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Received: 8 December 2022 | Revised: 24 February 2023 | Accepted: 1 March 2023

DOI: 10.1111/acem.14716

ORIGINAL ARTICLE

Survival by time-to-administration of amiodarone, lidocaine, or placebo in shock-refractory out-of-hospital cardiac arrest

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Funding information
Society for Academic Emergency Medicine, Grant/Award Number: RE2020-0000000167

Abstract

Background: Amiodarone and lidocaine have not been shown to have a clear survival benefit compared to placebo for out-of-hospital cardiac arrest (OHCA). However, randomized trials may have been impacted by delayed administration of the study drugs. We sought to evaluate how timing from emergency medical services (EMS) arrival on scene to drug administration affects the efficacy of amiodarone and lidocaine compared to placebo.

Method: This is a secondary analysis of the 10-site, 55-EMS-agency double-blind randomized controlled amiodarone, lidocaine, or placebo in OHCA study. We included patients with initial shockable rhythms who received the study drugs of amiodarone, lidocaine, or placebo before achieving return of spontaneous circulation. We performed logistic regression analyses evaluating survival to hospital discharge and secondary outcomes of survival to admission and functional survival (modified Rankin scale score ≤ 3). We evaluated the samples stratified by early (<8 min) and late administration groups (≥8 min). We compared outcomes for amiodarone and lidocaine compared to placebo and adjust for potential confounders.

Results: There were 2802 patients meeting inclusion criteria, with 879 (31.4%) in the early (<8 min) and 1923 (68.6%) in the late (≥8 min) groups. In the early group, patients receiving amiodarone, compared to placebo, had significantly higher survival to admission (62.0% vs. 48.5%, $p = 0.001$; adjusted OR [95% CI] 1.76 [1.24–2.50]), survival to discharge (37.1% vs. 28.0%, $p = 0.021$; 1.56 [1.07–2.29]), and functional survival (31.6% vs. 23.3%, $p = 0.029$; 1.55 [1.04–2.32]). There were no significant differences with early lidocaine compared to early placebo ($p > 0.05$). Patients in the late group who received amiodarone or lidocaine had no significant differences in outcomes at discharge compared to placebo ($p > 0.05$).

Conclusions: The early administration of amiodarone, particularly within 8 min, is associated with greater survival to admission, survival to discharge, and functional survival compared to placebo in patients with an initial shockable rhythm.

Supervising Editor: Dr. Jill Stoltzfus.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains a leading cause of morbidity and mortality in the United States, and more than 80,000 OHCA patients have an initial shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia [VF/pVT]).[1] Shock-refractory OHCA, defined as recurrence or persistence of VF/pVT after one defibrillation in the Amiodarone, Lidocaine, or Placebo Study (ALPS)[2,3] and the 2018 American Heart Association (AHA) update[4] and more recently as persistent shockable arrest despite three defibrillations,[5,6] occurs in up to 50% of patients with an initial shockable rhythm and is associated with increased mortality.[7] Current AHA and European Resuscitation Council (ERC) guidelines recommend the administration of an antiarrhythmic, amiodarone or lidocaine, after three defibrillation attempts, but quality evidence for the optimal timing of administration of these medications is lacking.[8,9] In practice, antiarrhythmics are often not administered until more than 20 min after emergency medical services (EMS) arrival on scene, and it is unclear if earlier administration would improve patient outcomes or if inclusion of large numbers of patients with delayed antiarrhythmic administrations biased results in past antiarrhythmic trials to the null.[10] As patients with shockable rhythms have the best odds of a full recovery,[1] if earlier antiarrhythmic administration in shock-refractory OHCA improved survival, it could save thousands of additional lives each year.

Six studies have noted that early, compared to late, amiodarone or lidocaine was associated with improved patient outcomes, including greater odds of return of spontaneous circulation (ROSC)[11,12] as well as survival to admission,[13,14] to discharge,[15] and with good neurologic status (functional survival)[16] when using 9-1-1 call or dispatch to drug administration time cutoffs of 15,[2] 16,[13] 20,[16] and 24 min.[17] These previous analyses had limitations, including varied time cutoffs, a lack of controlling for dispatch to EMS arrival times or routes of drug administration, and not accounting for the resuscitation time bias. A recent secondary analysis of the ALPS data suggested that earlier time from 9-1-1 call to antiarrhythmics was associated with greater odds of ROSC, with a significant interaction with time of drug administration, when comparing amiodarone to placebo.[11] However, this study did not evaluate survival outcomes, control for route of drug administration, or assess the ideal time interval from EMS arrival to drug delivery. Furthermore, it noted that longer times from the 9-1-1 call to drug administration were associated with a lower probability of ROSC for amiodarone compared to placebo, suggesting possible harm if amiodarone is administered later in a resuscitation.

Our objective was to evaluate if early antiarrhythmic administration was association with higher survival and survival with a favorable neurologic outcome for patients with shock-refractory OHCA compared to the placebo (normal saline) arm in ALPS while adjusting for potential confounding variables. We specifically sought to test two a priori cutoffs to define early drug administration. Our primary analysis used a timing-based early administration cutoff, defined as drug administration within 8 min of advanced life support (ALS) arrival on scene. Our secondary analysis used a sequence of care-based early administration cutoff, defined as drug administration with the initial dose of epinephrine.

METHODS

Study design

This was a secondary analysis of data from the randomized, double-blind ALPS trial whose methods and primary results have been previously published.[2,3] Data were obtained from the NHLBI BioLINCC repository after proposal approval and institutional review board determination of exemption for this secondary analysis. Briefly, ALPS enrolled adult patients (age ≥ 18 years) with nontraumatic shock-refractory OHCA. The intervention was a double-blinded study drug administration of either amiodarone, lidocaine, or placebo (normal saline). Drug administration was via two syringes of amiodarone (total 300 mg), lidocaine (total 120 mg), or placebo for the initial blinded intervention dose if a patient's weight was estimated to be over 45.3 kg. A subsequent blinded dose of one syringe of amiodarone (150 mg), lidocaine (60 mg), or placebo was to be administered for persistent shock-refractory OHCA.

Study setting

The ALPS trial enrolled adult (age ≥ 18) patients from 10 North American sites and 55 EMS agencies. These sites included two-tiered response models, consisting of basic life support (BLS) and ALS units and sites with single-tier dual-ALS EMS response.

