SUPPLEMENTAL MATERIAL

Data S1: Adjusted Per-protocol Analysis - Utstein Variables

We also repeated our primary analysis (per-protocol) adjusting for Utstein variables (age, sex, location of cardiac arrest [public versus non-public], witness status and bystander CPR [yes/no]). The study's findings were consistent even after adjustment for Utstein variables. In our adjusted analysis, the odds of ROSC at hospital arrival decreased as time to drug administration increased, in amiodarone (OR 0.92, 95% CI 0.90–0.94 per min increase in time interval), lidocaine (OR 0.95, 95% CI: 0.94-0.96), and placebo (OR 0.95, 95% CI: 0.94-0.96) treated patients. There was a significant time by treatment interaction for the comparison of amiodarone versus placebo (p=0.01) and lidocaine vs placebo (p=0.01). For each additional minute of wait time from 911 call to drug the odds of ROSC were lower in amiodarone versus placebo (OR=0.96, 95% CI 0.93–0.99) and amiodarone versus lidocaine (OR=0.96, 95% CI 0.93–0.99). Time was not significantly associated with ROSC when comparing lidocaine to placebo (1.00, 95% CI 0.97–1.03; p= 0.92).

Data S2: Probability of ROSC at Hospital Arrival Based on Time to the First Dose of the Trial Drug in Patients with Witnessed Cardiac Arrest

The probability of ROSC at hospital arrival based on time to the first dose of the trial drug in patients with witnessed cardiac arrest is shown in Figure S1. The result of a separate analysis of patients with witnessed cardiac arrest was similar to other analyses regarding time to trial drug administration effect.

Data S3: Intention-to-treat Population (patients with initial shockable rhythm or subsequently occurring shockable rhythm)

In the ROC ALPS trial intention-to-treat population, 4653 patients were enrolled in the three arms of the trial. Of those, 4209 (90.5%) patients with known drug administration times were included in this study analysis (1411 to the placebo arm, 1405 to the amiodarone arm and 1393 to the lidocaine arm). Baseline characteristics are summarised for all enrolled patients and are shown in Table S2. The time intervals between 911 emergency call (or time of cardiac arrest for paramedic witnessed cases) and trial drug administration were similar between all groups. As was expected in a large RCT, the baseline characteristics were well balanced between trial groups. Overall, 1322 (31.4%) patients had ROSC at hospital arrival (414 in the amiodarone arm, 475 in the lidocaine arm, and 433 in the placebo arm). A more comprehensive description of all baseline patient characteristics and outcomes in the per-protocol population has been reported, in the primary analysis of the study.[12]

The probability of ROSC at hospital arrival based on time to the first dose of the trial drug is shown in Figure S2. The odds of ROSC at hospital arrival decreased as time to drug administration increased, in amiodarone (OR 0.91, 95% CI 0.90–0.93 per min increase in time interval), lidocaine (OR 0.94, 95% CI: 0.93-0.95), and placebo (OR 0.94, 95% CI: 0.93-0.95) treated patients.

The change in probability of ROSC at hospital arrival based on time to the first dose of amiodarone (compared to placebo) is shown in Figure S3A. With short times to drug administration, the probability of ROSC was higher in amiodarone, whereas ROSC was higher with placebo at later times after drug administration. The change in probability of ROSC at hospital arrival based on time to the first dose of amiodarone (compared to lidocaine) is shown in Figure S3B. With short times to drug administration, ROSC at hospital arrival was no different in amiodarone versus

lidocaine, whereas ROSC was higher with lidocaine than amiodarone at later times after drug administration. Comparing lidocaine to placebo (Figure S3C), the likelihood of ROSC at hospital arrival increased irrespective of time to treatment (OR 1.20, 95% CI: 1.02-1.41).

There was a significant time by treatment interaction for the comparison of amiodarone versus placebo (p=0.002) and lidocaine vs placebo (p=0.001). For each additional minute of wait time from 911 call to drug the odds of ROSC were lower in amiodarone versus placebo (OR=0.96, 95% CI 0.94–0.99) and amiodarone versus lidocaine (OR=0.97, 95% CI 0.94–0.99). Time was not significantly associated with ROSC when comparing lidocaine to placebo (OR=1.00, 95% CI 0.98–1.02; p= 0.83).

Table S1: Distribution of patients' characteristics with regards to time to treatment (divided into quartiles based on time to the ALPS drug administration).

