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


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 (3.3%) 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.)
The trial was funded by the National Institute for Health Research HTA Programme (12/27).

The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.
30,000 people are treated for cardiac arrest in the community each year in the UK.

For every minute that passes without treatment, the chances of survival decrease by 10%.

Less than 1 in 10 (10%) patients survive to go home from hospital after a cardiac arrest. This number is even lower for patients where initial treatments do not work.
Where initial treatments do not work, adrenaline is sometimes given as a treatment. Adrenaline has been used for over 50 years, but it has never been properly tested to see whether it is beneficial or harmful.
Rationale for the trial

Epinephrine for resuscitation from cardiac arrest: A double-edged sword?*

Sutton, Robert M., MD; Berg, Robert A., MD; Helfaer, Mark A., MD

Critical Care Medicine: April 2009 - Volume 37 - Issue 4 - p 1518-1520
### Clinical Potpourri

**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 2014*

Rohit Seth Loomba, MD, Karan Nijhawan, BS, Saurabh Aggarwal, MD, Rohit Romesh Arora,

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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Epinephrine</th>
<th>No epinephrine</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Events</td>
<td>Total</td>
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<td>Total</td>
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<tr>
<td>Olausveengen et al</td>
<td>106</td>
<td>367</td>
<td>115</td>
</tr>
</tbody>
</table>

**Total (95% CI):**

- **Epinephrine:** 41754
- **No epinephrine:** 598504
- **Weight:** 100.0%
- **Odds Ratio:** 2.84 [2.28, 3.54]

**Total events:**

- **Epinephrine:** 8229
- **No epinephrine:** 32857

**Heterogeneity:**

- Tau² = 0.08; Chi² = 219.28, df = 8 (P < .00001); I² = 96%
- Test for overall effect: Z = 9.29 (P < .00001)

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Restart the heart
Clinical Potpourri

Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest really worth it?  

Rohit Seth Loomba, MDa, b, Karan Nijhawan, BSb, Saurabh Aggarwal, MDb, Rohit Romesh Arora, c

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<td>Fukuda et al</td>
<td>51</td>
<td>376</td>
<td>17.2%</td>
<td>1.12 [0.83, 1.51]</td>
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<td>718</td>
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<td>1.42 [1.34, 1.51]</td>
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<td>995</td>
<td>10906</td>
<td>21.8%</td>
<td>1.15 [1.07, 1.23]</td>
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<td>137</td>
<td>1013</td>
<td>19.2%</td>
<td>1.15 [0.92, 1.43]</td>
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<td>Holmberg et al</td>
<td>156</td>
<td>4566</td>
<td>19.9%</td>
<td>0.53 [0.44, 0.64]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>45055</strong></td>
<td><strong>602715</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.03 [0.79, 1.34]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 102.02, df = 4 (P < .00001); I² = 96%
Test for overall effect: Z = 0.19 (P = .85)

1 month survival
Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest really worth it?  

Rohit Seth Loomba, MD, Karan Nijhawan, BS, Saurabh Aggarwal, MD, Rohit Romesh Arora,

Survival with good brain function
Mechanism 1: Impaired microvascular blood flow

Adrenaline arm

Saline (placebo) arm

Courtesy of Giuseppe Ristagno,
Part 8: Advanced life support
2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations

Vasopressors

Despite the continued widespread use of adrenaline and increased use of vasopressin during resuscitation in some countries, there is no placebo-controlled study that shows that the routine use of any vasopressor during human cardiac arrest increases survival to hospital discharge.

Knowledge gaps
Placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed.
Dear Professor Perkins,

Re Proposed Trial of Adrenaline for Cardiac Arrest

The College of Paramedics namely supports and welcomes the proposed randomised placebo-controlled trial of adrenaline in cardiac arrest. We not only entirely ethical but also necessary - and, indeed, urgent. The College will support the trial in any way that it reasonably can.

Yours sincerely,

Andy Newton
Chairman
College of Paramedics

The need for a randomised, controlled trial of adrenaline versus placebo in out-of-hospital cardiac arrest

Recent reviews of published evidence on the use of vasopressors in the treatment of out-of-hospital cardiac arrest (OHCA) have concluded that administration of adrenaline increases the rate of short-term survival, as measured by return of spontaneous circulation but may cause worse long-term patient outcomes.