Patient population

The inclusion criteria for our study were the same as the parent ALPS trial's primary, per-protocol analysis. The per-protocol analysis in ALPS included adult (age ≥ 18 years) patients who received the randomized study drug and who had an initial shockable rhythm (VF/pVT) on EMS evaluation. The parent ALPS trial enrolled 4653 patients in the intention-to-treat analysis, with 3026 included in the preplanned per-protocol analysis. Of these 3026 eligible patients, we excluded all patients that achieved ROSC before the initial administration of the study drug ($n = 224$).

Variables

The primary intervention of interest was the study drug, amiodarone, lidocaine, or placebo, and how the *timing* of drug administration impacted the associations between the drug and outcomes. The timing of drug administration was determined as the time from ALS-capable EMS arrival on scene to initial study drug

administration or the time of arrest to initial study drug administration if an ALS-capable EMS unit witnessed the cardiac arrest. Subjects were subsequently divided into a priori determined early and late administration groups defined in the primary analysis by the cutoff of 8 min from ALS arrival on scene. We chose this interval as we felt it was the earliest reasonable interval for antiarrhythmic administration and from published mean and standard deviation (SD) data for time to study drug from the primary ALPS trial, which suggested that an 8-min cutoff would likely include one-third of patients in the early group. A secondary, sequence of care-based early group was defined by those receiving the study drug prior to or within 1 min of the initial epinephrine dose (*with-epinephrine* group) and those who received it 1 min or more after epinephrine (*after-epinephrine* group).

Adjusting variables used in the multivariable analysis included age; sex; arrest location (public or private); witnessed status (EMS, bystander, or none); bystander automated external defibrillator use; bystander cardiopulmonary resuscitation (CPR); route of drug administration (intravenous [IV] or intraosseous [IO]); and timing variables including dispatch to first EMS vehicle arrival (regardless of service level), first ALS arrival, and EMS arrival to first EMS defibrillation, to initial vascular access, and to initial epinephrine administration. These variables were selected using a direct approach via a directed acyclic graph,[18] as they were felt to represent variables associated with both the primary outcome (survival to discharge) and, potentially, the time to drug administration without being on the causal pathway (as they occur prior to the study drug administration).[7,19–23] We specifically did not adjust for downstream factors (e.g., length of total arrest, need for advanced airway placement) as these could potentially be on the causal pathway. We separately report, as part of a sensitivity analysis, results stratified by route of administration (IV vs. IO) given prior research suggesting this may be an effect modifier in the relationship between antiarrhythmics and patient outcomes.[24]

Outcomes

The primary outcome for this study was survival to hospital discharge, which was the same as the parent ALPS trial. The secondary outcomes were survival to admission and functional survival, defined as a modified Rankin scale score ≤ 3 at hospital discharge.

Statistical analysis

Prior to accessing the data and based on the available mean and SD from drug delivery time,[2] we estimated that our a priori cutoff of 8 min to define an early administration group would contain one-third of patients with approximately 300 in each treatment group (amiodarone, lidocaine, and placebo). Thus, this would be powered at 80% to detect a 10% difference ($\alpha = 0.05$) in survival to discharge between each separate intervention comparison and placebo. Assuming an R^2 contribution from other variables of 0.2, our calculated logistic regression power at this sample size was 90% for an odds ratio (OR) of 1.4.[25] To account for missing data and decrease bias,[26,27] we used multiple imputation[28] with chained equations using Stata's mi impute chained command to produce 10 multiply imputed datasets for subsequent analysis.[29,30] The proportion of missingness among individual variables ranged from 0% to 3.8%, yet a complete case analysis would require exclusion of 15.7% of eligible cases. We combined results from the 10 multiply imputed data sets accounting for variance.[31]

We stratified the data set into those with early study drug administration and late administration groups based on our a priori cutoff of 8 min from ALS arrival on scene to drug administration. We also compared a group that received the study drug on a sequence of care-based definition of within 1 min of initial epinephrine administration (with-epinephrine group) compared to those who received the study drug greater than 1 min after epinephrine administration (after-epinephrine group). We repeated analyses utilizing multivariable logistic regression to adjust for potential confounders using variables previously listed. We performed interaction testing for each comparison (amiodarone vs. placebo and lidocaine vs. placebo) as well as overall interaction with the treatment arm.

We next tested the interaction between time to drug as a continuous variable and treatment arm (amiodarone, lidocaine, or placebo) using logistic regression. We adjusted for standard confounders and predictors as listed above.[24] This was done modeling time to drug as a linear variable and separately as a nonlinear variable (using fractional polynomials and restricted cubic spline regressions,[32,33] as has been done previously in resuscitation research[34,35]) to account for a possible nonlinear relationship between time to drug and survival. We compared models quantitatively using likelihood ratio tests to compare nonlinear to linear variables for time to drug to determine statistical significance with an alpha level of 0.05. We tested for interaction between the time of drug administration and the treatment arm (amiodarone or lidocaine) compared to placebo on the entire data set and after excluding delayed administrations after the slope of the probability of survival to discharge over time of drug administration for amiodarone and lidocaine approximated that of placebo, as this may suggest a point of futility for any further administration after this time point. We additionally sought to determine if there was evidence of a more appropriate post hoc cutoff to guide optimal antiarrhythmic administration than the a priori chosen 8 min from ALS arrival.

