Congresso Nazionale IRC

2019

11 • 12 OTTOBRE

Centro Congressi **Veronafiere**

IRC | Italian Resuscitation Council

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11 - 12 OTTOBRE
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A come Adrenalina ed Amiodarone: quali farmaci?

Claudio Sandroni

ILCOR ALS Task Force - ERC ALS Science and Education Committee

Chair, ESICM Trauma and Emergency Medicine Section

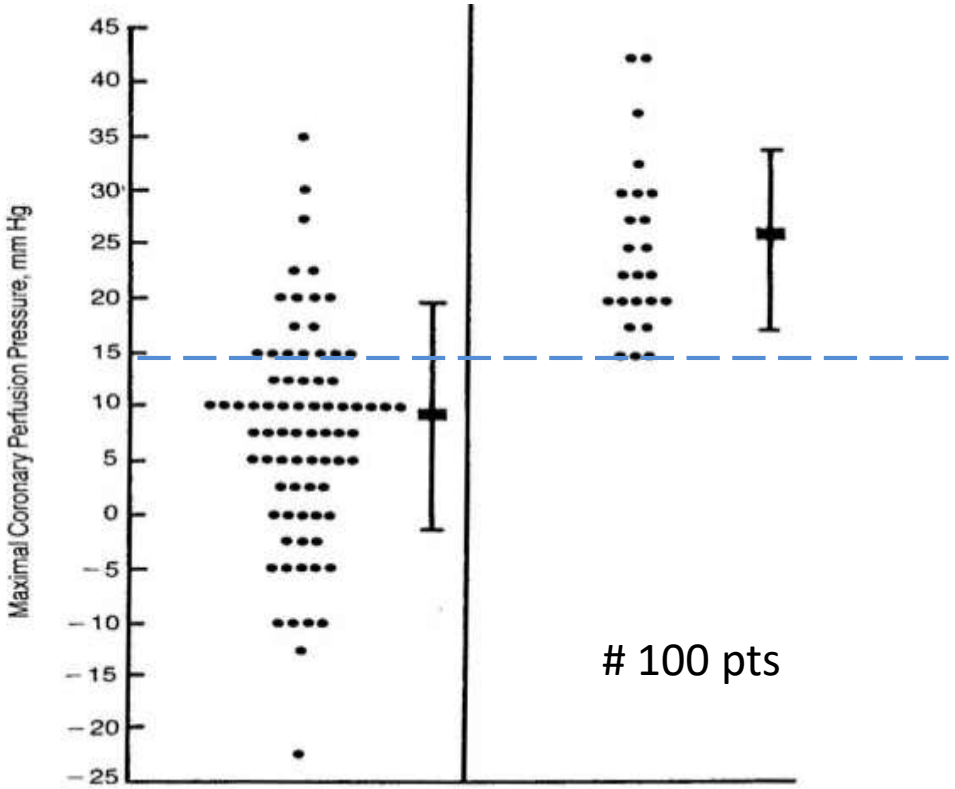
IRC Italian Resuscitation Council

COI

- Co-author, ERC guidelines, Advanced Life Support 2015
- Co-author, ERC guidelines on Post-Resuscitation Care, 2015

EPINEPHRINE

Coronary perfusion pressure (CPP)



ROSC only when
CPP≥15 mmHg

Paradis NA. JAMA 1990; 263: 1106-13

Epinephrine

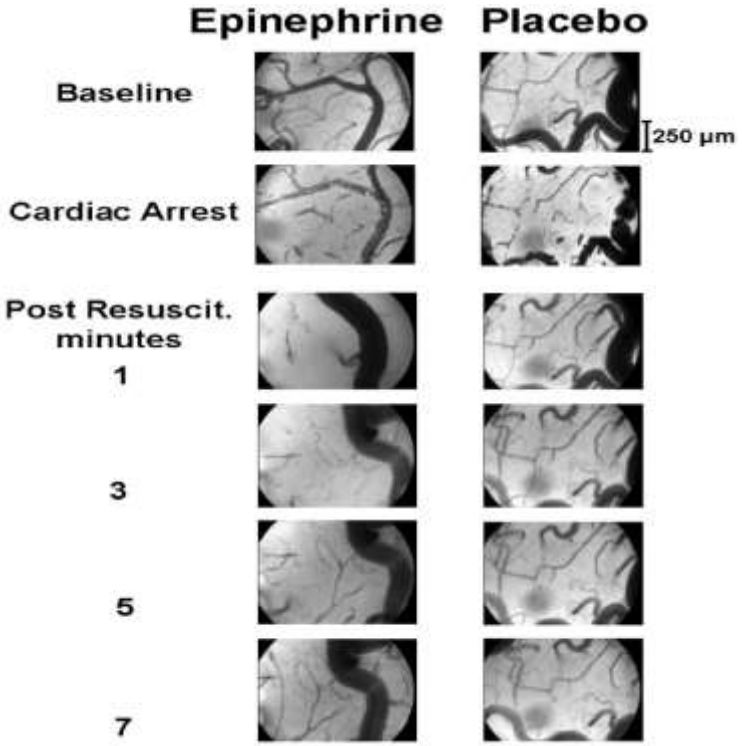
- It increases coronary blood flow
  - Michael JR et al. Circulation 1984;69:822-35
  - Brown CG et al. Circulation 1987;75:491-7
- It increases cerebral blood flow
  - Michael JR et al. Circulation 1984;69:822-35
  - Burnett AM et al. Resuscitation 2012; 83:1021–24
- Microcirculation?

Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation*

Giuseppe Ristagno, MD; Wanchun Tang, MD, FCCM; Lei Huang, MD; Alain Fymat, MD; Yun-Te Chang, MD; Shijie Sun, MD, FCCM; Carlos Castillo, MSEE; Max Harry Weil, MD, PhD, FCCM

Epinephrine:

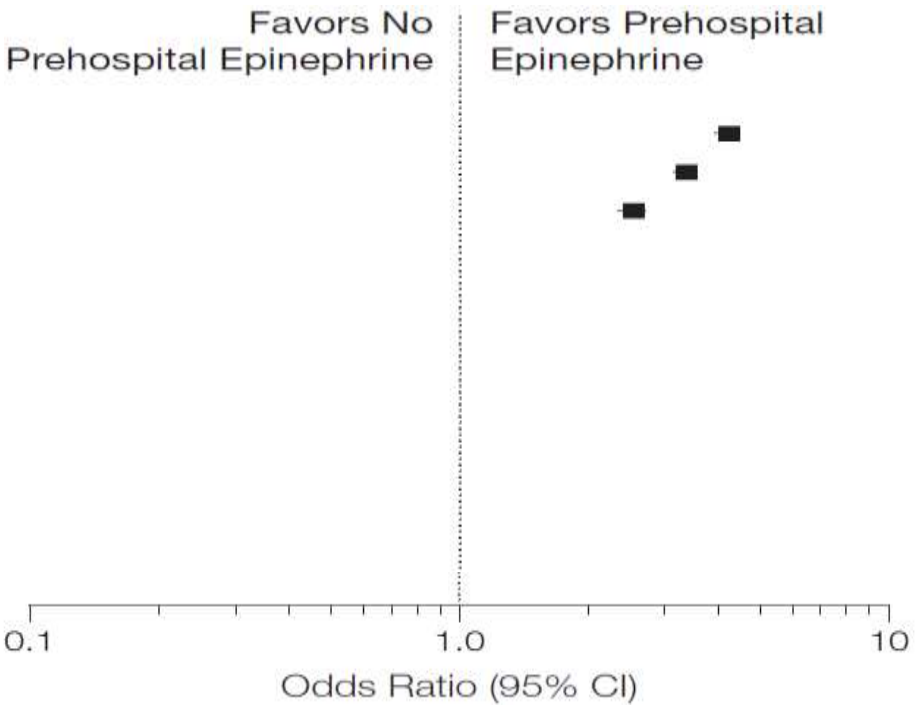
- Increases arterial pressure
- Decreases cerebral microcirculation
- Decreases oxygen pressure (PbO_2) inside cerebral tissue



Ristagno G et al Crit Care Med 2009;37:1408-15

JAMA Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases
ROSC	
Unadjusted	417 155
Adjusted for selected variables[a]	412 078
Adjusted for all covariates[b]	391 046



Hagihara A et al, JAMA. 2012;307(11):1161-116

BMJ

Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study

	Unadjusted*	Adjusted†
Ventricular fibrillation/ventricular tachycardia (1990 pairs)		
Overall survival	1.34 (1.12 to 1.60)‡	1.36 (1.13 to 1.63)
Neurologically intact survival	1.01 (0.78 to 1.30)§	1.02 (0.78 to 1.33)
Non-ventricular fibrillation/ventricular tachycardia (9058 pairs)		
Overall survival	1.72 (1.45 to 2.04)¶	1.78 (1.49 to 2.13)
Neurologically intact survival	1.57 (1.04 to 2.37)**	1.55 (0.99 to 2.41)

Nakahara S et al BMJ 2013;347:f6829

JAMA

Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest: A Randomized Trial

Theresa M. Olasveengen; Kjetil Sunde; Cathrine Brunborg; et al.

