone via intravenous (IV) or intraosseous (IO) access for inclusion in this study [Fig. 1]. All patients with an EMS witnessed OHCA, a resuscitation limiting advanced directive, or initial antiarrhythmic administration post-ROSC were excluded from our cohort. Patients who experienced OHCA in a healthcare facility (nursing home, rehabilitation center, etc.) or had ROSC without EMS resuscitation (bystander CPR and/or AED use only) were also excluded. We excluded patients who were >80 years of age or residents in healthcare facilities to avoid inclusion of a population of patients with a high burden of comorbidity that may preclude favorable outcomes despite antiarrhythmic administration and impair the ability to detect a treatment effect. EMS witnessed OHCA were excluded to enhance homogeneity of the cohort, as these patients represent a unique population that is more likely to respond to defibrillation, achieve ROSC, and survive. In alignment with target trial emulation methodology, we did not exclude patients who received both amiodarone and lidocaine because the need for a second 'rescue' antiarrhythmic agent could not have been known at the hypothetical time of randomization. The probability of receiving a second antiarrhythmic during resuscitation may be dependent on the first antiarrhythmic administered. Therefore, patients were classified into amiodarone and lidocaine groups by the first antiarrhythmic agent administered during resuscitation.

Variable definitions

Patients were classified as experiencing a shockable rhythm if their initial ECG rhythm was ventricular fibrillation, ventricular tachycardia, or an unknown AED shockable rhythm. Pre- and post-antiarrhythmic defibrillation was defined as any documented AED defibrillation, manual defibrillation, or double-sequential defibrillation delivered before or after the first documented administration of amiodarone or lidocaine. The response interval was defined as the time from EMS dispatch to scene arrival. The 'time to drug' was defined as the time from scene arrival to the first antiarrhythmic administration. The follow-up interval was defined as the time from drug administration to ROSC, hospital arrival, or termination of resuscitation. All other variables were derived from existing elements in the dataset.

Outcome measures

Our primary outcome for this study was prehospital ROSC. We chose this as our primary outcome due to availability for our entire sample and the proximity of this outcome to our intervention of interest. All patients with a documented ROSC time following EMS resuscitation were classified as having prehospital ROSC, regardless of duration. Secondary outcomes included the number of post-antiarrhythmic defibrillations, survival to hospital discharge, post-ROSC bradycardia, post-ROSC hypotension, and prehospital transcutaneous pacing. Within the subset of patients with hospital outcome data, patients were classified as experiencing mortality if their disposition suggested death prior to discharge. Hypotension was defined as a systolic blood pressure between 30 and 90 mmHg. Bradycardia was defined as a heart rate between 10 and 50 beats per minute.

Statistical analyses

For our unadjusted analyses, continuous variables were reported as medians with interquartile ranges and categorical variables were reported as percentages with frequencies. Continuous variables were compared using the Wilcoxon signed-rank sum test[16] and categorical variables were compared using McNemar's test or a chi-squared test with Yates' continuity correction, as appropriate. We performed propensity score matching analyses to examine the association between antiarrhythmic agent and outcomes. Propensity scores were generated from a logistic regression model including age, sex, OHCA etiology (presumed cardiac, respiratory/asphyxia, drug overdose, other), witnessed status, pre-first responder CPR, initial rhythm (VF, VT, unknown AED shockable), response interval (dispatch time to on-scene time), number of pre-antiarrhythmic defibrillations, medication interval (on-scene time to medication administration time), vascular access type through which the first dose of antiarrhythmic was administered (IV vs. IO), and OHCA location (private/home vs. public) without replacement.[17] The caliper width was set at 0.2 of the standard deviation of the logit of the propensity

