Adrenaline: The PARAMEDIC-2 Trial

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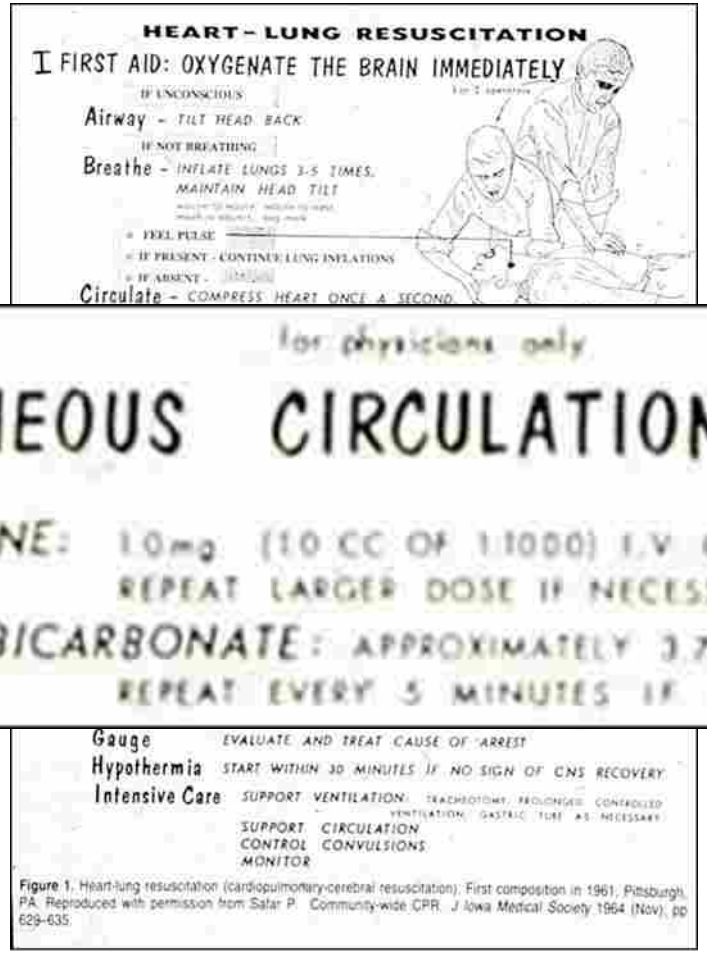
Declarations

Research funding from:

- National Institute for Health Research (UK) (Government)
- British Heart Foundation (Charity)
- Gas Safety Trust (Charity)



HEART – LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY

IF UNCONSCIOUS

Airway – TILT HEAD BACK

IF NOT BREATHING

Breathe – INFLATE LUNGS 3-5 TIMES.
MAINTAIN HEAD TILT

- FEEL PULSE
- IF PRESENT – CONTINUE LUNG INFLATIONS
- IF ABSENT –

Circulate – COMPRESS HEART ONCE A SECOND

for physicians only

II START SPONTANEOUS CIRCULATION

Drugs – EPINEPHRINE: 1.0 mg (10 CC OF 1:1000) I.V OR 0.5 mg INTRACARDIAC
REPEAT LARGER DOSE IF NECESSARY

SODIUM BICARBONATE: APPROXIMATELY 3.75 G/50 CC (1/2 DOSE IN CHILDREN) I.V.
REPEAT EVERY 5 MINUTES IF NECESSARY

Gauge EVALUATE AND TREAT CAUSE OF ARREST

Hypothermia START WITHIN 30 MINUTES IF NO SIGN OF CNS RECOVERY

Intensive Care SUPPORT VENTILATION: TRACHEOTOMY, PROLONGED CONTROLLED VENTILATION, GASTRIC TUBE AS NECESSARY
SUPPORT CIRCULATION
CONTROL CONVULSIONS
MONITOR

Figure 1. Heart-lung resuscitation (cardiopulmonary-cerebral resuscitation). First composition in 1961, Pittsburgh, PA. Reproduced with permission from Safar P. Community-wide CPR. *J Iowa Medical Society* 1964 (Nov); pp 629-635.

