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A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Concern about the use of epinephrine as a treatment for out-of-hospital cardiac arrest led the International Liaison Committee on Resuscitation to call for a placebo-controlled trial to determine whether the use of epinephrine is safe and effective in such patients.

METHODS

In a randomized, double-blind trial involving 8014 patients with out-of-hospital cardiac arrest in the United Kingdom, paramedics at five National Health Service ambulance services administered either parenteral epinephrine (4015 patients) or saline placebo (3999 patients), along with standard care. The primary outcome was the rate of survival at 30 days. Secondary outcomes included the rate of survival until hospital discharge with a favorable neurologic outcome, as indicated by a score of 3 or less on the modified Rankin scale (which ranges from 0 [no symptoms] to 6 [death]).

RESULTS

At 30 days, 130 patients (3.2%) in the epinephrine group and 94 (2.4%) in the placebo group were alive (unadjusted odds ratio for survival, 1.39; 95% confidence interval [CI], 1.06 to 1.82; P=0.02). There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (87 of 4007 patients [2.2%] vs. 74 of 3994 patients [1.9%]; unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61). At the time of hospital discharge, severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) had occurred in more of the survivors in the epinephrine group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]).

CONCLUSIONS

In adults with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was no significant between-group difference in the rate of a favorable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group. (Funded by the U.K. National Institute for Health Research and others; Current Controlled Trials number, ISRCTN73485024.)

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*A complete list of collaborators in the PARAMEDIC2 trial is provided in the Supplementary Appendix, available at NEJM.org.

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In attempting to reduce the rate of death and disability associated with cardiac arrest worldwide,[1,2] emergency medical workers have few effective treatments other than early initiation of cardiopulmonary resuscitation (CPR) and prompt defibrillation.[3] For more than 50 years, treatment strategies have included the use of various drugs, but there is limited evidence that such treatments are effective.[4]

Epinephrine (adrenaline) has potentially beneficial effects in cardiac arrest through the constriction of arterioles mediated by α-adrenergic receptors. Such constriction increases aortic diastolic pressure during CPR, thereby augmenting coronary blood flow and increasing the chance of a return of spontaneous circulation.[5] Potentially harmful effects on the heart are mediated through β-adrenergic stimulation, which causes dysrhythmias and increased myocardial oxygen demand and increases the risk of recurrent cardiac arrest.[6] In addition, α-adrenergic stimulation causes platelet activation, which promotes thrombosis[7] and impairs the microvascular blood flow in the cerebral cortex, which in turn increases the severity of cerebral ischemia during CPR and after a return of spontaneous circulation.[8]

Previous trials that have compared standard-dose epinephrine (1 mg) with high-dose epinephrine (5 to 10 mg), with epinephrine and vasopressin, or with placebo have not shown evidence of better outcomes.[9] Observational studies involving more than 500,000 patients have reported higher rates of return of spontaneous circulation but worse neurologic outcomes in patients who were treated with epinephrine.[10] The interpretation of these findings has been limited by conflicting results and the influence of unmeasured confounders. Thus, the International Liaison Committee on Resuscitation, a consortium of seven major organizations involved in the field of resuscitation worldwide, called for the initiation of a placebo-controlled trial to establish whether epinephrine is safe and effective as a treatment for cardiac arrest.[4,11] Subsequently, we initiated the PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest) trial to determine whether epinephrine is beneficial or harmful as a treatment for out-of-hospital cardiac arrest.[12]

Methods

Trial Design and Oversight

From December 2014 through October 2017, the multicenter, randomized, double-blind, placebo-controlled PARAMEDIC2 trial was conducted by five National Health Service ambulance services in the United Kingdom. The trial protocol (available with the full text of this article at NEJM.org) was developed by the investigators and has been published previously.[12] The South Central–Oxford C Research Ethics Committee and the Medicines and Healthcare Products Regulatory Authority approved the protocol. The trial was designed and conducted in accordance with Directive 2001/20/EC of the European Parliament and Council, which was transposed into legislation in the United Kingdom by the Medicines for Human Use (Clinical Trials) Regulations.

Because of the sudden and life-threatening nature of cardiac arrest, and in accordance with European legislation, the process of obtaining written informed consent was deferred until after the emergency had passed. We sought written informed consent to continue data collection after resuscitation from the patient or, if the patient lacked capacity, a legal representative. Additional details regarding the informed-consent process and patient and public involvement in the trial are provided in the Supplementary Appendix, available at NEJM.org.