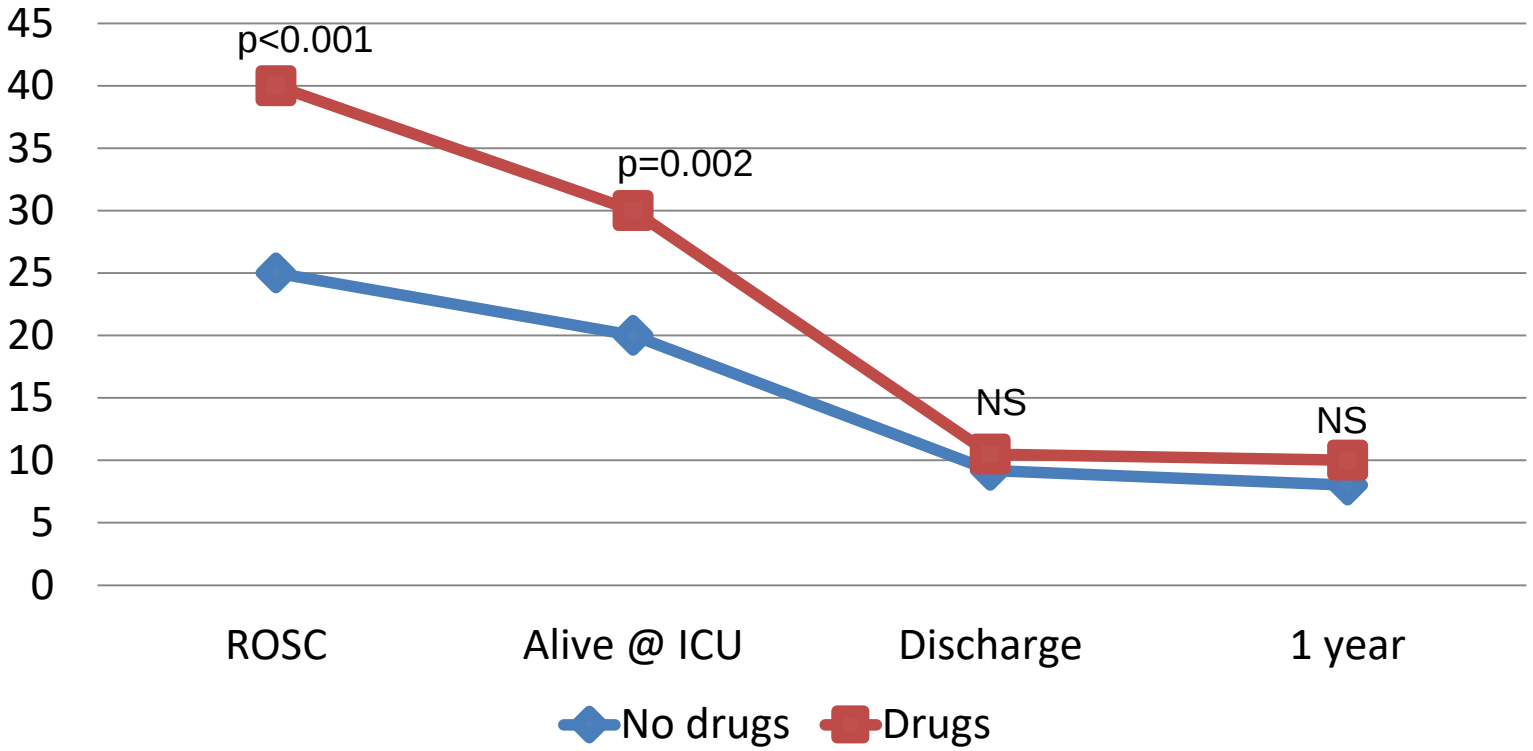
- Randomised trial, non-traumatic OHCA
- 851 adult patients
- Intervention:
  - ALS with drugs
  - ALS with no drugs (1st venous access 5' after ROSC)
- Strict control of CPR quality

Olasveengen, JAMA 2009; 302:2222-9

JAMA

Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest: A Randomized Trial

Theresa M. Olasveengen; Kjetil Sunde; Cathrine Brunborg; et al.



