

ORIGINAL ARTICLE

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

G.D. Perkins, C. Ji, C.D. Deakin, T. Quinn, J.P. Nolan, C. Scomparin, S. Regan, J. Long, A. Slowther, H. Pocock, J.J.M. Black, F. Moore, R.T. Fothergill, N. Rees, L. O'Shea, M. Docherty, I. Gunson, K. Han, K. Charlton, J. Finn, S. Petrou, N. Stallard, S. Gates, and R. Lall, for the PARAMEDIC2 Collaborators*

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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The Adrenaline Trial

Professor Tom Quinn FRCN FESC FAHA FACC
Kingston & St George's Joint Faculty, London, UK

On behalf of the PARAMEDIC-2 Collaborators



National Institute for Health Research WARWICK

improving the health and wealth of the nation through research

- 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.

Chain of survival

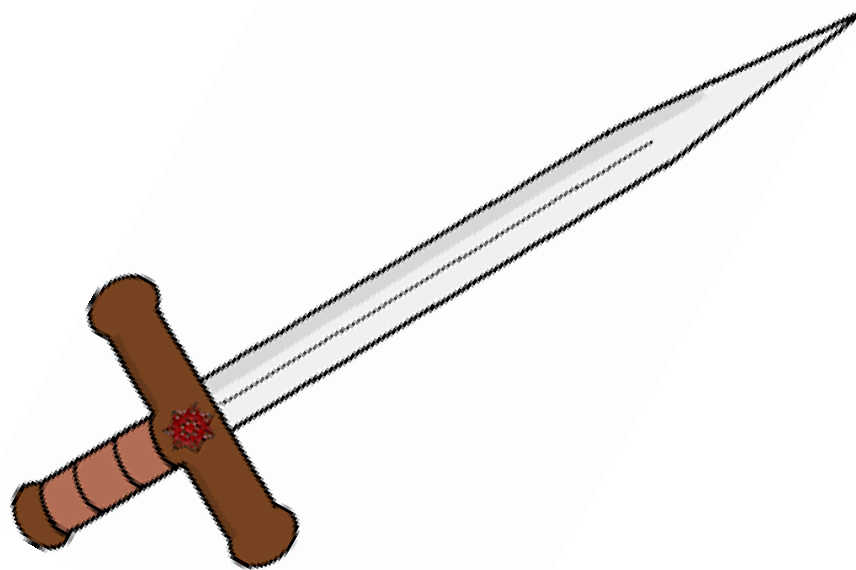
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Where initial treatments do not work, adrenaline is sometimes given as a treatment. Adrenaline has been used for over 50 years, but it has never been properly tested to see whether it is beneficial or harmful.

Rationale for the trial

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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](#)

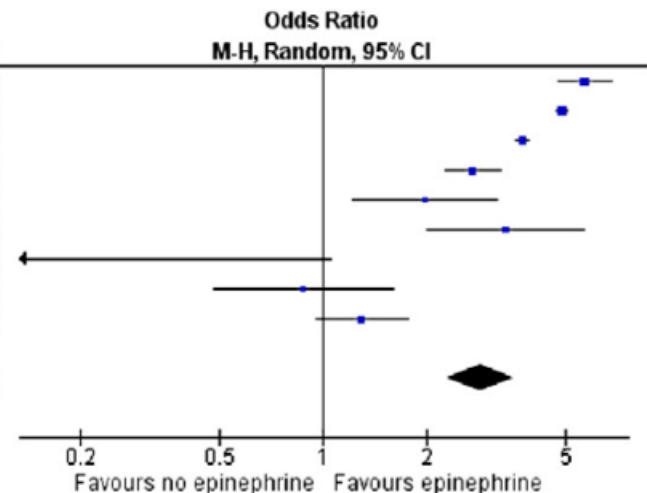
Clinical Potpourri

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^a,  , Karan Nijhawan, BS^b, Saurabh Aggarwal, MD^c, Rohit Romesh Arora,

Study or Subgroup	Epinephrine		No epinephrine		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Fukuda et al	235	770	453	6301	14.7%	5.67 [4.73, 6.79]
Goto et al	4563	23676	8674	185901	16.2%	4.88 [4.69, 5.07]
Hagihara et al	2786	15030	23042	402158	16.2%	3.74 [3.59, 3.91]
Hayashi et al	297	1013	287	2148	14.7%	2.69 [2.24, 3.23]
Herlitz et al	36	417	36	786	9.2%	1.97 [1.22, 3.18]
Jacobs et al	64	272	22	262	8.6%	3.36 [2.00, 5.64]
Kaji et al	121	160	24	24	0.6%	0.06 [0.00, 1.06]
Machida et al	21	49	204	443	7.4%	0.88 [0.48, 1.59]
Olasveengen et al	106	367	115	481	12.4%	1.29 [0.95, 1.76]
Total (95% CI)		41754		598504	100.0%	2.84 [2.28, 3.54]
Total events	8229		32857			
Heterogeneity: Tau ² = 0.08; Chi ² = 219.28, df = 8 (P < .00001); I ² = 96%						
Test for overall effect: Z = 9.29 (P < .00001)						





