ORIGINAL ARTICLE

Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Antiarrhythmic drugs are used commonly in out-of-hospital cardiac arrest for shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, but without proven survival benefit.

METHODS

In this randomized, double-blind trial, we compared parenteral amiodarone, lidocaine, and saline placebo, along with standard care, in adults who had nontraumatic out-of-hospital cardiac arrest, shock-refractory ventricular fibrillation or pulseless ventricular tachycardia after at least one shock, and vascular access. Paramedics enrolled patients at 10 North American sites. The primary outcome was survival to hospital discharge; the secondary outcome was favorable neurologic function at discharge. The per-protocol (primary analysis) population included all randomly assigned participants who met eligibility criteria and received any dose of a trial drug and whose initial cardiac-arrest rhythm of ventricular fibrillation or pulseless ventricular tachycardia was refractory to shock.

RESULTS

In the per-protocol population, 3026 patients were randomly assigned to amiodarone (974), lidocaine (993), or placebo (1059); of those, 24.4%, 23.7%, and 21.0%, respectively, survived to hospital discharge. The difference in survival rate for amiodarone versus placebo was 3.2 percentage points (95% confidence interval [CI], −0.4 to 7.0; P=0.08); for lidocaine versus placebo, 2.6 percentage points (95% CI, −1.0 to 6.3; P=0.16); and for amiodarone versus lidocaine, 0.7 percentage points (95% CI, −3.2 to 4.7; P=0.70). Neurologic outcome at discharge was similar in the three groups. There was heterogeneity of treatment effect with respect to whether the arrest was witnessed (P=0.05); active drugs were associated with a survival rate that was significantly higher than the rate with placebo among patients with bystander-witnessed arrest but not among those with unwitnessed arrest. More amiodarone recipients required temporary cardiac pacing than did recipients of lidocaine or placebo.

CONCLUSIONS

Overall, neither amiodarone nor lidocaine resulted in a significantly higher rate of survival or favorable neurologic outcome than the rate with placebo among patients with out-of-hospital cardiac arrest due to initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov number, NCT01401647.)

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Out-of-hospital cardiac arrest is responsible for more than 300,000 deaths each year in North America.[1] Many out-of-hospital cardiac arrests are attributable to ventricular fibrillation or pulseless ventricular tachycardia. Although ventricular fibrillation or pulseless ventricular tachycardia is regarded as the most treatable presentation of out-of-hospital cardiac arrest because of its responsiveness to shock,[2] most defibrillation attempts do not result in sustained return of spontaneous circulation.[3] Ventricular fibrillation or pulseless ventricular tachycardia commonly persists or recurs after shock, and there is a significant inverse relationship between the duration of ventricular fibrillation or pulseless ventricular tachycardia, or the frequency of acute recurrences, and resuscitation outcome.[4-6]

Amiodarone and lidocaine are used commonly to promote successful defibrillation of shock-refractory ventricular fibrillation or pulseless ventricular tachycardia and prevent recurrences. In controlled trials involving patients with out-of-hospital cardiac arrest, those who received amiodarone were more likely than those who received placebo or lidocaine to have a return of spontaneous circulation and to survive to be admitted to the hospital,[7,8] but the effects of amiodarone on survival to hospital discharge or neurologic outcome remain uncertain. To address this knowledge gap, we compared the effects of amiodarone, lidocaine, and placebo on survival to hospital discharge after out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.

Methods

Trial Conduct and Oversight

The background and methods of the trial were described previously.[9] Paramedics from 55 emergency medical services (EMS) agencies enrolled patients with out-of-hospital cardiac arrest at 10 North American sites participating in the Resuscitation Outcomes Consortium (ROC).[10] The trial was conducted under exception from informed consent in emergency research in accordance with applicable regulatory requirements, oversight by the Food and Drug Administration and Health Canada, approval by institutional review boards in participating communities, and monitoring by an independent data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute (NHLBI).

The trial was sponsored by the NHLBI, the Canadian Institutes of Health Research, and others (see the support statement at the end of the article). In addition, Baxter Healthcare provided the trial drugs without cost and tested the stability of these products over the trial duration but otherwise played no role in the trial. The investigators designed and conducted the trial; gathered, analyzed, and interpreted the data; wrote the manuscript draft (the first author); and made the decision to submit it for publication. The trial statisticians had full access to all trial data and take responsibility for their integrity, analytic accuracy, and completeness and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