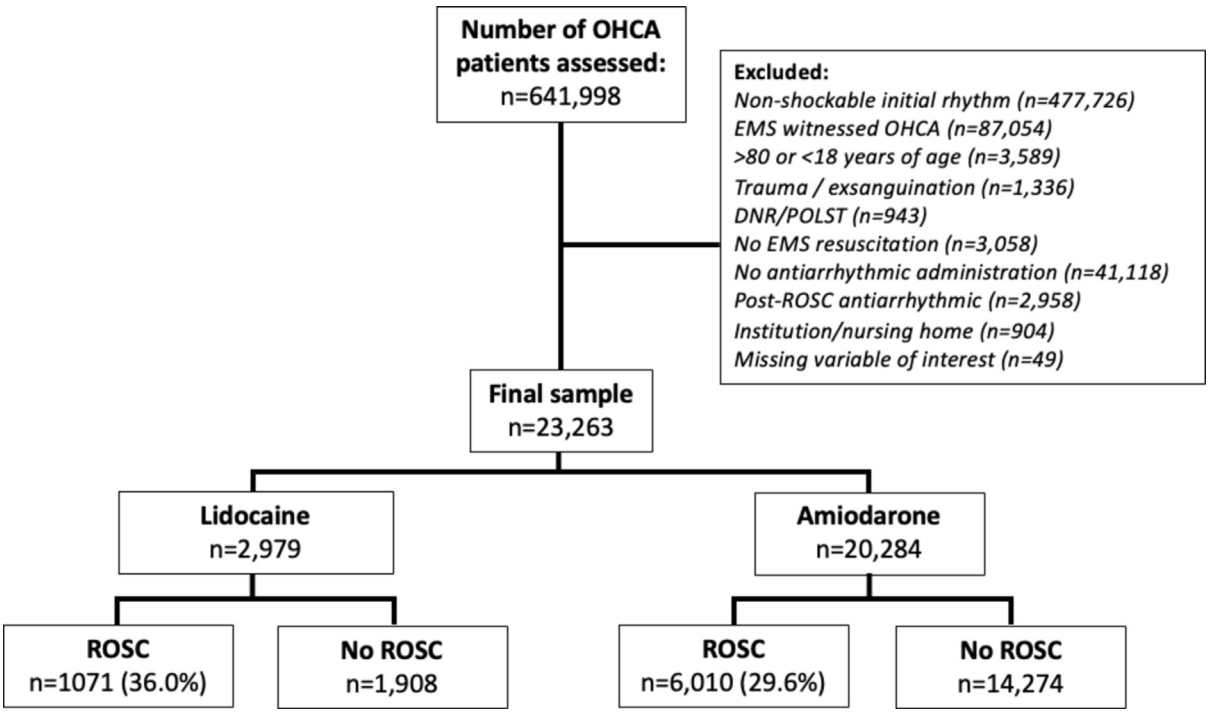

Fig. 1 – Flow diagram detailing derivation of cohort.

score.[18] To assess the quality of matching, the standardized percentage bias (standardized mean difference expressed as a percentage) between groups was calculated for each covariable.[19] [Table 1, Supplemental Table 2] This method of generating a propensity matched cohort was repeated for each secondary outcome of interest and within each analyzed subgroup. For example, for the outcome of mortality, a propensity score matched cohort was generated from the subgroup of patients with hospital outcome data. Stata SE/18 was used for all data management and statistical analyses.

To investigate whether the outcomes of patients treated by EMS agencies that administered primarily lidocaine differed from agencies that administered primarily amiodarone, we examined the outcomes of all patients treated by each agency in this study, the group of patients treated by each agency in this study who had shockable rhythms and did not receive lidocaine or amiodarone, and the group of patients treated by each agency in this study that had non-shockable initial rhythms. EMS agencies were classified as 'amiodarone predominant' agencies if >80% of included patients received amiodarone as the first-line anti-arrhythmic agent, and 'lidocaine predominant' agencies if >80% of included patients received lidocaine. Multivariable logistic regression modeling (adjusted for including age, sex, OHCA etiology, witnessed status, pre-first responder CPR, initial rhythm [asystole, PEA, unknown AED non-shockable, ventricular fibrillation, ventricular tachycardia, unknown AED shockable], response interval, and OHCA location) was used to determine whether being treated by a 'lidocaine predominant' EMS agency was associated with the odds of prehospital ROSC among all OHCA patients and the subgroup of OHCA patients with non-shockable initial rhythms. The same cohort derivation strategy was used for this subgroup analysis with the exception of excluding patients with non-shockable initial rhythms and excluding patients who did not receive antiarrhythmics.

Finally, we performed several post-hoc sensitivity analyses using additional modeling techniques. We performed post-matching multilevel mixed effects logistic regression modeling[20] with treating EMS agency as a random effect to determine whether clustering of outcomes by EMS agency may have contributed to our results. We also performed propensity score matching including the dispatch to defibrillation interval, the on-scene to epinephrine interval, and the initial airway management strategy (endotracheal intubation, i-gel, King Laryngeal Tube, LMA, no advanced airway) as covariables.

Results

After application of exclusion criteria, 23,263 patients from 1,707 EMS agencies were included in the analysis. The majority of patients (20,284; 87.2%) received amiodarone as their first antiarrhythmic during resuscitation. [Fig. 1] Overall, 7,081 (30.4%) patients achieved ROSC, 2,530 (35.7%) experienced post-ROSC bradycardia, 1,348 (19.0%) experienced post-ROSC hypotension, and 529 (7.5%) received post-ROSC transcutaneous pacing. Among the subset of transported patients with hospital disposition data, 25.6% (992/3,869) survived to hospital discharge. Table 1 describes the characteristics and outcomes of our cohort stratified by antiarrhythmic agent before and after propensity score matching. The distribution of propensity scores in each treatment group before and after matching are displayed in Supplemental Fig. 1.

