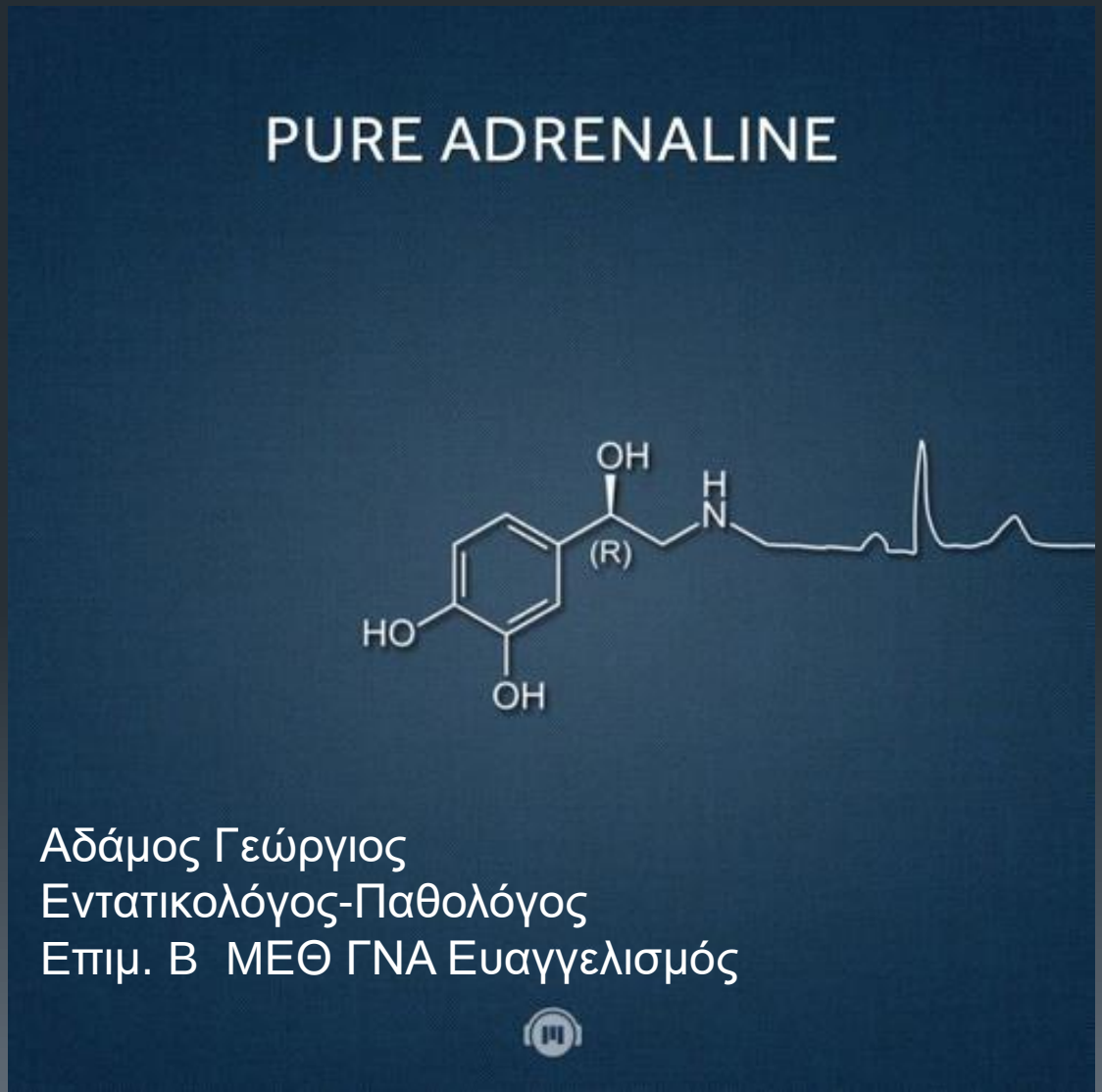
Αγγειοσυσπαστικά και αναζωογόνηση



Αδάμος Γεώργιος
Εντατικολόγος-Παθολόγος
Επιμ. Β ΜΕΘ ΓΝΑ Ευαγγελισμός

Αγγειοσυσπαστικά και αναζωογόνηση

- Rationale
- Drawbacks
- Evidence
- Questions (timing, dose)
- 2021 Guidelines

Αγγειοσυσπαστικά και αναζωογόνηση

- Rationale

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

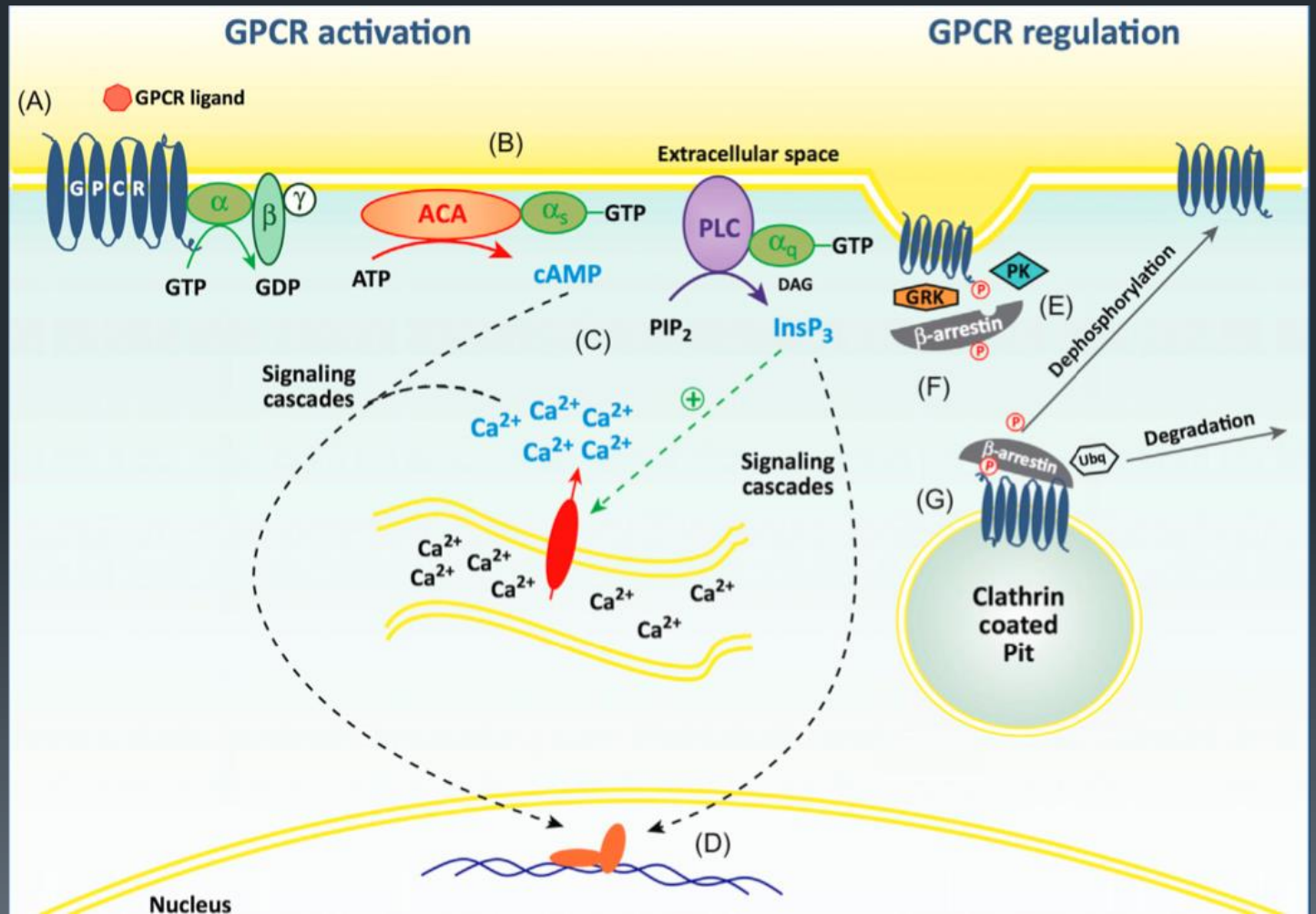
- Adrenaline is a powerful agonist at both α and β-adrenergic receptors (⬇doses- β effects predominate)