The treatment recommendation on the use of vasopressors in cardiac arrest, published in 2010 by the International Liaison Committee on Resuscitation (ILCOR), stated: "Although there is evidence that vasopressors (adrenaline or vasopressin) may improve return of spontaneous circulation (ROSC) and short-term survival, there is insufficient evidence to suggest that vasopressors improve survival to discharge and neurological outcome. The insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment adult cardiac arrest. Given the observed benefit in short-term outcomes, the use of adrenergic vasopressor may be considered in adult cardiac arrest."

ILCOR stated that placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed.

The current Resuscitation Council (UK) Guidelines and the UK Ambulance Services Care Practice Guidelines include the recommendation that adrenaline is given routinely every minutes during the management of cardiac arrest. The long-term safety and effectiveness of this recommendation is unknown. The Resuscitation Council (UK) supports the need to randomised, controlled trial of adrenaline versus placebo in adults sustaining out-of-hospital cardiac arrest. In the context of such a trial, comparing adrenaline with placebo is considered ethically justified.

Researchers to test cardiac arrest treatment in first ever trial

The practice of giving heart patients an adrenaline shot following a cardiac arrest will be put to the test by researchers for the very first time.

Patients whose hearts have stopped beating are routinely given the drug by paramedics to help resuscitate the heart on the assumption that it improves the chances of survival.

But doctors are concerned that this practice may be causing severe brain damage in survivors of cardiac arrest.

Researchers at Warwick University and the University of Surrey will be conducting a study to establish whether or not the use of adrenaline causes more harm than good.

In the trial, 8,000 patients who have a cardiac arrest in Wales, the West Midlands, North East, the south coast and London will be given either an adrenaline injection or an injection of a placebo.

Neither the patients nor the paramedics administering the injection will know which the patient has received.

An advertising drive will take place before the trial begins in autumn in which patients will be given the opportunity to opt out of the study.

Our Medical Director, Professor Peter Weil, said: "It is important to remember that whilst adrenaline is routinely used to treat a cardiac arrest, we don't actually know whether this is a safe and effective practice. The concern is that it could be doing patients more harm than good. The only way to answer this crucially important question is to do a well-designed clinical trial."

"It is always difficult to conduct trials in situations where people are too ill to give their consent. But there are well established ethical guidelines for undertaking such studies. What is unacceptable is to continue giving a treatment that could be doing more harm than good."

"Only by undertaking studies of this kind can we be sure that patients are receiving the highest possible standard of care and have the best chance of a good outcome."
Public consultation

In a community survey, 86% agreed on the need for the trial, 8% neutral, 6% disagreed

75% willing to participate

95% of survey respondents thought that long-term survival without brain damage was more important than survival alone or restarting the heart
Ethical considerations

• When a person suffers cardiac arrest, loss of consciousness occurs within seconds.

• The attending paramedics must focus on immediate treatments that are known to be effective. This will give the patient the best chance of survival.

• It is therefore not possible to seek consent from the patient or their next of kin in the emergency situation.
Ethical considerations

• Sought the views of:
  – Patients and public
  – Doctors, nurses and paramedics
  – Research Ethics Committee
  – Health Research Authority

• Complied with legal and regulatory frameworks
Ethical approach

- Approval for deferred consent from the Research Ethics Committee
- Shared information about the trial with the public
- Provided a mechanism for a person to indicate they did not want to participate in the trial
Ethical approach

• Informed the patient (if possible) or their next of kin as soon as possible after the emergency had passed about their involvement in the trial, and seek their consent to continue

• After careful consideration and consultation with patients, the public and the Research Ethics Committee, it was decided not to write to the next of kin of those who did not survive. Information was made available and a process put in place to respond to enquires from relatives
Objective

• Primary objective
  – The primary objective of this trial is to determine the clinical effectiveness of adrenaline in the treatment of OHCA measured as primary outcome: 30 day survival.