Olasveengen, JAMA 2009; 302:2222-9

However

- Not blinded
- Not only epinephrine
  - Antiarrhythmics
  - Atropine

Olasveengen, JAMA 2009; 302:2222-9

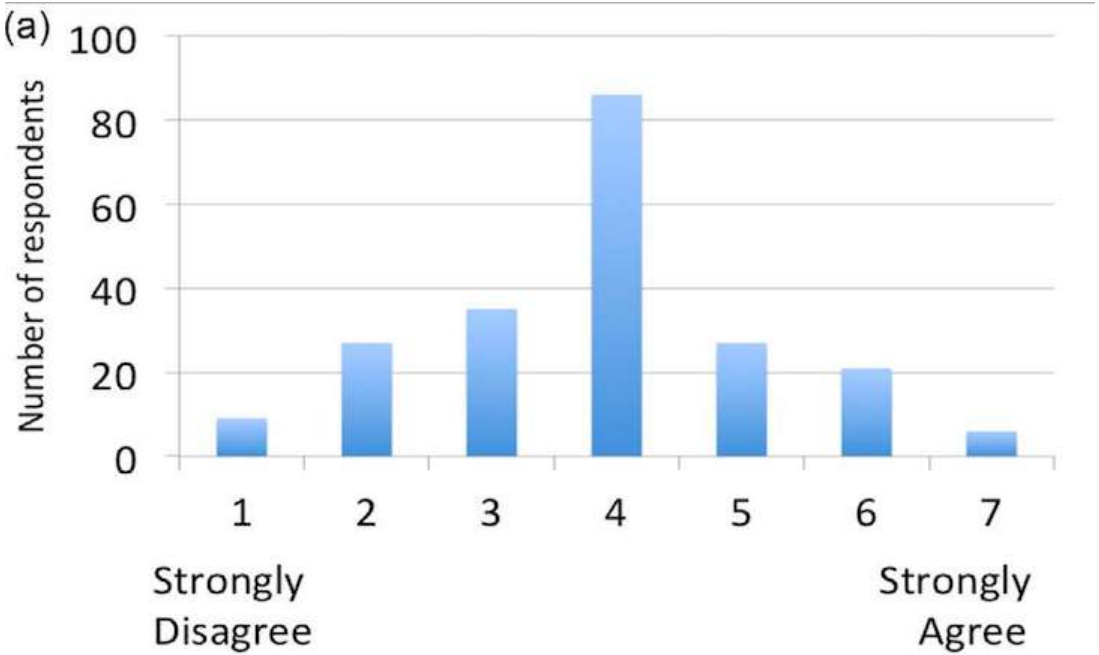
PARAMEDIC2
The Adrenaline Trial

ORIGINAL ARTICLE

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

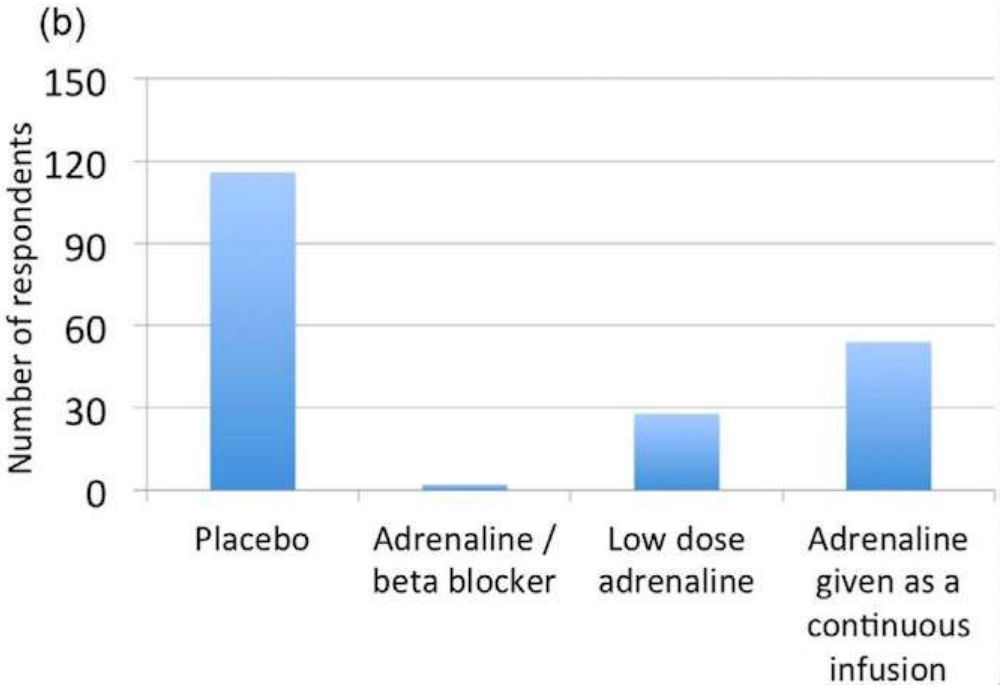
G.D. Perkins, C. Ji, C.D. Deakin, T. Quinn, J.P. Nolan, C. Scomparin, S. Regan, J. Long, A. Slowther, H. Pocock, J.J.M. Black, F. Moore, R.T. Fothergill, N. Rees, L. O'Shea, M. Docherty, I. Gunson, K. Han, K. Charlton, J. Finn, S. Petrou, N. Stallard, S. Gates, and R. Lall, for the PARAMEDIC2 Collaborators*

“Do i.v. adrenaline use risks in cardiac arrest outweigh benefit?”