The trial was funded by the Health Technology Assessment Programme of the National Institute for Health Research, with legal sponsorship provided by the University of Warwick. The funders had no role in the trial design, in the collection or analysis of the data, or in the writing of the manuscript. The Warwick Clinical Trials Unit undertook data management. The trial statisticians had full access to all the data and assume responsibility for the integrity of the data, the completeness and accuracy of the data and analysis, and the fidelity of the trial to the protocol.

Patient Population

Adult patients who had sustained an out-of-hospital cardiac arrest for which advanced life support was provided by trial-trained paramedics were eligible for inclusion. Criteria for exclusion were known or apparent pregnancy, an age of less than

16 years, cardiac arrest from anaphylaxis or asthma, or the administration of epinephrine before the arrival of the trial-trained paramedic. In one ambulance service, traumatic cardiac arrests were also excluded in accordance with local protocols.

RANDOMIZATION AND TREATMENT

Paramedic resuscitation protocols as outlined in the European Resuscitation Council Guidelines are described in the Supplementary Appendix.[13] If initial attempts at resuscitation (CPR and defibrillation) were unsuccessful, the patient was randomly assigned to receive either parenteral epinephrine or saline placebo by the opening of a trial pack containing either agent. Uniquely numbered but otherwise identical-appearing trial packs contained 10 prefilled syringes, with each syringe containing either 1 mg of epinephrine or 0.9% saline. Single doses of epinephrine or saline were administered by an intravenous or intraosseous route every 3 to 5 minutes. The programming team at the Warwick Clinical Trials Unit provided randomization with concealed assignment. A randomization sequence was computer-generated by the minimization method with an overall assignment ratio of 1:1.

Ambulance services entered data into a secure electronic portal. Data definitions followed the Utstein recommendations.[14] Data regarding the quality of the CPR results were obtained with the use of defibrillator downloads when available (Physiocontrol). Treatments were continued until a sustained pulse was achieved, resuscitation was discontinued, or care was handed over to clinicians in the hospital. Hospital-based care was not specified in the trial protocol but was informed by national guidelines, which covered targeted temperature management, hemodynamic and ventilatory criteria, and prognostication, as described in the Supplementary Appendix.[15]

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the rate of survival at 30 days. The secondary outcomes were the rate of survival until hospital admission, the lengths of stay in the hospital and in the intensive care unit (ICU), the rates of survival at hospital discharge and at 3 months, and the neurologic outcomes at hospital discharge and at 3 months. We defined survival with a favorable neurologic outcome as a score of 3 or less on the modified Rankin scale (which ranges from 0 [no symptoms] to 6 [death]).[16] Outcomes were assessed by research paramedics, who were unaware of treatment assignments. We recorded serious adverse events (death, hospitalization, and disability) as trial outcomes. Other adverse events were reported directly to the trial office.

STATISTICAL ANALYSIS

We determined that the enrollment of 8000 patients would provide the best threshold to balance precision and practicality. With this target sample size, if the risk ratio for the epinephrine group was estimated to be 1.25, the corresponding 95% confidence interval would range from 1.07 to 1.46. A risk ratio of 1.25 corresponds to a rate of 30-day survival of 6.0% in the placebo group and 7.5% in the epinephrine group. Further information regarding the sample-size calculations is provided in the Supplementary Appendix.

The data and safety monitoring committee performed interim reviews every 3 months. We used the Lan–DeMets, O'Brien–Fleming, and Pocock alpha spending methods to determine the upper and lower stopping boundaries for the primary outcome, with no adjustment in the final analysis.

The primary analysis was performed without adjustment in the modified intention-to-treat population, which included all the patients who had undergone randomization and were confirmed to have received the assigned intervention. Trial data were summarized by the calculation of means and standard deviations for normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequency and percentage for categorical variables.