Restart the heart



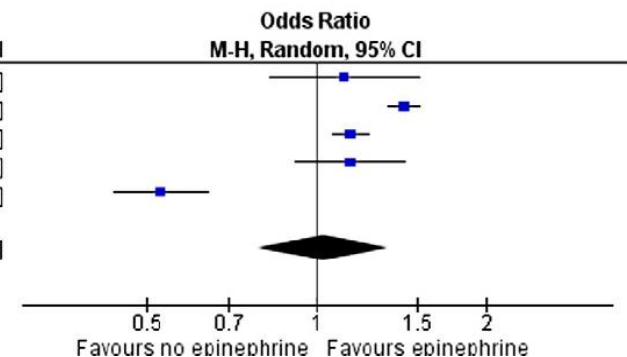
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Study or Subgroup	Epinephrine		No epinephrine		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Fukuda et al	51	770	376	6301	17.2%	1.12 [0.83, 1.51]
Goto et al	1277	23676	7157	185901	21.9%	1.42 [1.34, 1.51]
Hagihara et al	805	15030	18906	402158	21.8%	1.15 [1.07, 1.23]
Hayashi et al	137	1013	258	2148	19.2%	1.15 [0.92, 1.43]
Holmberg et al	156	4566	388	6207	19.9%	0.53 [0.44, 0.64]
Total (95% CI)		45055		602715	100.0%	1.03 [0.79, 1.34]
Total events	2426		27085			
Heterogeneity: Tau ² = 0.08; Chi ² = 102.02, df = 4 (P < .00001); I ² = 96%						
Test for overall effect: Z = 0.19 (P = .85)						





1 month survival

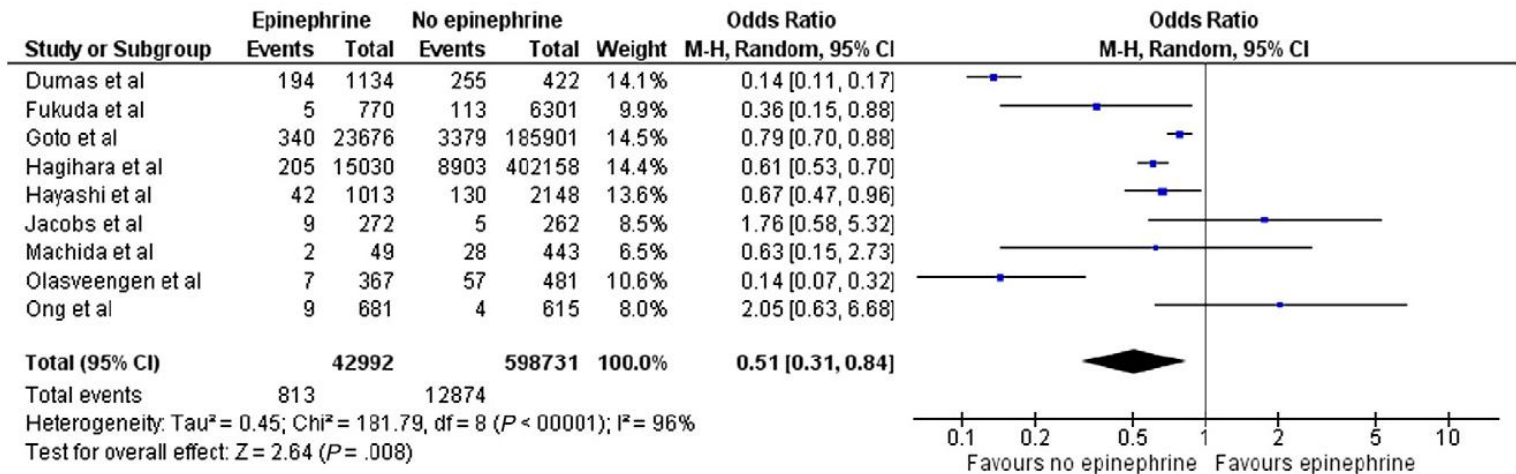


Clinical Potpourri

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

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Survival with good brain function



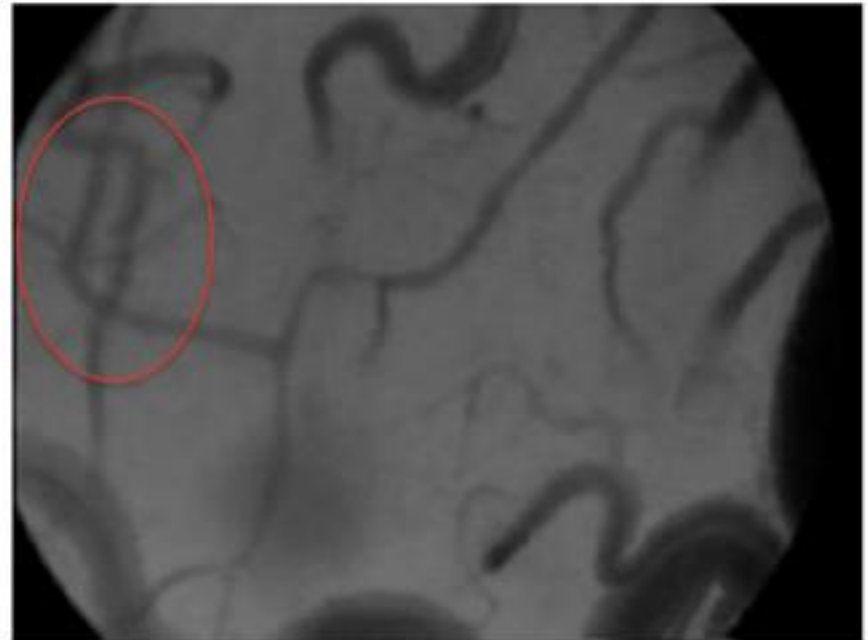
Mechanism 1: Impaired microvascular blood flow

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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^{ALS-D-023B}

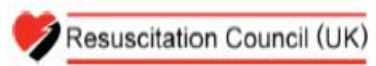
Despite the continued widespread use of adrenaline and increased use of vasopressin during resuscitation in some countries, there is no placebo-controlled study that shows that the routine use of any vasopressor during human cardiac arrest increases survival to hospital discharge.

Knowledge gaps

Placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed.



Prof. Gavin Perkins
Warwick Medical School
University of Warwick
Gibbett Hill
Warwick
Coventry CV4 7AL



Dear Professor Perkins,

Re Proposed Trial of Adrenaline for Cardiac Arrest

The College of Paramedics warmly supports and welcomes the proposed randomised placebo-controlled trial of adrenaline in cardiac arrest. We believe this is 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 outcomes¹⁻³.

