

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 thrombosis⁷ 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

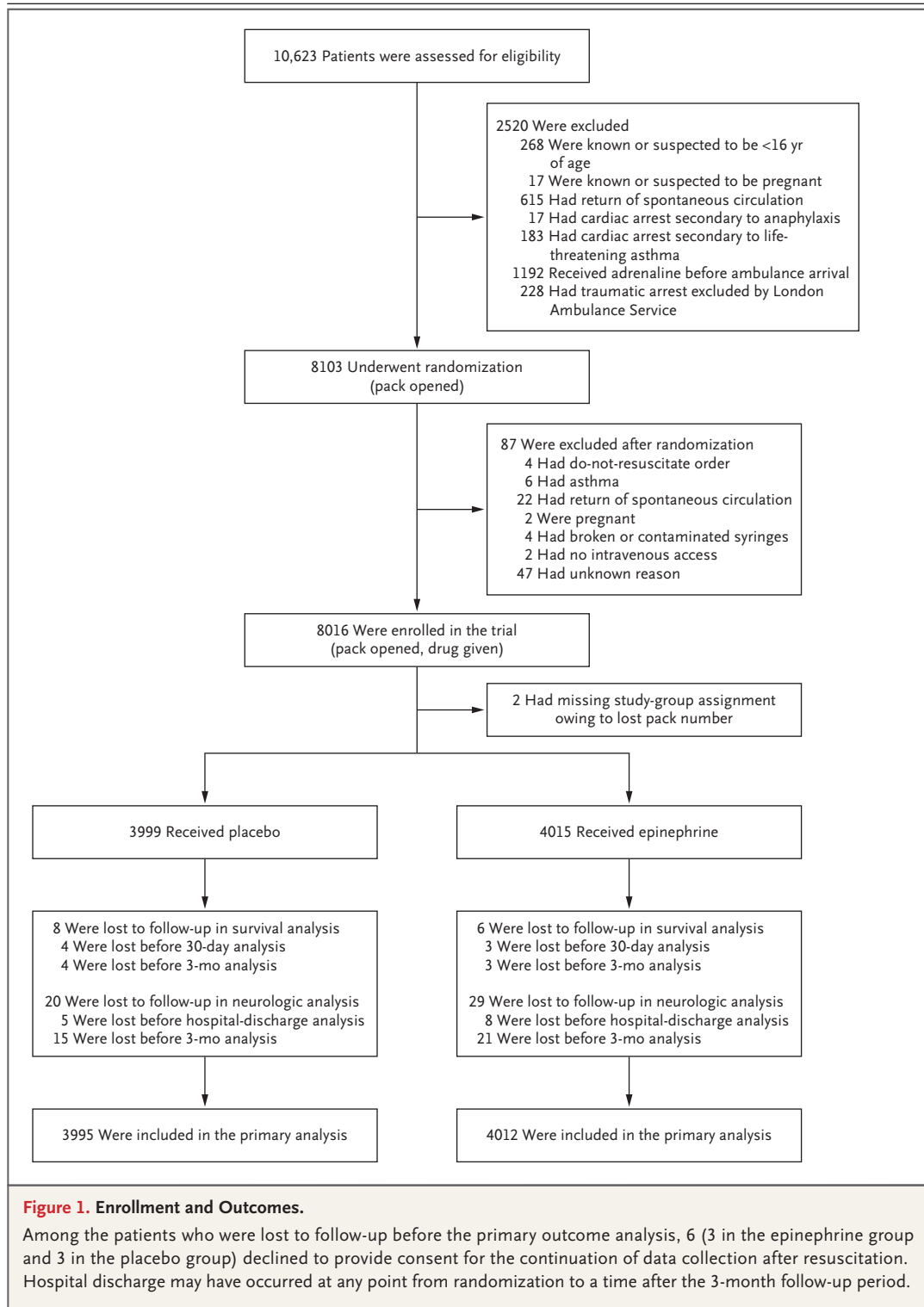
service (e.g., between the emergency call and ambulance arrival) were also similar in the two groups (Table 2). In the two groups, the median time from the emergency call to ambulance arrival was 6.6 minutes (interquartile range, 4.2 to 9.7), with a further 13.8 minutes (interquartile range, 9.5 to 19.0) 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



at least 1 percentage point higher in the epinephrine group than in the placebo group was 37% (Fig. S3 in the Supplementary Appendix). The prob-

ability 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 \pm SD — yr	69.7 \pm 16.6	69.8 \pm 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)
Nons shockable	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 sponta-

neous 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 Pre-hospital 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 clinicians¹⁶; 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