Patients

The trial included patients 18 years of age or older with nontraumatic out-of-hospital cardiac arrest and shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, defined as confirmed persistent (nonterminating) or recurrent (restarting after successful termination) ventricular fibrillation or pulseless ventricular tachycardia after one or more shocks anytime during resuscitation (inclusive of rhythms interpreted as being shockable by an automated external defibrillator). Eligible patients were also required to have intravenous or intraosseous vascular access. We excluded patients who had already received open-label intravenous lidocaine or amiodarone during resuscitation or had known hypersensitivity to these drugs. A complete list of trial inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

The trial protocol specified that the primary analysis population (the per-protocol population) would include only those randomly assigned participants who actually met the eligibility criteria, who received any dose of a trial drug during shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, and who were confirmed to have an initial (rather than secondary) cardiac-arrest rhythm of ventricular fibrillation or pulseless ventricular tachycardia. Analyses were also performed in all randomly assigned patients (the intention-to-treat population).

INTERVENTIONS

The trial evaluated licensed parenteral preparations of lidocaine, normal saline and a recently approved Captisol-based formulation of amiodarone (Nexterone, Baxter Healthcare) that is designed to reduce hypotensive effects.[11,12] Trial drugs were packaged in identically appearing, sealed kits each having three identically formulated syringes. Each syringe held 3 ml of colorless fluid containing 150 mg of amiodarone (totaling 450 mg in the amiodarone kit), 60 mg of lidocaine (180 mg in the lidocaine kit), or normal saline. Kits and their syringe contents were indistinguishable except by numerical code and were randomly distributed to EMS providers in a ratio of 1:1:1. Randomization was performed in permuted blocks of concealed size and was stratified according to participating site and agency. Trial drugs were tested regularly for stability and were confirmed to maintain their integrity in the simulated climates of trial communities.[9]

TREATMENT PROTOCOL

Patients with out-of-hospital cardiac arrest were treated in accordance with local EMS protocols that complied with American Heart Association (AHA) guidelines for advanced life support.[13] Some patients were coenrolled in a concurrent trial comparing continuous chest compressions with interrupted chest compressions during cardiopulmonary resuscitation (CPR).[14]

After the failure of one or more shocks to terminate ventricular fibrillation or pulseless ventricular tachycardia or prevent its recurrence, eligible patients received a vasopressor and were then enrolled in the trial by the EMS personnel's act of opening a trial-drug kit whose masked contents (amiodarone, lidocaine, or placebo) determined the patient's random assignment (details are provided in the Supplementary Appendix). Patients, investigators, and trial personnel were unaware of the trial-drug assignments. The initial dose of a trial drug, approximating current clinical practice, consisted of two syringes (one syringe if the estimated body weight was <100 lb [45.4 kg]) that were administered by rapid bolus.[10,15,16] If ventricular fibrillation or pulseless ventricular tachycardia persisted after the initial dose of the trial drug, standard resuscitation measures, and additional shocks, a supplemental dose (one syringe) of the same drug was administered. Thereafter, standard interventions for advanced life support ensued according to local practice, excluding open-label lidocaine or amiodarone before hospitalization.

POST–CARDIAC ARREST CARE

All trial interventions were completed before hospital arrival. On arrival, hospital care providers were notified of the patient's enrollment in the trial and encouraged to provide usual post–cardiac arrest care in accordance with published AHA guidelines,[17] including open-label amiodarone or lidocaine if necessary. Components of hospital care were monitored but were not standardized by the trial protocol, and their performance was reported back to hospitals periodically. A patient's trial-drug assignment was not disclosed to care providers, investigators, or site personnel unless emergency unblinding was requested, and then only to the treating physicians.

DATA COLLECTION AND OUTCOMES

Data from prehospital patient care records, CPR-process measures, and data from hospital medical records were collected as described in the Supplementary Appendix. The primary outcome of the trial was survival to hospital discharge. The main aim was to compare survival in amiodarone recipients versus placebo recipients, with secondary comparisons of survival in lidocaine recipients versus placebo recipients and in amiodarone recipients versus lidocaine recipients. The secondary outcome was survival with favorable neurologic status at discharge, defined as a score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) of 3 or less, indicating the ability to conduct daily activities independently or with minimal assistance.[18] These outcomes were determined in both the per-protocol population (the primary analysis) and in the intention-to-treat population.