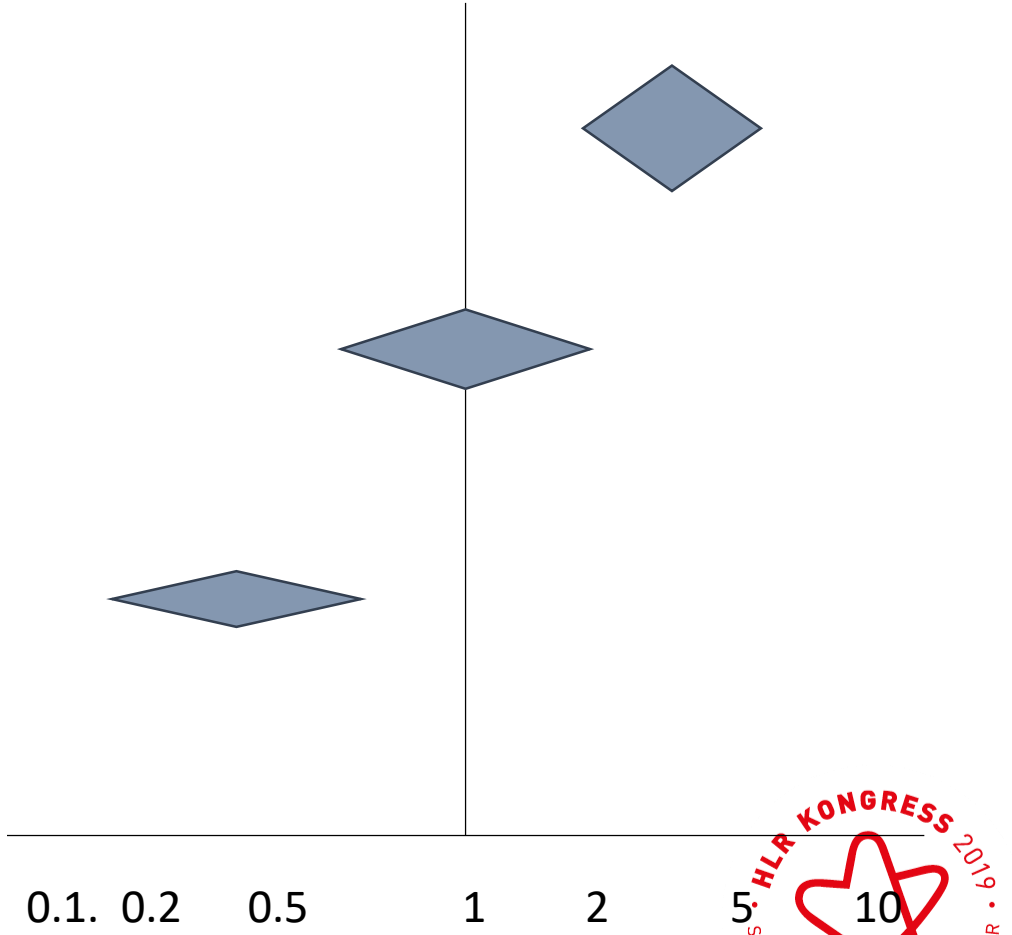
Peter Safar 1961

Chain of survival

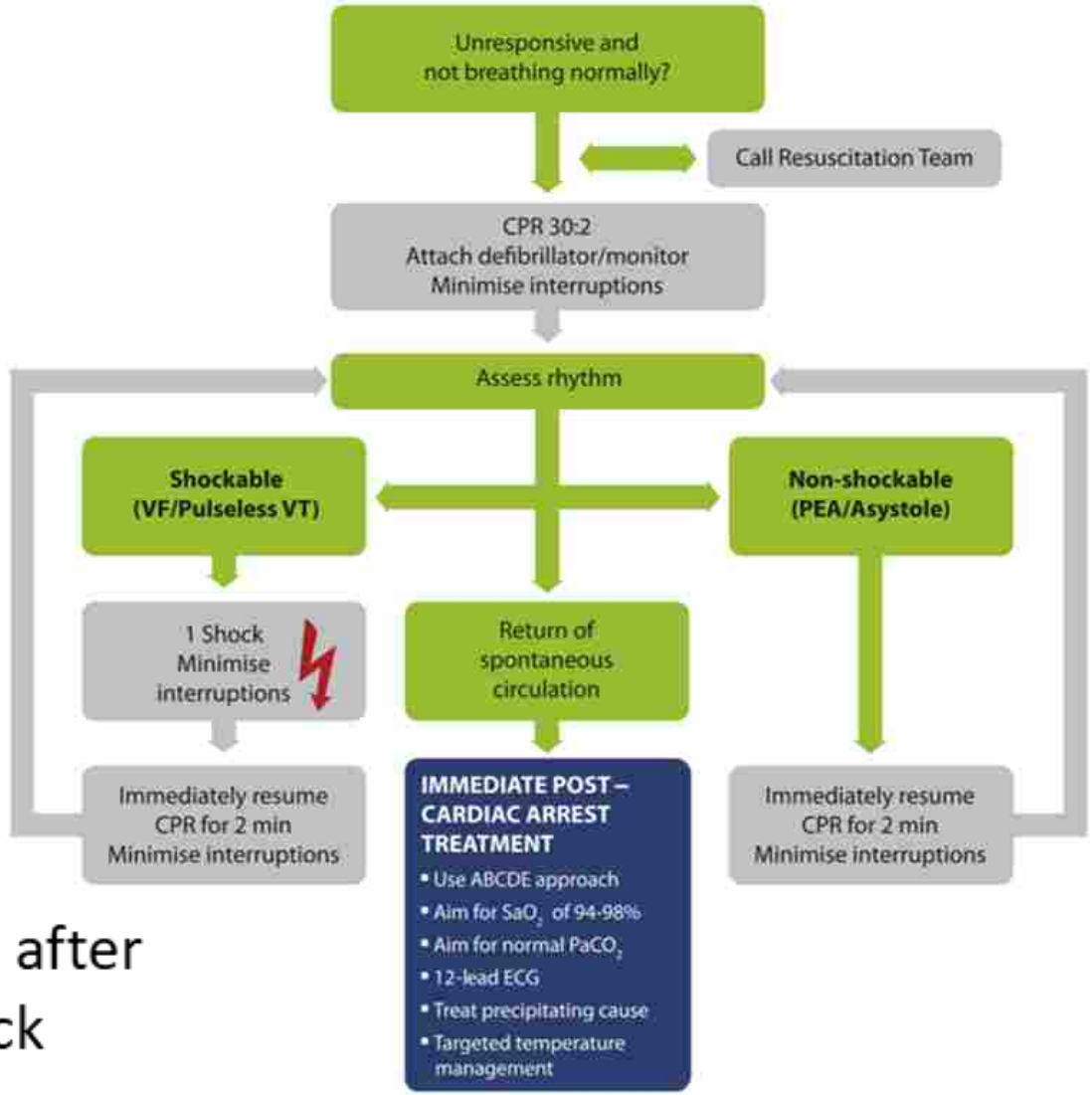
Where initial treatments do not work, adrenaline is sometimes given as a treatment. Adrenaline has been used for over 50 years, but it has never been properly tested to see whether it is beneficial or harmful.

Evidence before PARAMEDIC2

- ROSC (n=9)
- Survival to discharge (n=5)
- Favourable neurological outcome (n=9)



Loomba J Crit care 2014



Adrenaline after 3rd shock

Airway
IV/IO Access
Adrenaline

The NEW ENGLAND JOURNAL of MEDICINE

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.)

PARAMEDIC2

The Adrenaline Trial

South Central Ambulance Service NHS
NHS Foundation Trust

West Midlands Ambulance Service NHS
NHS Foundation Trust

London Ambulance Service NHS
NHS Trust

North East Ambulance Service NHS
NHS Foundation Trust

Welsh Ambulance Service NHS
NHS Trust

HLR KONGRESS 2019
STOCKHOLM 24-25 SEPTEMBER

National Institute for Health Research

improving the health and wealth of the nation through research

- The trial was funded by the National Institute for Health Research HTA Programme (12/27/126)

- The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.

FUNDED BY
NIHR | National Institute for Health Research

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.

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

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

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

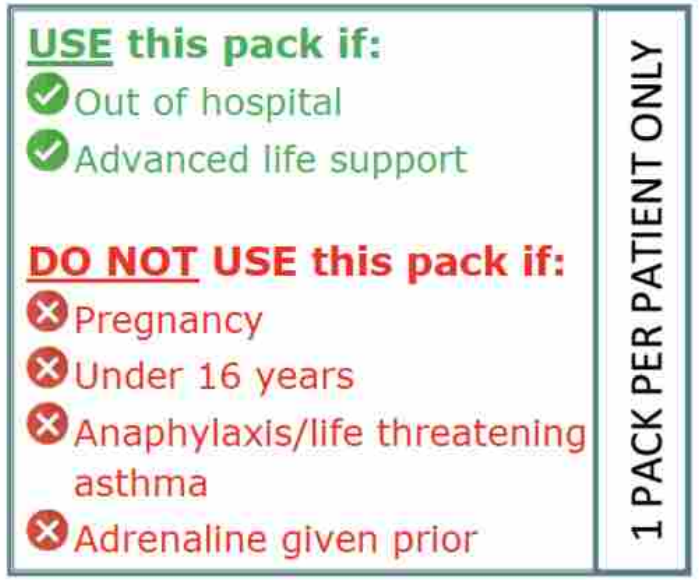
- After careful consideration and consultation with patients, the public and the Research Ethics Committee, it was decided not to write to the next of kin of those who did not survive. Information was made available and a process put in place to respond to enquires from relatives