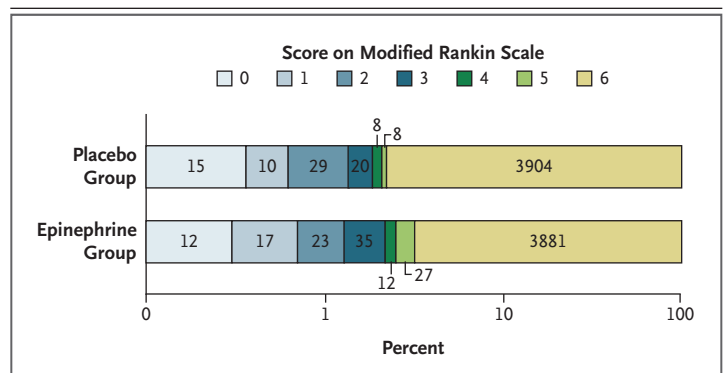


Figure 2. Survival with a Favorable Neurologic Outcome at Hospital Discharge.

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.

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.

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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REFERENCES

- Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics — 2018 update: a report from the American Heart Association. *Circulation* 2018;137(12):e67-e492.
- Gräsner JT, Lefering R, Koster RW, et al. Corrigendum to “EuReCa ONE — 27 Nations, ONE Europe, ONE Registry A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe” [Resuscitation 105 (2016) 188-195]. *Resuscitation* 2016;109:145-6.
- Perkins GD, Travers AH, Berg RA, et al. Adult basic life support and automated external defibrillation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2015;95:e43-e69.
- Soar J, Callaway CW, Aibiki M, et al. Advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2015;95:e71-e120.
- Perkins GD, Cottrell P, Gates S. Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest? *BMJ* 2014;348:g2435.
- Callaway CW. Epinephrine for cardiac arrest. *Curr Opin Cardiol* 2013;28:36-42.
- Larsson PT, Wallén NH, Egberg N, Hjemdahl P. Alpha-adrenoceptor blockade by phentolamine inhibits adrenaline-induced platelet activation in vivo without affecting resting measurements. *Clin Sci (Lond)* 1992;82:369-76.
- Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med* 2009;37:1408-15.
- Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. *Resuscitation* 2014;85:732-40.
- Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? *J Crit Care* 2015;30:1376-81.
- Kleinman ME, Perkins GD, Bhanji F, et al. ILCOR scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care: a consensus statement. *Resuscitation* 2018;127:132-46.
- Perkins GD, Quinn T, Deakin CD, et al. Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): trial protocol. *Resuscitation* 2016;108:75-81.
- Monsieurs KG, Nolan JP, Bossaert LL, et al. European Resuscitation Council guidelines for resuscitation 2015. 1. Executive summary. *Resuscitation* 2015;95:1-80.
- Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry templates for out-of-hospital cardiac arrest. *Resuscitation* 2014;96:328-40.
- Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council guidelines for resuscitation 2015. *Resuscitation* 2015;95:202-22.
- Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Resuscitation* 2018;127:147-63.
- Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. 6. Advanced cardiovascular life support: section 6: pharmacology II: agents to optimize cardiac output and blood pressure. *Circulation* 2000;102:Suppl:1-129-1-135.
- Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation* 2011;82:1138-43.
- Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. *Lancet* 2018;391:980-8.
- Berdowski J, Beekhuis F, Zwiderman AH, Tijssen JG, Koster RW. Importance of the first link: description and recognition of an out-of-hospital cardiac arrest in an emergency call. *Circulation* 2009;119:2096-102.
- Hasselqvist-Ax I, Riva G, Herlitz J, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2015;372:2307-15.
- Kitamura T, Kiyohara K, Sakai T, et al. Public-access defibrillation and out-of-hospital cardiac arrest in Japan. *N Engl J Med* 2016;375:1649-59.
- Deakin CD, Yang J, Nguyen R, et al. Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: a prospective cohort study. *Resuscitation* 2016;109:138-44.
- Casas AI, Geuss E, Kleikers PWM, et al. NOX4-dependent neuronal autotoxicity and BBB breakdown explain the superior sensitivity of the brain to ischemic damage. *Proc Natl Acad Sci U S A* 2017;114:12315-20.
- Busl KM, Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. *NeuroRehabilitation* 2010;26:5-13.
- Hoke RS, Chamberlain D. Skeletal chest injuries secondary to cardiopulmonary resuscitation. *Resuscitation* 2004;63:327-38.
- Nolan JP, Ferrando P, Soar J, et al. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. *Crit Care* 2016;20:219.
- Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004;30:2126-8.