Mechanistic outcomes that were assessed for exploratory purposes included the number of defibrillation shocks administered after receipt of the trial drug, return of spontaneous circulation at hospital arrival, hospital admission, hospital treatments, and time to withdrawal of life-sustaining treatments. Prespecified subgroups were defined according to status with respect to witnessing of the cardiac arrest (witnessed by EMS, witnessed by bystander, or unwitnessed), receipt of bystander-initiated CPR (yes or no), location of the arrest (public or private), time to trial-

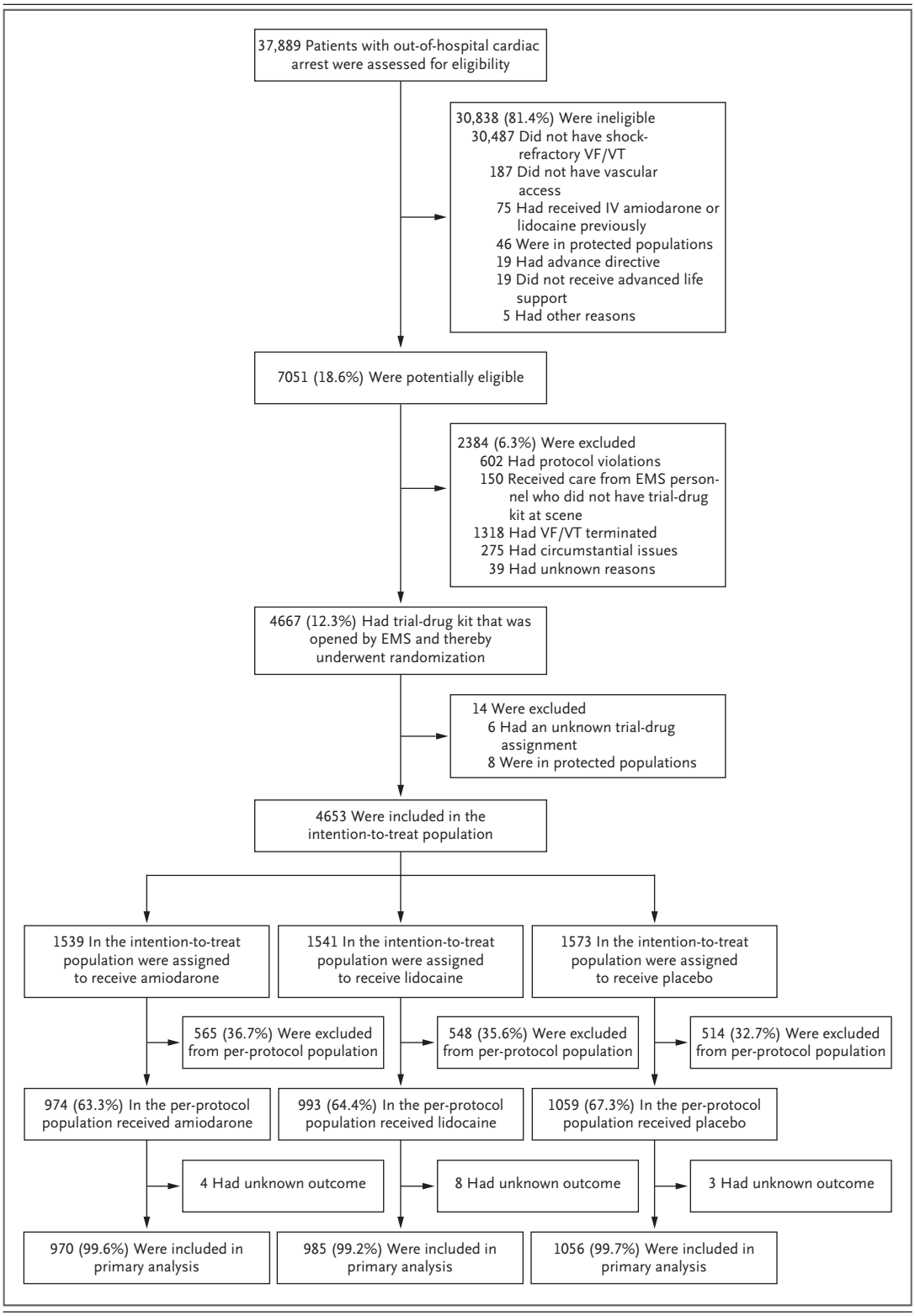

Figure 1 (facing page). Screening and Randomization.
The inclusion and exclusion of patients depended on their clinical and cardiac-rhythm characteristics at the time of potential trial-drug receipt. Of 46 patients in protected populations who were determined to be ineligible before enrollment, 33 were children, 12 were prisoners, and 1 was pregnant. Of 5 patients who had "other reasons" for ineligibility, 3 had exsanguination and 2 had a history of allergy to amiodarone or lidocaine. Circumstantial issues that were reasons for nonenrollment included safety concerns at the scene, arrival at the hospital before the trial-drug kit was opened, debatable asystole, shocks from an implanted defibrillator, infiltration or loss of intravenous (IV) access, and a need for extrication of the patient. The intention-to-treat population excluded patients in protected populations. There were 8 such patients (6 children and 2 prisoners) who were enrolled; 3 were assigned to amiodarone, 1 to lidocaine, and 4 to placebo. The intention-to-treat population included all patients for whom a trial-drug kit was opened, regardless of their eligibility, initial cardiac-arrest rhythm, or actual receipt of the trial drug. A total of 1627 patients in the intention-to-treat population were excluded from the per-protocol population (Table S1 in the Supplementary Appendix). The per-protocol population was composed of randomly assigned, trial-eligible patients whose initial cardiac-arrest rhythm was ventricular fibrillation or pulseless ventricular tachycardia (VF/VT), who continued to have shock-refractory VF/VT, and who received any dose of a trial drug. EMS denotes emergency medical services.

drug administration (<15 or ≥15 minutes), route of trial-drug administration (intravenous or intraosseous), treatment group in the concurrent trial of continuous or interrupted chest compressions during CPR, baseline survival rate at the trial site (in quartiles), and EMS drug-administration practice (see the Supplementary Appendix).

Adverse events were considered to be drug-related if they were reported previously with these medications[19,20] (e.g., anaphylaxis, thrombophlebitis requiring therapeutic intervention, clinical seizure activity, and bradycardia requiring temporary cardiac pacing) and if they occurred within 24 hours after trial-drug administration. Serious or unexpected adverse events attributable to trial interventions[21] and complications related to vascular access were also assessed. Other adverse events such as pulmonary edema, hypotension, or pneumonia, which are common after out-of-hospital cardiac arrest, were monitored but were not considered to be drug-related unless imbalanced between trial groups.

STATISTICAL ANALYSIS