• Secondary objective
  – Secondary objectives of the trial are to evaluate the effects of adrenaline on survival, cognitive and neurological outcomes of survivors and to establish the cost-effectiveness of using adrenaline.
Eligibility Criteria

• **Inclusion Criteria:**
  – Cardiac arrest in out of hospital environment
  AND
  – Advanced life support initiated and / or continued by ambulance service clinician

• **Exclusion criteria at the time of arrest will be:**
  – Known or apparent pregnancy
  – Known or apparently aged under 16 years
  – Cardiac arrest caused by anaphylaxis or life threatening asthma
  – Adrenaline given prior to arrival of ambulance service clinician
**Treatment of shockable rhythms (VF/VT)**

1. Confirm cardiac arrest — check for signs of life and normal breathing, and if trained to do so check for breathing and a pulse simultaneously.
2. Call resuscitation team.
3. Perform uninterrupted chest compressions while applying self-adhesive defibrillation/monitoring pads — one below the right clavicle and the other in the V6 position in the midaxillary line.
4. Plan actions before pausing CPR for rhythm analysis and communicate these to the team.
5. Stop chest compressions; confirm VF/pVT from the ECG. This pause in chest compressions should be brief and no longer than 5 seconds.
6. Resume chest compressions immediately; warn all rescuers other than the individual performing the chest compressions to “stand clear” and remove any oxygen delivery device as appropriate.
7. The designated person selects the appropriate energy on the defibrillator and presses the charge button. Choose an energy setting of at least 150 J for the first shock, the same or a higher energy for subsequent shocks, or follow the manufacturer’s guidance for the particular defibrillator. If unsure of the correct energy level for a defibrillator choose the highest available energy.
8. Ensure that the rescuer giving the compressions is the only person touching the patient.
9. Once the defibrillator is charged and the safety check is complete, tell the rescuer doing the chest compressions to “stand clear”; when clear, give the shock.
10. After shock delivery immediately restart CPR using a ratio of 30:2, starting with chest compressions. Do not pause to reassess the rhythm or feel for a pulse. The total pause in chest compressions should be brief and no longer than 5 seconds.
11. Continue CPR for 2 min; the team leader prepares the team for the next pause in CPR.
12. Pause briefly to check the monitor.
13. If VF/pVT, repeat steps 5–12 above and deliver a second shock.
14. If VF/pVT persists, repeat steps 6–8 above and deliver a third shock. Resume chest compressions immediately. Give adrenaline 1 mg IV and amiodarone 300 mg IV while performing a further 2 min CPR. Withhold adrenaline if there are signs of return of spontaneous circulation (ROSC) during CPR.
15. Repeat this 2 min CPR — rhythm/pulse check — defibrillation sequence if VF/pVT persists.
16. Give further adrenaline 1 mg IV after alternate shocks (i.e. approximately every 3–5 min).
**Treatment of PEA and asystole**

1. Start CPR 30:2
   - **Give adrenaline 1 mg IV as soon as intravascular access is achieved**
2. Return of spontaneous circulation:
   - **Continue CPR 30:2 until the airway is secured – then continue chest compressions without pausing during ventilation**
3. Recheck the rhythm after 2 min:
   - a. If electrical activity compatible with a pulse is seen, check for a pulse and/or signs of life
      - i. If a pulse and/or signs of life are present, start post-resuscitation care
      - ii. If no pulse and/or no signs of life are present (PEA or asystole):
         - 1. **Continue CPR**
         - 2. Recheck the rhythm after 2 min and proceed accordingly
         - 3. Give further adrenaline 1 mg IV every 3–5 min (during alternate 2-min loops of CPR)
   - b. If VF/pVT at rhythm check, change to shockable side of algorithm.
Randomisation

- Randomisation – opening drug pack

- Post randomization exclusions
  - ROSC
  - ROLE
  - Exclusion

- Drug administration
Outcomes

• **Primary outcome**
  – Survival to 30 days post randomisation

• **Secondary outcomes**
  – Survived event (sustained ROSC, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)
  – Survival to hospital discharge post randomisation
  – Neurological outcome (modified Rankin Scale (mRS)) at hospital discharge.
  – Hospital length of stay post randomisation
  – Intensive care length of stay post randomisation
  – Hospital free survival in 30 days post randomisation
  – ICU free survival in 30 days post randomisation
The study population