- Adrenergic receptors belong to G protein–coupled receptor (GPCR) superfamily, and are membrane receptors that activate heterotrimeric G proteins

- G proteins typically stimulate (via Gs protein) or inhibit (via Gi protein) the enzyme adenylyl-cyclase or activate (via Gq protein) phospholipase C (PLC)

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline



Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

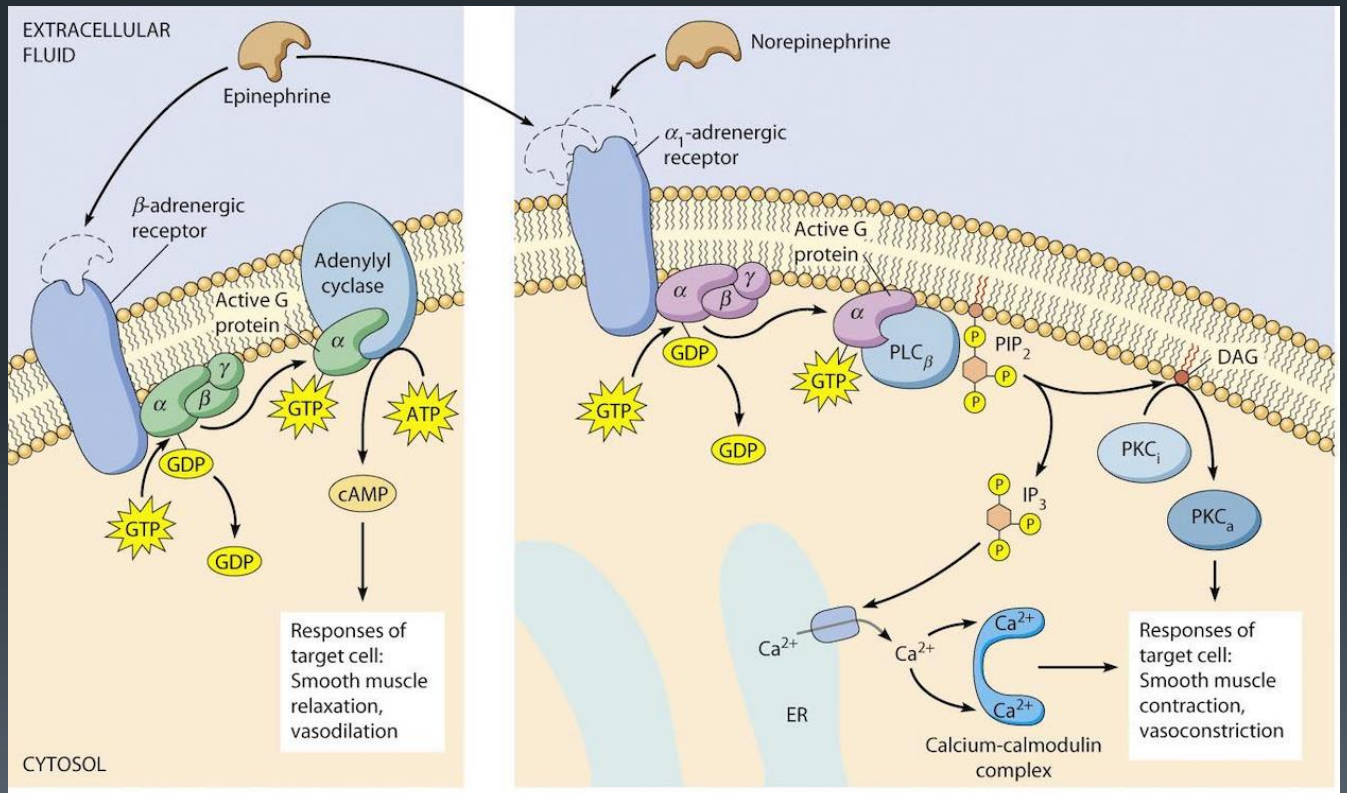
α-adrenergic receptor

- Can be classified into α1 and α2
- α1-receptors are concentrated around arterial and venous trees, smooth muscles in GI and urogenital tract.
- α2-receptors are distributed both presynaptically and post-synaptically.
- Presynaptic α2 receptor inhibit secretion of noradrenaline from sympathetic neurones (also mediate hypnotic-analgesic effects)
- Postsynaptic α2 receptors are responsible for inhibition of adrenaline from adrenal medulla

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

α-adrenergic receptor



(a) cAMP pathway initiated by activation of β-adrenergic receptor

(b) Inositol-phospholipid-calcium pathway initiated by activation of α_1-adrenergic receptor

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

β-adrenergic receptor

- Three subtypes of β-ARs have been characterized (β1 -AR, β2 -AR, β3 - AR)
- In the healthy human heart, there is approximately a 4:1 ratio of β1 -AR to β2 -AR, with minimal expression of β3 - AR
- β1-ARs are present in all cardiomyocytes , low level of expression in non-myocyte cells
- β2 -AR and β3 -AR are frequently absent in myocytes but are abundant in non- myocyte cells (relaxation of smooth muscles)

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

β-adrenergic receptor

- While all β-ARs are associated with the stimulatory G protein (G_s) activation, it is known that β2 -AR and β3 -AR can be coupled to inhibitory G_i protein