Survival outcomes were analyzed with the use of fixed-effect regression models with and without adjustment for age, sex, the interval between the emergency call and the ambulance arrival at the scene, the interval between the ambulance arrival and the administration of a trial agent, the cause of cardiac arrest, the initial cardiac rhythm, whether the cardiac arrest was witnessed, and whether CPR was performed by a bystander. The Hodges–Lehmann method was used to estimate median differences with 95% confidence intervals for length-of-stay outcomes. In cases in which the proportional odds assumption was violated in

modeling of the score on the modified Rankin scale, partial proportional odds models were used. Scores on the modified Rankin scale were also analyzed as a binary outcome (with scores of 0 to 3 classified as "good" and scores of 4 to 6 classified as "poor"). Unadjusted and adjusted odds ratios with 95% confidence intervals and mean differences with 95% confidence intervals were reported for categorical and continuous outcomes, respectively. The number needed to treat and its 95% confidence interval were calculated for survival at 30 days. To aid in interpretation, we included a Bayesian analysis for the primary outcome and for survival with a favorable neurologic outcome.

Prespecified subgroup analyses included the patient's age, cause of cardiac arrest, initial cardiac rhythm, whether the cardiac arrest was witnessed, whether CPR was performed by a bystander, interval between the emergency call and ambulance arrival at the scene, interval between ambulance arrival and the trial-agent administration, and the interval between the emergency call and trial-agent administration. A P value for interaction was reported in each analysis. Post hoc sensitivity analyses (which incorporated best-case and worst-case scenarios and multiple imputation) were conducted for survival at 30 days, survival at hospital discharge, and survival with a good neurologic outcome at discharge. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and RStan.

RESULTS

PATIENTS AND INTERVENTIONS

Of 10,623 patients who were screened for eligibility, 8103 (76.3%) were eligible, and trial packs were opened. The reasons for trial exclusion are shown in Figure 1. Between the opening of the trial packs and administration of epinephrine or placebo, further information indicated that 87 patients (1.1%) were ineligible to participate in the trial. Another 2 patients had unknown trial-group assignments because of missing trial-pack numbers. The remaining 8014 patients were assigned to the epinephrine group (4015 patients) or to the placebo group (3999 patients).

The characteristics of patients were well balanced at baseline (Table 1), and concurrent treatments were similar (Table S1 in the Supplementary Appendix). The key intervals in providing service (e.g., between the emergency call and ambulance arrival) were also similar in the two groups (Table 2). In the two groups, the median time from the emergency call to ambulance arrival was 6.6 minutes (interquartile range, 4.2 to 9.7), with a further 13.8 minutes (interquartile range, 9.5 to 19.0) elapsing until administration of the trial agent. The proportion of patients who had a return of spontaneous circulation during the prehospital resuscitation phase was higher in the epinephrine group than in the placebo group (36.3% vs. 11.7%), as was the proportion who were transported to the hospital (50.8% vs. 30.7%). The course of events for all the patients from initial enrollment to in-hospital death or hospital discharge is shown in Figure S1 in the Supplementary Appendix.

PRIMARY AND SECONDARY OUTCOMES

Data for the primary outcome were available for 4012 patients (99.9%) in the epinephrine group and 3995 patients (99.9%) in the placebo group. In the epinephrine group, 130 patients (3.2%) were alive at 30 days, as compared with 94 patients (2.4%) in the placebo group (unadjusted odds ratio for survival, 1.39; 95% confidence interval [CI], 1.06 to 1.82; P=0.02) (Table 3). The number of patients who would need to be treated with epinephrine to prevent one death at 30 days was 112 (95% CI, 63 to 500). The Kaplan–Meier curves for survival at day 30 are shown in Figure S2 in the Supplementary Appendix.

There was no evidence of a significant difference between the epinephrine group and the placebo group in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (87 of 4007 patients [2.2%] and 74 of 3994 patients [1.9%], respectively; unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61) (Table 3, and Table S2 in the Supplementary Appendix). Severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) was more common among survivors in the epinephrine group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]) (Fig. 2). The results with respect to survival at 3 months and neurologic outcomes at 3 months were similar in the two groups (Table 3, and Table S3 in the Supplementary Appendix).