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 of adult cardiac arrest. Given the observed benefit in short-term outcomes, the use of adrenaline or vasopressin may be considered in adult cardiac arrest⁴'.

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 Clinical Practice Guidelines include the recommendation that adrenaline is given routinely every 3-5 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 for a 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.



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Research: Our pioneering research
Community: Share your experience with others

Home Media News from the BHF Adrenaline trial

August 13, 2014

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 Weissberg, 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 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 a trial 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."



“What is unacceptable is to continue giving a treatment that could be doing more harm than good”

"Only by undertaking difficult 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."



ASSOCIATION OF
AMBULANCE
CHIEF EXECUTIVES

NAsMeD
National Ambulance Service Medical Directors

Public consultation

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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



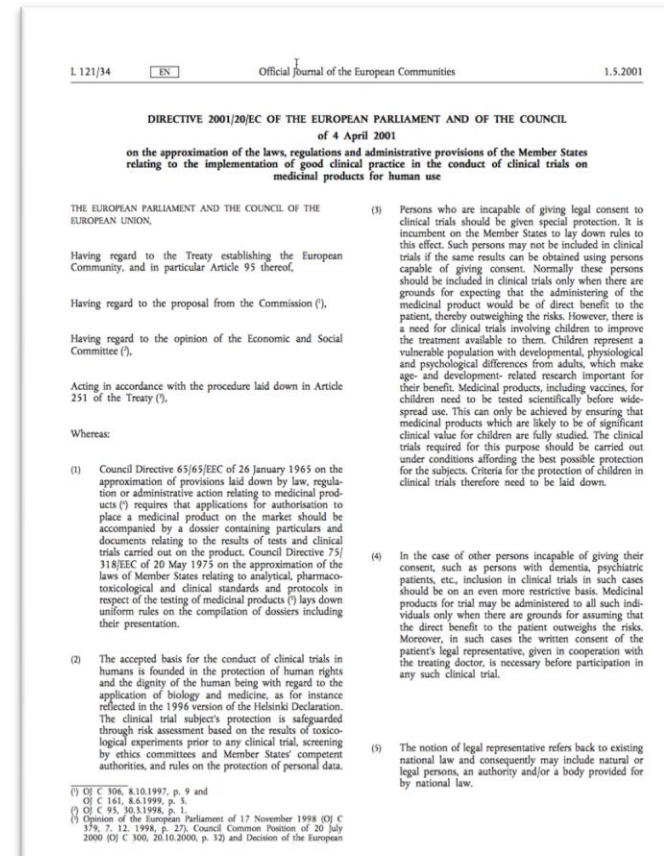
Ethical considerations

- 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

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- 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

10 Facts about the PARAMEDIC2 Trial **PARAMEDIC2 The Adrenaline Trial**

1 Should we use Adrenaline? Doctors, nurses, paramedics and... that adrenaline which is some... heart may actually damage... less likely a patient... It has never... any p...

2 Re-starting the Heart "Resuscitation" is an attempt... the heart, ultimate... the patient's... and

10 Facts about Cardiac Arrest

1 Cardiac Arrest and Heart Attack A "cardiac arrest" is when the heart suddenly stops beating. A "heart attack" is when the heart muscle is damaged. A heart does not necessarily stop beating.

2 Cardiac Arrest and Heart Attack

3 Risk Factors Family history, smoking, high blood pressure, obesity, diabetes, sedentary lifestyle, P... High salt, sugar, and fat diets, alcohol, and... Non-steroidal anti-inflammatory drugs (NSAIDs) and other medications, such as lo...

4 What to do if you witness a cardiac arrest

10 Facts about Resuscitation

1 CPR (Cardio-pulmonary resuscitation) Often called "the kiss of life" or "resuscitation" or "heart massage" CPR actually is both chest compressions AND rescue breaths

2 Chest Compressions

3 Rescue Breaths

4 DEFIBRILLATION (electric shocks) Also called "AED" - automated external defibrillator. Anyone can use a defib.

5 Immediate CPR can double, or even triple, a victim's chance of survival

6 Every minute delay can mean a 10% drop in your chance of surviving

7 Get training <https://www.bhf.org.uk/heart-health/haction-of-livesavers>

8 Bystander CPR saves lives! I.e. YOU

10 Improving survival

6 Taking Part in PARAMEDIC2

The PARAMEDIC2 trial is investigating whether adrenaline is beneficial or harmful in the treatment of cardiac arrest. Answering this question will help to improve the treatment of people who have a cardiac arrest.

If you were to have a cardiac arrest and be resuscitated by a paramedic at one of the five ambulance services taking part in Paramedic 2 you may receive adrenaline as part of your treatment or you may not. You will receive all treatments that are proven to work and it is only the adrenaline which will not be given to everyone.

If you would not want to take part in the trial, should you suffer a cardiac arrest, you can contact the study team who will send a "No Study" bracelet to wear.

8 Oversight for PARAMEDIC2

PARAMEDIC2 has been assessed and approved by an independent Research Ethics Committee and Medicines and Healthcare Products Regulatory Agency (MHRA).

The trial is further monitored by an independent committee that includes patient and public representation. There is a quote from one of the representatives: "After talking to the research team I am fully convinced of the need for the trial... I can't believe it hasn't been done already."

This trial is funded (and managed) by the National Institute for Health Research (NIHR) and is being managed by the University of Warwick.

PARAMEDIC2 The Adrenaline Trial

Should we use adrenaline when someone's heart stops?