Finally, we sought to evaluate the impact of delays to drug administration timing on each individual drug to itself rather than comparing amiodarone or lidocaine to placebo to put our results in context of prior published analyses of antiarrhythmic timing that did not have a placebo arm for comparison.[12,15,16] Due to the resuscitation time bias, we anticipated that these comparisons would show significantly better outcomes with early drug administration compared to late drug administration in unadjusted analysis, even when comparing early placebo to late placebo. Thus, our primary focus was on multivariable logistic regression evaluating the impact

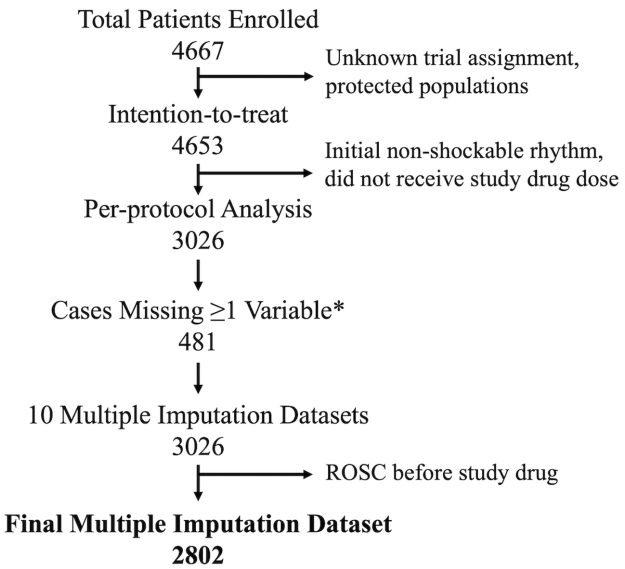
of early compared to late drug administration with adjustment for potential confounders.

For statistical significance, a two-tailed *p*-value of 0.05 was used as a cutoff without correction for multiple comparisons. We assessed data for normality and data transformed as appropriate. We assessed for specification error using linktest (Stata) and collinearity through evaluation of variance inflation factors and evaluated for influential data points in our logistic regression model using Pearson's residuals and predicted probabilities. All statistical analyses were conducted using Stata 17.0.

RESULTS

There were 3026 adult patients in the per-protocol analysis who received the study drug of amiodarone, lidocaine, or placebo and had an initial shockable rhythm. A total of 224 cases were excluded from the final analysis due to achieving ROSC prior to the initial study drug administration (Figure 1). This left 2802 patients for the primary analysis, and the characteristics of the primary sample are reported in Table 1.

Approximately one-third (n = 879, 31.4%) of patients received the study drug within 8 min of ALS arrival on scene. In this early group, amiodarone, compared to placebo, had higher survival to admission (62.0% vs. 48.5%, p = 0.001), survival to discharge (37.1% vs. 28.0%, p = 0.021), and functional survival (31.6% vs. 23.3%, p = 0.029; Figure 2). These correspond to a number needed to treat (NNT) for one additional survivor to admission of 8, survivor to discharge of 11, and survivor with a good functional outcome of 12. Late amiodarone had no significant differences across outcomes compared to placebo (Figure 2). There were no differences in survival to admission, survival to discharge, or functional survival for early lidocaine compared to early placebo or for late lidocaine compared to late placebo except for higher survival to admission (40.0% vs. 33.9%, p = 0.023). Multivariable logistic regression analyses adjusting for potential confounders found significantly higher odds (adjusted OR [aOR] [95% CI]) of survival to admission (1.75 [1.24–2.50]), survival to discharge (1.56 [1.07–2.29]), and functional survival (1.55 [1.04–2.32]) for early amiodarone compared to early placebo utilizing this 8-min cutoff (Table 2). There were no differences with multivariable analysis for late (≥8 min) amiodarone compared to late placebo. There were also no significant differences for lidocaine compared to placebo, regardless of early or late administration, with the exception again of late lidocaine compared to late placebo for survival to admission (1.35 [1.07–1.71]).



***Missing (n [%]):** Age (1 [0.03%]); Sex (1 [0.03%]); Bystander Witness Status (84 [2.78%]); Bystander CPR (51 [1.69%}); Bystander AED (53 [1.75%]); Arrest Location (3 [0.10%]); Time of 1st EMS arrival (113 [3.73%]); Time of ALS arrival (23 [0.76%]); Time of 1st EMS Shock (114 [3.77%]); Time of 1st EMS Vascular Access (75 [2.48%]); Time of 1st EMS Epinephrine (62 [2.05%]); Time of 1st Randomized Study Drug (35 [1.16%]); Survival to Discharge (16 [0.53%]); Functional Survival (20 [0.66%]).

FIGURE 1 Flow of inclusion and exclusion of cases for analysis and missing data. AED, automated external defibrillator; ROSC, return of spontaneous circulation.

To use a sequence of care-based cutoff to define early drug administration, we evaluated patients who received the study drug within 1 min of the initial epinephrine dose (with epinephrine). One-quarter of patients received the study drug prior to or within 1 min after the initial epinephrine dose (n = 712, 25.4%) with a mean (95% CI) time of randomized drug administration of 8.4 (8.1–8.7) min after ALS arrival on scene compared to 11.9 (11.7–12.2) min for the after epinephrine group (p <0.001). In the administered-with-epinephrine group, amiodarone had higher survival to discharge (32.2% vs. 23.5%, p = 0.038) and functional survival (27.0% vs. 19.2%, p = 0.046) compared to placebo (Figure 3). There were no differences in amiodarone compared to placebo in the after epinephrine group receiving the study drug more than 1 min after the initial epinephrine administration. There were no differences in outcomes for lidocaine compared to placebo when given with or after initial epinephrine administration except for higher survival to admission for lidocaine compared to placebo in the after-epinephrine group (45.7% vs. 37.1%, p = 0.001). Multivariable logistic regression analyses adjusting for potential confounders found significantly higher odds (OR [95% CI]) of survival to admission (1.85 [1.25–2.74]), survival to discharge (1.59 [1.02–2.49]), and functional survival (1.65 [1.02–2.67]) for amiodarone administered with epinephrine compared to placebo administered with epinephrine (Table 3). There were no differences with multivariable analysis for amiodarone compared to placebo when both were given after epinephrine or for lidocaine regardless of administration timing in relation to epinephrine except for lidocaine compared to placebo for survival to admission (1.42 [1.14–1.78]) when both were given after epinephrine.

We next sought to evaluate time to drug as a continuous variable via logistic regression analyses evaluating the interaction between study drugs and minutes to study drug administration from ALS arrival on scene (Figure 4). The comparison of amiodarone to placebo had a significant interaction with time to drug for survival to admission (p = 0.043) without reaching statistical significance for survival to discharge (p = 0.082) and functional survival (p = 0.064).

TABLE 1 Characteristics of sample by randomized drug from the multiply imputed data sets excluding those with ROSC prior to initial study drug administration.