In a Bayesian analysis that used an assumption of no benefit from adrenaline, the posterior probability that the absolute rate of survival was

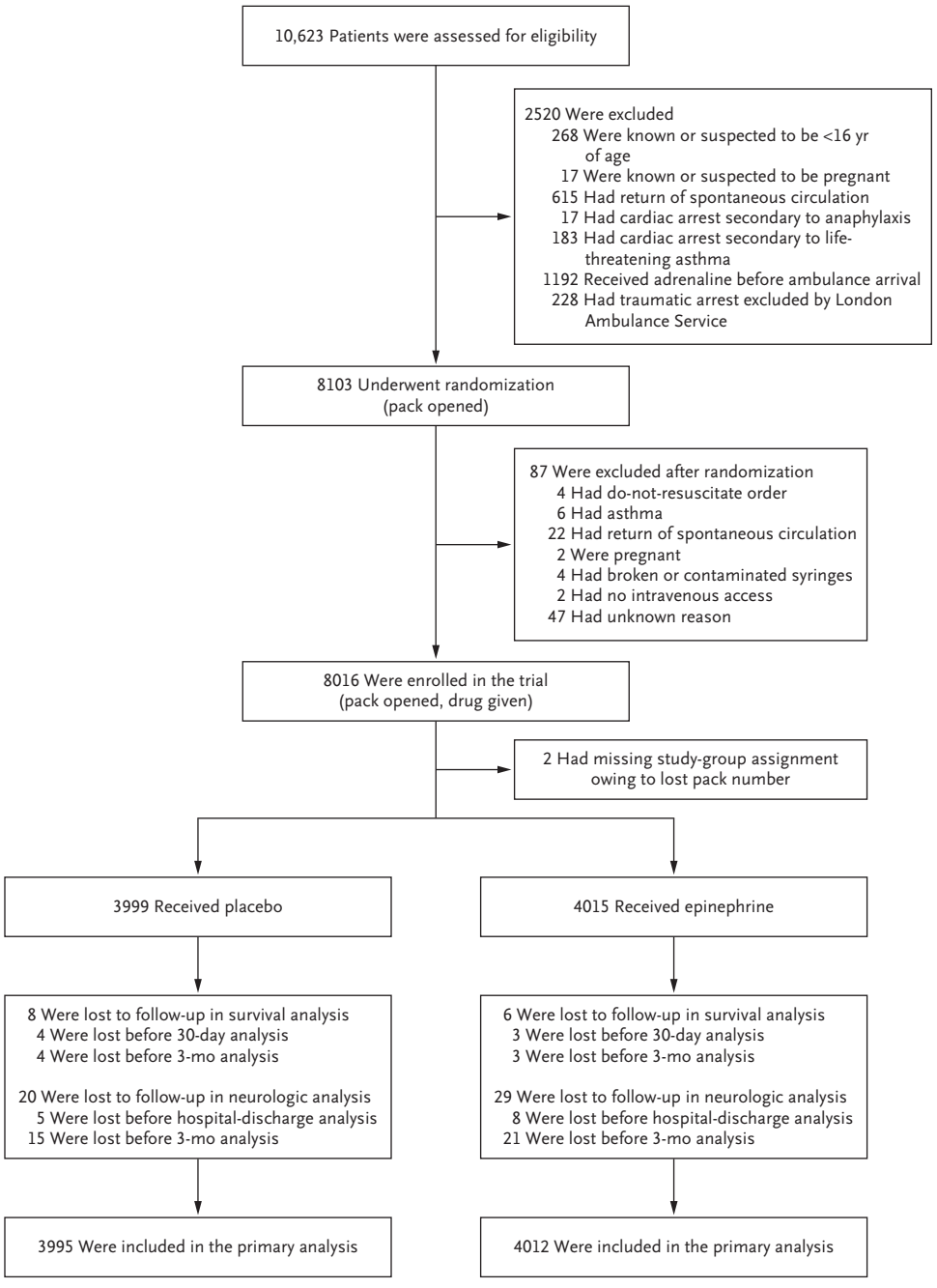

Figure 1. Enrollment and Outcomes.

Among the patients who were lost to follow-up before the primary outcome analysis, 6 (3 in the epinephrine group and 3 in the placebo group) declined to provide consent for the continuation of data collection after resuscitation. Hospital discharge may have occurred at any point from randomization to a time after the 3-month follow-up period.

at least 1 percentage point higher in the epinephrine group than in the placebo group was 37% (Fig. S3 in the Supplementary Appendix). The probability that the absolute survival rate was at least 2 percentage points higher was 0.2%. With respect to the rate of survival with a favorable neurologic