Perkins GD et al. N Engl J Med. 2018; 379:711-721

“In a trial, the standard dose of adrenaline should be compared with which of the following?”



Perkins GD et al. N Engl J Med. 2018; 379:711-721

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

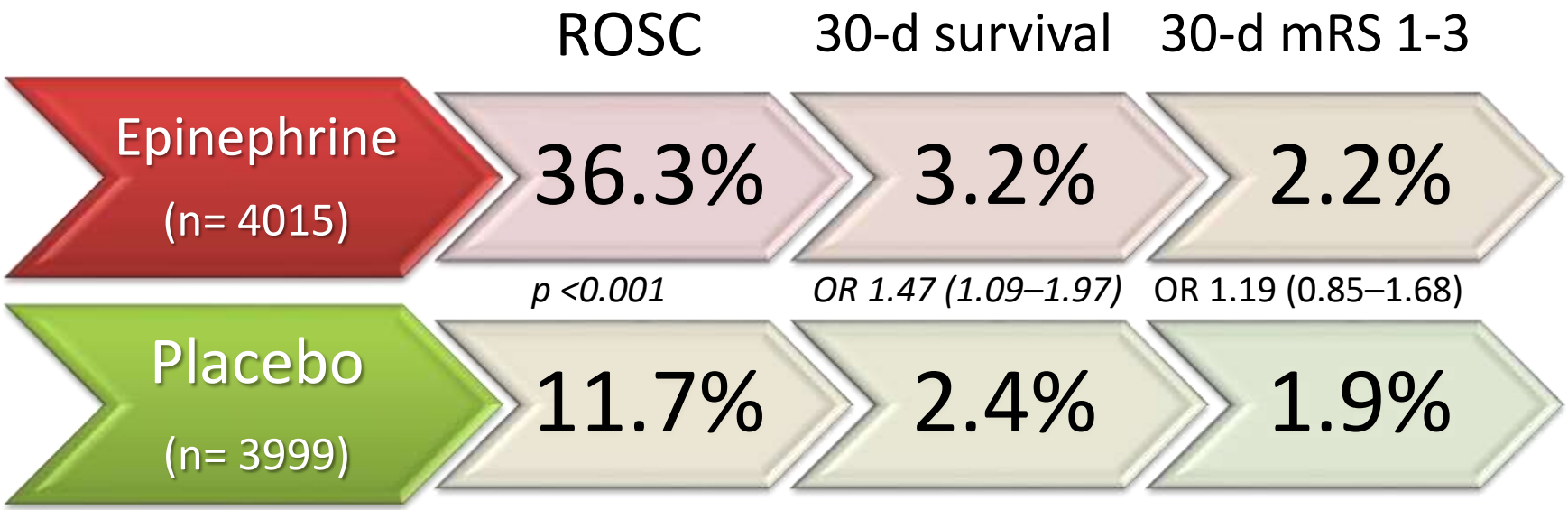
- 8014 adult OHCA in UK
- Epinephrine vs. placebo (double-blinded)
- Primary outcome: survival @30 days
- Secondary outcome: discharge w/mRS 1-3

Perkins GD et al. N Engl J Med. 2018; 379:711-721

modified Rankin Score (mRS)