29. Nichol G, Brown SP, Perkins GD, et al. What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey. *Resuscitation* 2016;107:115-20.
30. Morrison LJ, Visentin LM, Kiss A, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2006;355:478-87.
31. Fried TR, Bradley EH, Towle VR. Assessment of patient preferences: integrating treatments and outcomes. *J Gerontol B Psychol Sci Soc Sci* 2002;57:S348-S354.
32. Hanger HC, Fogarty B, Wilkinson TJ, Sainsbury R. Stroke patients' views on stroke outcomes: death versus disability. *Clin Rehabil* 2000;14:417-24.
33. Angelos MG, Butke RL, Panchal AR, et al. Cardiovascular response to epinephrine varies with increasing duration of cardiac arrest. *Resuscitation* 2008;77:101-10.
34. Kudenchuk PJ. Early epinephrine in out-of-hospital cardiac arrest: is sooner better than none at all? *Resuscitation* 2013;84:861-2.
35. Andersen LW, Kurth T, Chase M, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis. *BMJ* 2016;353:i1577.
36. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008;359:21-30.

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EDITORIALS



Testing Epinephrine for Out-of-Hospital Cardiac Arrest

Clifton W. Callaway, M.D., Ph.D., and Michael W. Donnino, M.D.

The administration of epinephrine has been part of the resuscitation of patients with cardiac arrest since the 1960s. The rationale for the use of epinephrine includes evidence from studies in animals and from clinical trials in humans that increasing vasomotor tone during circulatory collapse and chest compressions improves coronary perfusion pressure, shunts more blood to the heart, and increases the likelihood of restoring spontaneous circulation.¹ However, epinephrine also decreases microvascular blood flow in some organs, increases cardiac dysrhythmias, and increases myocardial oxygen demand during critical ischemia.² These deleterious effects can result in long-term organ dysfunction or hypoperfusion of the heart and brain. Despite decades of epinephrine use, data on the benefit of the drug comes primarily from conflicting observational studies with a high risk of bias.

The PARAMEDIC2 trial³ reported now in the *Journal* provides the largest set of randomized data on epinephrine use in out-of-hospital cardiac arrest so far. In this trial, patients with cardiac arrest were randomly assigned to receive parenteral epinephrine or saline, with trial-group assignments concealed from both the treating teams and the outcome assessors. All but 7 of 8014 patients were included in the primary analysis at 30 days. Groups were well balanced with respect to most baseline characteristics. These features greatly reduced the risk of bias, and this pragmatic trial provides the most rigorous data on patient-centered outcomes with respect to epinephrine to date.

Patients who received epinephrine had a higher rate of 30-day survival than those who

received placebo (adjusted odds ratio, 1.47; 95% confidence interval [CI], 1.09 to 1.97), but the overall survival rate in this trial was disappointingly small (3.2% and 2.4%, respectively). There was no clear improvement in functional recovery among the survivors in the epinephrine group as compared with the placebo group (adjusted odds ratio, 1.19; 95% CI, 0.85 to 1.68), and the proportion of survivors with severe neurologic impairment was actually higher in the epinephrine group (31.0% vs. 17.8%), which raised concern that some of the additional survivors did not have a desirable quality of life. Epinephrine robustly improved a return of spontaneous circulation (36.3% vs. 11.7%), a finding that was consistent with the results of observational studies and with a previous smaller randomized trial (adjusted odds ratio, 3.4; 95% CI, 2.0 to 5.6).⁴ The small magnitude of the higher rate of survival and absence of functional recovery will prompt debate about whether epinephrine is truly beneficial for improving meaningful clinical outcomes.