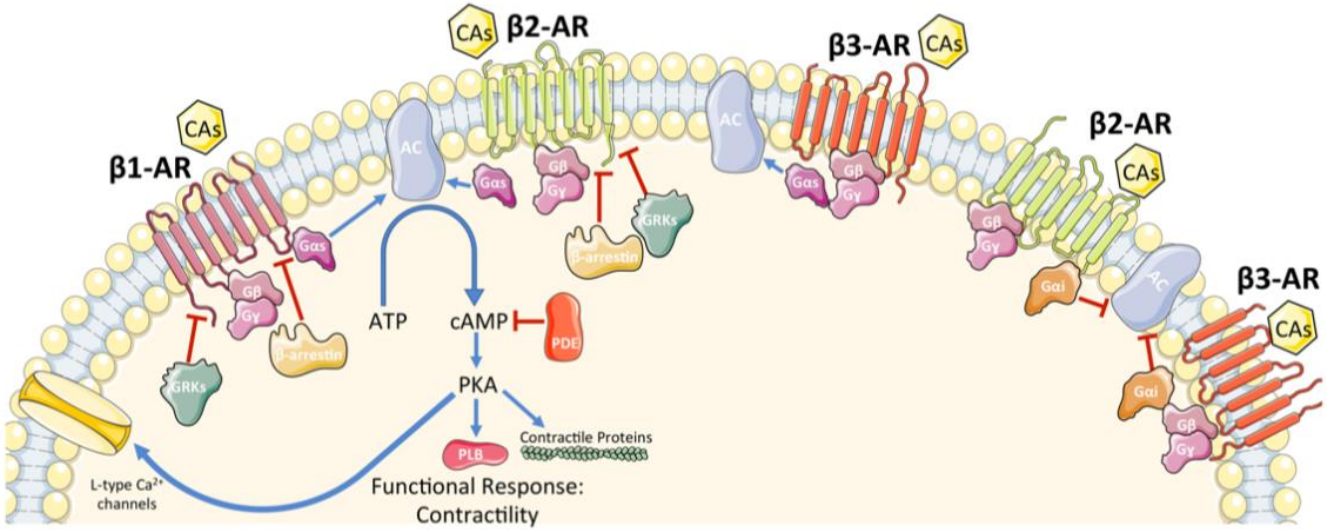


FIGURE 1 | Schematic representation of β-AR signaling in cardiomyocytes. See main text for details. CAs, catecholamines; β-AR, β-adrenergic receptor; G-protein subunits: G_α ($G_{\alpha s}$ or $G_{\alpha i}$), G_β, G_γ; GRK2, G protein-coupled receptor kinase 2; AC, adenylyl cyclase; ATP, adenosine tri-phosphate; cAMP, cyclic adenosine mono-phosphate; PDE, phosphodiesterase; PKA, protein kinase A. A blue arrow is used when a stimulatory mechanism is involved while a red bar-headed line is used for an inhibitory mechanism.

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

- After more than a few minutes of CA arterial tone collapses and a vasoconstrictor is essential

- Adrenaline augments coronary blood flow generated by chest compressions during CPR

- Coronary perfusion pressure defined as the difference between aortic diastolic blood pressure and the right atrial pressure is the major determinant of coronary blood flow.

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

- Through its action of increasing coronary and cerebral perfusion pressure, is thought to increase the chance of restoring a heartbeat (return of spontaneous circulation (ROSC)) and of improving long-term neurological outcome

- Adrenaline has been included in resuscitation guidelines worldwide since the 1960s

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

Epinephrine in cardiac resuscitation

*John W. Pearson, B.M.**
Joseph S. Redding, M.D.
Baltimore, Md.

The acceptance of closed-chest cardiac massage as an effective measure in the treatment of cardiac arrest necessitates a re-evaluation of other measures which might also be used in this situation. Most of our information in regard to closed-chest cardiac massage is based on clinical reports. It is known experimentally, however, that closed-chest cardiac massage combined with intermittent positive pressure ventilation will reoxygenate the arterial blood even when asphyxia is profound.[1] This artificial circulation is much less than normal,[2] and, therefore, a spontaneous circulation must be restored at the earliest possible moment.

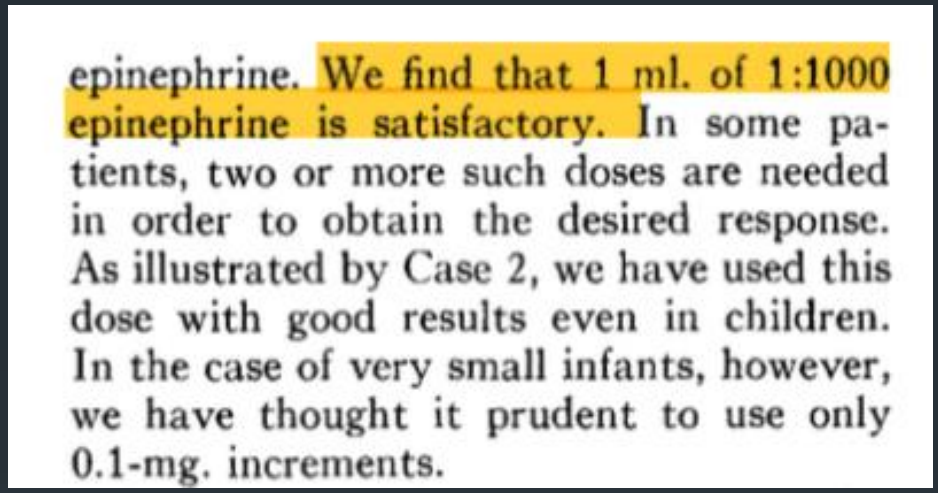
The use of intracardiac injections of epinephrine to restore heart action has been advocated for years. There are conflicting directions as to the dosage and manner of use, and almost no data about its effectiveness. The following experiments were performed to correct this deficiency.

Methods

Seventy mongrel dogs were anesthetized with pentobarbital (25 mg. per kilogram of body weight) given intravenously. Each animal was intubated with a cuffed endotracheal tube. Aortic pressure and electrocardiogram were recorded continuously in all animals. With the animal secured in the supine position and breathing room air, the endotracheal tube was occluded at the end of an exhalation. At first there were increasing efforts to breathe, accompanied by great fluctuations in aortic pressure. Between 2 and 4 minutes after airway obstruction the animals became apneic. Circulation then gradually deteriorated, with the development of hypotension and bradycardia. From 6 to 8 minutes after airway obstruction, fluctuations in aortic systolic blood pressure stopped in each animal. Cessation of circulation at this point had been confirmed in other experiments by the absence of measurable myocardial contractile force and by cessation of blood flow in the carotid artery.

The dogs were divided into 7 groups of 10 dogs each (see Table I). In Group 1, intermittent positive pressure ventilation with room air (25 ml. per kilogram of body weight at a rate of 20 breaths per minute) was begun when the aortic systolic pressure fell to 25 mm. Hg. In Group 2, ventilation was begun at a systolic pressure of 25 mm. Hg, and 1 ml. of 1:1000 epinephrine was injected into one of the ventricles as ventilation was begun. It made no difference in the final results whether the injection was made into the right or the left ventricle. In Group 3, ventilation of the lungs and closed-chest cardiac massage, performed by compressing the sternum

From the Department of Anesthesiology, Baltimore City Hospitals, Baltimore, Md.
This investigation was supported by Research Grant H-5439 from the National Heart Institute, United States Public Health Service.
Received for publication Sept. 17, 1962.
*Address: Department of Anesthesiology, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore 24, Md.



epinephrine. We find that 1 ml. of 1:1000 epinephrine is satisfactory. In some patients, two or more such doses are needed in order to obtain the desired response. As illustrated by Case 2, we have used this dose with good results even in children. In the case of very small infants, however, we have thought it prudent to use only 0.1-mg. increments.

Am Heart J. 1963 Aug;66:210-4

Αγγειοσυσπαστικά και αναζωογόνηση

- Adrenaline

- Early study of 100 patients with invasive monitoring (catheterization of RA and aortic arch) during cardiac arrest recorded much ↑CPP in patients who had ROSC

- No patient with maximal CPP <15mmHg had ROSC.

- Thus adrenaline might ↑ROSC through ↑CPP

JAMA. 1990;263:1106–13.