Score	Definition
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Results

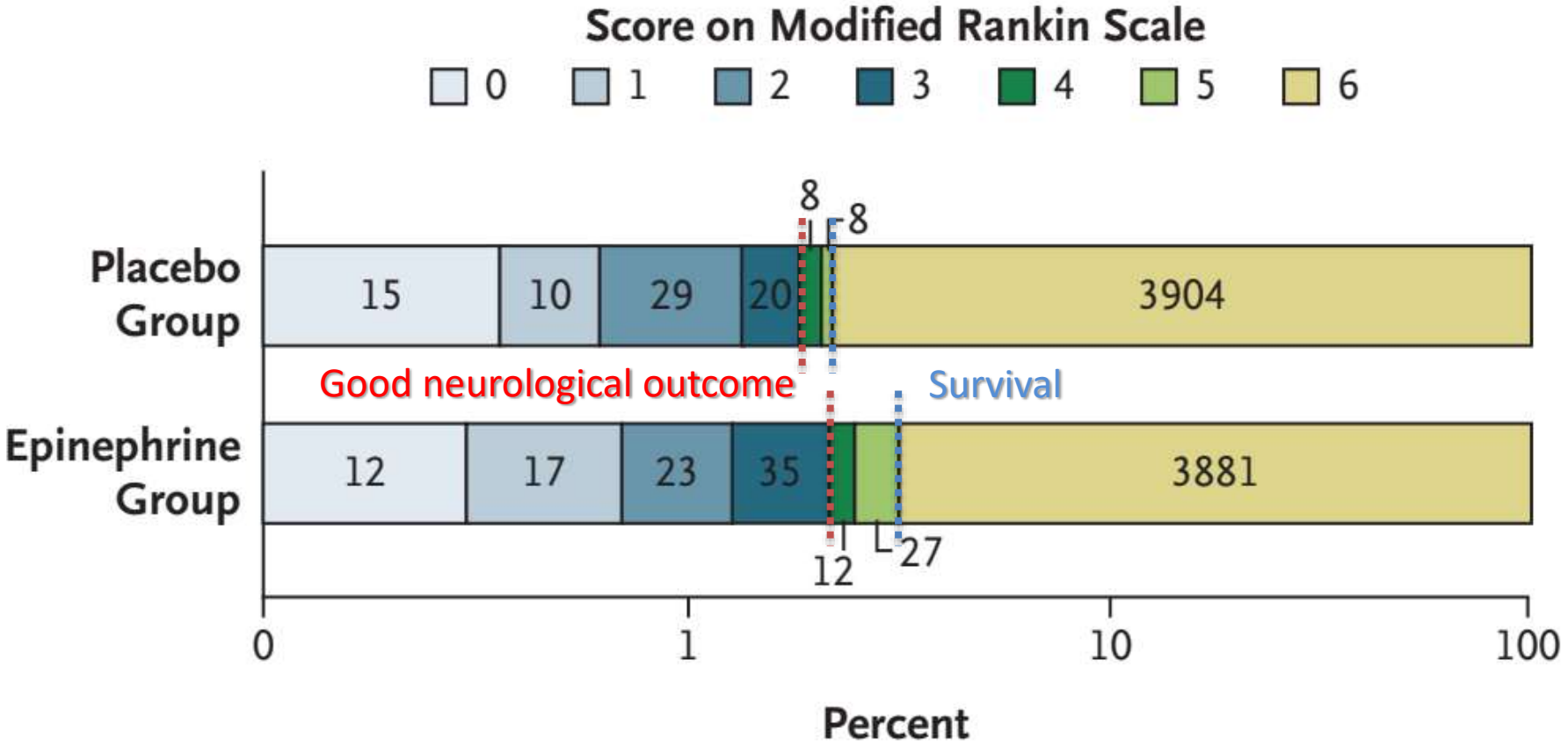


Perkins GD et al. N Engl J Med. 2018; 379:711-721

Epinephrine: benefits?

- Significant increase of survival to discharge
  - Quantitatively modest (0.8%)
  - NNT = 113
- Nonsignificant increase of survival with good neurological outcome
  - Higher rate of poor neurological outcome *in survivors*

Perkins GD et al. N Engl J Med. 2018; 379:711-721



Perkins GD et al. N Engl J Med. 2018; 379:711-721

Future sub-studies

- Timing of epinephrine
- Administration route
- Cost analysis

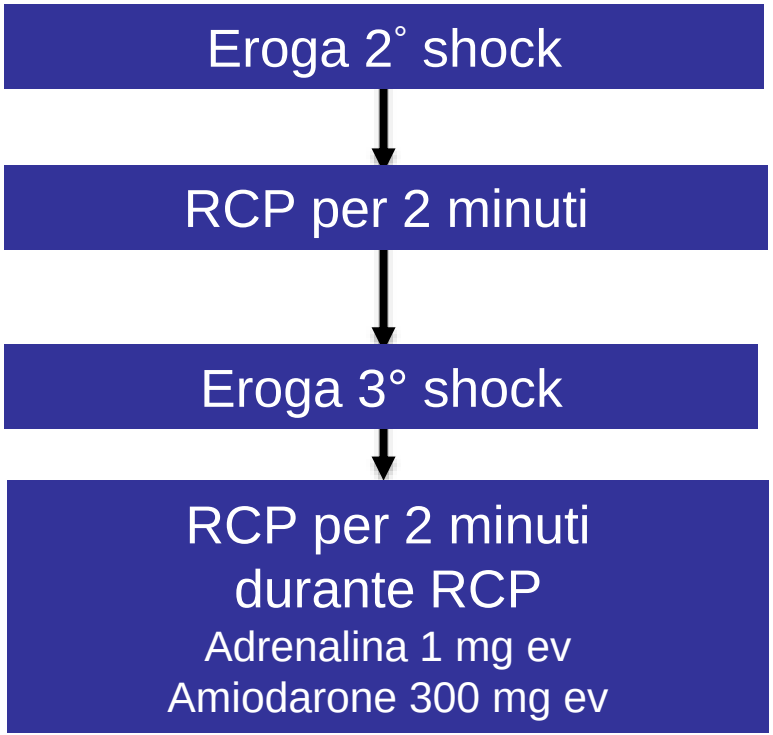
Perkins GD et al. N Engl J Med. 2018; 379:711-721