65% male

Average age 69 (years)

6 out of 10 people received CPR from bystanders or family members before the ambulance arrived.
50% witnessed by bystander
10% witnessed by paramedics
40% unwitnessed

20% initially shockable rhythms

90% medical cause of cardiac arrest
10,623 Patients were assessed for eligibility

2,520 Were excluded
  268 Were known or suspected to be <16 yr of age
  17 Were known or suspected to be pregnant
  615 Had return of spontaneous circulation
  17 Had cardiac arrest secondary to anaphylaxis
  133 Had cardiac arrest secondary to life-threatening asthma
  1,192 Received adrenaline before ambulance arrival
  228 Had traumatic arrest excluded by London Ambulance Service

8,103 Underwent randomization
  (pack opened)

8,016 Were enrolled in the trial
  (pack opened, drug given)

87 Were excluded after randomization
  4 Had do-not-resuscitate order
  6 Had asthma
  22 Had return of spontaneous circulation
  2 Were pregnant
  4 Had broken or contaminated syringes
  2 Had no intravenous access
  47 Had unknown reason

2 Had missing study-group assignment owing to lost pack number

3,999 Received placebo

8 Were lost to follow-up in survival analysis
  4 Were lost before 30-day analysis
  4 Were lost before 3-mo analysis

20 Were lost to follow-up in neurologic analysis
  5 Were lost before hospital-discharge analysis
  15 Were lost before 3-mo analysis

3,995 Were included in the primary analysis

4,015 Received epinephrine

6 Were lost to follow-up in survival analysis
  1 Were lost before 30-day analysis
  1 Were lost before 3-mo analysis

20 Were lost to follow-up in neurologic analysis
  1 Were lost before hospital-discharge analysis
  21 Were lost before 3-mo analysis

4,012 Were included in the primary analysis
10,623 Patients were assessed for eligibility

2520 Were excluded
   268 Were known or suspected to be <16 yr of age
   17 Were known or suspected to be pregnant
   615 Had return of spontaneous circulation
   17 Had cardiac arrest secondary to anaphylaxis
   183 Had cardiac arrest secondary to life-threatening asthma
   1192 Received adrenaline before ambulance arrival
   228 Had traumatic arrest excluded by London Ambulance Service

8103 Underwent randomization (pack opened)
8103 Underwent randomization (pack opened)

87 Were excluded after randomization
   4 Had do-not-resuscitate order
   6 Had asthma
   22 Had return of spontaneous circulation
   2 Were pregnant
   4 Had broken or contaminated syringes
   2 Had no intravenous access
   47 Had unknown reason

8016 Were enrolled in the trial (pack opened, drug given)
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3995 Were included in the primary analysis

4015 Received epinephrine

6 Were lost to follow-up in survival analysis
3 Were lost before 30-day analysis
3 Were lost before 3-mo analysis
29 Were lost to follow-up in neurologic analysis
8 Were lost before hospital-discharge analysis
21 Were lost before 3-mo analysis

4012 Were included in the primary analysis
Return of spontaneous circulation

Adrenaline
36.3%
n=1457/3975

Placebo
11.7%
n=468/3960
Admitted to hospital

Adrenaline

23.8%

n=947/3973

Placebo

8.0%

n=319/3982

Significantly more in adrenaline group

Odds ratio 3.83 (95% CI 3.30-4.43)
Survival to 30 days

Adrenaline

3.2%
n=130/4012

Placebo

2.4%
n=94/3995

Significantly more in adrenaline group

Odds ratio 1.39 (95% CI 1.06-1.82)
P=0.02
Favourable neurological outcome

Adrenaline: 2.2% (n=87/4007)

Placebo: 1.9% (n=74/3994)

No significant difference

Odds ratio: 1.18 (95% CI 0.86-1.61)
Poor neurological outcome

Adrenaline: 31.0% (n=39/126)

Placebo: 17.8% (n=16/90)