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

- Although global cerebral and coronary blood flow is increased by epinephrine, microcirculatory flow may be impaired

- Beta-adrenergic effects are generally undesirable for cardiac arrest patients (tachycardia, dysrhythmias, ↑myocardial O_2 demand)

- Epinephrine can promote thrombogenesis and platelet activation

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Animal studies

- Animal studies have documented ↓cerebral tissue oximetry values with epinephrine vs placebo despite ↑MAP and cerebral perfusion pressure

Resuscitation. 2016;101:77–83

- Microcirculatory blood flow was evaluated with **OPS** imaging in 10 pigs randomized in adrenaline vs vasopressin during CPR.

Post ROSC cerebral O_2 tension and microvascular flows were lower with epinephrine while cerebral CO_2 tension was higher.

Crit Care Med. 2007;35:2145–9

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Animal studies

➢ Another study in pigs recorded ↓cerebral O_2 tension and ↑cerebral CO_2 tension post ROSC in adrenaline group vs placebo despite higher MAP

➢ Microcirculatory alterations were evident in favor of placebo group

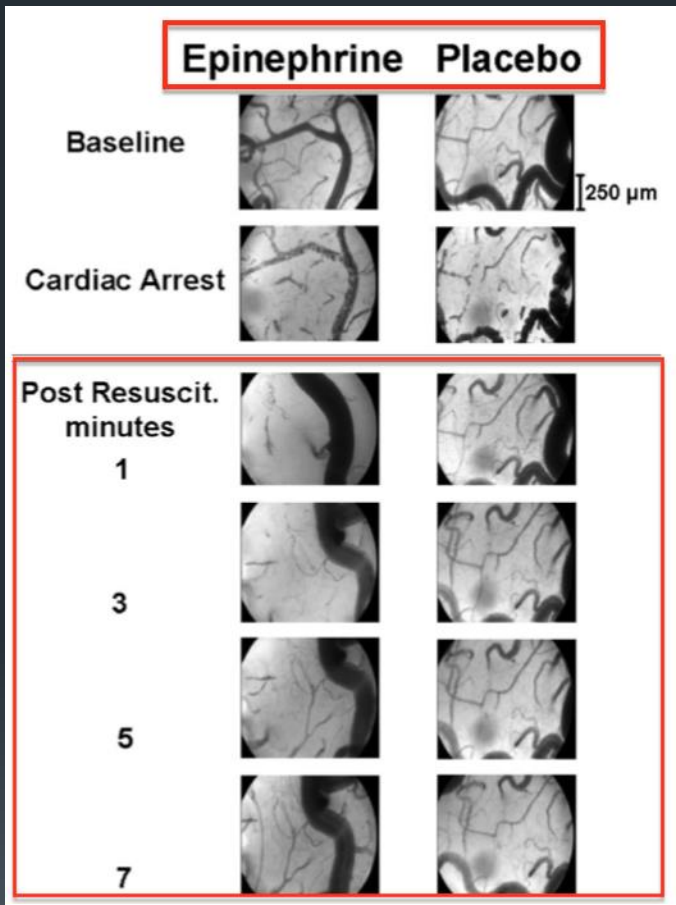


Figure 5. Cerebral cortical circulation. Microphotographs of the frontal cortex at baseline, during cardiac arrest, and following resuscitation after epinephrine and in comparison with placebo. In contrast to venules, microvessels <20 μm largely disappear after epinephrine and reappear within 5–7 minutes.

Crit Care Med 2009; 37:1408 –1415

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Animal studies

➢ Microcirculatory Alterations (MBF)

Table 1. Experimental groups

Group	Drugs	Symbol	Number of Animals Per Group
1	Placebo + Placebo	□	5
2	Placebo + Epinephrine	■	5
3	Propranolol + Prazosin + Epinephrine	△	5
4	Propranolol + Yohimbine + Epinephrine	▲	5

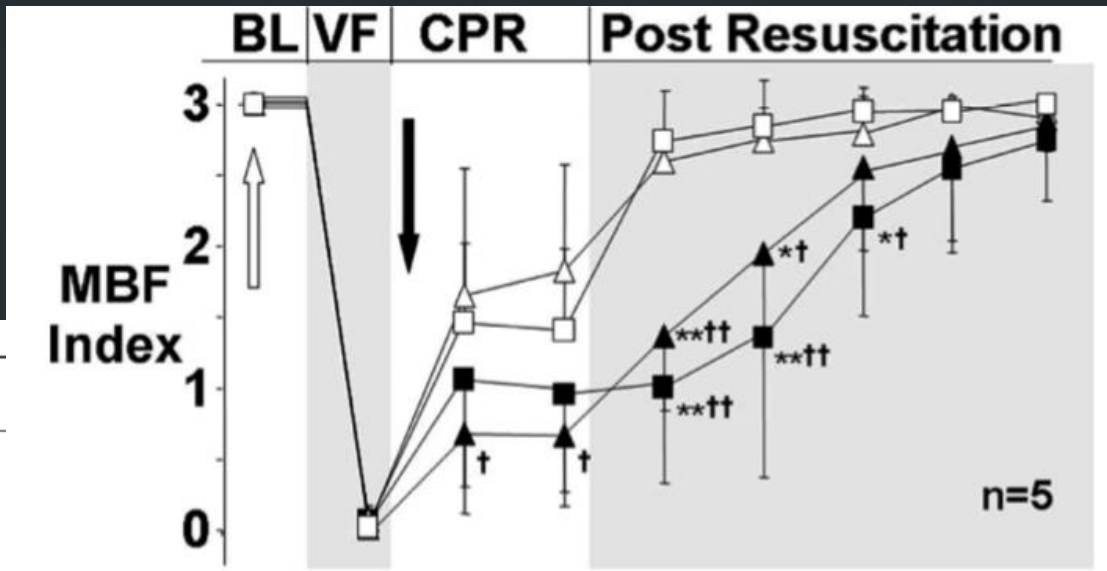


Figure 4. *Top*, Microcirculatory blood flow index (*MBF*). *Bottom*, number of capillaries during post-resuscitation, assessed with orthogonal polarization spectral imaging applied to the cerebral cortical surface (mean ± SD). *BL*, baseline; *VF*,

Crit Care Med 2009; 37:1408 –1415

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Animal studies

➢ ↑ Lactate

Table 4. Blood gas measurements at baseline (BL) and after resuscitation (PR)

	Placebo + Placebo □ (5)	Placebo + Epinephrine ■ (5)	Propranolol + Prazosin + Epinephrine Δ (5)	Propranolol + Yohimbine + Epinephrine ▲ (5)
Hemoglobin, g/dL				
BL	8.9 ± 1	8.8 ± 1.4	8.7 ± 1	8.8 ± 1.2
pH				
BL	7.56 ± 0.03	7.56 ± 0.01	7.56 ± 0.03	7.53 ± 0.03
PR 5 min	7.5 ± 0.06[a]	7.41 ± 0.04	7.48 ± 0.02[b]	7.43 ± 0.05
Arterial PO_2, Torr				
BL	109 ± 19	103 ± 15	101 ± 31	98 ± 4
PR 5 min	364 ± 61	353 ± 66	309 ± 65	401 ± 43
Arterial Pco_2, Torr				
BL	35.4 ± 5	35 ± 2	35.5 ± 4	35.4 ± 3
PR 5 min	35.2 ± 5	35.2 ± 5	35 ± 7	36.8 ± 3
Mixed venous saturation, %				
BL	84 ± 4	81 ± 8	78 ± 7	83 ± 5
PR 5 min	91 ± 2	89 ± 4	87 ± 9	89 ± 6
Arterial lactate, mmol/L				
BL	1.2 ± 0.2	1.1 ± 0.4	1 ± 0.1	1.8 ± 1.7
PR 5 min	5.1 ± 1.3[b]	8.3 ± 1.5	4.5 ± 0.7[b]	7 ± 3.1
Arterial glucose, mg/dL				
BL	100 ± 28	88 ± 27	83 ± 18	94 ± 15
PR 5 min	250 ± 102	168 ± 99	140 ± 52	199 ± 93

[a] $p < 0.02$ and [b] $p < 0.01$ vs. Placebo + Epinephrine group.