Adjusted outcomes

After matching, more patients who received lidocaine had prehospital ROSC in comparison to patients who received amiodarone (36.0% lidocaine vs. 30.4% amiodarone, absolute difference: 5.6%). Lidocaine administration was associated with greater odds of prehospital

Table 1 – Cohort characteristics before and after propensity score matching.

	Pre-Matching		Post-Matching		
	Amiodarone	Lidocaine	Amiodarone	Lidocaine	SMD
N	20,284 (87.2%)	2,979 (12.8%)	2,976 (50.0%)	2,976 (50.0%)	
Age (years)					
Missing: n = 0	62.0 (53.0–70.0)	63.0 (53.0–70.0)	62.0 (53.0–70.0)	63.0 (53.0–70.0)	0.008
Sex	–	–			
Male	15,703 (77.4%)	2,316 (77.7%)	2,345 (78.8%)	2,315 (77.8%)	0.024
Female	4,577 (22.6%)	659 (22.1%)	629 (21.1%)	659 (22.1%)	
Unknown	4 (0.0%)	4 (0.1%)	2 (0.1%)	2 (0.1%)	
Witnessed	–	–			
No	5,271 (26.0%)	723 (24.3%)	706 (23.7%)	722 (24.3%)	0.030
Yes	13,478 (66.4%)	2,017 (67.7%)	2,007 (67.4%)	2,015 (67.7%)	
Unknown	1,535 (7.6%)	239 (8.0%)	263 (8.8%)	239 (8.0%)	
Response interval (min.)					
Missing: n = 22	6.0 (4.3–8.6)	6.6 (4.6–9.5)	6.6 (4.6–9.4)	6.6 (4.6–9.5)	0.009
Pre-EMS CPR	–	–			
No	11,583 (57.1%)	1,632 (54.8%)	1,600 (53.8%)	1,630 (54.8%)	0.033
Yes	7,961 (39.2%)	1,230 (41.3%)	1,241 (41.7%)	1,229 (41.3%)	
Unknown	740 (3.6%)	117 (3.9%)	135 (4.5%)	117 (3.9%)	
Initial rhythm	–	–			
Ventricular fibrillation	18,053 (89.0%)	2,578 (86.5%)	2,572 (86.4%)	2,575 (86.5%)	0.010
Ventricular tachycardia	1,161 (5.7%)	166 (5.6%)	162 (5.4%)	166 (5.6%)	
AED Shockable	1,070 (5.3%)	235 (7.9%)	242 (8.1%)	235 (7.9%)	
Etiology	–	–			
Presumed cardiac	18,890 (93.1%)	2,791 (93.7%)	2,790 (93.8%)	2,788 (93.7%)	0.012
Respiratory/asphyxia	685 (3.4%)	93 (3.1%)	93 (3.1%)	93 (3.1%)	
Drug overdose	232 (1.1%)	35 (1.2%)	37 (1.2%)	35 (1.2%)	
Other	468 (2.3%)	58 (1.9%)	54 (1.8%)	58 (1.9%)	
Missing	9 (0.0%)	2 (0.1%)	2 (0.1%)	2 (0.1%)	
Location	–	–	–	–	–
Private/home	14,861 (73.3%)	2,158 (72.4%)	2,118 (71.2%)	2,158 (72.5%)	0.030
Public	5,423 (26.7%)	821 (27.6%)	858 (28.8%)	818 (27.5%)	
Drug dose (mg)					
Missing: n = 95	300.0 (300.0–300.0)	100.0 (100.0–100.0)	300.0 (300.0–300.0)	100.0 (100.0–100.0)	
Vascular access	–	–	–	–	–
Intravenous	9,252 (45.6%)	1,702 (57.1%)	1,683 (56.6%)	1,700 (57.1%)	0.012
Intraosseous	11,032 (54.4%)	1,277 (42.9%)	1,293 (43.4%)	1,276 (42.9%)	
Time to drug (min.)					
Missing: n = 49	12.2 (9.0–16.9)	11.5 (8.2–16.5)	11.9 (8.6–16.4)	11.5 (8.3–16.5)	0.015
Pre-drug shocks	4.0 (2.0–6.0)	3.0 (2.0–4.0)	4.0 (2.0–4.0)	3.0 (2.0–4.0)	0.005
					P values
Post-drug shocks	2.0 (0.0–6.0)	2.0 (0.0–4.0)	2.0 (0.0–6.0)	2.0 (0.0–4.0)	<0.001*
Time to ROSC					
N/A: 16,182	28.4 (21.8–37.8)	27.6 (20.9–36.7)	28.4 (21.4–37.9)	27.6 (20.9–36.7)	0.194*
Follow-up interval					
Missing: n = 760	21.4 (13.1–30.6)	21.8 (13.3–31.6)	21.5 (13.6–30.6)	21.8 (13.3–31.6)	0.225*
DSD					
No	19,766 (97.4%)	2,962 (99.4%)	2,896 (97.3%)	2,959 (99.4%)	<0.001+
Yes	518 (2.6%)	17 (0.6%)	80 (2.7%)	17 (0.6%)	
Post-ROSC bradycardia					
No	3,816 (63.5%)	735 (68.6%)	578 (63.9%)	735 (68.6%)	0.031#
Yes	2,194 (36.5%)	336 (31.4%)	326 (36.1%)	336 (31.4%)	
Post-ROSC hypotension					
No	4,832 (80.4%)	901 (84.1%)	717 (79.3%)	901 (84.1%)	0.007#
Yes	1,178 (19.6%)	170 (15.9%)	187 (20.7%)	170 (15.9%)	
Post-ROSC bradycardia and hypotension					
No	5,450 (90.7%)	994 (92.8%)	822 (90.9%)	994 (92.8%)	0.135#
Yes	560 (9.3%)	77 (7.2%)	82 (9.1%)	77 (7.2%)	
Post-ROSC pacing					
No	5,526 (91.9%)	1,026 (95.8%)	839 (92.8%)	1,026 (95.8%)	0.005#