Eligibility Criteria

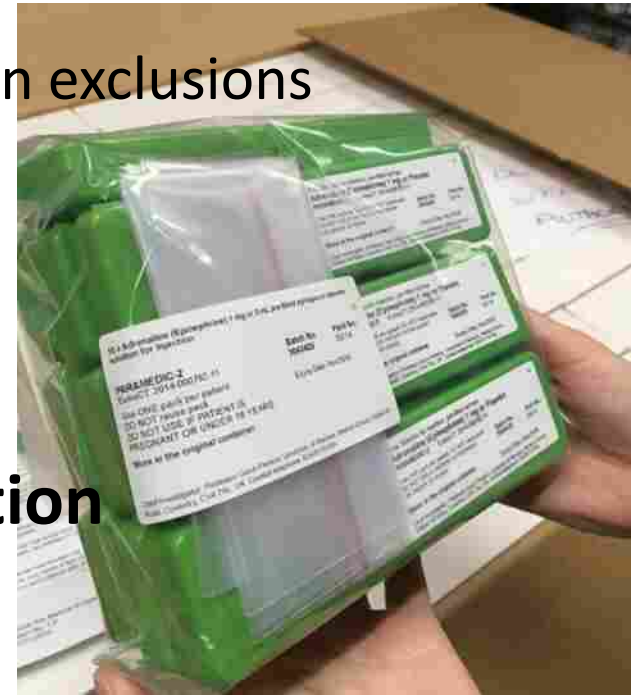
- **Inclusion Criteria:**
  - OHCA

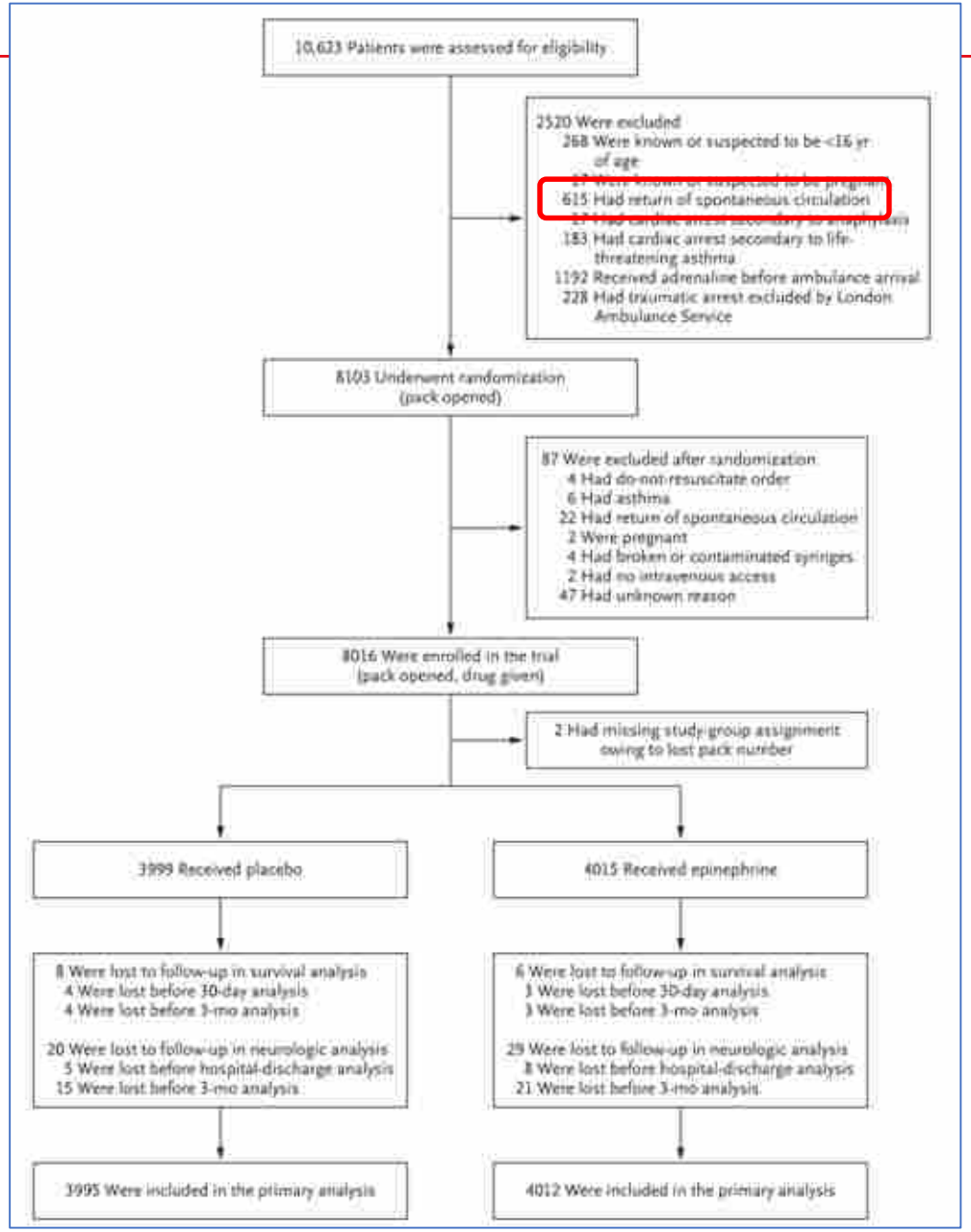
  AND
  - ALS initiated and / or continued by ambulance service clinician

- **Exclusion criteria:**
  - Known or apparent pregnancy
  - Known or apparently <16 years
  - Anaphylaxis or life threatening asthma
  - Adrenaline given prior to arrival of ambulance service clinician



- Randomisation – opening drug pack
  - Post randomization exclusions
    - ROSC
    - ROLE
    - Exclusion
- **Drug administration**