Information about the Paramedic2 Trial

www2.warwick.ac.uk
E paramedictrial@w...
T 024 7615
PARAMED
Warwick Clinical T...
Cobbet Hill Road, Univer...
Coventry, CV

NIHR
SORSBY
Warwick

Tel: 024 7615 1164 paramedictrial@warwick.ac.uk www.warwick.ac.uk/paramedic2

South Central Ambulance Service NHS Foundation Trust West Midlands Ambulance Service NHS Foundation Trust

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

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- **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

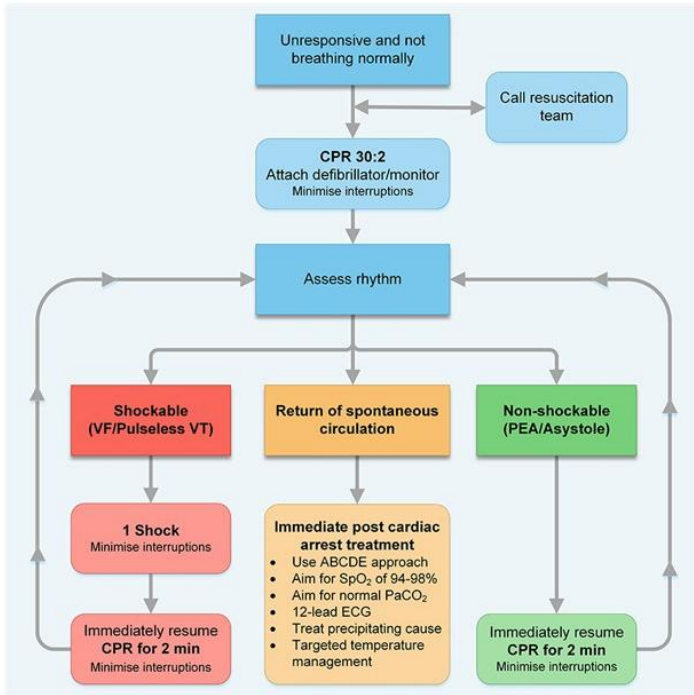
USE this pack if:

- ✓ Out of hospital
- ✓ Advanced life support

DO NOT USE this pack if:

- ✗ Pregnancy
- ✗ Under 16 years
- ✗ Anaphylaxis/life threatening asthma
- ✗ Adrenaline given prior

1 PACK PER PATIENT ONLY



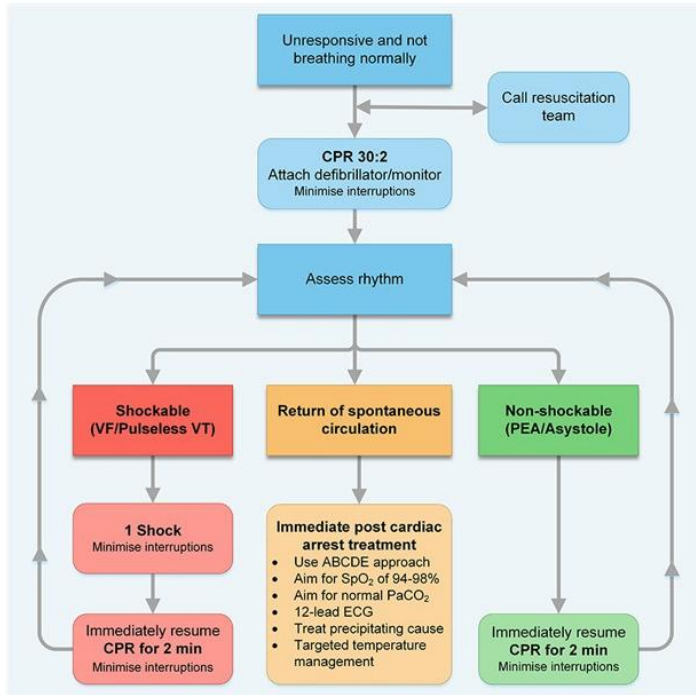
- During CPR**
- Ensure high quality chest compressions
 - Minimise interruptions to compressions
 - Give oxygen
 - Use waveform capnography
 - Continuous compressions when advanced airway in place
 - Vascular access (intravenous or intraosseous)
 - Give adrenaline every 3-5 min
 - Give amiodarone after 3 shocks

- Treat Reversible Causes**
- Hypoxia
 - Hypovolaemia
 - Hypo-/hyperkalaemia/metabolic
 - Hypothermia
 - Thrombosis - coronary or pulmonary
 - Tension pneumothorax
 - Tamponade - cardiac
 - Toxins

- Consider**
- Ultrasound imaging
 - Mechanical chest compressions to facilitate transfer/treatment
 - Coronary angiography and percutaneous coronary intervention
 - Extracorporeal CPR

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 6–12 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
2. Give adrenaline 1 mg IV as soon as intravascular access is achieved
3. Continue CPR 30:2 until the airway is secured – then continue chest compressions without pausing during ventilation
4. 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.

- During CPR**
- Ensure high quality chest compressions
 - Minimise interruptions to compressions
 - Give oxygen
 - Use waveform capnography
 - Continuous compressions when advanced airway in place
 - Vascular access (intravenous or intraosseous)
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- Treat Reversible Causes**
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 - Hypothermia
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 - Tamponade – cardiac
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- Consider**
- Ultrasound imaging
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 - Extracorporeal CPR

Randomisation

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- 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