We estimated that a sample size of 3000 in the per-protocol population (1000 patients per group) would provide 90% power to detect an absolute difference of 6.3 percentage points in the rate of survival to hospital discharge between the amiodarone group and the placebo group (29.7% vs. 23.4%). The baseline survival rate was estimated from patients with a first recorded rhythm of ventricular fibrillation or pulseless ventricular tachycardia who received at least two shocks in previous ROC trials.[22,23] The projected difference in survival with amiodarone was estimated from a previous trial database[7] and was the comparison for which this trial was powered.

Survival was evaluated across groups with the use of the z-test for comparison of binomial proportions with pooled variance, with a one-sided significance level of 0.025 for comparisons between an active drug and placebo (based on the monitoring plan of the trial) and a two-sided significance level of 0.05 when comparing amiodarone with lidocaine.[9] All comparisons in this report, including testing interactions, were recalculated as two-sided with P values of less than or equal to 0.05 considered to indicate statistical significance (as most comparisons were initially performed), which did not substantially change the results.

The data and safety monitoring board performed interim reviews twice a year with the use of group sequential methods with formal stopping boundaries; final differences and 95% confidence intervals for the primary outcome were adjusted accordingly.[9] Apart from this, there were no adjustments for multiple comparisons.

RESULTS

TRIAL POPULATIONS

The trial began on May 7, 2012 and completed enrollment on October 25, 2015. Of 37,889 patients with nontraumatic out-of-hospital cardiac arrest, 7051 (18.6%) had shock-refractory ventricular fibrillation or pulseless ventricular tachycardia at some time and were potentially eligible for enrollment in the trial (Fig. 1). The intention-to-treat population of 4653 patients was composed of 4667 with opened drug kits, excluding 6 with an unknown trial-drug assignment and 8 in protected populations. Of these, 3026 comprised the per-protocol population of trial-eligi-

Table 1. Prerandomization Characteristics of the Per-Protocol Population.*

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)
Age — yr	63.7±14.0	63.0±14.7	62.7±14.6
Male sex — no./total no. (%)	762/973 (78.3)	816/993 (82.2)	844/1059 (79.7)
Cardiac arrest occurred in public location — no./total no. (%)	303/974 (31.1)	312/993 (31.4)	316/1056 (29.9)
Cardiac arrest witnessed — no./total no. (%)			
By EMS	57/950 (6.0)	44/965 (4.6)	54/1027 (5.3)
By bystander	621/950 (65.4)	636/965 (65.9)	687/1027 (66.9)
Bystander-initiated PAD shock — no./total no. (%)	62/905 (6.9)	51/927 (5.5)	57/988 (5.8)
Bystander-initiated CPR — no./total no. (%)	556/905 (61.4)	549/927 (59.2)	595/988 (60.2)
Time from initial call†			
To first arrival of EMS — min	5.8±2.6	5.6±2.4	5.8±2.6
To first arrival of EMS ≤4 min — no./total no. (%)	209/973 (21.5)	237/992 (23.9)	244/1058 (23.1)
To first arrival of ALS — min	8.0±5.1	7.8±4.3	8.0±4.6
Trial site — no. (%)			
A	104 (10.7)	97 (9.8)	92 (8.7)
B	154 (15.8)	158 (15.9)	162 (15.3)
C	74 (7.6)	77 (7.8)	80 (7.6)
D	59 (6.1)	60 (6.0)	66 (6.2)
E	4 (0.4)	8 (0.8)	7 (0.7)
F	215 (22.1)	223 (22.5)	260 (24.6)
G	21 (2.2)	14 (1.4)	15 (1.4)
H	163 (16.7)	149 (15.0)	169 (16.0)
I	63 (6.5)	85 (8.6)	80 (7.6)
J	117 (12.0)	122 (12.3)	128 (12.1)