Patient Characteristics	Time From 911 Call to First Dose of ALPS Drug (min) (N = 2994*)			
	≤ 14.0 min	**14.0 -17.5 min**	**17.5 -22.0 min**	**> 22.0 min**
Mean age, year (SD)	62.8 (13.5)	63.5 (14.4)	62.7 (14.5)	64.5 (14.2)
Male, n (%)	618 (20.6)	590 (19.4)	611 (20.4)	580 (19.4)
Witnessed, n (%)	553 (19.0)	490 (16.8)	541 (18.6)	491 (16.9)
Public location, n (%)	273 (9.1)	206 (6.9)	229 (7.7)	213 (7.1)
Bystander CPR, n (%)	490 (16.6)	457(15.5)	464 (15.8)	429(14.6)

SD = standard deviation; CPR= cardiopulmonary resuscitation

*May vary depending on missing values

Table S2: Intention-to-treat population characteristics and outcomes by treatment arm (N = 4209).

Patient characteristics	**Placebo (n=1411*)**	**Amiodarone (n=1405*)**	**Lidocaine (n=1393*)**
Mean age, year (SD)	63.6 (15.2)	64.4 (14.7)	63.5 (15.6)
Median time to drug, min (IQR)	19.0 (9.6)	19.5 (10.7)	19.2 (10.3)
Male, n (%)	1076 (76.3)	1078 (76.8)	1098 (78.8)
Witnessed, n (%)	931 (67.7)	892 (65.1)	900 (66.5)
Public location, n (%)	408 (26.0)	404 (26.3)	409 (26.5)
Bystander CPR, n (%)	724 (51.3)	768 (54.7)	712 (51.1)
Outcomes			
ROSC at hospital arrival, n (%)	433 (30.7)	414 (29.5)	475 (34.1)
Number of EMS shocks after first dose of the trial drug, median (IQR)	4 (3)	4 (3)	4 (3)
Number of EMS shocks after first dose of the trial drug, median (IQR)	5 (6)	5 (4)	4 (3)

IQR= interquartile range; SD = standard deviation; CPR= cardiopulmonary resuscitation; EMS= emergency medical services; ROSC= return of spontaneous circulation

*may vary depending on missing values

Figure S1: Probability (shaded area shows 95% CI) of ROSC at hospital arrival based on time to the first dose of the trial drug in witnessed cardiac arrest cases. CI= confidence interval; ROSC= return of spontaneous circulation.