Crit Care Med 2009; 37:1408 –1415

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Animal studies

- Microcirculatory changes in the **sublingual mucosa** were evaluated post ROSC in a separate study of 15 pigs subjected to 5' of CPR.
- Adrenaline group had reduced microcirculatory blood flow which persisted for several minutes.

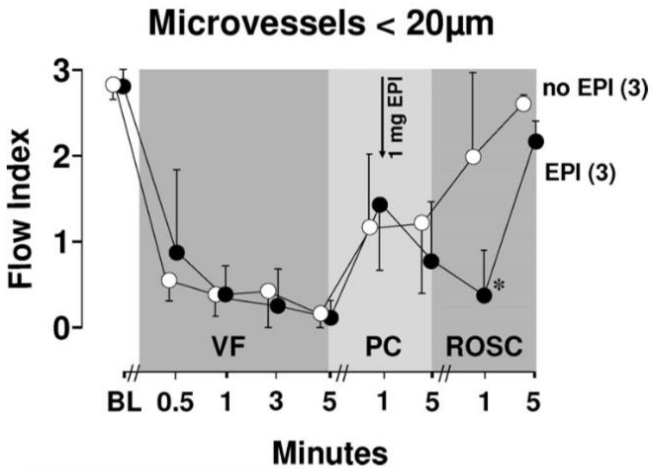


Figure 1. Progression of microvascular blood flow at baseline (*BL*), during ventricular fibrillation (*VF*) and precordial compression (*PC*), and after return of spontaneous circulation (*ROSC*) when 1 mg of epinephrine (*EPI*) was administered during PC. *$p < .05$ vs. no EPI.

Crit Care Med. 2006;34:S454–7

Αγγειοσυσπαστικά και αναζωογόνηση

- Drawbacks

Human physiogical studies

- An observational study of regional cerebral O_2 measured by NIRS in 36 patients with IHCA documented an ↑ rSO_2 by 1.4% during post adrenaline injection 5 min period

However the investigators noticed that rSO_2 values were actually already increasing prior to adrenaline injection (a trend not altered significantly by adrenaline, p=0.583)

Resuscitation. 2016;104:1–5

- In an Oslo study of 174 patients with OHCA adrenaline ↑ the rate transition from PEA to ROSC and vise versa (ROSC to PEA or VT/VF)

Resuscitation. 2012;83:946–52

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- AHA and ERC have included the use of vasopressors in their cardiac arrest resuscitation algorithms since the inception of their guidelines

- Despite the common and widespread use of vasopressor agents during CPR, the evidence base supporting their effectiveness is still evolving

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- In a 2015 review of existing science published by the International Liaison Committee on Resuscitation (ILCOR), the administration of standard-dose epinephrine (1 mg bolus dose) during CPR was given a weak recommendation supported by only very-low quality evidence

- when standard-dose epinephrine is given during CPR for patients with non-shockable rhythms, a weak recommendation based on low-quality evidence was made to administer the epinephrine as soon as possible

- PARAMEDIC2 trial followed the ERC ALS 2015 Guidelines

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

PARAMEDIC2

- Represents the **largest RCT** trial on epinephrine use in OHCA
- 8014 patients were randomized either to epinephrine or placebo group
- Groups were well balanced with respect to baseline characteristics reducing the risk of bias

N Engl J Med 2018;379:711-21

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

PARAMEDIC2

Primary outcome

-Rate of survival at 30 days

Secondary outcomes

-Rate of survival until hospital admission

-LOS in the hospital and in the intensive care unit (ICU)

-Rates of survival at hospital discharge and at 3 months

-Neurologic outcomes at hospital discharge and at 3 months.

N Engl J Med 2018;379:711-21

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

PARAMEDIC2

- Overall survival rate in this trial was disappointingly small* (3.2% and 2.4%, respectively)
- Epinephrine robustly improved ROSC (36.3% vs. 11.7%), a finding consistent with observational studies and a previous smaller RCT (aOR, 3.4; 95% CI, 2.0 to 5.6)
- Patients who received epinephrine had a higher rate of 30-day survival than those who received placebo (aOR, 1.47; 95% CI, 1.09 to 1.97)

N Engl J Med 2018;379:711-21

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

PARAMEDIC2

- There was no 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* (unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61)

- The proportion of survivors with severe neurologic impairment was actually higher in the epinephrine group (31.0% vs. 17.8%)

N Engl J Med 2018;379:711-21

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

PARAMEDIC2

-Paramedics administered the trial agent a median of 21 minutes after the emergency call

-The mean (±SD) total dose of epinephrine in this trial was 4.9±2.5 mg

-No subgroup analysis examining the timing of epinephrine dosing relative to the onset of arrest.

N Engl J Med 2018;379:711-21

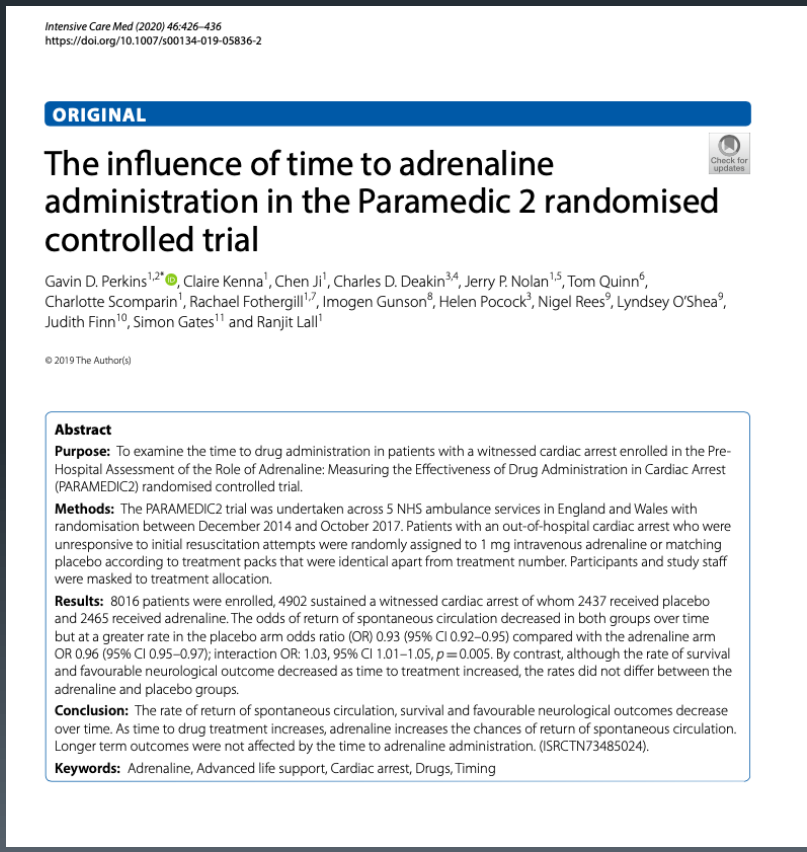
Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- Models of time to drug administration showed a pattern which suggests that the relative effects of adrenaline to placebo on ROSC increased over time