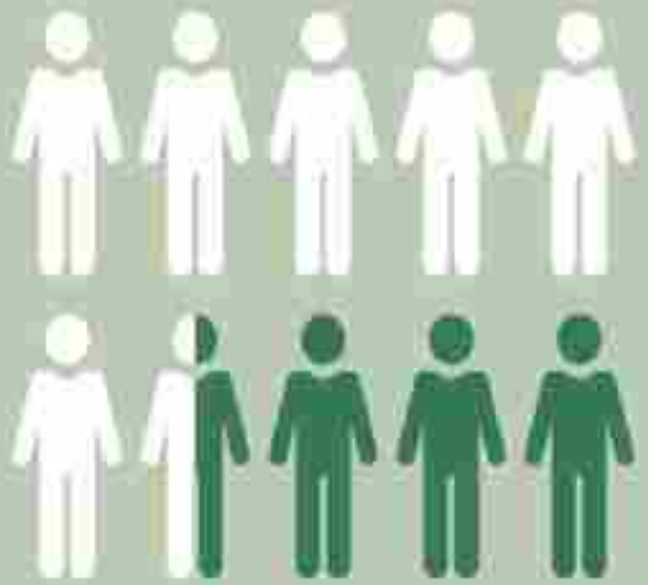




- Patients refractory to initial attempts at resuscitation
- Registry data / previous trials suggest circa 3% survival
- 3999 placebo, 4013 intervention
- 99% follow-up of primary outcome
- 23% loss to follow-up for neurological outcomes by 3 months

PARAMEDIC2
The Adrenaline Trial

The study population



65% male

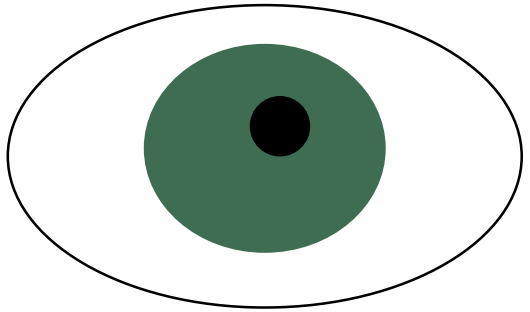
Average age

69

(years)

6 out of **10**

people received CPR from bystanders or family members before the ambulance arrived



50% bystander witnessed

10% witnessed by paramedics, 40% unwitnessed

20%

initially shockable rhythms

90%

medical cause of cardiac arrest

Median time to adrenaline administration 21 minutes
Mean dose 5mg

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

Return of spontaneous circulation

Adrenaline

Placebo

36.3%

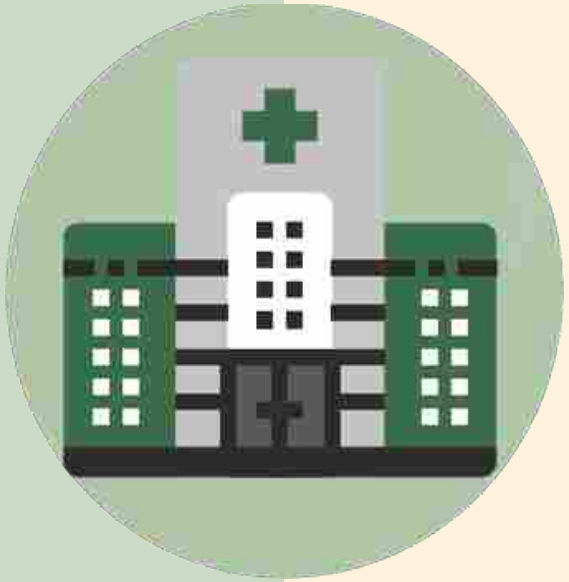
n=1457/3975

11.7%

n=468/3960

Admitted to hospital

Adrenaline



Placebo

23.8%

n=947/3973

Significantly more in adrenaline group

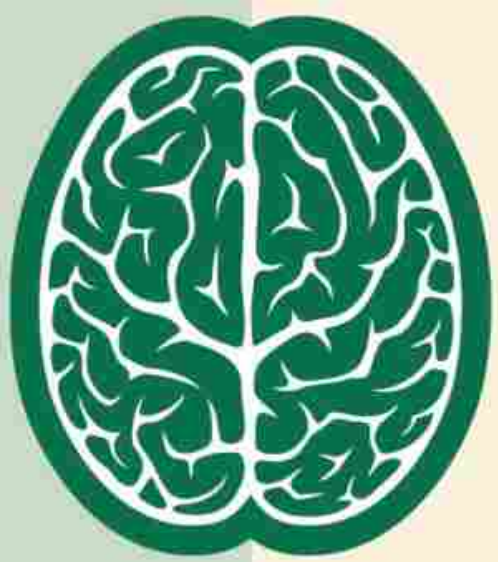
Odds ratio
3.83 (95% CI 3.30-4.43)

8.0%

n=319/3982

Favourable neurological outcome

Adrenaline



Placebo

2.2%

n=87/4007

No significant difference

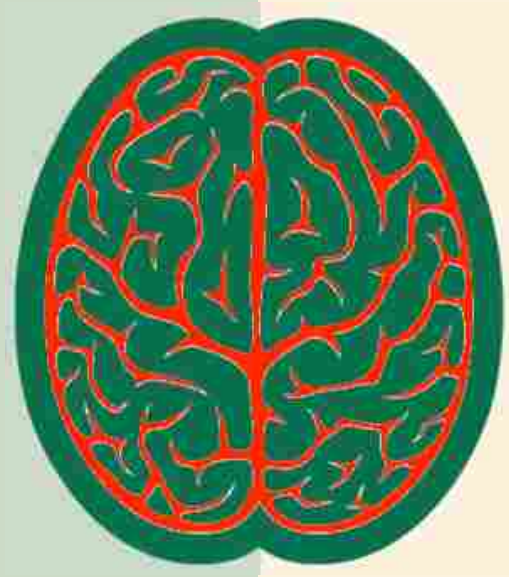
Odds ratio
1.18 (95% CI 0.86-1.61)