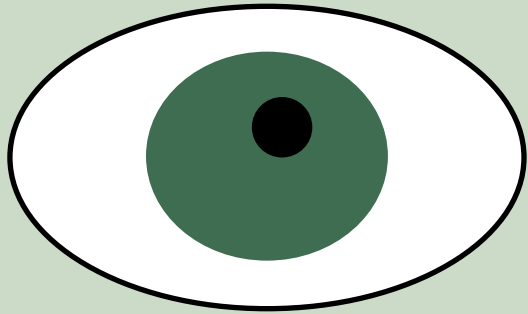
69

(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

%

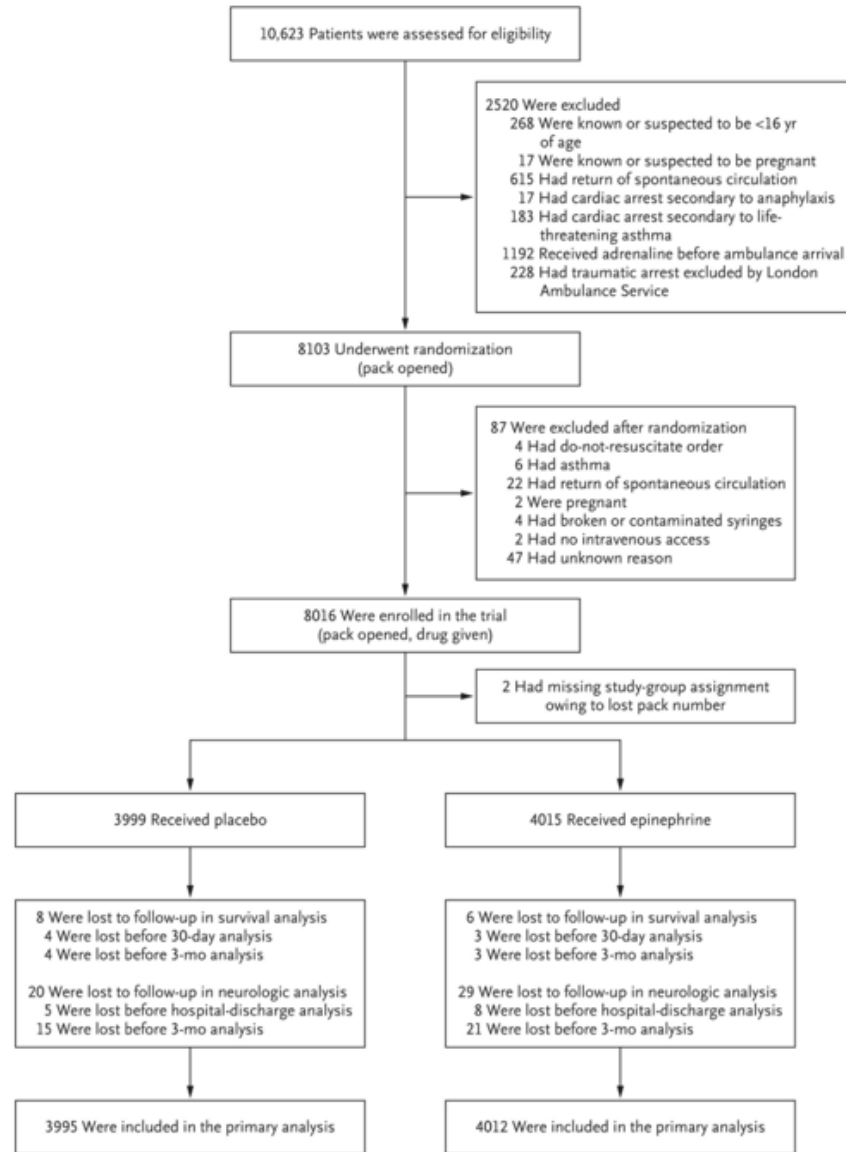
initially
shockable
rhythms