	Randomized study drug ($n = 2802$)					
	Placebo ($n = 981$)		Lidocaine ($n = 926$)		Amiodarone ($n = 895$)	
	Early (<8 min)	Late (≥8 min)	Early (<8 min)	Late (≥8 min)	Early (<8 min)	Late (≥8 min)
Age (years)	63.0 (54.0 to 72.0)	63.0 (54.0 to 73.0)	63.0 (54.0 to 72.5)	63.0 (54.0 to 74.0)	65.0 (54.0 to 74.0)	63.0 (55.0 to 74.0)
Male (%)	82.8 (78.5 to 87.1)	77.5 (74.3 to 80.6)	84.7 (80.7 to 88.8)	82.1 (79.1 to 85.1)	83.1 (78.6 to 87.6)	76.2 (72.8 to 79.7)
Witness status						
Bystander (%)	67.5 (62.1 to 73.0)	66.4 (62.8 to 70.1)	67.0 (61.7 to 72.4)	64.6 (60.7 to 68.4)	72.0 (66.5 to 77.4)	63.0 (59.2 to 66.9)
EMS (%)	5.9 (3.2 to 8.6)	3.6 (2.1 to 5.0)	5.4 (2.8 to 7.9)	3.5 (2.0 to 4.9)	5.8 (2.9 to 8.7)	4.9 (3.1 to 6.6)
Bystander CPR (%)	56.6 (51.0 to 62.2)	57.0 (53.3 to 60.8)	61.1 (55.6 to 66.6)	54.5 (50.4 to 58.4)	65.4 (59.7 to 71.1)	55.3 (51.3 to 59.2)
Bystander AED (%)	1.7 (0.2 to 3.1)	7.2 (5.3 to 9.2)	8.0 (4.9 to 11.1)	4.3 (2.6 to 5.9)	8.6 (5.2 to 12.0)	5.7 (3.8 to 7.5)
Public location (%)	31.6 (26.3 to 36.9)	28.9 (25.5 to 32.3)	33.4 (28.1 to 38.8)	30.3 (26.6 to 33.9)	34.3 (28.6 to 40.0)	29.3 (25.7 to 32.9)
9-1-1 call to arrival						
First vehicle (min)	5.2 (4.0 to 6.9)	5.2 (4.1 to 6.6)	5.2 (4.0 to 6.5)	5.2 (4.0 to 6.5)	5.2 (4.2 to 6.3)	5.3 (4.1 to 6.8)
First ALS (min)	7.8 (5.2 to 10.5)	6.5 (4.8 to 9.3)	7.5 (5.0 to 10.4)	6.5 (4.7 to 9.0)	7.5 (5.5 to 10.1)	6.5 (4.7 to 9.0)
ALS arrival to care[a]						
First shock (min)	1.4 (−1.1 to 3.0)	3.8 (1.4 to 6.0)	1.8 (−0.8 to 3.3)	3.6 (1.1 to 5.8)	1.7 (−0.9 to 3.4)	3.9 (1.4 to 6.0)
First access (min)	3.6 (2.5 to 4.7)	6.6 (4.9 to 8.8)	3.8 (2.6 to 5.0)	6.5 (4.9 to 8.8)	3.7 (2.7 to 4.7)	6.5 (4.7 to 8.5)
First epinephrine (min)	5.0 (4.0 to 6.0)	8.2 (6.7 to 10.6)	5.0 (4.0 to 6.1)	8.1 (6.3 to 10.3)	5.0 (3.8 to 6.0)	8.1 (6.3 to 10.3)
First study drug (min)	6.2 (5.2 to 7.2)	11.8 (9.8 to 14.9)	6.5 (5.5 to 7.2)	12.0 (9.9 to 15.4)	6.3 (5.1 to 7.2)	11.7 (9.7 to 15.3)
Study drug route						
IO (%)	17.7 (13.4 to 22.0)	23.9 (20.7 to 27.1)	14.7 (10.7 to 18.7)	26.5 (23.0 to 30.0)	16.3 (11.9 to 20.7)	24.0 (20.6 to 27.4)

Note: Values reported are means (95% CIs) combined from the 10 multiply imputed data sets combined using Rubin's rules for binary variable and median (IQR) for continuous variables.

Abbreviations: AED, automated external defibrillator; ALS, advanced life support; IO, intraosseous; ROSC, return of spontaneous circulation .

[a]ALS arrival or time of arrest for EMS-witnessed arrests.