* Plus–minus values are means ±SD. No baseline factors varied significantly according to trial group (P>0.05). ALS denotes advanced life support, CPR cardiopulmonary resuscitation, EMS emergency medical services, and PAD public-access defibrillation.
† Initial call refers to the initial notification of an occurrence of cardiac arrest to an emergency call center.

ble patients with out-of-hospital cardiac arrest and initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia who were randomly assigned recipients of amiodarone (974 patients), lidocaine (993), or placebo (1059), excluding 1627 who did not meet the per-protocol criteria (Table S1 in the Supplementary Appendix). Emergency unblinding of the trial-drug assignment was requested in 24 patients (0.8%) and was proportionately similar across trial groups.

The baseline patient characteristics and event characteristics in the per-protocol population were well balanced across trial groups (Tables 1 and 2). The first dose of the trial drugs was given a mean (±SD) of 19.3±7.4 minutes after the initial call to EMS and after a median of three shocks (interquartile range, two to four) had been administered.

OUTCOMES

Outcomes were available for 99.5% of all patients in the per-protocol population (Fig. 1). Among amiodarone recipients in the per-protocol population, 237 (24.4%) survived to hospital discharge (the primary outcome), as compared to 233 (23.7%) who received lidocaine and 222 (21.0%) who received placebo. The absolute risk difference for the primary comparison of amiodarone versus placebo was 3.2 percentage points (95% confidence interval [CI], −0.4 to 7.0; P=0.08). For the secondary comparison of lidocaine versus placebo, the risk difference was 2.6 percent-

Table 2. Event Characteristics and Treatments Received in the Per-Protocol Population.*

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Overall P Value
Time from initial call to first dose of trial drug in patients with non–EMS-witnessed cardiac arrest — min	19.3±7.1	19.3±7.6	19.3±7.3	0.81
Time from cardiac arrest to first dose of trial drug in patients with EMS-witnessed arrest — min	11.7±5.8	12.1±6.6	12.1±6.6	0.91
Time from initial call to first dose of epinephrine — min	16.1±6.5	15.8±6.1	16.2±6.4	0.35
Trial drug given through intraosseous access — no./total no. (%)†	212/974 (21.8)	220/991 (22.2)	229/1054 (21.7)	0.96
Syringes of trial drug given — no./total no. (%)				<0.001
3 syringes	621/967 (64.2)	594/981 (60.6)	758/1051 (72.1)	
2 syringes	327/967 (33.8)	368/981 (37.5)	273/1051 (26.0)	
1 syringe	19/967 (2.0)	19/981 (1.9)	20/1051 (1.9)	
Prehospital advanced airway management successful — no. (%)	819 (84.1)	854 (86.0)	893 (84.3)	0.45
CPR-process measures in first 10 min after pad placement				
Pre-shock pause — sec‡	10.2±10.7	10.2±9.0	10.2±9.0	0.99
Post-shock pause — sec‡	5.1±6.7	5.2±10.6	5.8±10.0	0.19
Compression rate/min	110.3±10.7	110.7±10.5	110.7±10.9	0.63
Compression depth — mm	50.9±9.2	51.5±10.5	52.0±9.8	0.22
CPR fraction§	0.83±0.09	0.84±0.09	0.83±0.10	0.58
No. of EMS shocks — median (IQR)	5 (3–7)	5 (3–7)	6 (4–9)	<0.001
No. of shocks before first dose of trial drug — median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.73
No. of EMS shocks after first dose of trial drug — median (IQR)	2 (1–4)	2 (1–3)	3 (1–6)	<0.001
Prehospital drugs administered				
Epinephrine — no. (%)	961 (98.7)	981 (98.8)	1046 (98.8)	1.00
Vasopressin — no./total no. (%)	67/974 (6.9)	60/992 (6.0)	55/1059 (5.2)	0.28
Bicarbonate — no. (%)	271 (27.8)	258 (26.0)	308 (29.1)	0.29
Atropine — no./total no. (%)	52/974 (5.3)	43/992 (4.3)	33/1059 (3.1)	0.04
Beta-blocker — no./total no. (%)	6/974 (0.6)	2/992 (0.2)	10/1059 (0.9)	0.09
Open-label lidocaine — no./total no. (%)	4/974 (0.4)	6/992 (0.6)	13/1059 (1.2)	0.08
Open-label amiodarone — no./total no. (%)	7/974 (0.7)	13/992 (1.3)	15/1059 (1.4)	0.29
Procainamide — no./total no. (%)	67/974 (6.9)	57/992 (5.7)	92/1059 (8.7)	0.03
Magnesium — no./total no. (%)	78/974 (8.0)	68/992 (6.8)	119/1059 (11.2)	0.001
Coenrollment in CPR trial — no./total no. (%)¶				0.95
Received continuous chest compressions	234/973 (24.0)	249/993 (25.1)	253/1059 (23.9)	
Received interrupted chest compressions	264/973 (27.1)	259/993 (26.1)	290/1059 (27.4)	
Were not enrolled in CPR trial	475/973 (48.8)	485/993 (48.8)	516/1059 (48.7)	