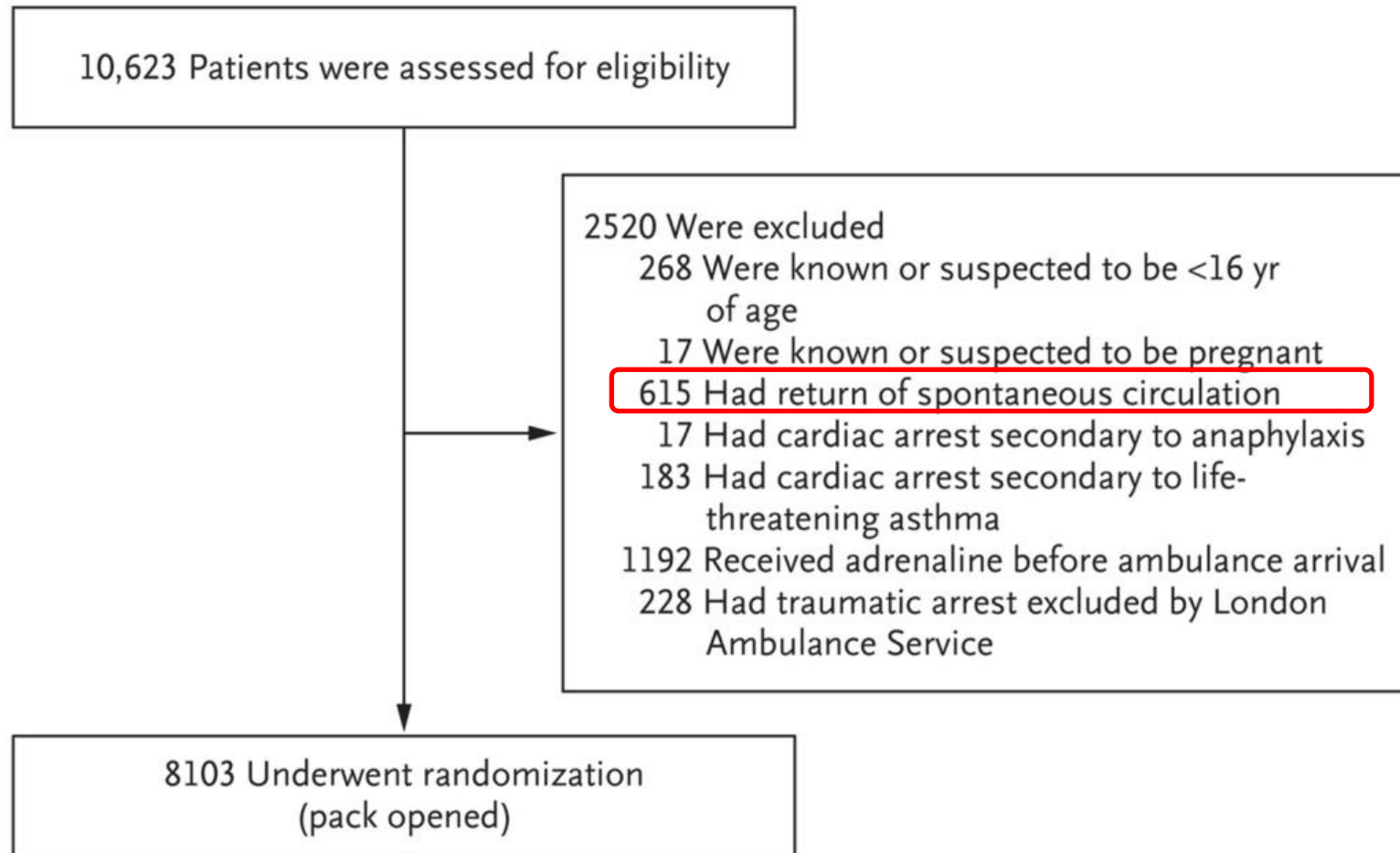


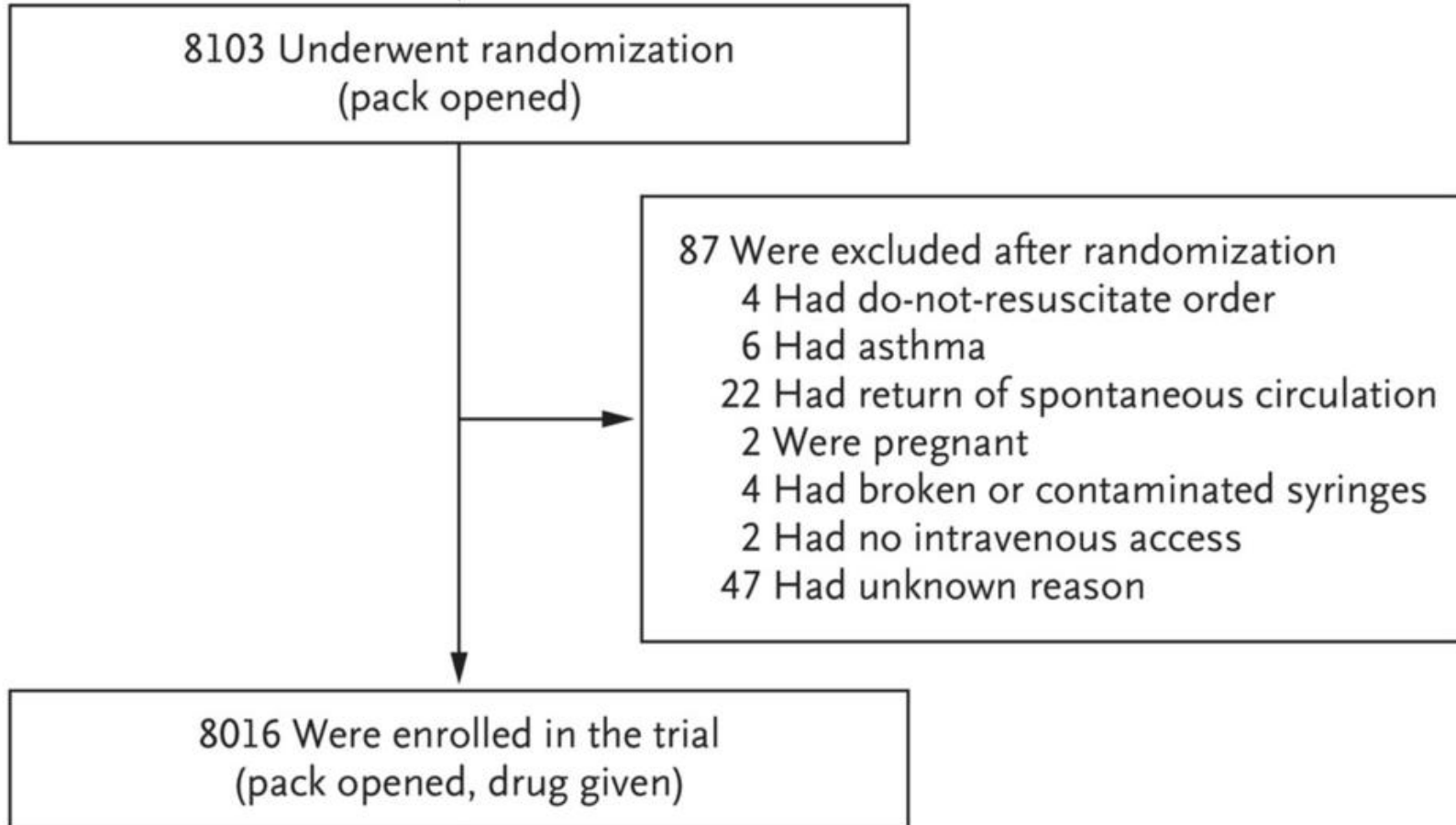
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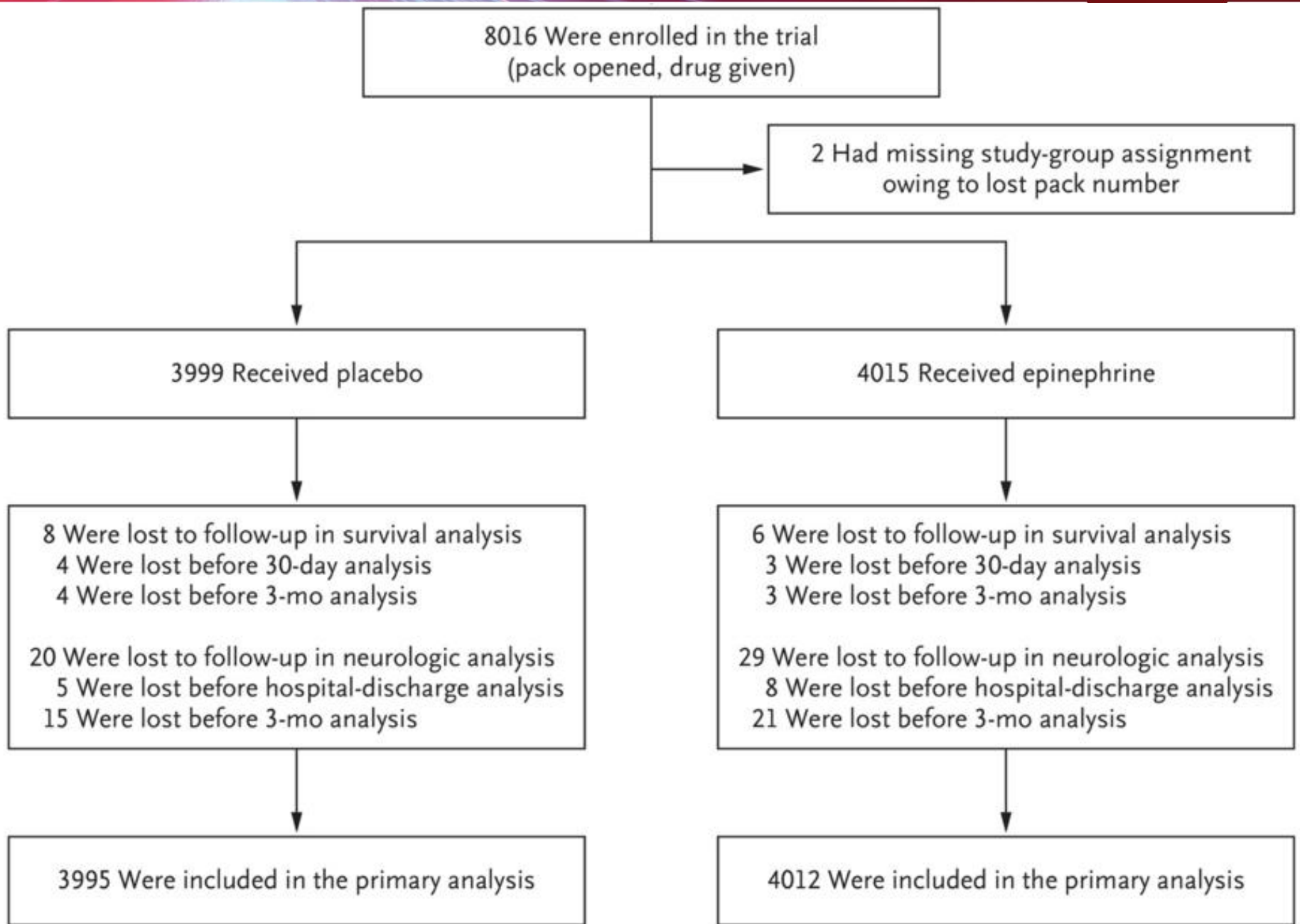
%