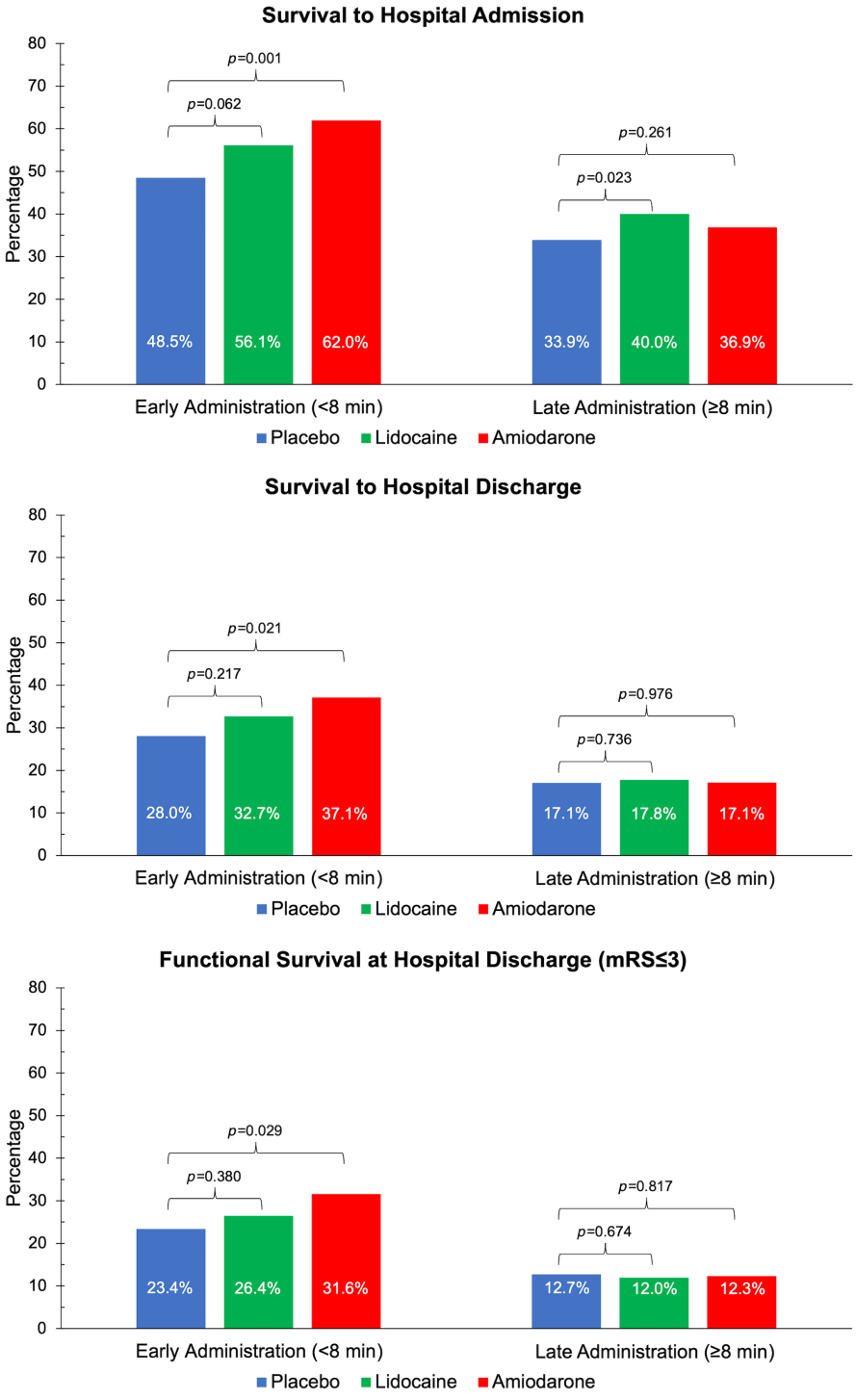


FIGURE 2 Unadjusted outcomes after early and late amiodarone, lidocaine, and placebo as treatment for shock-refractory OHCA. mRS, modified Rankin scale score; OHCA, out-of-hospital cardiac arrest.

Lidocaine, compared to placebo, had no significant interaction with time to drug for survival to admission ($p = 0.248$), survival to discharge ($p = 0.710$), or functional survival (0.510). There was not a more optimal time cutoff to define early antiarrhythmic administration than the a priori chosen 8 min from ALS arrival, as earlier administrations appear to, without plateau, be associated with higher probabilities of favorable outcomes.

To facilitate comparison to prior studies on the association between the timing of antiarrhythmics and outcomes in OHCA that did not have a data set with a placebo arm for comparison,[12,15,16] we evaluated the impact of delays to delivery among patients receiving each study drug. After multivariable analyses, the odds (95% CI) for survival to admission, survival to discharge, and functional survival were significantly lower per 1-min delay in drug administration for placebo (0.94 [0.90–0.98], 0.92 [0.87–0.97], and 0.90 [0.84–0.96]), lidocaine (0.91 [0.87–0.95], 0.89 [0.85–0.94], and 0.86 [0.80–0.92]), and amiodarone (0.87 [0.83–0.91], 0.80 [0.74–0.86], and 0.77 [0.71–0.84]), respectively, with the greatest magnitude of decreased odds per 1-min delay in the amiodarone group (Figure 5). Evaluating the interaction between

TABLE 2 Outcomes after early and late amiodarone, lidocaine, and placebo as treatment for shock-refractory OHCA.

	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
	Lidocaine vs. Placebo	Amiodarone vs. Placebo	Lidocaine vs. Placebo	Amiodarone vs. placebo
Survival to hospital admission				
Administration timing				
Early (<8 min)	1.36 (0.99–1.87)	1.73 (1.24–2.42)*	1.36 (0.97–1.90)	1.76 (1.24–2.50)*
Late (≥8 min)	1.30 (1.04–1.63)	1.14 (0.91–1.43)	1.35 (1.07–1.71)*	1.16 (0.91–1.46)
	Interaction $p = 0.829$	Interaction $p = 0.044$*	Interaction $p = 0.976$	Interaction $p = 0.057$
	Overall interaction $p = 0.090$		Overall interaction $p = 0.097$	
Survival to hospital discharge				
Administration timing				
Early (<8 min)	1.24 (0.88–1.76)	1.52 (1.07–2.16)*	1.24 (0.85–1.80)	1.56 (1.07–2.29)*
Late (≥8 min)	1.05 (0.79–1.40)	1.00 (0.75–1.34)	1.05 (0.78–1.43)	1.05 (0.78–1.42)
	Interaction $p = 0.351$	Interaction $p = 0.075$	Interaction $p = 0.463$	Interaction $p = 0.078$
	Overall interaction $p = 0.208$		Overall interaction $p = 0.283$	
Functional survival to hospital discharge (mRS ≤ 3)				
Administration timing				
Early (<8 min)	1.18 (0.82–1.71)	1.51 (1.04–2.20)*	1.16 (0.78–1.73)	1.55 (1.04–2.32)*
Late (≥8 min)	0.93 (0.67–1.30)	0.96 (0.69–1.34)	0.92 (0.65–1.30)	1.00 (0.70–1.40)
	Interaction $p = 0.351$	Interaction $p = 0.075$	Interaction $p = 0.375$	Interaction $p = 0.098$
	Overall interaction $p = 0.205$		Overall interaction $p = 0.255$	

Note: *p*-values reported for the unadjusted and adjusted logistic regressions represent interaction *p*-values adding for each comparison with placebo (amiodarone vs. placebo and separately lidocaine vs. placebo) and across all treatment arms (overall) with time to drug administration.

Abbreviations: mRS, modified Rankin scale; OHCA, out-of-hospital cardiac arrest.

*Significant associations.

time to drug and study drug treatment on the association with patient outcomes using nonlinear logistic regressions to model time to drug resulted in models that were not significantly better than the linear approach quantitatively (all likelihood ratio test *p*-values > 0.05) or qualitatively (Figure S1); thus, linear modeling was used throughout.