ILCOR Statement: Vasopressors

- We recommend administration of epinephrine during CPR
  - (strong recommendation, low to moderate certainty of evidence).
- For PEA/asystole, we recommend administration of epinephrine as soon as feasible during CPR
  - (strong recommendation, very low certainty of evidence).
- For VF/pVT, we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during CPR
  - (weak recommendation, very low certainty of evidence).

ANTIARRHYTHMICS

In caso di FV / TV refrattaria



- Somministra **adrenalina** e **amiodarone 300 mg** dopo il 3° shock
- In alternativa all'amiodarone: **lidocaina 1-1,5 mg/kg**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 5, 2016 VOL. 374 NO. 18

Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest

- Double-blind RCT (*ALPS* trial) in VF/pVT OHCA
- Shock-resistant (≥1) VF/pVT were randomised (1:1:1):
  - Amiodarone (Nexterone®) 300 mg (+ 150)
  - Lidocaine 120 mg (+ 60)
  - Placebo
- Primary endpoint: survival to discharge
  - Secondary endpoint: survival to discharge with good mRS

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

ALPS trial: characteristics

- Captisol-enabled amiodarone (Nexterone® Baxter)
  - To avoid the haemodynamic effects of Polysorbate-80
- Either i.v. or i.o. administration route
- Powered to detect a 6% absolute difference between amiodarone and placebo
  - 3000 patients needed

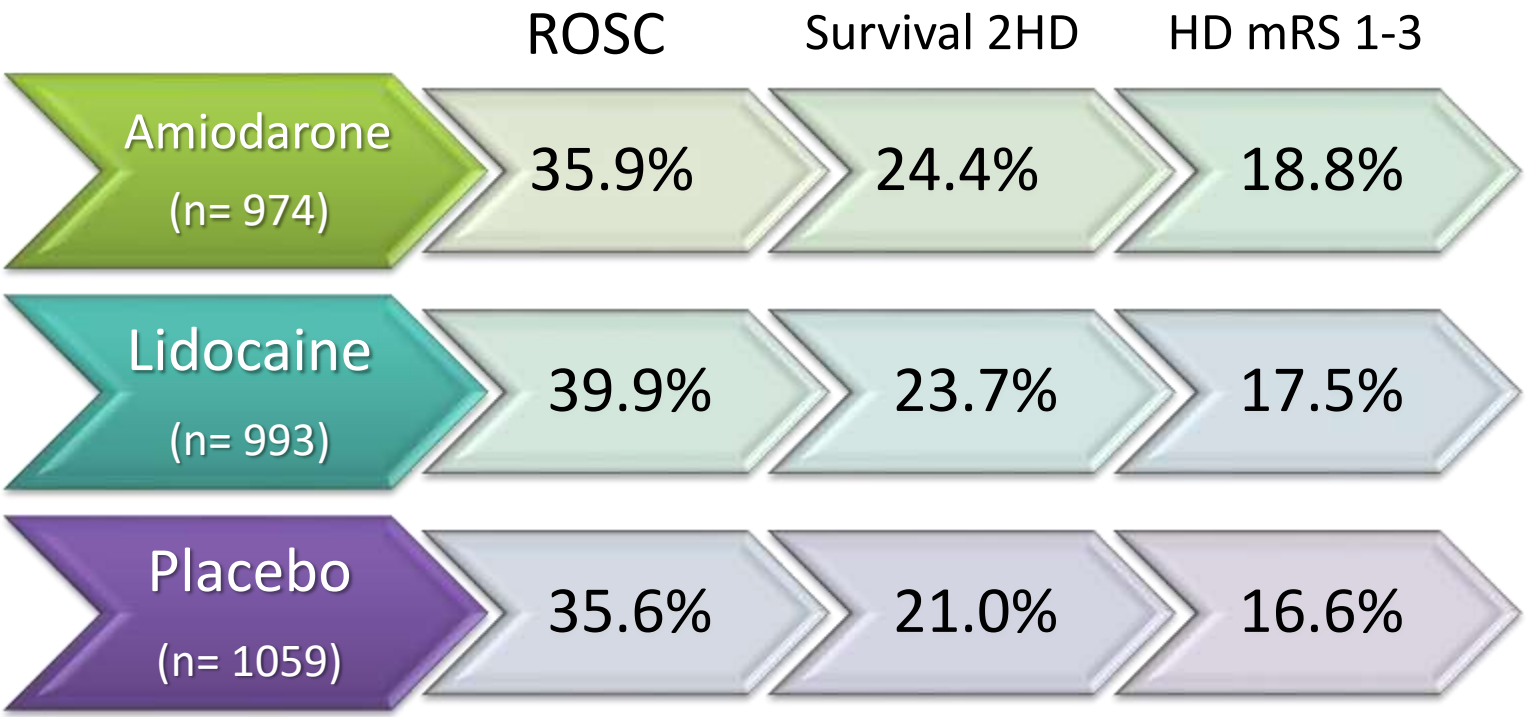
Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