1.9%

n=74/3994

Poor neurological outcome

Adrenaline



Placebo

31.0%

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

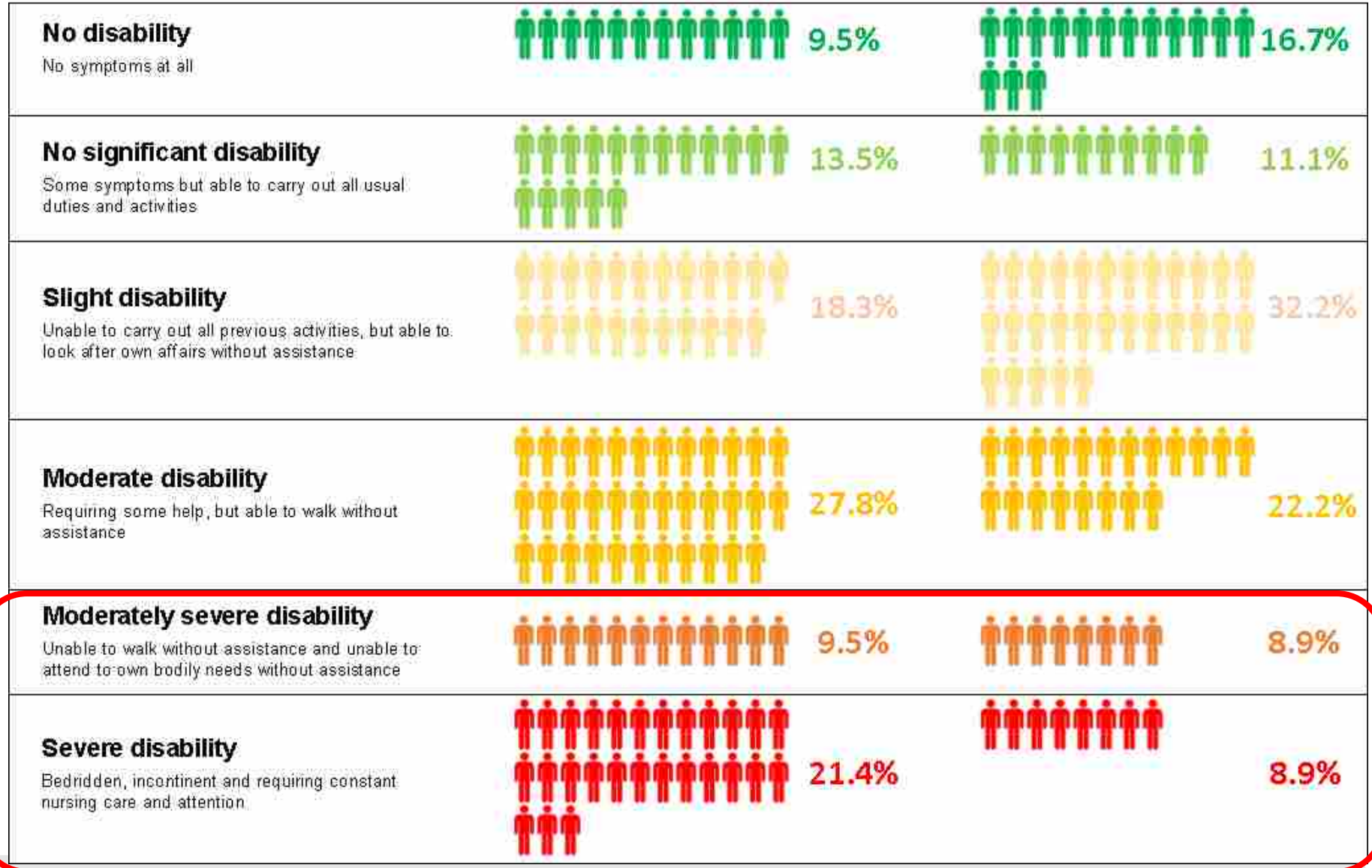
17.8%

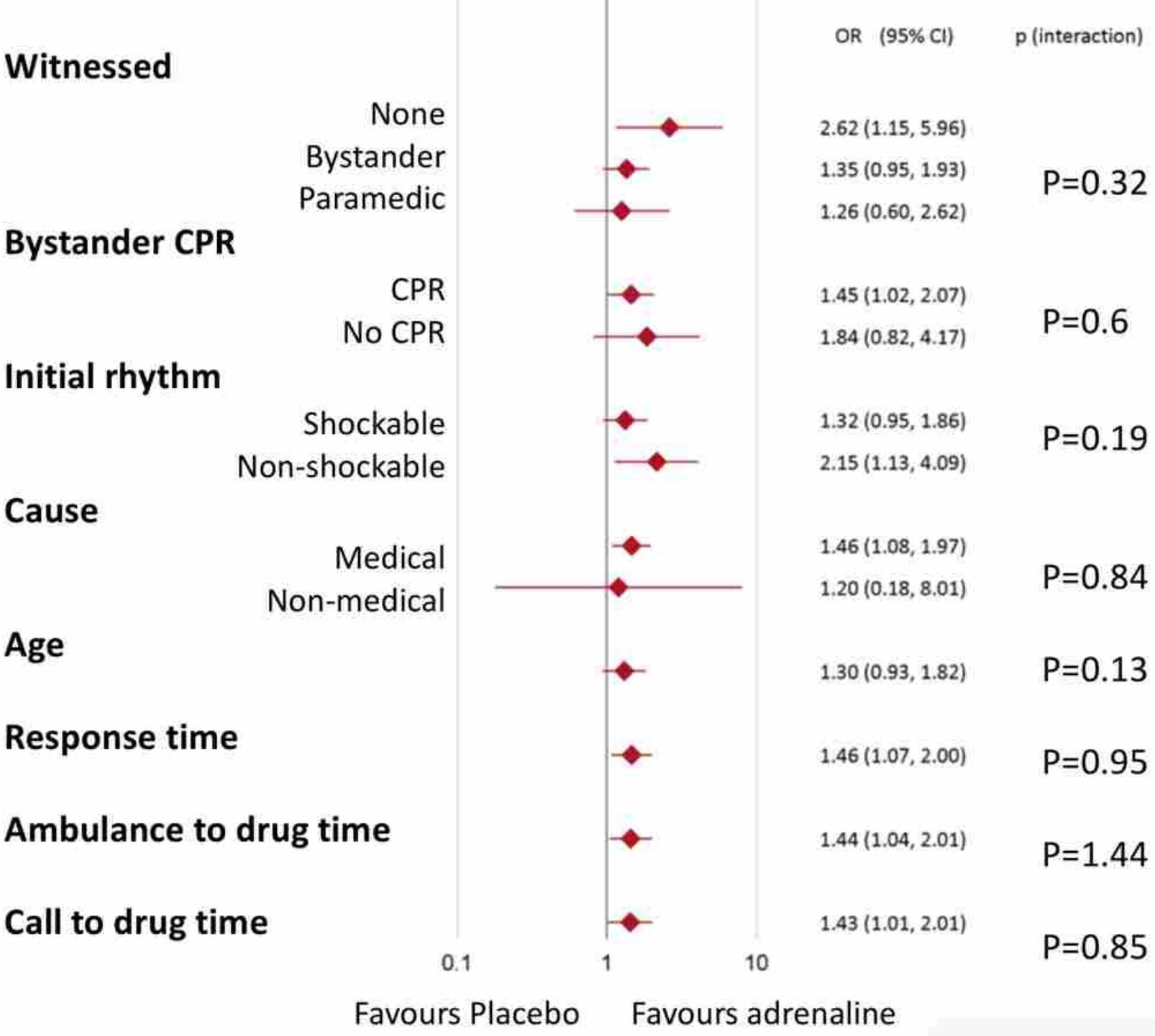
n=39/126

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)