Sensitivity analyses were performed to evaluate the robustness of the results. Excluding 126 cases with EMS-witnessed arrests and repeating the analyses resulted in unchanged significance with the exception that the interaction term between each 1-min delay in time to drug and the comparison between amiodarone and placebo became significant for functional survival ($p = 0.032$). The exclusion of 501 cases receiving the study drug more than 15 min from ALS arrival, since it may be after a point of futility any effect modification of the treatment by the time to drug administration no longer occurs, resulted in significant interaction for each 1-min delay in time to drug and the comparison between amiodarone and placebo for survival to discharge ($p = 0.039$). Similarly, utilizing a post hoc cut-off to define early and late drug administration of 10 min resulted in significant interaction by time to drug as a binary variable (<10 min vs. ≥10 min) for the amiodarone and placebo comparison for survival to discharge ($p = 0.039$). Stratifying the analysis by route of study drug administration (IV or IO) resulted in larger effect sizes that remained significant in the IV group (Table S1; $n = 2183$) for amiodarone compared to placebo and near significant interaction in this comparison group with each 1-min delay in time to drug for survival to discharge (Figure S2; $p = 0.051$). Significance was lost in all comparisons when evaluating the IO group (Table S2; $n = 619$, all $p > 0.20$). Finally, we repeated our analyses using the closest physiologic equivalent of arrest time, defined as the time of the 9-1-1 call for bystander-witnessed arrests or the time of EMS starting CPR for EMS-witnessed arrests. Using this physiologic-based time from arrest to drug timing, rather than ALS arrival to drug delivery, did not alter the association between time to drug and the probability of survival to discharge (Figure S3) or our results when defining the early administration group as drug delivery within 15 min of the 9-1-1 call (aOR [95% CI] survival to discharge 1.65 [1.10–2.49] and 1.35 [0.89–2.05] for amiodarone and lidocaine compared to placebo, respectively).

DISCUSSION

In this post hoc secondary analysis of the ALPS double-blind randomized trial, we found that amiodarone was associated with significantly greater odds of survival to admission, survival to discharge, and functional survival compared to placebo when given within 8 min of ALS arrival on scene or with the initial dose of epinephrine.

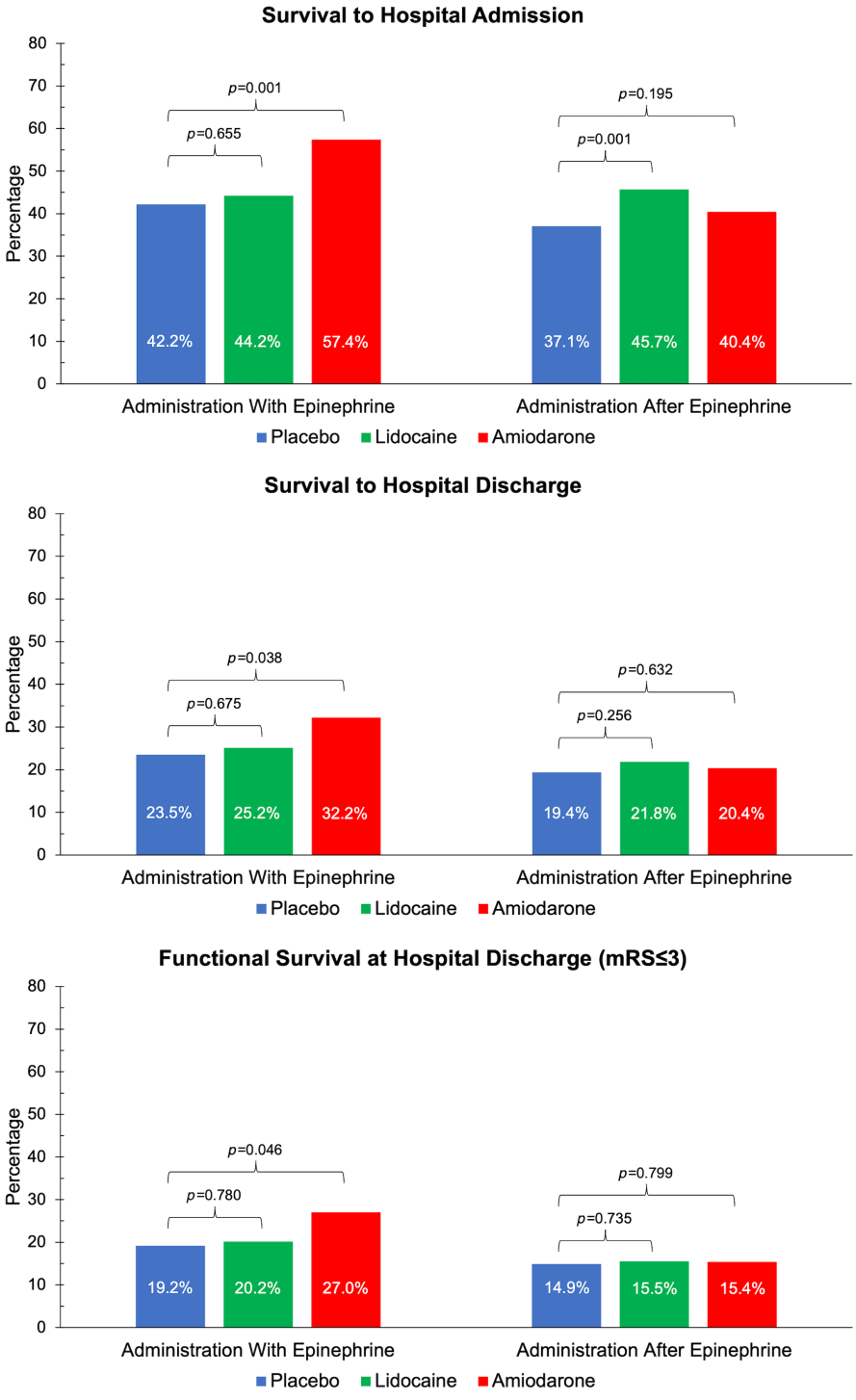


FIGURE 3 Unadjusted outcomes after administration of amiodarone, lidocaine, and placebo with epinephrine and after epinephrine for shock-refractory OHCA. mRS, modified Rankin scale score; OHCA, out-of-hospital cardiac arrest.