Table 1 (continued)

	Pre-Matching		Post-Matching		
	Amiodarone	Lidocaine	Amiodarone	Lidocaine	SMD
Yes	484 (8.1%)	45 (4.2%)	65 (7.2%)	45 (4.2%)	
ROSC					
No	14,274 (70.4%)	1,908 (64.0%)	2,072 (69.6%)	1,905 (64.0%)	<0.001[+]
Yes	6,010 (29.6%)	1,071 (36.0%)	904 (30.4%)	1,071 (36.0%)	
Mortality	–	–			
No	803 (24.1%)	189 (35.0%)	124 (25.7%)	189 (35.1%)	0.001[+]
Yes	2,526 (75.9%)	351 (65.0%)	358 (74.3%)	350 (64.9%)	

SMD = standardized mean difference, EMS = emergency medical services, AED = automated external defibrillator, mg = milligrams, DSD = double sequential defibrillation, ROSC = return of spontaneous circulation.

[*] Wilcoxon signed-rank sum test.

[+] McNemar's test.

[#] Chi-squared test with Yates continuity correction.

ROSC in comparison to amiodarone administration (OR: 1.29 [1.16, 1.44], 2,976 matched pairs). Based on this estimate of effect size, 18 [12,31] patients would need to be treated with lidocaine instead of amiodarone to obtain prehospital ROSC in 1 additional patient with shock refractory or recurrent VF/VT.

Secondary outcomes

Patients who received lidocaine received fewer post-antiarrhythmic defibrillations in comparison to patients who received amiodarone (median: 2 [0–4] vs. 2 [0–6]; 2,976 matched pairs, mean: 3.3 vs. 3.9, $p < 0.001$). Among patients who had documented prehospital ROSC, lidocaine administration was associated with decreased odds of experiencing post-ROSC bradycardia (OR: 0.80 [0.67, 0.95], 1,067 matched pairs), post-ROSC hypotension (OR: 0.77 [0.61, 0.96], 1,067 matched pairs) and decreased odds of receiving prehospital transcutaneous pacing (OR: 0.50 [0.34, 0.72], 1,067 matched pairs).

After propensity score matching, more patients who received lidocaine survived to hospital discharge in comparison to patients who received amiodarone (35.1% lidocaine vs. 25.7% amiodarone, absolute difference: 9.4%). Administration of lidocaine was associated with greater odds of survival to hospital discharge in comparison to amiodarone administration (OR: 1.54 [1.19, 2.00], 538 matched pairs).

The directionality of the association between lidocaine administration, ROSC, and survival to hospital discharge was consistent