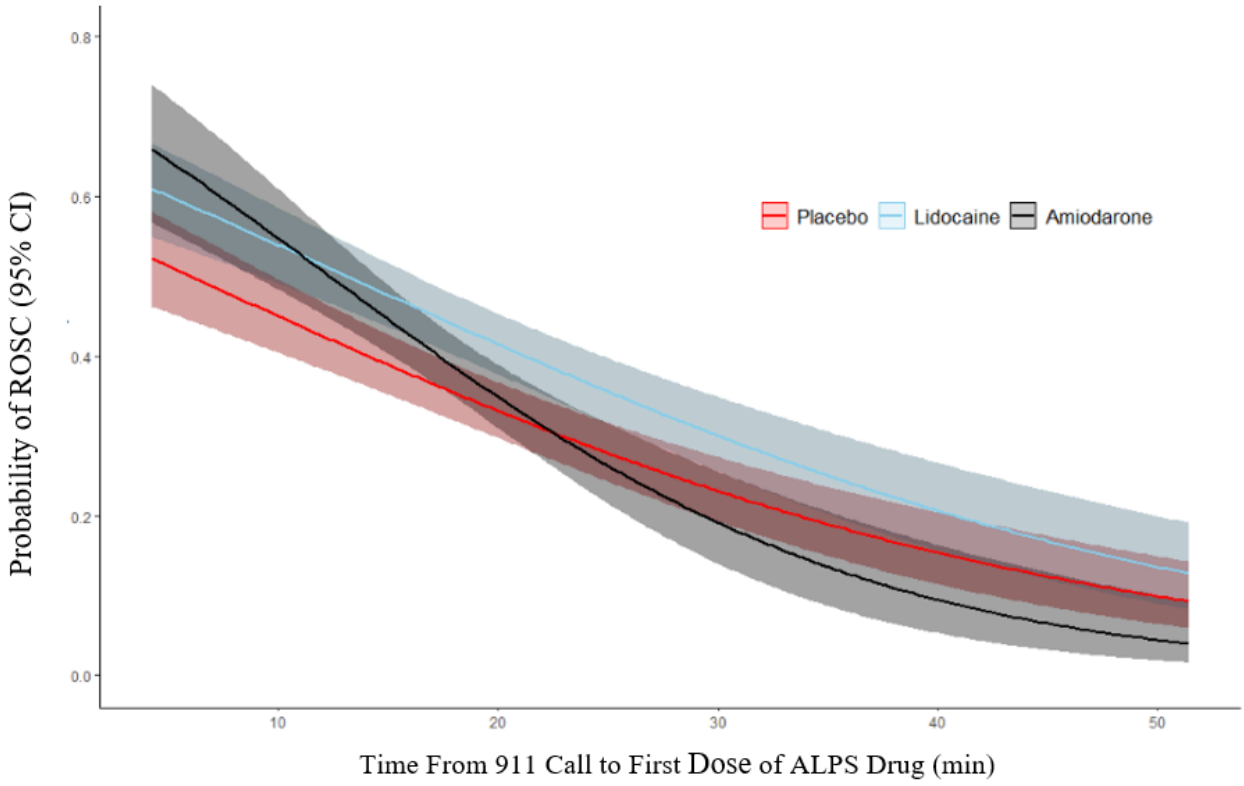

Figure S2: Probability (shaded area shows 95% CI) of ROSC at hospital arrival based on time to the first dose of the trial drug in the intention-to-treat population. CI= confidence interval; ROSC= return of spontaneous circulation.

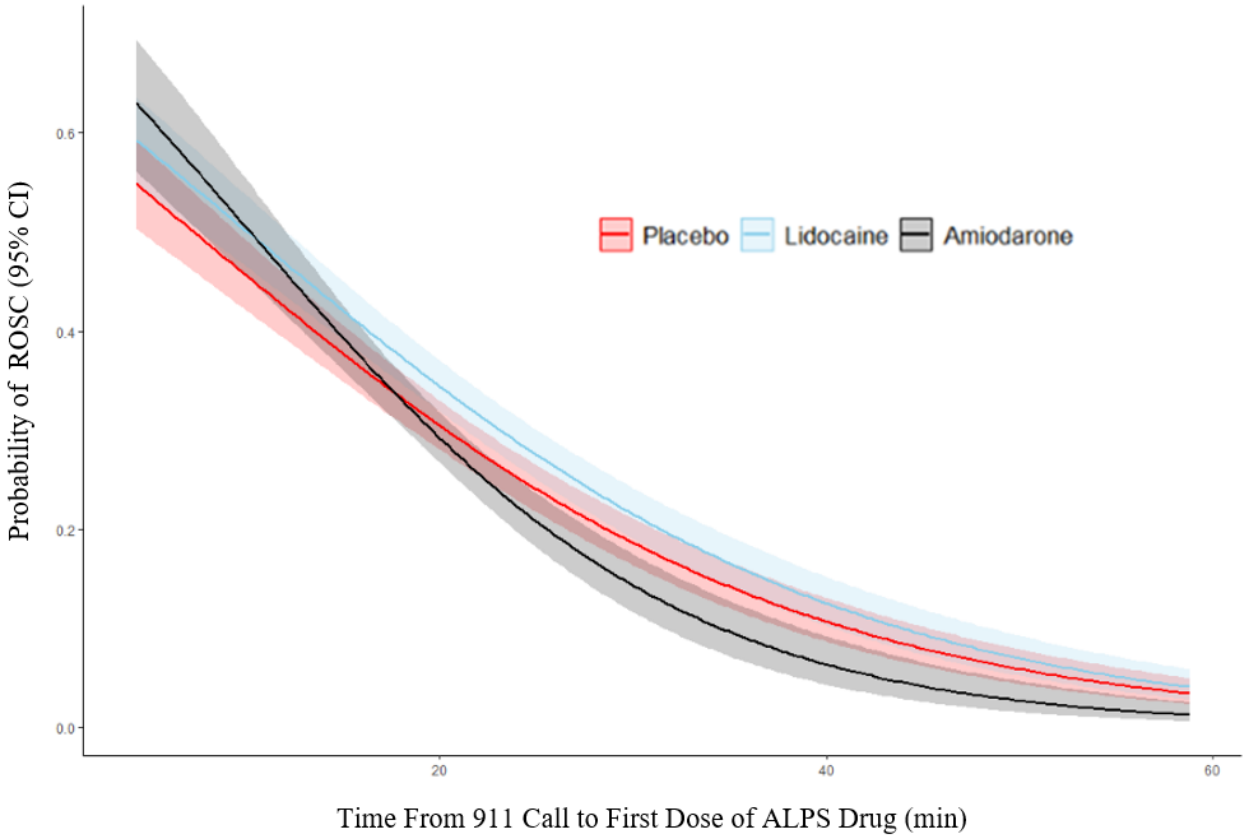

Figure S3: Change in OR of ROSC at hospital arrival in the intention-to-treat population based on time to the first dose of A) amiodarone (compared to placebo). B) Amiodarone (compared to lidocaine). C) Lidocaine (compared to placebo). Shaded area shows 95% CI. OR= odds ration; CI= confidence interval; ROSC= return of spontaneous circulation.