OR (95% CI)
p (interaction)
Witnessed
None
2.62 (1.15, 5.96)
Bystander
1.35 (0.95, 1.93)
P=0.32
Paramedic
1.26 (0.60, 2.62)
Bystander CPR
CPR
1.45 (1.02, 2.07)
No CPR
1.84 (0.82, 4.17)
P=0.6
Initial rhythm
Shockable
1.32 (0.95, 1.86)
Non-shockable
2.15 (1.13, 4.09)
P=0.19
Cause
Medical
1.46 (1.08, 1.97)
Non-medical
1.20 (0.18, 8.01)
P=0.84
Age
1.30 (0.93, 1.82)
P=0.13
Response time
1.46 (1.07, 2.00)
P=0.95
Ambulance to drug time
1.44 (1.04, 2.01)
P=1.44
Call to drug time
1.43 (1.01, 2.01)
P=0.85
0.1
1
10
Favours Placebo
Favours adrenaline

Comparative effectiveness

10 times more effective

8 times more effective

20 times more effective

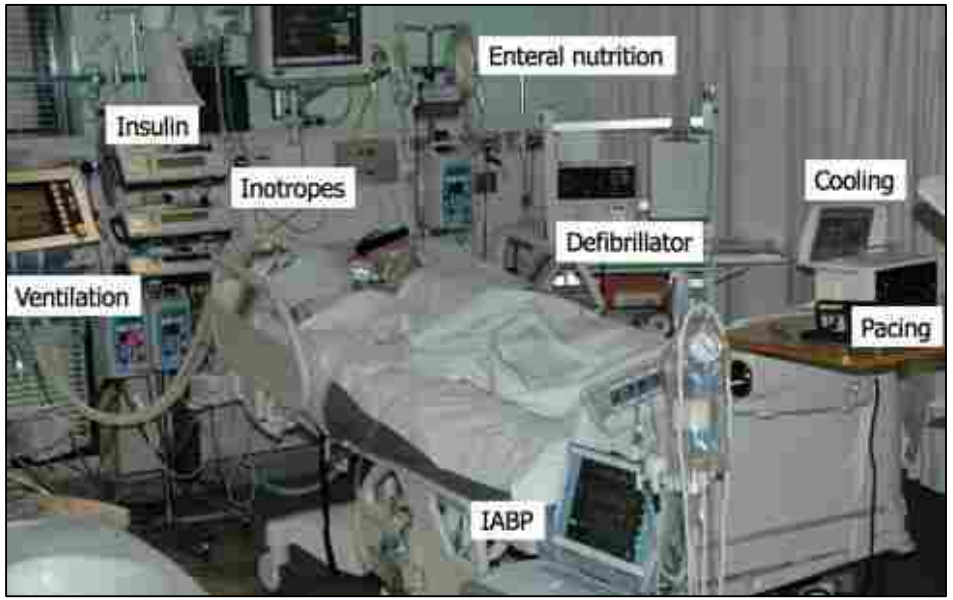
Adrenaline Reference (1)

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.)

A national perspective from the NHS - 22,500 people treated with adrenaline

Outcome	Additional patients
ROSC	5602
Admission	3555
ICU admission	1643
Discharged alive	203
Favourable outcome	**68**
Unfavourable outcome	**135**



5143 ICU days

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with standard-dose adrenaline				
Survival to hospital discharge	Study population		RR 1.44 (1.11 to 1.86)	8538 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	OHCA only
	23 per 1000	32 per 1000 (25 to 42)				
Survival to hospital admission	Study population		RR 2.51 (1.67 to 3.76)	8489 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	OHCA only
	83 per 1000	209 per 1000 (139 to 313)				
Favourable neurological outcomes	Study population		RR 1.21 (0.90 to 1.62)	8535 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Favourable neurological outcomes were defined as a CPC score of < 3 or mRS < 4 OHCA only
	19 per 1000	22 per 1000 (17 to 30)				
Return of spontaneous circulation	Study population		RR 2.86 (2.21 to 3.71)	8663 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]	OHCA and IHCA
	115 per 1000	329 per 1000 (254 to 427)				

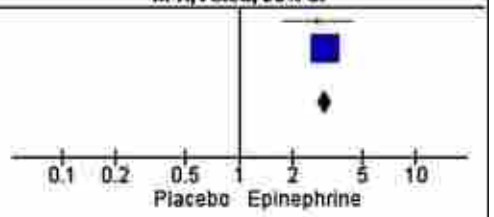
Cochrane Library

Adrenaline and vasopressin for cardiac arrest (Review)

A Return of Spontaneous Circulation

Study or Subgroup	Epinephrine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Jacobs	64	272	22	262	4.6%	2.80 [1.78, 4.41]	2011
Perkins	1457	3975	468	3960	95.4%	3.10 [2.82, 3.41]	2018
Total (95% CI)		**4247**		**4222**	**100.0%**	**3.09 [2.82, 3.39]**	
Total events	1521		490				

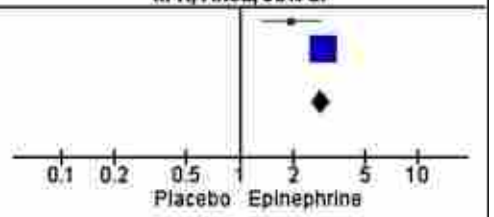
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 23.91 (P < 0.00001)



B Survival to Hospital Admission

Study or Subgroup	Epinephrine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Jacobs	69	272	34	262	9.8%	1.95 [1.34, 2.84]	2011
Perkins	947	3973	319	3982	90.2%	2.98 [2.64, 3.35]	2018
Total (95% CI)		**4245**		**4244**	**100.0%**	**2.88 [2.57, 3.22]**	
Total events	1016		353				

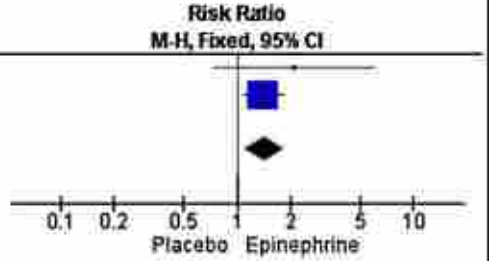
Heterogeneity: Chi² = 4.41, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 18.27 (P < 0.00001)



C Survival to Hospital Discharge

Study or Subgroup	Epinephrine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Jacobs	11	272	5	262	5.3%	2.12 [0.75, 6.02]	2011
Perkins	128	4009	91	3995	94.7%	1.40 [1.08, 1.83]	2018
Total (95% CI)		**4281**		**4257**	**100.0%**	**1.44 [1.11, 1.86]**	
Total events	139		96				

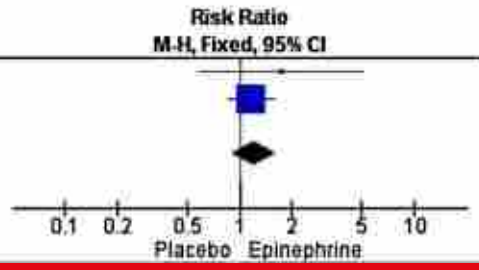
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)