* IQR denotes interquartile range.
† Data are based on the initial dose of the trial drug.
‡ Shown is the mean pause with respect to the first three shocks.
§ The CPR fraction is the proportion of each minute in which compressions are given.
¶ In this randomized trial involving patients with out-of-hospital cardiac arrest, one group received continuous chest compressions with positive-pressure ventilation, and the other group received compressions that were interrupted for ventilations at a ratio of 30 compressions to two ventilations.

Table 3. Outcomes According to Trial Group in the Per-Protocol Population.*

Outcome	Amiodarone (N = 974)	Lidocaine (N = 993)	Placebo (N = 1059)	Amiodarone vs. Placebo		Lidocaine vs. Placebo		Amiodarone vs. Lidocaine	
				Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
				percentage points		*percentage points*		*percentage points*	
Primary outcome: survival to discharge — no./total no. (%)†	237/970 (24.4)	233/985 (23.7)	222/1056 (21.0)	3.2 (–0.4 to 7.0)	0.08	2.6 (–1.0 to 6.3)	0.16	0.7 (–3.2 to 4.7)	0.70
Secondary outcome: modified Rankin score ≤3 — no./total no. (%)‡	182/967 (18.8)	172/984 (17.5)	175/1055 (16.6)	2.2 (–1.1 to 5.6)	0.19	0.9 (–2.4 to 4.2)	0.59	1.3 (–2.1 to 4.8)	0.44
Mechanistic (exploratory) outcomes									
Return of spontaneous circulation at ED arrival — no./total no. (%)	350/974 (35.9)	396/992 (39.9)	366/1059 (34.6)	1.4 (–2.8 to 5.5)	0.52	5.4 (1.2 to 9.5)	0.01	–4.0 (–8.3 to 0.3)	0.07
Admitted to hospital — no. (%)	445 (45.7)	467 (47.0)	420 (39.7)	6.0 (1.7 to 10.3)	0.01	7.4 (3.1 to 11.6)	<0.001	–1.3 (–5.7 to 3.1)	0.55
Modified Rankin score in all patients‡	5.0±1.9	5.1±1.8	5.2±1.8	–0.14 (–0.30 to 0.02)	0.09	–0.06 (–0.22 to 0.10)	0.45	–0.08 (–0.24 to 0.08)	0.34
Modified Rankin score in survivors‡	2.0±2.7	2.2±2.7	2.0±2.6						
Distribution of modified Rankin scores — no./total no. (%)‡									
0	60/966 (6.2)	49/981 (5.0)	55/1053 (5.2)						
1	47/966 (4.9)	37/981 (3.8)	39/1053 (3.7)						
2	41/966 (4.2)	46/981 (4.7)	40/1053 (3.8)						
3	34/966 (3.5)	37/981 (3.8)	41/1053 (3.9)						
4	31/966 (3.2)	36/981 (3.7)	27/1053 (2.6)						
5	21/966 (2.2)	24/981 (2.4)	18/1053 (1.7)						
6	732/966 (75.8)	752/981 (76.7)	833/1053 (79.1)						

* CI denotes confidence interval, and ED emergency department.
† The difference and 95% CI were adjusted for sequential monitoring.
‡ Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death). A score of 3 or less indicates the ability to conduct daily activities independently or with minimal assistance.