- By contrast, the effects of adrenaline relative to placebo on survival and favourable neurological outcomes did not change over time

*examined within the group of patients whose cardiac arrest was EMS or bystander witnessed (n=4,852)



Intensive Care Med (2020) 46:426–436
https://doi.org/10.1007/s00134-019-05836-2

ORIGINAL

The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial

Gavin D. Perkins[1,2*], Claire Kenna[1], Chen Ji[1], Charles D. Deakin[3,4], Jerry P. Nolan[1,5], Tom Quinn[6], Charlotte Scomparin[1], Rachael Fothergill[1,7], Imogen Gunson[8], Helen Pocock[3], Nigel Rees[9], Lyndsey O'Shea[9], Judith Finn[10], Simon Gates[11] and Ranjit Lall[1]

Abstract

Purpose: To examine the time to drug administration in patients with a witnessed cardiac arrest enrolled in the Pre-Hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2) randomised controlled trial.

Methods: The PARAMEDIC2 trial was undertaken across 5 NHS ambulance services in England and Wales with randomisation between December 2014 and October 2017. Patients with an out-of-hospital cardiac arrest who were unresponsive to initial resuscitation attempts were randomly assigned to 1 mg intravenous adrenaline or matching placebo according to treatment packs that were identical apart from treatment number. Participants and study staff were masked to treatment allocation.

Results: 8016 patients were enrolled, 4902 sustained a witnessed cardiac arrest of whom 2437 received placebo and 2465 received adrenaline. The odds of return of spontaneous circulation decreased in both groups over time but at a greater rate in the placebo arm odds ratio (OR) 0.93 (95% CI 0.92–0.95) compared with the adrenaline arm OR 0.96 (95% CI 0.95–0.97); interaction OR: 1.03, 95% CI 1.01–1.05, $p = 0.005$. By contrast, although the rate of survival and favourable neurological outcome decreased as time to treatment increased, the rates did not differ between the adrenaline and placebo groups.

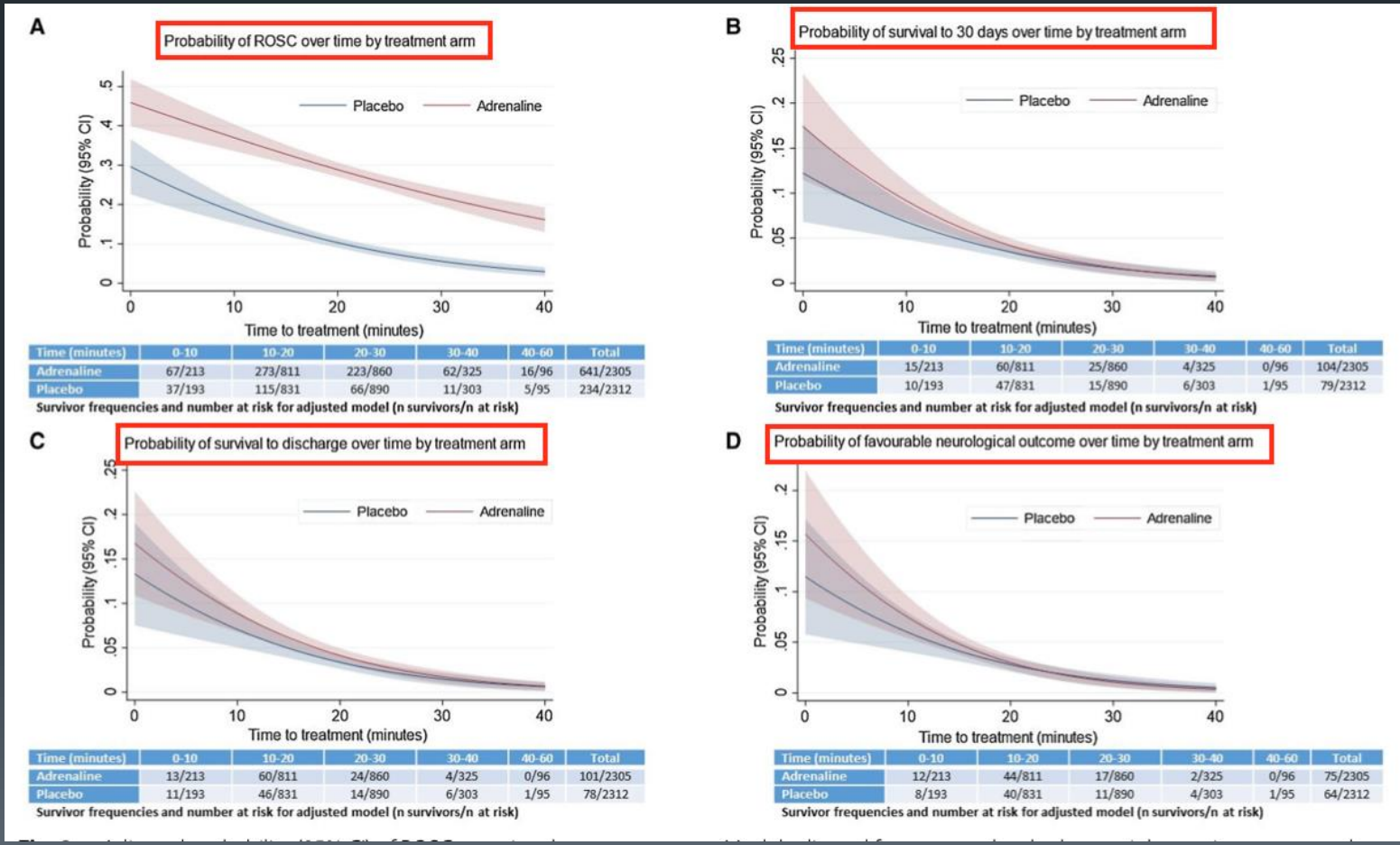
Conclusion: The rate of return of spontaneous circulation, survival and favourable neurological outcomes decrease over time. As time to drug treatment increases, adrenaline increases the chances of return of spontaneous circulation. Longer term outcomes were not affected by the time to adrenaline administration. (ISRCTN73485024).