In our study, the NNT with amiodarone, compared to placebo, if given within 8 min of ALS arrival or with epinephrine was 11 and 12 for survival to discharge and 12 and 13 for good neurologic outcome at discharge, respectively. Overall, our findings suggest the timing of antiarrhythmic administration, specifically for amiodarone, may be crucial to its efficacy in shock-refractory OHCA.

Amiodarone and lidocaine are the currently recommended antiarrhythmic medications for shock-refractory OHCA.[8,9] Amiodarone was found in two trials to improve survival to admission compared to placebo but had no difference for survival to hospital discharge or neurologically intact survival, though both were underpowered to detect these outcomes.[13,14] The more recent ALPS trial found higher survival to admission for amiodarone and lidocaine compared to placebo but not higher survival to discharge or functional survival.[2] In prespecified subgroup analyses in ALPS, amiodarone and lidocaine, compared to placebo, had significantly greater survival to discharge for bystander-witnessed arrests ($p = 0.04$ and $p = 0.03$, respectively) and EMS-witnessed arrests for amiodarone ($p = 0.01$). The absolute risk reduction for amiodarone compared to placebo with an EMS-witnessed arrest was 21.9% and for a bystander-witnessed arrest 5%,

TABLE 3 Outcomes after administration of amiodarone, lidocaine, and placebo with epinephrine and after epinephrine for shock-refractory OHCA.

	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
	Lidocaine vs. Placebo	Amiodarone vs. Placebo	Lidocaine vs. Placebo	Amiodarone vs. Placebo
Survival to hospital admission				
Administration timing				
With epinephrine	1.09 (0.76–1.56)	1.85 (1.27–2.68)*	1.11 (0.76–1.62)	1.85 (1.25–2.74)*
After epinephrine	1.43 (1.15–1.77)	1.15 (0.93–1.43)	1.42 (1.14–1.78)*	1.17 (0.94–1.47)
	Interaction $p = 0.199$	Interaction $p = 0.032$*	Interaction $p = 0.323$	Interaction $p = 0.045$*
	Overall interaction $p = 0.003$*		Overall interaction $p = 0.012$	
Survival to hospital discharge				
Administration timing				
With epinephrine	1.09 (0.72–1.65)	1.54 (1.02–2.32)*	1.18 (0.76–1.83)	1.59 (1.02–2.49)*
After epinephrine	1.16 (0.90–1.51)	1.07 (0.82–1.39)	1.07 (0.81–1.42)	1.08 (0.81–1.42)
	Interaction $p = 0.803$	Interaction $p = 0.140$	Interaction $p = 0.746$	Interaction $p = 0.113$
	Overall interaction $p = 0.177$		Overall interaction $p = 0.247$	
Functional survival to hospital discharge (mRS ≤ 3)				
Administration timing				
With epinephrine	1.06 (0.68–1.66)	1.56 (1.01–2.41)*	1.16 (0.72–1.88)	1.65 (1.02–2.67)*
After epinephrine	1.05 (0.78–1.41)	1.04 (0.77–1.40)	0.94 (0.69–1.29)	1.04 (0.76–1.42)
	Interaction $p = 0.971$	Interaction $p = 0.134$	Interaction $p = 0.500$	Interaction $p = 0.083$
	Overall interaction $p = 0.235$		Overall interaction $p = 0.220$	

Note: *p*-values reported for the unadjusted and adjusted logistic regressions represent interaction *p*-values adding for each comparison with placebo (amiodarone vs. placebo and separately lidocaine vs. placebo) and across all treatment arms (overall) with time to drug administration.

Abbreviations: mRS, modified Rankin scale; OHCA, out-of-hospital cardiac arrest.

*Significant associations.

suggesting NNTs for survival to discharge of 4.6 and 20, respectively. Our study builds on this initial analysis and shows that perhaps the increased efficacy in witnessed arrests is in part due to the shorter time intervals from arrest to antiarrhythmic administration, as we found an overall NNT of 11 for amiodarone compared to placebo in all-comers with initial shockable rhythms if the drugs were given within 8 min of ALS arrival or arrest (for EMS-witnessed arrests).

A recent study found that shorter time from 9-1-1 call to amiodarone had a higher probability of ROSC at ED arrival than placebo.[11] This study also reported that delayed administration of amiodarone was associated with lower probabilities of ROSC compared to placebo. However, this study did not account for route of drug administration, which has been shown to possibly impact antiarrhythmic efficacy and may impact the time of drug delivery,[24] nor did it evaluate survival outcomes. Our study independently confirms the importance of early amiodarone, and we further show clear associations with greater survival to discharge and functional survival for early amiodarone compared to placebo. Our results also agree with published retrospective studies finding reduced odds of survival with each 1-min delay in amiodarone administration (aOR 0.93[15] vs. 0.80 in our study) and neurologic outcomes (unadjusted OR 0.89[16] vs. aOR 0.77 in our study). We also provide reassuring evidence that there is no association with worse survival to discharge or functional outcomes for late amiodarone administration compared to placebo. Finally, we identified a clear, targeted goal time for antiarrhythmic administration of no later than 8 min from ALS arrival on scene with evidence that amiodarone administered with epinephrine, rather than after another cycle of CPR, may be a modifiable change in cardiac arrest guidelines to test in future studies.

The current recommended administration time for antiarrhythmics, after the third shock, was developed due to precedence of timing in prior studies without clear evidence that delaying administration of these medications would result in better outcomes or that earlier administration would cause harm.[4] A recent retrospective study evaluated patients who received amiodarone after obtaining ROSC from a single defibrillation rather than administration after three defibrillations as recommended by current guidelines.[36] The authors found this early amiodarone administration occurred in nearly one-quarter of cases and was not associated with harm and instead was associated with lower VF recurrence and improved survival to admission compared to the usual sequence of amiodarone administration.[36] Future studies are needed to prospectively confirm the association between earlier amiodarone and better patient outcomes, and a randomized trial may be necessary to evaluate the efficacy of an algorithm that calls for amiodarone as soon as vascular access is obtained or with the initial epinephrine dose compared to current guidelines. These trials and future