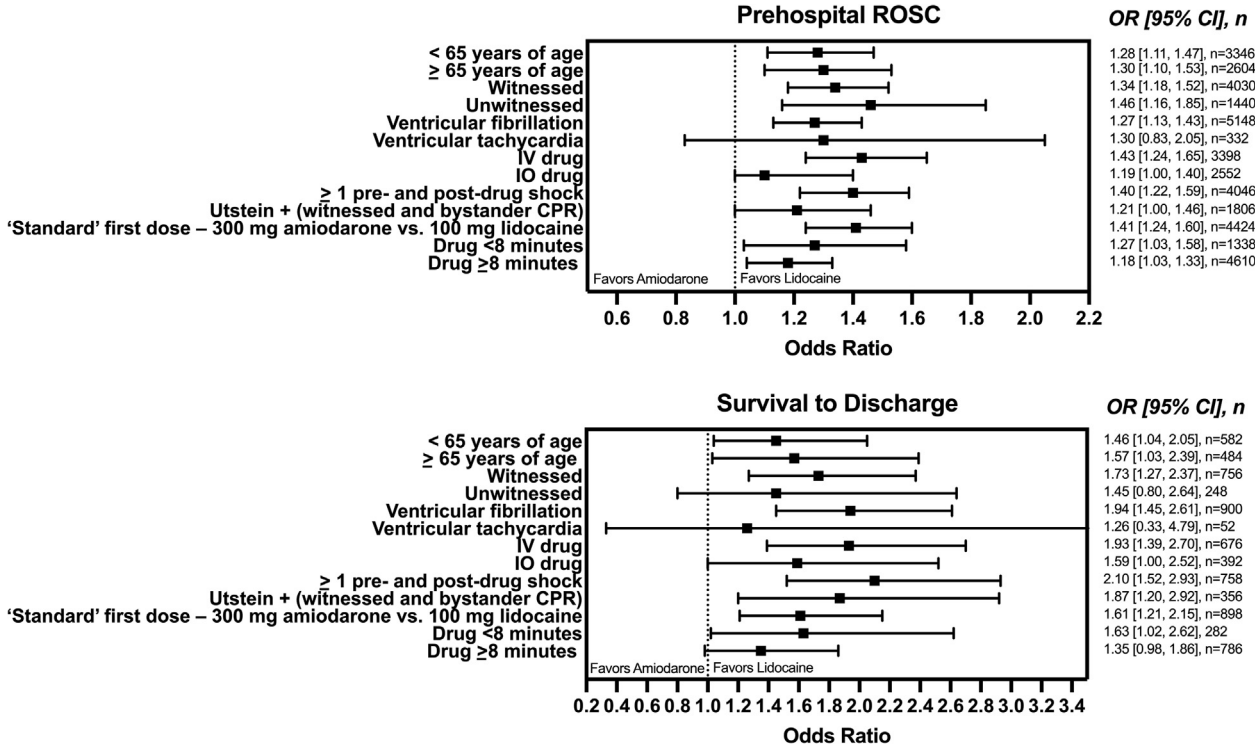

Fig. 2 – Subgroup analyses. OR = odds ratio, CI = confidence interval, ROSC = return of spontaneous circulation IV = intravenous, IO = intraosseous, mg = milligrams.

across subgroups defined by age, witnessed status, initial cardiac rhythm, documented pre- and post-antiarrhythmic defibrillation, vascular access type, initial antiarrhythmic dose, and the timing of antiarrhythmic administration. [Fig. 2] Additional analyses, including a mixed-effects multi-level multivariable logistic regression model and a propensity score matched analysis that included the dispatch to defibrillation interval, on-scene to epinephrine interval, and the initial airway management strategy were also consistent with the directionality of effect suggested by our primary analysis. [Supplemental Table 3].

Agency-level analyses

Lidocaine was the preferred antiarrhythmic for 157 EMS agencies, and 1,373 agencies administered primarily amiodarone [Supplemental Fig. 2]. For this analysis, our cohort consisted of 240,509 patients (218,623 treated by 'amiodarone predominant' agencies, 21,886 treated by 'lidocaine predominant' agencies). We found that resuscitation by a 'lidocaine predominant' EMS agency was associated with *decreased* odds of ROSC among all patients (aOR: 0.92 [0.89, 0.96]), within the subgroup of OHCA patients who had initially shockable rhythms and did not receive a prehospital antiarrhythmic (aOR: 0.83 [0.76, 0.90]; $n = 47{,}906$) and within the subgroup of patients with initially non-shockable rhythms (aOR: 0.89 [0.85, 0.93]; $n = 180{,}638$) in comparison to resuscitation by an 'amiodarone predominant' EMS agency.

Discussion

In this nationwide retrospective study, we found that the administration of lidocaine for shock-refractory OHCA was associated with greater odds of prehospital ROSC in comparison to amiodarone administration. We also found mechanistic support for the validity of this association – patients who received intra-arrest lidocaine received fewer post-ROSC defibrillations than patients who received amiodarone. Among other secondary outcomes, we also found that lidocaine administration was associated with greater odds of survival to hospital discharge and lesser odds of experiencing prehospital bradycardia, hypotension, and transcutaneous pacing.