Keywords: Adrenaline, Advanced life support, Cardiac arrest, Drugs, Timing

Intensive Care Med (2020) 46:426–436

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	67/213	273/811	223/860	62/325	16/96	641/2305
Placebo	37/193	115/831	66/890	11/303	5/95	234/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	15/213	60/811	25/860	4/325	0/96	104/2305
Placebo	10/193	47/831	15/890	6/303	1/95	79/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	13/213	60/811	24/860	4/325	0/96	101/2305
Placebo	11/193	46/831	14/890	6/303	1/95	78/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	12/213	44/811	17/860	2/325	0/96	75/2305
Placebo	8/193	40/831	11/890	4/303	1/95	64/2312

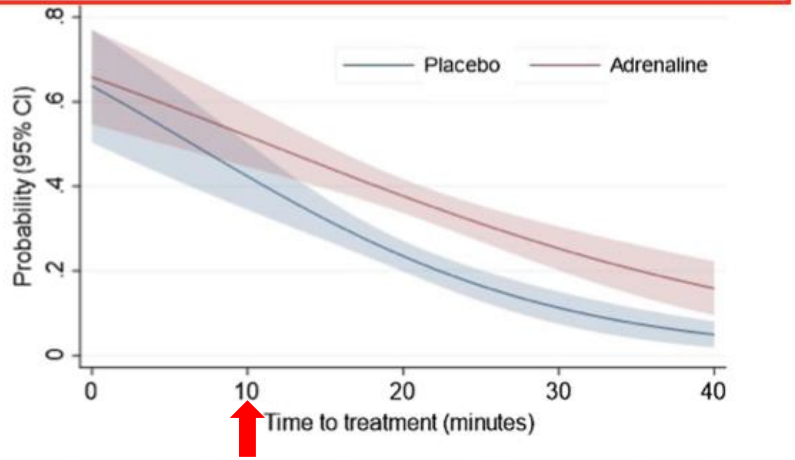
Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Intensive Care Med (2020) 46:426–436

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

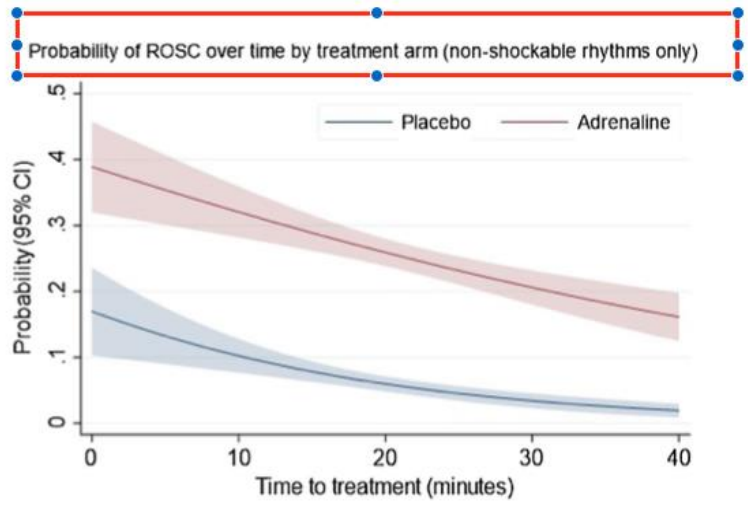
A



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	16/37	102/239	74/211	16/72	2/20	210/579
Placebo	16/32	76/235	32/238	6/65	2/17	132/587

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

B



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	51/176	171/572	149/649	46/253	14/76	431/1726
Placebo	21/161	39/596	34/652	5/238	3/78	102/1725

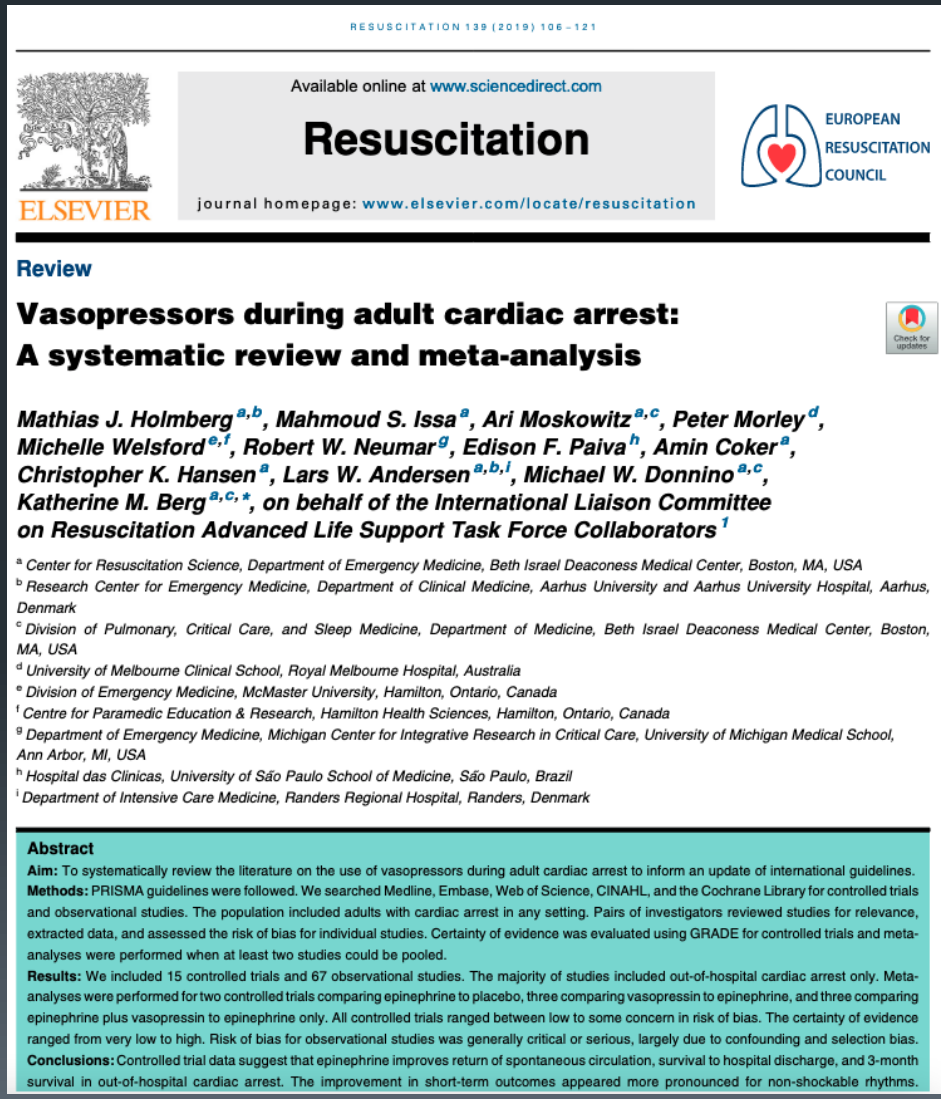
Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Intensive Care Med (2020) 46:426–436

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

-ILCOR reviewed the use of vasopressors in cardiac arrest following the publication of the PARAMEDIC2 trial



RESUSCITATION 139 (2019) 106–121

Available online at www.sciencedirect.com

Resuscitation

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

ELSEVIER

EUROPEAN RESUSCITATION COUNCIL

Review

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

Mathias J. Holmberg[a,b], Mahmoud S. Issa[a], Ari Moskowitz[a,c], Peter Morley[d], Michelle Welsford[e,f], Robert W. Neumar[g], Edison F. Paiva[h], Amin Coker[a], Christopher K. Hansen[a], Lars W. Andersen[a,b,i], Michael W. Donnino[a,c], Katherine M. Berg[a,c,], on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force Collaborators[1]*

[a] *Center for Resuscitation Science, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA*
[b] *Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark*
[c] *Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA*
[d] *University of Melbourne Clinical School, Royal Melbourne Hospital, Australia*
[e] *Division of Emergency Medicine, McMaster University, Hamilton, Ontario, Canada*
[f] *Centre for Paramedic Education & Research, Hamilton Health Sciences, Hamilton, Ontario, Canada*
[g] *Department of Emergency Medicine, Michigan Center for Integrative Research in Critical Care, University of Michigan Medical School, Ann Arbor, MI, USA*
[h] *Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil*
[i] *Department of Intensive Care Medicine, Randers Regional Hospital, Randers, Denmark*

Abstract

Aim: To systematically review the literature on the use of vasopressors during adult cardiac arrest to inform an update of international guidelines.