ALPS trial: key process variables

Characteristic	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)
Time from initial call to first dose of trial drug in patients with non–EMS-witnessed cardiac arrest — min	19.3±7.1	19.3±7.6	19.3±7.3
Time from cardiac arrest to first dose of trial drug in patients with EMS-witnessed arrest — min	11.7±5.8	12.1±6.6	12.1±6.6
Trial drug given through intraosseous access — no./total no. (%)†	212/974 (21.8)	220/991 (22.2)	229/1054 (21.7)
No. of shocks before first dose of trial drug — median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

Results



Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

Rates of hospital admission

n = 3026

Amiodarone vs. Placebo		Lidocaine vs. Placebo		Amiodarone vs. Lidocaine	
Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value
6.0 (1.7 to 10.3)	0.01	7.4 (3.1 to 11.6)	<0.001	−1.3 (−5.7 to 3.1)	0.55

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

Rates of survival to discharge

n = 3026

Amiodarone vs. Placebo		Lidocaine vs. Placebo		Amiodarone vs. Lidocaine	
Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value	Difference (95% CI) *percentage points*	P Value
3.2 (–0.4 to 7.0)	0.08	2.6 (–1.0 to 6.3)	0.16	0.7 (–3.2 to 4.7)	0.70

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

Limitations

- Underpowered
  - Predicted absolute difference in survival to discharge 6.3%; actual 3.4%)
  - ≈ 9,000 patients needed
- Generalisability?
  - Nexterone used instead of Amiodarone
  - Drugs used after 1 unsuccessful shock
- Survival according to administration route?

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

Survival according to administration route

	Amiodarone	Lidocaine	Placebo	Amiodarone vs Placebo Difference (95% CI) P	Lidocaine vs Placebo Difference (95% CI) P	Amiodarone vs Lidocaine Difference (95% CI) P
Route of access[2]						
IO, n (%) [N=212;218;227]	41 (19.3%)	45 (20.6%)	51 (22.5%)	-3.1% (-10.7%, 4.5%) P=0.42	-1.8% (-9.5%, 5.8%) P=0.64	-1.3% (-8.9%, 6.3%) P=0.74
IV, n (%) [N=758;765;824]	196 (25.9%)	188 (24.6%)	170 (20.6%)	5.2% (1.1%, 9.4%) P=0.01	3.9% (-0.2%, 8.1%) P=0.06	1.3% (-3.1%, 5.6%) P=0.56

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

ALPS trial: conclusions

- In patients with VF/pVT resistant to ≥1 shock, both amiodarone and lidocaine are associated with increased survival to hospital admission as compared to placebo
- There is a non-significant trend towards increased survival to discharge as well
- Amiodarone ≡ Lidocaine

Kudenchuck PJ. et al., NEJM 2016;374:1711-22.

ILCOR COSTR: Antiarrhythmics

- We suggest the use of amiodarone or lidocaine in adults with shock refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT)
  - (weak recommendation, low quality evidence).

Statement paper

European Resuscitation Council Guidelines for Resuscitation: 2018 Update– Antiarrhythmic drugs for cardiac arrest

- The ILCOR CoSTR suggests that any beneficial effects of amiodarone or lidocaine are similar.
- This ERC update does not make any major changes to the recommendations for the use of antiarrhythmic drugs during advanced life support for shock refractory cardiac arrest.

Soar J et al. Resuscitation 2019; 134:99-103

Conclusions

- Epinephrine increases survival to discharge
  - Trend towards better neurological outcome
- Both amiodarone and lidocaine increase ROSC
  - No effect on good neurological survival
- Both trials underpowered
  - No reason to change guidelines for now

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