One major limitation of the trial is that the protocol neither controlled nor measured in-hospital treatments. The most common cause of in-hospital death is iatrogenic limitation of life support, which may result in the death of potentially viable patients.⁵ Conversely, treating teams may work harder to treat or reduce injury in the sickest patients in the intensive care unit, thereby minimizing differences created by prehospital therapy. Measuring or regimenting hospital care is both difficult and expensive, but some trials have shown that it is possible.⁶ The success of those trials supports the inclusion of such data or protocols as a standard part of any trial involv-

ing patients who are critically ill, even though this idea is contrary to the current preference for cheaper pragmatic designs.

The benefits of the use of epinephrine during cardiac arrest may depend on timing, initial electrocardiographic rhythm, and dose. With regard to timing, paramedics administered the trial agent a median of 21 minutes after the emergency call, which is slightly longer than the interval in other out-of-hospital trials.⁷ This timing is dramatically different for in-hospital cardiac arrest, where epinephrine is administered a median of 3 minutes after resuscitation starts,⁸ and the results should not be extrapolated to this setting. Effects of very early epinephrine administration in out-of-hospital arrest remain unknown and may be impossible to test with current delivery systems.

Epinephrine increased 30-day survival in patients with nonshockable rhythms (adjusted odds ratio, 2.15; 95% CI, 1.13 to 4.09) but had unclear benefit in those with shockable rhythms (adjusted odds ratio, 1.33; 95% CI, 0.95 to 1.86). Rapid epinephrine use is associated with better outcomes in patients with nonshockable rhythms during in-hospital cardiac arrest,⁸ but early administration immediately after the first rescue shock is associated with worse outcomes in patients with shockable rhythms.⁹ Shockable rhythms are more likely to occur in patients with cardiac or cardiovascular causes of arrest, which epinephrine may exacerbate. The data support the principle that drug administration should not compete with or delay defibrillation and that epinephrine may have different effects in patients with different electrocardiographic rhythms.

The mean (\pm SD) total dose of epinephrine in this trial was 4.9 ± 2.5 mg. Higher epinephrine doses produce much smaller incremental increases in return of spontaneous circulation and do not improve long-term survival.¹⁰ These results do not encourage studying higher epinephrine doses but suggest that it would be desirable to have more data on whether smaller doses of epinephrine could promote a return of spontaneous circulation with fewer adverse effects.

Despite having a powerful effect on restoring

spontaneous circulation after out-of-hospital cardiac arrest, epinephrine produced only a small absolute increase in survival with no increase in favorable functional recovery as compared with placebo. We now must ponder whether additional treatments after a return of spontaneous circulation could improve functional recovery, whether drug use should differ on the basis of cardiac rhythm, and whether lower doses of epinephrine would be superior to higher doses among patients with out-of-hospital cardiac arrest.

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

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1. Paradis NA, Martin GB, Rosenberg J, et al. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. *JAMA* 1991;265:1139-44.
2. Ristagno G, Sun S, Tang W, Castillo C, Weil MH. Effects of epinephrine and vasopressin on cerebral microcirculatory flows during and after cardiopulmonary resuscitation. *Crit Care Med* 2007;35:2145-9.
3. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018; 379:711-21.
4. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation* 2011;82:1138-43.
5. Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. *Resuscitation* 2016; 102:127-35.
6. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197-206.
7. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med* 2016;374:1711-22.
8. Donnino MW, Saliccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ* 2014;348:g3028.
9. Andersen LW, Kurth T, Chase M, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis. *BMJ* 2016;353:i1577.
10. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. *Resuscitation* 2014;85:732-40.

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