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Epinephrine (N=4015)	Placebo (N=3999)
Mean age ±SD — yr	69.7±16.6	69.8±16.4
Sex — no. (%)		
Male	2609 (65.0)	2584 (64.6)
Female	1406 (35.0)	1415 (35.4)
Initial cardiac rhythm — no. (%)		
Shockable	770 (19.2)	748 (18.7)
Ventricular fibrillation	716 (17.8)	684 (17.1)
Pulseless ventricular tachycardia	25 (0.6)	20 (0.5)
Not otherwise identified with AED	29 (0.7)	44 (1.1)
Nonshockable	3149 (78.4)	3181 (79.5)
Asystole	2135 (53.2)	2194 (54.9)
Pulseless electrical activity	955 (23.8)	937 (23.4)
Bradycardia	20 (0.5)	16 (0.4)
Not otherwise identified with AED	39 (1.0)	34 (0.9)
Undetermined		
Not identified	4 (0.1)	1 (<0.1)
Missing data	92 (2.3)	69 (1.7)
Cause of cardiac arrest — no. (%)		
Medical cause	3656 (91.1)	3691 (92.3)
Traumatic cause	66 (1.6)	57 (1.4)
Drowning	10 (0.2)	10 (0.3)
Drug overdose	74 (1.8)	72 (1.8)
Electrocution	0	1 (<0.1)
Asphyxia	117 (2.9)	81 (2.0)
Not identified	1 (<0.1)	2 (0.1)
Missing data	91 (2.3)	85 (2.1)
Witness of cardiac arrest — no. (%)		
None	1498 (37.3)	1505 (37.6)
Paramedic	452 (11.3)	470 (11.8)
Bystander	2013 (50.1)	1967 (49.2)
Not identified	1 (<0.1)	1 (<0.1)
Missing data	51 (1.3)	56 (1.4)
CPR performed — no. (%)		
By bystander	2382 (59.3)	2349 (58.7)
By paramedic during witnessed event	452 (11.3)	470 (11.8)
Not identified	1 (<0.1)	1 (<0.1)
Missing data	69 (1.7)	84 (2.1)

* There were no significant between-group differences in any of the baseline characteristics. AED denotes automated external defibrillator, and CPR cardiopulmonary resuscitation.

outcome at hospital discharge, the probabilities that the rate was at least 1 or 2 percentage points higher with epinephrine were 1.9% and 0%, respectively (Fig. S4 in the Supplementary Appendix).

The other secondary outcomes are presented in Table 3. Among the patients who were admitted to the hospital, there were no significant between-group differences in the length of stay in the hospital or ICU (Figs. S5 and S6 in the Supplementary Appendix). There was no statistical evidence of a modification in treatment effect by such factors as the patient's age, whether the cardiac arrest was witnessed, whether CPR was performed by a bystander, initial cardiac rhythm, or response time or time to trial-agent administration (Fig. S7 in the Supplementary Appendix).

Table 2. Intervals between Key Events and Initial Response to Resuscitation.*

Variable	Epinephrine (N = 4015)	Placebo (N = 3999)
Interval between emergency call and ambulance arrival at scene		
No. of patients in analysis	4015	3999
Median (IQR) — min†	6.7 (4.3–9.7)	6.6 (4.2–9.6)
Interval between emergency call and administration of trial agent		
No. of patients in analysis	3975	3949
Median (IQR) — min†	21.5 (16.0–27.3)	21.1 (16.1–27.4)
Interval between ambulance arrival at scene and departure		
No. of patients in analysis	2039	1226
Mean — min	50.1±21.8	44.5±18.3
Interval between ambulance departure from scene and hospital arrival		
No. of patients in analysis	2038	1225
Mean — min	12.9±9.8	12.4±8.9
Median interval between initiation of advanced life support and cessation (IQR) — min	47.5 (35.1–64.0)	43.1 (33.5–56.1)
Return of spontaneous circulation — no. (%)		
Yes	1457 (36.3)	468 (11.7)
No	2518 (62.7)	3492 (87.3)
Missing data	40 (1.0)	39 (1.0)
Transportation of patient to hospital — no. (%)		
Yes	2041 (50.8)	1227 (30.7)
No	1974 (49.2)	2772 (69.3)
Declaration of death by emergency department staff — no. (%)		
Yes	988 (24.6)	689 (17.2)
No	614 (15.3)	290 (7.3)
Not applicable because not transported	1974 (49.2)	2772 (69.3)
Missing data	439 (10.9)	248 (6.2)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Among cardiac arrests that were witnessed by paramedics, the interval between the emergency call and the cardiac event was considered to be 0 minutes.