D Favorable Neurological Outcome at Hospital Discharge

Study or Subgroup	Epinephrine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Jacobs	9	272	5	262	6.4%	1.73 [0.59, 5.11]	2011
Perkins	87	4007	74	3994	93.6%	1.17 [0.86, 1.59]	2018
Total (95% CI)		**4279**		**4256**	**100.0%**	**1.21 [0.90, 1.62]**	
Total events	96		79				

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)



Resuscitation

Review

Vasopressors during adult cardiac arrest: A systematic review and meta-analysis

Mathias J. Holmberg, Mahmoud S. Issa, Ari Moskowitz, Peter Morley, Michelle Welsford, Robert W. Neumar, Edison F. Paiva, Amin Coker, Christopher K. Hansen, Lars W. Andersen, Michael W. Donnino, Katherine M. Berg, on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force Collaborators

Available online at www.sciencedirect.com

Resuscitation

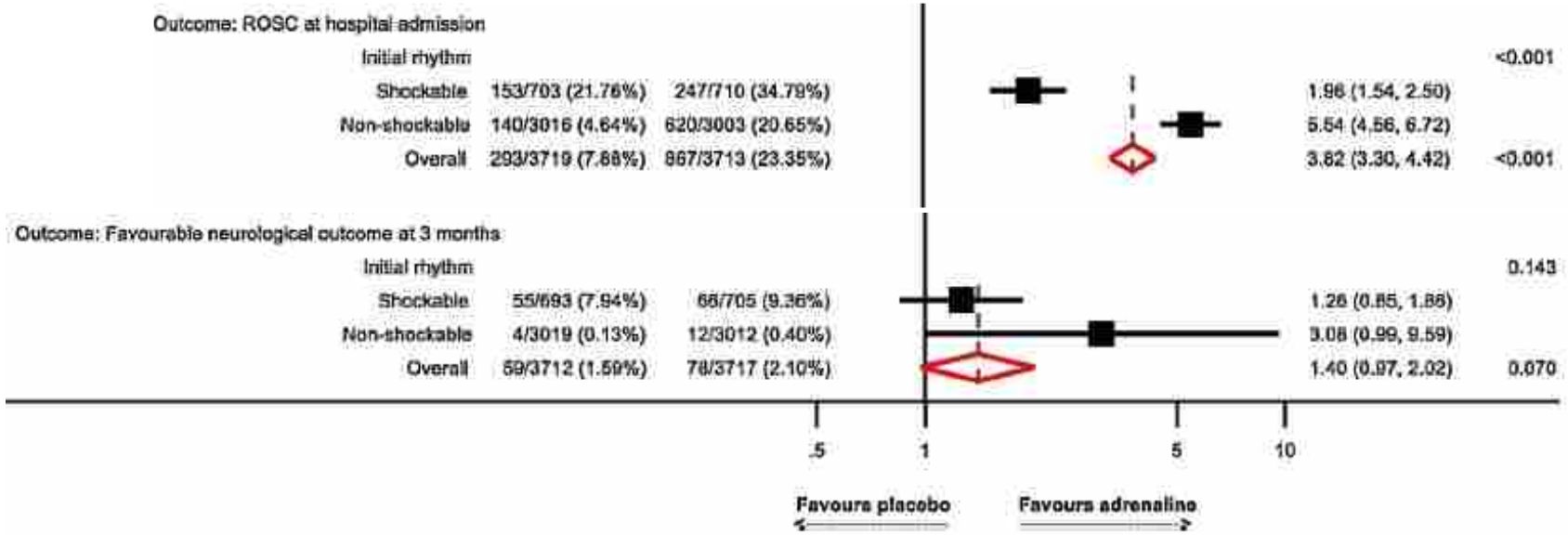
journal homepage: www.elsevier.com/locate/resuscitation

EUROPEAN RESUSCITATION COUNCIL

Clinical paper

The effects of adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms: Findings from the PACA and PARAMEDIC-2 randomised controlled trials

Gavin D. Perkins[a,b,], Claire Kenna[a], Chen Ji[a], Charles D. Deakin[c,d], Jerry P. Nolan[a,e], Tom Quinn[f], Rachael Fothergill[g], Imogen Gunson[h], Helen Pocock[c], Nigel Rees[i], Karl Charlton[j], Judith Finn[k], Simon Gates[l], Ranjit Lall[a]*



Vasopressors in Adult Cardiac Arrest

We **recommend administration of epinephrine** during cardiopulmonary resuscitation (strong recommendation, low to moderate certainty of evidence).

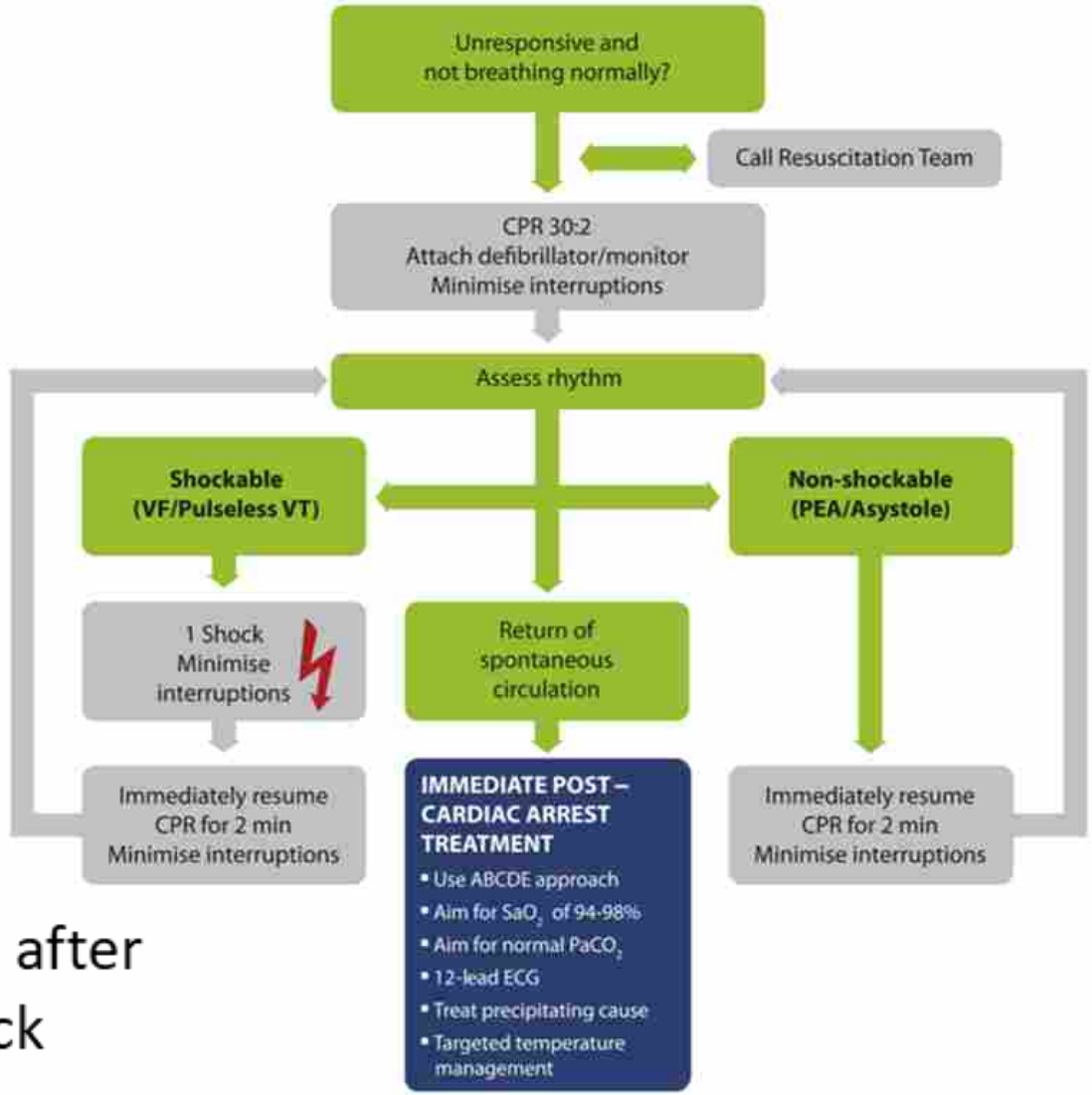
The task force made a strong recommendation given that the intervention may reduce mortality in a life-threatening situation and adverse events are not prohibitive.