medical
cause of
cardiac
arrest









Return of spontaneous circulation

Adrenaline



Placebo

36.3%

n=1457/3975

11.7%

n=468/3960

Admitted to hospital

Adrenaline



Placebo

23.8%

n=947/3973

Significantly more in
adrenaline group

Odds ratio
3.83 (95% CI 3.30-4.43)

8.0%

n=319/3982

Survival to 30 days

Adrenaline



Placebo

3.2%

n=130/4012

Significantly more in
adrenaline group

Odds ratio
1.39 (95% CI 1.06-1.82)

P=0.02

2.4%

n=94/3995

Favourable neurological outcome

Adrenaline

Placebo



2.2%

n=87/4007

No significant
difference

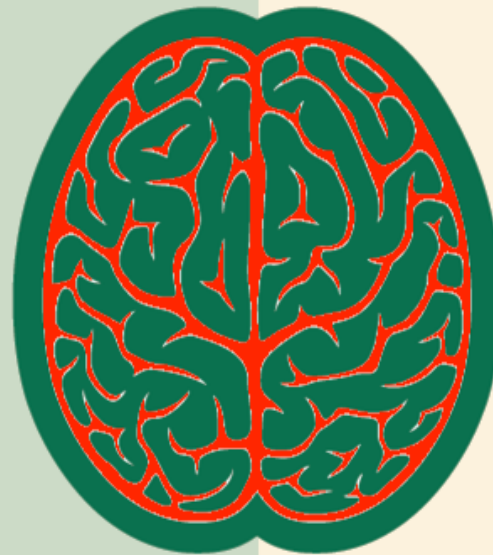
Odds ratio
1.18 (95% CI 0.86-1.61)