Sensitivity analyses that incorporated the best-case and worst-case scenarios and multiple imputation confirmed the findings of the main trial results (Table S3 in the Supplementary Appendix). No additional serious adverse events were reported.

DISCUSSION

In this trial, the use of epinephrine during resuscitation for out-of-hospital cardiac arrest resulted in a significantly higher rate of survival at 30 days than the use of placebo. Patients in the epinephrine group had a higher rate of return of spontaneous circulation, a higher frequency of transport to the hospital, and a higher rate of treatment in the ICU. However, although the rate of survival was slightly better, the trial did not show evidence of a between-group difference in the rate of survival with a favorable neurologic outcome. This result was explained by a higher proportion of patients who survived with severe neurologic disability in the epinephrine group.

A meta-analysis of six randomized trials involving 6174 patients in which investigators compared standard-dose epinephrine (1 mg) with high-dose epinephrine (5 to 10 mg) showed better

Table 3. Primary and Secondary Outcomes.*

Outcome	Epinephrine	Placebo	Odds Ratio (95% CI)†	
			Unadjusted	Adjusted
Primary outcome				
Survival at 30 days — no./total no. (%)‡	130/4012 (3.2)	94/3995 (2.4)	1.39 (1.06–1.82)	1.47 (1.09–1.97)
Secondary outcomes				
Survival until hospital admission — no./total no. (%)§	947/3973 (23.8)	319/3982 (8.0)	3.59 (3.14–4.12)	3.83 (3.30–4.43)
Median length of stay in ICU (IQR) — days				
Patients who survived	7.5 (3.0–15.0)	7.0 (3.5–12.5)	NA	NA
Patients who died¶	2.0 (1.0–5.0)	3.0 (1.0–5.0)	NA	NA
Median length of hospital stay (IQR)				
Patients who survived	21.0 (10.0–41.0)	20.0 (9.0–38.0)	NA	NA
Patients who died‖	0	0	NA	NA
Survival until hospital discharge — no./total no. (%)	128/4009 (3.2)	91/3995 (2.3)	1.41 (1.08–1.86)	1.48 (1.10–2.00)
Favorable neurologic outcome at hospital discharge — no./total no. (%)	87/4007 (2.2)	74/3994 (1.9)	1.18 (0.86–1.61)	1.19 (0.85–1.68)
Survival at 3 mo — no./total no. (%)	121/4009 (3.0)	86/3991 (2.2)	1.41 (1.07–1.87)	1.47 (1.08–2.00)
Favorable neurologic outcome at 3 mo — no./total no. (%)	82/3986 (2.1)	63/3979 (1.6)	1.31 (0.94–1.82)	1.39 (0.97–2.01)

* ICU denotes intensive care unit, and NA not applicable.
† The odds ratio is for the epinephrine group as compared with the placebo group. Odds ratios were adjusted for patients' age, sex, interval between emergency call and ambulance arrival at scene, interval between ambulance arrival at scene and administration of the trial agent, initial cardiac rhythm, cause of cardiac arrest, whether the cardiac arrest was witnessed, and whether CPR was performed by a bystander.
‡ P=0.02 for the between-group comparison in the primary analysis.
§ Survival until hospital admission was defined as a sustained return of spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital (also defined as "survived event").
¶ Among the patients who died, the length of stay in the ICU is for all the patients who were admitted to and died in the ICU.
‖ Among the patients who died, the length of stay in the hospital is for all the patients who died before hospital discharge.

rates of return of spontaneous circulation and hospital admission with the high-dose regimen but no significant between-group difference in the rates of survival until hospital discharge or survival with a favorable neurologic outcome.[9] These data, combined with evidence of greater myocardial dysfunction after a return of spontaneous circulation with high-dose epinephrine, led to international recommendations against the use of high-dose epinephrine in 2000.[17] In the Prehospital Adrenaline for Cardiac Arrest (PACA) trial comparing standard-dose epinephrine with placebo,[18] the result was inconclusive, since only 10% of the intended patients were recruited and information regarding treatment assignment was unavailable for 10% of the patients who underwent randomization.