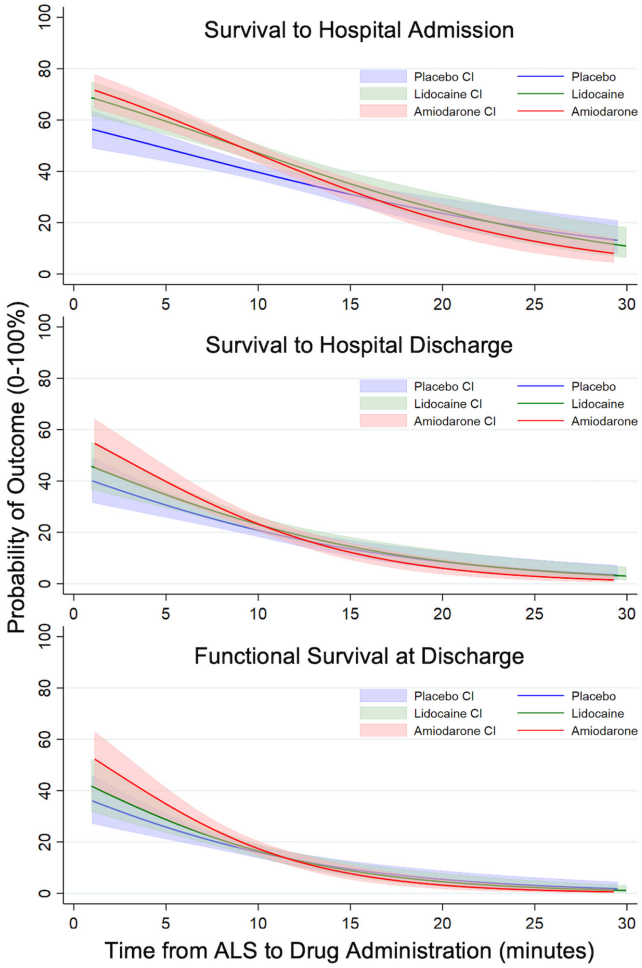


FIGURE 4 Time from ALS arrival on scene to administration of study drug and its impact on the probability of survival to admission; survival to discharge; and functional survival stratified by reception of placebo, lidocaine, or amiodarone. ALS, advanced life support.

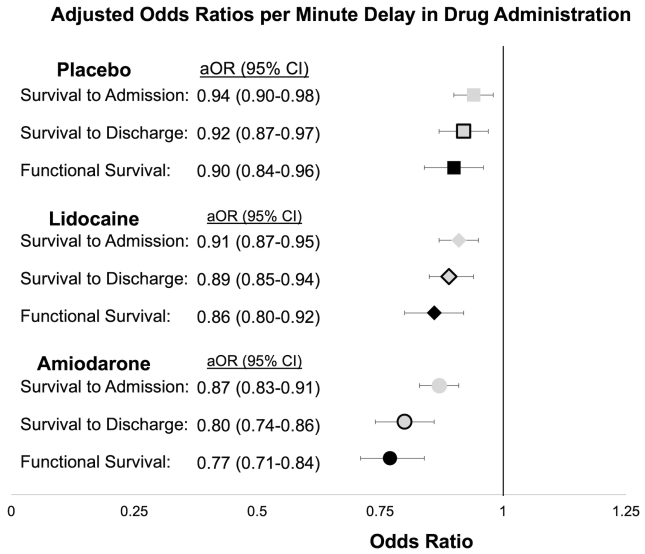


FIGURE 5 Adjusted odds of survival to discharge and functional survival per-minute increase in time from ALS arrival to randomized study drug administration. ALS, advanced life support; aOR, adjusted odds ratio.

guidelines should also carefully consider the route of administration, as amiodarone appears to lose all associations with favorable outcomes if given via the tibial IO route.[24] Finally, local EMS agencies and the Cardiac Arrest Registry to Enhance Survival (CARES) should also consider adding the timing of antiarrhythmic administration to facilitate confirmative observational studies in larger data sets and to allow for quality improvement efforts.

LIMITATIONS

Our study has several limitations as it is a secondary analysis of a large, double-blind, randomized trial. Fortunately, after adjusting for confounders, our primary results comparing outcomes across the study drug given in the parent ALPS trial (amiodarone, lidocaine, or placebo) minimally changed from unadjusted analyses. However, we were unable to adjust for clustering by agency or site, as site or agency are not available in the public use ALPS data set. In the primary ALPS trial, there were similar distributions across the three study drug arms at each site in the per-protocol design. Although our study is a secondary analysis of this randomized trial predominately across the double-blind study drug (amiodarone, lidocaine, or placebo), we cannot evaluate if our secondary analysis stratifying patients into early groups (whether using an 8-min cutoff or those given with epinephrine) results in differences across sites of care. We are also limited in that the data set does not have values of other potential confounding factors, such as comorbidities of patients, CPR fraction, or CPR pauses, that could impact results. Our study is also limited by what may be inaccuracies of time measurements of drug delivery recorded during OHCA treatment in the prehospital setting. The ALPS data set also contains a low proportion of IO routes of administration (<25%) and a very low proportion of humeral IO routes (<5%), both of which are increasingly utilized by EMS agencies and could impact antiarrhythmic efficacy in current practice. Thus, this limits the applicability of our findings to current practice and likely necessitates a prospective study to confirm the importance of timing for amiodarone efficacy.

CONCLUSIONS

Administration of amiodarone within 8 min of advanced life support arrival or with the initial dose of epinephrine in shock-refractory out-of-hospital cardiac arrest appears to be associated with significantly improved odds of survival to discharge and survival with a favorable outcome compared to placebo in this post hoc secondary analysis of a large randomized, double-blind trial. Future prospective studies are needed to confirm these findings and evaluate if earlier amiodarone improves patient-oriented outcomes after shock-refractory out-of-hospital cardiac arrest.

ACKNOWLEDGMENTS

The authors thank the participating EMS agencies in the Amiodarone, Lidocaine, and Placebo Study and the National Heart, Lung, and Blood Institute data repository for making data accessible for researchers.

FUNDING INFORMATION

This project was supported by a grant from the Society for Academic Emergency Medicine (RE2020-0000000167).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lupton JR, Neth MR, Sahni R, et al. Survival by time-to-administration of amiodarone, lidocaine, or placebo in shock-refractory out-of-hospital cardiac arrest. *Acad Emerg Med*. 2023;30:906-917. doi:10.1111/acem.14716

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