1.9%

n=74/3994

Poor neurological outcome

Adrenaline



Placebo

31.0%

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

17.8%













n=39/126

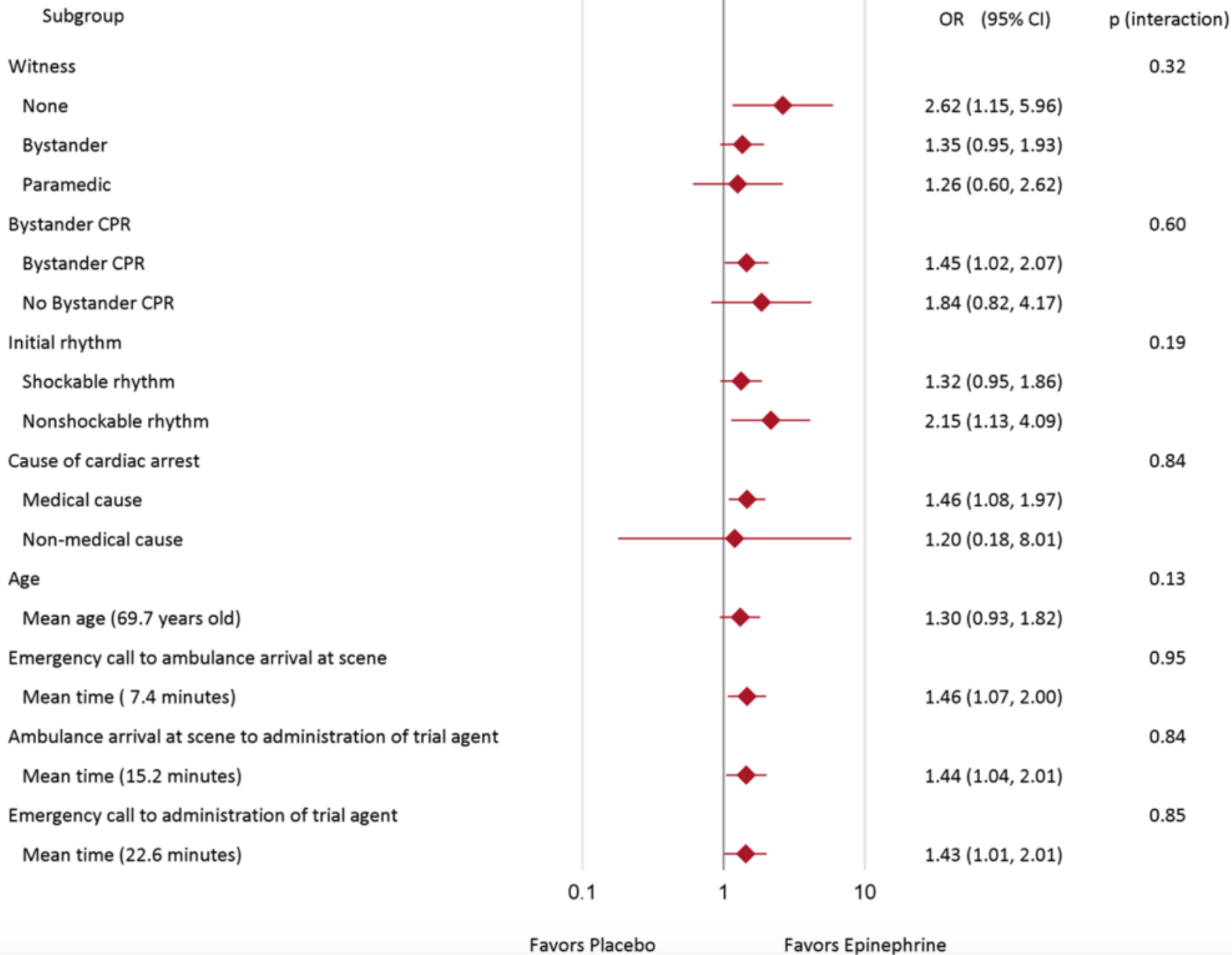
Post-hoc comparison

Odds ratio

0.51 (95% CI 0.27-0.96)

n=16/90

Survivors at hospital discharge	Adrenaline (n=126)	No adrenaline (n=90)
No disability No symptoms at all	 9.5%	 16.7%
No significant disability Some symptoms but able to carry out all usual duties and activities	 13.5%	 11.1%
Slight disability Unable to carry out all previous activities, but able to look after own affairs without assistance	 18.3%	 32.2%
Moderate disability Requiring some help, but able to walk without assistance	 27.8%	 22.2%
Moderately severe disability Unable to walk without assistance and unable to attend to own bodily needs without assistance	 9.5%	 8.9%
Severe disability Bedridden, incontinent and requiring constant nursing care and attention	 21.4%	 8.9%
Classified by modified Rankin Scale	100%	100%



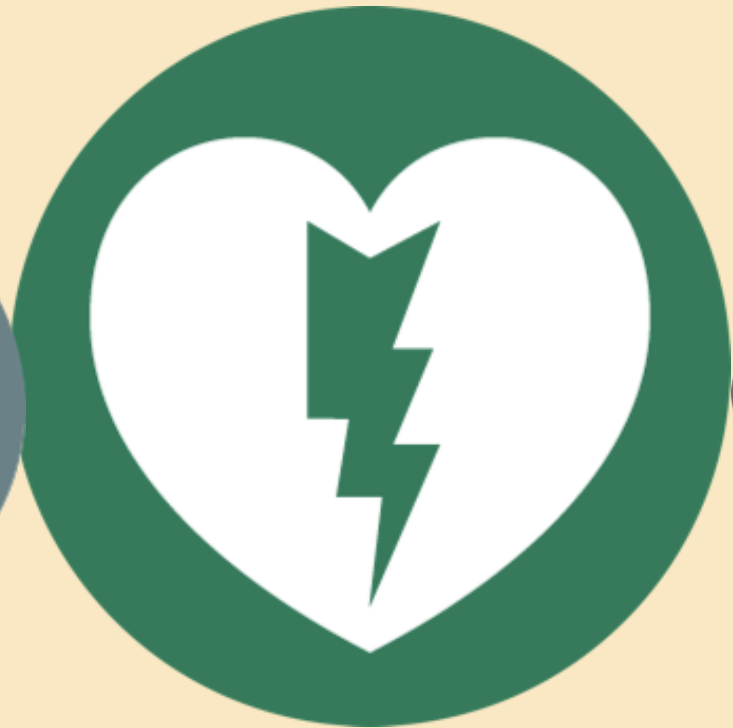
Comparative effectiveness



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 Bengier, 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.