Table 4. Adverse Events in the Per-Protocol Population.*

Event	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	Overall P Value
	number (percent)			
Thrombophlebitis within 24 hr	1 (0.1)	3 (0.3)	2 (0.2)	0.61
Anaphylaxis within 24 hr	0	0	0	NA
Clinical seizure activity within 24 hr	31 (3.2)	51 (5.1)	39 (3.7)	0.07
Temporary cardiac pacing within 24 hr†	48 (4.9)	32 (3.2)	29 (2.7)	0.02
Complications of intravenous or intraosseous access within 24 hr	2 (0.2)	0	2 (0.2)	0.37
Any nonfatal serious adverse event within 24 hr‡§	11 (1.1)	12 (1.2)	4 (0.4)	0.09
Any nonfatal adverse event within 24 hr§	81 (8.3)	84 (8.5)	69 (6.5)	0.18
Death before hospital discharge	733 (75.3)	752 (75.7)	834 (78.8)	0.16
Any adverse event within 24 hr or death before hospital discharge	763 (78.3)	775 (78.0)	851 (80.4)	0.20

* Adverse events were defined as drug-related if they occurred in the first 24 hours after randomization. NA denotes not applicable.
† Excluded were patients in whom pacing was initiated before the trial drug was given.
‡ Nonfatal serious adverse events were defined as events that were life-threatening or potentially resulting in prolonged hospitalization or disability, as designated by a trial site, excluding death.
§ Shown is the total number of patients (some patients may have had >1 event).

age points (95% CI, –1.0 to 6.3; P=0.16), and for the secondary comparison of amiodarone versus lidocaine, it was 0.7 percentage points (95% CI, –3.2 to 4.7; P=0.70) (Table 3). Rates of survival with favorable neurologic status (the secondary outcome) were similar in the amiodarone group (182 patients [18.8%]), lidocaine group (172 [17.5%]), and placebo group (175 [16.6%]). The risk difference for the secondary outcome for amiodarone versus placebo was 2.2 percentage points (95% CI, –1.1 to 5.6; P=0.19); for lidocaine versus placebo, 0.9 percentage points (95% CI, –2.4 to 4.2; P=0.59); and for amiodarone versus lidocaine, 1.3 percentage points (95% CI, –2.1 to 4.8; P=0.44).

SUBGROUPS

There was heterogeneity of treatment effect with respect to whether or not the out-of-hospital cardiac arrest was witnessed (P=0.05 for interaction); active drugs were associated with a higher rate of survival to hospital discharge than the rate with placebo among patients with witnessed out-of-hospital cardiac arrest (Table S2 in the Supplementary Appendix). Among 1934 patients with bystander-witnessed arrest, the survival rate was higher with amiodarone (27.7%) or lidocaine (27.8%) than with placebo (22.7%). This absolute risk difference was significant for amiodarone versus placebo (5.0 percentage points; 95% CI, 0.3 to 9.7; P=0.04) and for lidocaine versus placebo (5.2 percentage points; 95% CI, 0.5 to 9.9; P=0.03), but did not differ significantly between amiodarone and lidocaine (–0.1 percentage points; 95% CI, –5.1 to 4.9; P=0.97). The survival rate was also higher among amiodarone recipients than placebo recipients with EMS-witnessed arrest, a risk difference of 21.9 percentage points (95% CI, 5.8 to 38.0; P=0.01). Conversely, among 839 patients in whom out-of-hospital cardiac arrest was unwitnessed, survival did not differ significantly between trial groups. No other significant interaction with treatment was found in other prespecified subgroups.

MECHANISTIC OUTCOMES

After randomization, placebo recipients were more likely to require an additional dose of blinded trial drug than recipients of amiodarone or lidocaine, and they received a greater number of subsequent shocks and other rhythm-control medications (Table 2). More lidocaine recipients than placebo recipients had sustained return of spontaneous circulation on hospital arrival (Table 3). Patients were more likely to survive to hospital admission after receipt of amiodarone

or lidocaine than after receipt of placebo. Fewer recipients of amiodarone or lidocaine than of placebo required CPR during hospitalization (Table S3 in the Supplementary Appendix). Use of open-label antiarrhythmic drugs (particularly open-label amiodarone) during the first 24 hours of hospitalization was also less common in the amiodarone group than in the lidocaine or placebo groups.

ADVERSE EVENTS

In the per-protocol population, the overall frequency of prespecified drug-related adverse events did not differ significantly among patients who received amiodarone, lidocaine, or placebo, nor did serious adverse events (Table 4, and Table S4 in the Supplementary Appendix). There was a greater need for temporary cardiac pacing after receipt of amiodarone (4.9%) than after receipt of lidocaine (3.2%) or placebo (2.7%).