A very high value is placed on an uncertain but potentially life preserving benefit.

However, the **impact on neurologic outcome remains uncertain**, with no statistically significant evidence of benefit or harm on neurologic outcome at 3 months.

ILCOR (contd.)

- For non-shockable rhythms (PEA/asystole), we recommend administration of epinephrine as soon as feasible during cardiopulmonary resuscitation (**strong recommendation, very low certainty of evidence**).
- For shockable rhythms (VF/VT), we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during cardiopulmonary resuscitation (**weak recommendation, very low certainty of evidence**).



Adrenaline after 3rd shock

Airway
IV/IO Access
Adrenaline

More questions!

- Are we giving the ‘right’ dose?
- Are we giving the right way (bolus vs. continuous infusion)?
- Could we give adrenaline sooner, and would this change outcome?
- Could we protect the brain intra-arrest (and how)?
- Will funders support trials large enough to give us adequate power for long term neurological outcomes?

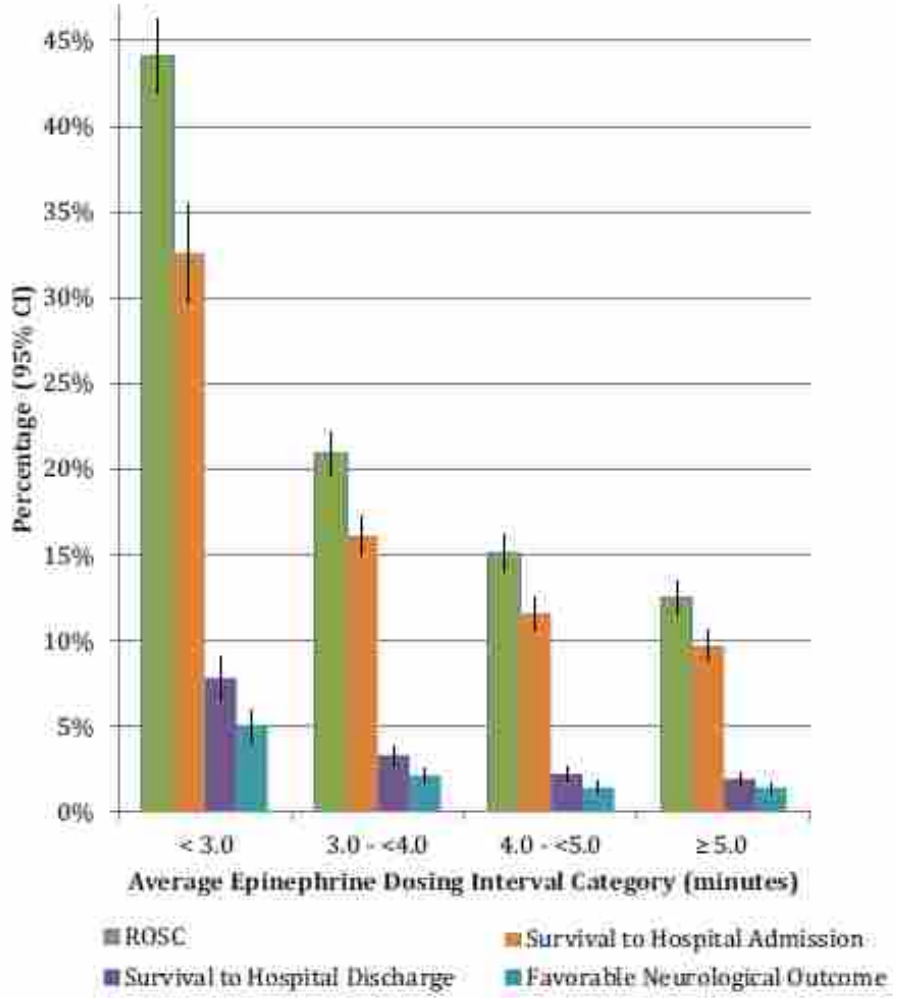


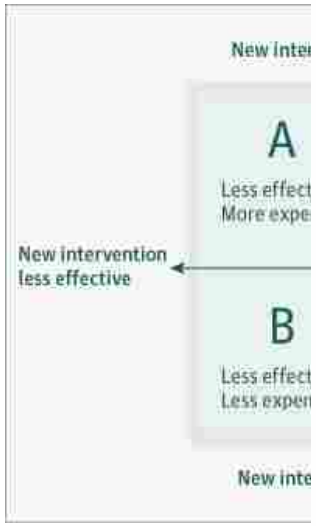
Figure 2. Patient outcomes stratified by average epinephrine dosing interval.

Circulation

ILCOR ADVISORY STATEMENT

COSCA (Core Outcome Set for Cardiac Arrest) in Adults

An Advisory Statement From the International Liaison Committee on Resuscitation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HUMAN
ORGAN

ACCA
Acute Cardiovascular
Care Association

ACUTE CARDIOVASCULAR CARE2020

7-9 March 2020
Athens, Greece

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