Significantly more with severe brain damage (mRS 4/5) in adrenaline group

Post-hoc comparison
Odds ratio: 0.51 (95% CI 0.27-0.96)
<table>
<thead>
<tr>
<th>Disability Level</th>
<th>Adrenaline (n=126)</th>
<th>No adrenaline (n=90)</th>
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<tr>
<td>No disability</td>
<td>9.5%</td>
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<tr>
<td>No significant disability</td>
<td>13.5%</td>
<td>11.1%</td>
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<td>Slight disability</td>
<td>18.3%</td>
<td>32.2%</td>
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<tr>
<td>Moderate disability</td>
<td>27.8%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Moderately severe disability</td>
<td>9.5%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Severe disability</td>
<td>21.4%</td>
<td>8.9%</td>
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Classified by modified Rankin Scale 100% 100%
<table>
<thead>
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<th>Subgroup</th>
<th>OR (95% CI)</th>
<th>p (interaction)</th>
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<tr>
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<td>2.62 (1.15, 5.96)</td>
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<td>1.35 (0.95, 1.93)</td>
<td>0.60</td>
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<td>1.26 (0.60, 2.62)</td>
<td>1.84 (0.82, 4.17)</td>
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<td>Initial rhythm</td>
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<td>Shockable rhythm</td>
<td>1.45 (1.02, 2.07)</td>
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<td>Non-medical cause</td>
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<tr>
<td>Age</td>
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<td></td>
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<tr>
<td>Mean age (69.7 years old)</td>
<td>1.30 (0.93, 1.82)</td>
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<td>Emergency call to ambulance arrival at scene</td>
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<td></td>
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<tr>
<td>Mean time (7.4 minutes)</td>
<td>1.46 (1.07, 2.00)</td>
<td>1.44 (1.04, 2.01)</td>
</tr>
<tr>
<td>Ambulance arrival at scene to administration of trial agent</td>
<td>1.46 (1.07, 2.00)</td>
<td>1.44 (1.04, 2.01)</td>
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<tr>
<td>Mean time (15.2 minutes)</td>
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<td>Emergency call to administration of trial agent</td>
<td>1.43 (1.01, 2.01)</td>
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Comparative effectiveness

- 10 times more effective
- 8 times more effective
- 20 times more effective
- Adrenaline
Reference (1)
Conclusion

Adrenaline can restart the heart but it’s no good for the brain

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.)
Implications for practice

Values and preferences of the communities we serve
Conversation and dialogue
PARAMEDIC2 collaborators

PARAMEDIC 2 collaborators: Matthew Cooke, Sarah Lamb, Andrew Carson (RIP), Ian Jacobs (RIP), Ed England, Nicola Brock, Claire Godfrey, Sarah Taylor, Michelle Thomson, Isabel Rodriguez-Bachiller, Claire King, Johanna Lazarus, Helen Werts, Joshua Golding, Alex Boda, Richard Whitfield, Laura Galligan, Rob Lovett, Jennifer Bradley, Gill Price, Andy Rosser, Garry Parcell, Mindy Jhamat, Josh Miller, Jenny Sears Brown, Alice Pretty, Emma Harris, Jenny Lumley-Holmes, Rhiannon Boldy, Prudence Horwood, Sonia Byers, Gary Shaw, Matt Limmer, Craig Wynne, Michelle Jackson, Emma Bell, Oliver Gupta, Rima Gupta, Susie Hennings, Jessica Horton, James Buck, Sarah Rumble, Hayley Johnson, Eva Kritzer, Chockalingham Muthiah, Adrian Willis, Claire Daffern, Louise Clarkson, Felix Achana, Nicola Cashin, Emma Skilton, Malvenia Richmond, Martin Underwood, Natalie Strickland, Sarah Duggan, Mike Smyth, Marie Stevens; Trial Steering Committee (Jon Nicholl, Neil Bayliss, Helen Snooks, Jonathan Benger, Robert Andrews, David Pitcher); Data Monitoring Committee (Marion Campbell, Jasmeet Soar, Kathy Rowan, Sue Mason).

We would also like to thank collaborators at all receiving hospitals, all staff involved at participating ambulance services and our patient and public partners.