The benefit of epinephrine for survival that we found in our trial should be considered in comparison with other treatments in the chain of survival.[19] The number of patients who would need to be treated with epinephrine to prevent one death after cardiac arrest was 112, as compared with early recognition of cardiac arrest (number needed to treat, 11),[20] CPR performed by a bystander (number needed to treat, 15),[21] and early defibrillation (number needed to treat, 5).[22]

The reasons that the use of epinephrine did not improve neurologic outcome in this trial are uncertain. One explanation is that although epinephrine increases macroscopic cerebral blood flow, it paradoxically impairs cerebral microvascular blood flow and thus has the potential to worsen brain injury after a return of spontaneous circulation.[8,23] An alternative explanation is that the brain is more sensitive to ischemia and reper-

fusion injury and less able to functionally recover after restoration of circulation than are the heart and other organs.[24,25] No specific therapies other than targeted temperature management have been shown to reduce the severity of brain injury after cardiac arrest.[15]

Clinical decision making must balance the burdens and benefits of treatment. The burdens of treatment are high in cardiac arrest, since resuscitation is an invasive procedure with substantial risks of complications.[26] If resuscitation is initially successful, most patients require continuation of life-sustaining therapies in the ICU for several days.[27] Treatment is withdrawn in one third of patients, and a further third of patients die,[27] predominantly from the consequences of severe brain injury.[28] In such patients, the benefits of epinephrine that were identified in our trial are small, since they would result in 1 extra survivor for every 112 patients treated. This number is less than the minimal clinically important difference that has been defined in previous studies.[29,30] Among the survivors, almost twice the number in the epinephrine group as in the placebo group had severe neurologic impairment.

Our work with patients and the public before starting the trial (as summarized in the Supplementary Appendix) identified survival with a favorable neurologic outcome to be a higher priority than survival alone. The Core Outcome Set for Cardiac Arrest (COSCA) was developed by patients and clinicians[16]; neurologic outcome and health-related quality of life were prioritized along with survival as the most important outcomes. Patients may be less willing to accept burdensome treatments if the chances of recovery are small or the risk of survival with an impaired neurologic outcome is high.[31,32]

Our trial has several limitations. According to the protocol, paramedics administered intermittent 1-mg boluses of epinephrine, whereas other strategies (e.g., different doses or dosing intervals) might have produced different results. Earlier administration of epinephrine could also have influenced the results, although data concerning the benefit of early drug administration are conflicting.[33-35] We did not collect information regarding the patients' baseline neurologic status, although the number of patients who had impaired neurologic function before cardiac arrest is likely to have been very small and balanced between the two groups. The original protocol anticipated a higher survival rate than the one that was observed. This result probably reflects the overall poor prognosis among patients who do not have a response to initial CPR and defibrillation and is similar to findings in other studies.[7,36] Information about the quality of CPR was limited to the first 5 minutes of cardiac arrest and involved fewer than 5% of the enrolled patients. Although national guidelines inform the care that patients receive after resuscitation, we did not mandate or monitor for adherence with specific protocols.

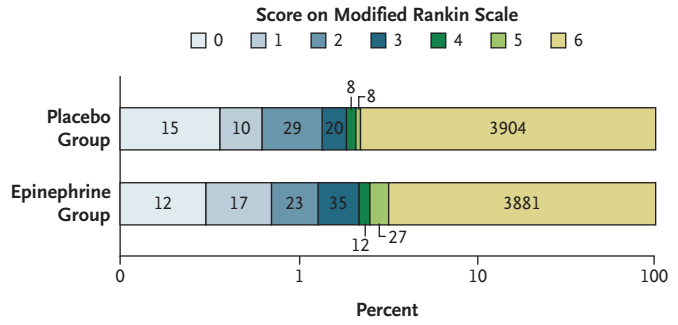

Figure 2. Survival with a Favorable Neurologic Outcome at Hospital Discharge.

Shown is the distribution of patients' scores on the modified Rankin scale, which ranges from 0 (no symptoms) to 6 (death). Survival until hospital discharge with a favorable neurologic outcome, as indicated by a score of 3 or less on the modified Rankin scale, occurred in 87 of 4007 patients (2.2%) in the epinephrine group and in 74 of 3994 patients (1.9%) in the placebo group. However, severe neurologic impairment (a score of 4 or 5) was more frequent in the epinephrine group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]). The patients who died before hospital discharge are indicated by a score of 6 on the scale. The data are presented on a $\log_{10}$ scale of the percentages of patients in each group.

In conclusion, in this randomized trial involving patients with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of survival at 30 days than the use of placebo, but there was no significant between-group difference in the rate of a favorable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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