INTENTION-TO-TREAT POPULATION

Patients enrolled in the intention-to-treat population had balanced baseline characteristics across trial groups (Table S5 in the Supplementary Appendix). There were no significant differences between the trial groups in the rates of the primary and secondary outcomes (Table S6 in the Supplementary Appendix). There were also no significant differences between the trial groups in the rates of drug-related adverse events or serious adverse events (Tables S7 and S8 in the Supplementary Appendix).

DISCUSSION

In this randomized, double-blind, placebo-controlled, prehospital trial, we found that treatment with amiodarone or lidocaine did not result in a significantly higher rate of survival to hospital discharge or favorable neurologic outcome at discharge than the rate with placebo after out-of-hospital cardiac arrest caused by shock-refractory initial ventricular fibrillation or pulseless ventricular tachycardia. There were also no significant differences in these outcomes between amiodarone and lidocaine.

Two previous small, randomized trials showed significantly higher rates of return of spontaneous circulation and hospital admission with amiodarone than with placebo or lidocaine after shock-refractory out-of-hospital cardiac arrest.[7,8] The current trial, which was larger and performed in the context of well-executed CPR, showed similar benefits with respect to short-term outcomes, but with both drugs. The time to treatment with these drugs was typically late across all the trials, averaging 19 minutes from the initial call to EMS in this trial and 21 to 25 minutes in the others.[7,8] Such delays may attenuate the effectiveness of antiarrhythmic interventions as patients progress to the metabolic phase of out-of-hospital cardiac arrest, when cellular injury and physiological derangements may be irreversible despite restored circulation.[24]

Our results could be interpreted in several ways. First, antiarrhythmic drugs may simply be ineffective in this population because they lack antiarrhythmic or restorative effects on circulation. This explanation seems unlikely, given that both amiodarone and lidocaine facilitated termination of ongoing or recurrent ventricular fibrillation or pulseless ventricular tachycardia with fewer shocks than placebo, were associated with higher rates of hospital admission, and resulted in a lesser need for CPR or antiarrhythmic therapies during hospitalization, which could even be taken as potential mechanisms for improved survival. Drug-related adverse events could also have mitigated survival. This too seems unlikely, because no significant between-group differences were observed in the frequency of adverse events. Conversely, because hospital care was not standardized, treatment imbalances between trial groups might have attenuated the survival benefit from amiodarone or lidocaine. However, the trial was randomized and blinded throughout, and the frequency of coronary catheterization, therapeutic hypothermia, and withdrawal of life-sustaining treatments did not differ significantly across trial groups.

The effectiveness of active treatment could also depend on physiological conditions, timing, and patient characteristics. We observed an interaction of treatment with the witnessed status of out-of-hospital cardiac arrest, which is often taken as a surrogate for early recognition of cardiac arrest, a short interval between the patient's collapse from cardiac arrest and the initiation of treatment, and a greater likelihood of therapeutic responsiveness. Though prespecified, this subgroup analysis was performed in the context of an insignificant difference for the overall analysis, and the P value for heterogene-

ity in this subgroup analysis was not adjusted for the number of subgroup comparisons. Nonetheless, the suggestion that survival was improved by drug treatment in patients with witnessed out-of-hospital cardiac arrest, without evidence of harm in those with unwitnessed arrest, merits thoughtful consideration.

Finally, the point estimates of the survival rates in the placebo group and the amiodarone group differed less than anticipated when the trial was designed, which suggests that the trial may have been underpowered. If amiodarone has a true treatment effect of 3 percentage points, approximately 9000 patients across the three trial groups would be needed to establish this difference in outcome with 90% power. Though seemingly small, a confirmed overall difference of 3 percentage points in survival with drug therapy would mean that 1800 additional lives could be saved each year in North America alone after out-of-hospital cardiac arrest.

Several limitations of this trial should be considered. Selection bias could have influenced trial enrollment. However, reasons for nonenrollment were systematically tracked, and questionable instances of exclusion were numerically small. The trial tested only one administration strategy without active-treatment crossover; other strategies may produce different results. Last, enrollment of patients whose condition at randomization afforded little or no chance of survival irrespective of treatment may have diluted the presence of a more robust treatment effect in others, resulting in a smaller overall benefit than had eligibility been more selective.[25]

In conclusion, in this randomized trial, we found that overall neither amiodarone nor lidocaine resulted in a significantly higher rate of survival to hospital discharge or favorable neurologic outcome than the rate with placebo among patients with out-of-hospital cardiac arrest due to initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.

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APPENDIX

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