Our results are consistent with the ALPS randomized controlled trial,[8] which demonstrated that patients who received lidocaine had ROSC more frequently at emergency department arrival than patients who received amiodarone, although the difference did not reach statistical significance. The absolute difference in favor of lidocaine was 4.0%, (39.9 vs. 35.9%), which is comparable to the 5.6% absolute difference observed in this study (36.0 vs. 30.4%). In addition, our results align with a recent nationwide observational study of adult IHCA that suggested lidocaine administration was associated with greater odds of ROSC.[10] Similar findings were also previously reported in a cohort of pediatric IHCA patients.[11]

In contrast to our study the ALPS trial did not suggest a difference between amiodarone and lidocaine for the outcome of survival to hospital discharge. One possible reason for this disparity may be the polysorbate-free formulation of amiodarone used in the ALPS study, which was chosen to reduce the risk of hypotensive effects.[8] This polysorbate free formulation is not widely available for intra-arrest use in the prehospital setting in the United States. Therefore, negative hemodynamic effects from amiodarone diluted in polysorbate 80[21] may explain this disparity in outcomes. In addition to compromising hemodynamics during ongoing CPR, post-ROSC hypotension may exacerbate secondary injury following ischemia and reperfusion and has been repeatedly associated with increased mortality following OHCA.[22–27] More of the patients who received amiodarone experienced post-ROSC bradycardia and hypotension in our cohort, which supports this hypothesis.

Slightly more of the patients who received amiodarone received double-sequential defibrillation (DSD), which has been shown to improve outcomes from shock-refractory cardiac arrest.[28] We hypothesize that DSD was used more frequently during the resuscitation of patients who received amiodarone because more patients who received lidocaine achieved ROSC prior to the deployment of this procedure late in the course of resuscitation as a rescue technique. The use of DSD may also be tied to agency-level practices, which could be associated with antiarrhythmic preference.

Previous retrospective studies excluded patients who received both amiodarone and lidocaine.[29–32] Patients who receive both antiarrhythmic agents represent an important treatment refractory population, as the first antiarrhythmic administered may modify the probability of needing a second antiarrhythmic. Therefore, for our study, we classified patients into groups based on the first documented antiarrhythmic administered.

Limitations

These data are subject to the limitations of all retrospective observational studies, including chance, bias, residual confounding, and the influence of unknown or unmeasured confounders. Despite our efforts to account for sources of bias common to observational studies, unknown confounders or confounding variables not captured by this dataset may have influenced the relationship between antiarrhythmic medications and outcome. Future work that incorporates known predictors of ROSC and survival to hospital discharge not available to our study group (e.g. CPR quality metrics[33–37], *peri*-shock pause duration[38,39], pad position[28,40]) may be warranted.

The minority of patients in this study received lidocaine (12.8%), which suggests that treatment with this antiarrhythmic may also be associated with other deviations from nationwide practice patterns. As a result of this observation, we hypothesized that the quality of resuscitation provided by EMS agencies that routinely administer lidocaine may differ in an important way from the quality of resuscitation provided by EMS agencies that primarily administer amiodarone. To test this hypothesis, we compared the outcomes of patients treated by 'lidocaine preferred' EMS agencies to the outcomes of patients treated by 'amiodarone preferred' agencies. To our surprise, we found that OHCA patients who did not receive lidocaine but were treated by EMS agencies that routinely administered lidocaine had *lower* odds of ROSC. Therefore, we are not able to attribute the association between lidocaine and greater odds of ROSC in our cohort to agency-level characteristics tied to antiarrhythmic administration practices.

One common limitation of retrospective studies is hidden in the 'follow-up interval.' For prehospital outcomes such as ROSC or rearrest, the probability of observing the outcome is partially dependent on the amount of time the patient is being treated by EMS providers. For example, EMS providers in urban environments have shorter transport times and are therefore less likely to observe a rearrest event prior to transfer of care, whereas EMS providers in rural environments with longer transport times spend much longer observing the clinical state of a patient during transport and are more likely to observe a rearrest. To address this source of bias, we compared

the 'follow-up interval' for each antiarrhythmic group and found no significant difference.

The results of this study are only generalizable to community dwelling patients between 18 and 80 years of age who experience cardiac arrest prior to the arrival of EMS, have an initially shockable ECG rhythm, and do not respond to defibrillation prior to the administration of antiarrhythmic drugs. Future studies comparing antiarrhythmic agents in other populations may be warranted. Importantly, the ALPS randomized controlled trial found a significant improvement in survival to hospital discharge for patients who received amiodarone in comparison to placebo in the subgroup of patients with EMS witnessed OHCA, but did not observe a similar relationship for patients who received lidocaine in comparison to placebo.

Approximately 20% of all transported patients in the ESO Data Collaborative annual datasets have associated hospital disposition data that was used to derive the secondary outcome of survival to hospital discharge. This may introduce selection bias for our survival analyses in several ways. First, prehospital termination of resuscitation in the absence of ROSC has become the standard of care in many parts of the United States. Therefore, the population of transported patients with hospital disposition data likely have more favorable baseline characteristics and outcomes than the true population of OHCA patients, and antiarrhythmic drug may modify the probability of ROSC and therefore transport. This source of bias may be limited because patients with shockable rhythms do not qualify for standard ALS[41] or BLS[42,43] termination of resuscitation rules. In addition, better resourced and more urban healthcare systems are more likely to participate in the bi-directional health data exchange that provides ESO with hospital outcome data. These factors may limit the generalizability and validity of our secondary survival analyses. The characteristics of transported patients with outcome data in our cohort were similar to the characteristics of transported patients without outcome data. [Supplemental Table 4].

Conclusion

Our retrospective, multi-agency 'target trial emulation' suggested that lidocaine was associated with increased odds of prehospital ROSC in comparison to amiodarone when administered during resuscitation.

CRediT authorship contribution statement

Tanner Smida: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Remle Crowe:** Writing – review & editing. **Bradley S. Price:** Writing – review & editing, Methodology. **James Scheidler:** Writing – review & editing. **P.S. Martin:** Writing – review & editing. **Micheal Shukis:** Writing – review & editing. **James Bardes:** Writing – review & editing.

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.

Acknowledgements

We would like express our appreciation for the many EMS providers who resuscitated the patients and collected the data included in this study. In addition, we would like to thank the ESO Data Collaborative for access to the data that made this study possible. JB receives support from the National Institute of General Medical Sciences of the National Institutes of Health under Award Number 5U54GM104942-05. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2025.110515.

Author details

[a]*West Virginia University School of Medicine MD/PhD Program, Morgantown, WV, United States*[b]*ESO Solutions, Austin, TX, United States*[c]*West Virginia University, John Chambers School of Business and Economics, Morgantown, WV, United States* [d]*West Virginia University School of Medicine, Department of Emergency Medicine, Division of Prehospital Medicine, United States*

REFERENCES

1. CARES. *2023 Annual Report - Cardiac Arrest Registry to Enhance Survival*; 2024.
2. Holmen J, Hollenberg J, Claesson A, et al. Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation. Resuscitation 2017;113:33–8.
3. Coult J, Yang BY, Kwok H, et al. Prediction of shock-refractory ventricular fibrillation during resuscitation of out-of-hospital cardiac arrest. Circulation 2023;148:327–35.
4. Tateishi K, Saito Y, Kitahara H, et al. Impact of number of defibrillation attempts on neurologically favourable survival rate in patients with out-of-Hospital cardiac arrest. Resuscitation 2023;186:109779.
5. Ko BS, Kim YJ, Han KS, et al. Association between the number of prehospital defibrillation attempts and a sustained return of spontaneous circulation: a retrospective, multicentre, registry-based study. Emerg Med J 2023;40:424–30.
6. Panchal AR, Berg KM, Kudenchuk PJ, et al. 2018 American Heart Association Focused Update on Advanced Cardiovascular Life Support Use of Antiarrhythmic Drugs During and Immediately After Cardiac Arrest: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2018;138:e740–9.
7. Soar J, Perkins GD, Maconochie I, et al. European Resuscitation Council Guidelines for Resuscitation: 2018 Update - Antiarrhythmic drugs for cardiac arrest. Resuscitation 2019;134:99–103.
8. Kudenchuk PJ, Daya M, Dorian P. and Resuscitation Outcomes Consortium I. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. N Engl J Med 2016;375:802–3.

9. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341:871–8.
10. Wagner D, Kronick SL, Nawer H, Cranford JA, Bradley SM, Neumar RW. Comparative effectiveness of amiodarone and lidocaine for the treatment of: in-hospital cardiac arrest. Chest 2022.
11. Valdes SO, Donoghue AJ, Hoyme DB, et al. Outcomes associated with amiodarone and lidocaine in the treatment of in-hospital pediatric cardiac arrest with pulseless ventricular tachycardia or ventricular fibrillation. Resuscitation 2014;85:381–6.
12. ESO. *Data and Research - ESO*. 2023; Available from: https://www.eso.com/data-and-research/.
13. NEMSIS. *NEMSIS Data Dictionary - NHTSA v3.4.0*. 2020 3/14/2024]; Available from: https://nemsis.org/media/nemsis_v3/release-3.4.0/DataDictionary/PDFHTML/DEMEMS/index.html.
14. Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. BMJ 2022;378:e071108.
15. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016;183:758–64.
16. StataCorp. *signrank — Equality tests on matched data*. 2023 [cited 2024; Available from: https://www.stata.com/manuals/rsignrank.pdf#page=2.56.
17. Leuven E, Sianesi B. *PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing*. 2003; Available from: http://repec.org/bocode/p/psmatch2.html.
18. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–61.
19. Leuven E. *pstest: Covariate imbalance testing and graphing*; 2003. Available from: http://fmwww.bc.edu/repec/bocode/p/pstest.html.
20. StataCorp. *melogit — Multilevel mixed-effects logistic regression*; 2023 3/14/2023]. Available from: https://www.stata.com/manuals/memelogit.pdf.
21. Torres-Arraut E, Singh S, Pickoff AS. Electrophysiologic effects of Tween 80 in the myocardium and specialized conduction system of the canine heart. J Electrocardiol 1984;17:145–51.
22. Bray JE, Bernard S, Cantwell K, Stephenson M, Smith K, Committee VS. The association between systolic blood pressure on arrival at hospital and outcome in adults surviving from out-of-hospital cardiac arrests of presumed cardiac aetiology. Resuscitation 2014;85:509–15.
23. Chiu YK, Lui CT, Tsui KL. Impact of hypotension after return of spontaneous circulation on survival in patients of out-of-hospital cardiac arrest. Am J Emerg Med 2018;36:79–83.
24. Javaudin F, Desce N, Le Bastard Q, et al. Impact of pre-hospital vital parameters on the neurological outcome of out-of-hospital cardiac arrest: Results from the French National Cardiac Arrest Registry. Resuscitation 2018;133:5–11.
25. Lacocque J, Siegel L, Sporer KA. Prehospital, post-ROSC blood pressure and associated neurologic outcome. Am J Emerg Med 2021;49:195–9.
26. Smida T, Menegazzi JJ, Crowe RP, et al. The Association of Combined Prehospital Hypotension and Hypoxia with Outcomes following Out-of-Hospital Cardiac Arrest Resuscitation. Prehosp Emerg Care 2023:1–6.
27. Smida T, Menegazzi JJ, Crowe RP, Weiss LS, Salcido DD. Association of prehospital hypotension depth and dose with survival following out-of-hospital cardiac arrest. Resuscitation 2022;180:99–107.
28. Cheskes S, Verbeek PR, Drennan IR, et al. Defibrillation strategies for refractory ventricular fibrillation. N Engl J Med 2022;387:1947–56.
29. Wagner D, Kronick SL, Nawer H, Cranford JA, Bradley SM, Neumar RW. Comparative effectiveness of amiodarone and lidocaine for the treatment of in-hospital cardiac arrest. Chest 2023;163:1109–19.
30. Tagami T, Matsui H, Tanaka C, et al. Amiodarone compared with lidocaine for out-of-hospital cardiac arrest with refractory ventricular fibrillation on hospital arrival: a nationwide database study. Cardiovasc Drugs Ther 2016;30:485–91.
31. Holmberg MJ, Ross CE, Atkins DL, et al. Lidocaine versus amiodarone for pediatric in-hospital cardiac arrest: an observational study. Resuscitation 2020;149:191–201.
32. Kishihara Y, Kashiura M, Amagasa S, Fukushima F, Yasuda H, Moriya T. Comparison of the effects of lidocaine and amiodarone for out-of-hospital cardiac arrest patients with shockable rhythms: a retrospective observational study from a multicenter registry. BMC Cardiovasc Disord 2022;22:466.
33. Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. Circulation 2012;125:3004–12.
34. Idris AH, Guffey D, Pepe PE, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med 2015;43:840–8.
35. Nichol G, Daya MR, Morrison LJ, et al. Compression depth measured by accelerometer vs. outcome in patients with out-of-hospital cardiac arrest. Resuscitation 2021;167:95–104.
36. Stiell IG, Brown SP, Nichol G, et al. What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients?. Circulation 2014;130:1962–70.
37. Vadeboncoeur T, Stolz U, Panchal A, et al. Chest compression depth and survival in out-of-hospital cardiac arrest. Resuscitation 2014;85:182–8.
38. Cheskes S, Schmicker RH, Christenson J, et al. Perishock pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. Circulation 2011;124:58–66.
39. Cheskes S, Schmicker RH, Verbeek PR, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. Resuscitation 2014;85:336–42.
40. Lupton JR, Newgard CD, Dennis D, et al. Initial defibrillator pad position and outcomes for shockable out-of-hospital cardiac arrest. JAMA Netw Open 2024;7:e2431673.
41. Morrison LJ, Verbeek PR, Vermeulen MJ, et al. Derivation and evaluation of a termination of resuscitation clinical prediction rule for advanced life support providers. Resuscitation 2007;74:266–75.
42. Morrison LJ, Visentin LM, Kiss A, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. N Engl J Med 2006;355:478–87.
43. Verbeek PR, Vermeulen MJ, Ali FH, Messenger DW, Summers J, Morrison LJ. Derivation of a termination-of-resuscitation guideline for emergency medical technicians using automated external defibrillators. Acad Emerg Med 2002;9:671–8.