Methods: PRISMA guidelines were followed. We searched Medline, Embase, Web of Science, CINAHL, and the Cochrane Library for controlled trials and observational studies. The population included adults with cardiac arrest in any setting. Pairs of investigators reviewed studies for relevance, extracted data, and assessed the risk of bias for individual studies. Certainty of evidence was evaluated using GRADE for controlled trials and meta-analyses were performed when at least two studies could be pooled.

Results: We included 15 controlled trials and 67 observational studies. The majority of studies included out-of-hospital cardiac arrest only. Meta-analyses were performed for two controlled trials comparing epinephrine to placebo, three comparing vasopressin to epinephrine, and three comparing epinephrine plus vasopressin to epinephrine only. All controlled trials ranged between low to some concern in risk of bias. The certainty of evidence ranged from very low to high. Risk of bias for observational studies was generally critical or serious, largely due to confounding and selection bias.

Conclusions: Controlled trial data suggest that epinephrine improves return of spontaneous circulation, survival to hospital discharge, and 3-month survival in out-of-hospital cardiac arrest. The improvement in short-term outcomes appeared more pronounced for non-shockable rhythms.

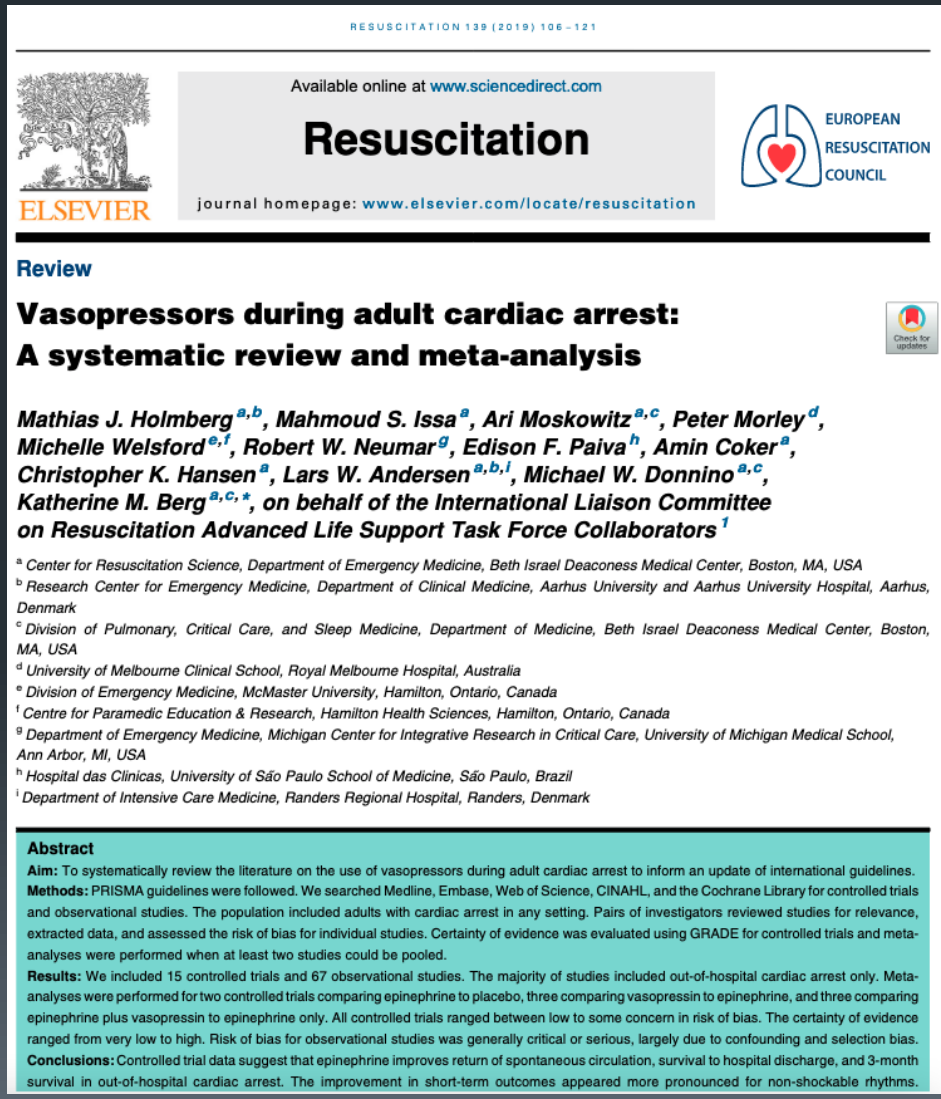
Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

-RCTs, non-randomized controlled trials, and observational studies with a comparison group were included

-Studies comparing different doses or timing of vasopressors were also included



RESUSCITATION 139 (2019) 106–121

Available online at www.sciencedirect.com

Resuscitation

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

ELSEVIER

EUROPEAN RESUSCITATION COUNCIL

Review

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

Mathias J. Holmberg[a,b], Mahmoud S. Issa[a], Ari Moskowitz[a,c], Peter Morley[d], Michelle Welsford[e,f], Robert W. Neumar[g], Edison F. Paiva[h], Amin Coker[a], Christopher K. Hansen[a], Lars W. Andersen[a,b,i], Michael W. Donnino[a,c], Katherine M. Berg[a,c,], on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force Collaborators[1]*

[a] Center for Resuscitation Science, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
[b] Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark
[c] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
[d] University of Melbourne Clinical School, Royal Melbourne Hospital, Australia
[e] Division of Emergency Medicine, McMaster University, Hamilton, Ontario, Canada
[f] Centre for Paramedic Education & Research, Hamilton Health Sciences, Hamilton, Ontario, Canada
[g] Department of Emergency Medicine, Michigan Center for Integrative Research in Critical Care, University of Michigan Medical School, Ann Arbor, MI, USA
[h] Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil
[i] Department of Intensive Care Medicine, Randers Regional Hospital, Randers, Denmark

Abstract

Aim: To systematically review the literature on the use of vasopressors during adult cardiac arrest to inform an update of international guidelines.

Methods: PRISMA guidelines were followed. We searched Medline, Embase, Web of Science, CINAHL, and the Cochrane Library for controlled trials and observational studies. The population included adults with cardiac arrest in any setting. Pairs of investigators reviewed studies for relevance, extracted data, and assessed the risk of bias for individual studies. Certainty of evidence was evaluated using GRADE for controlled trials and meta-analyses were performed when at least two studies could be pooled.

Results: We included 15 controlled trials and 67 observational studies. The majority of studies included out-of-hospital cardiac arrest only. Meta-analyses were performed for two controlled trials comparing epinephrine to placebo, three comparing vasopressin to epinephrine, and three comparing epinephrine plus vasopressin to epinephrine only. All controlled trials ranged between low to some concern in risk of bias. The certainty of evidence ranged from very low to high. Risk of bias for observational studies was generally critical or serious, largely due to confounding and selection bias.

Conclusions: Controlled trial data suggest that epinephrine improves return of spontaneous circulation, survival to hospital discharge, and 3-month survival in out-of-hospital cardiac arrest. The improvement in short-term outcomes appeared more pronounced for non-shockable rhythms.

Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

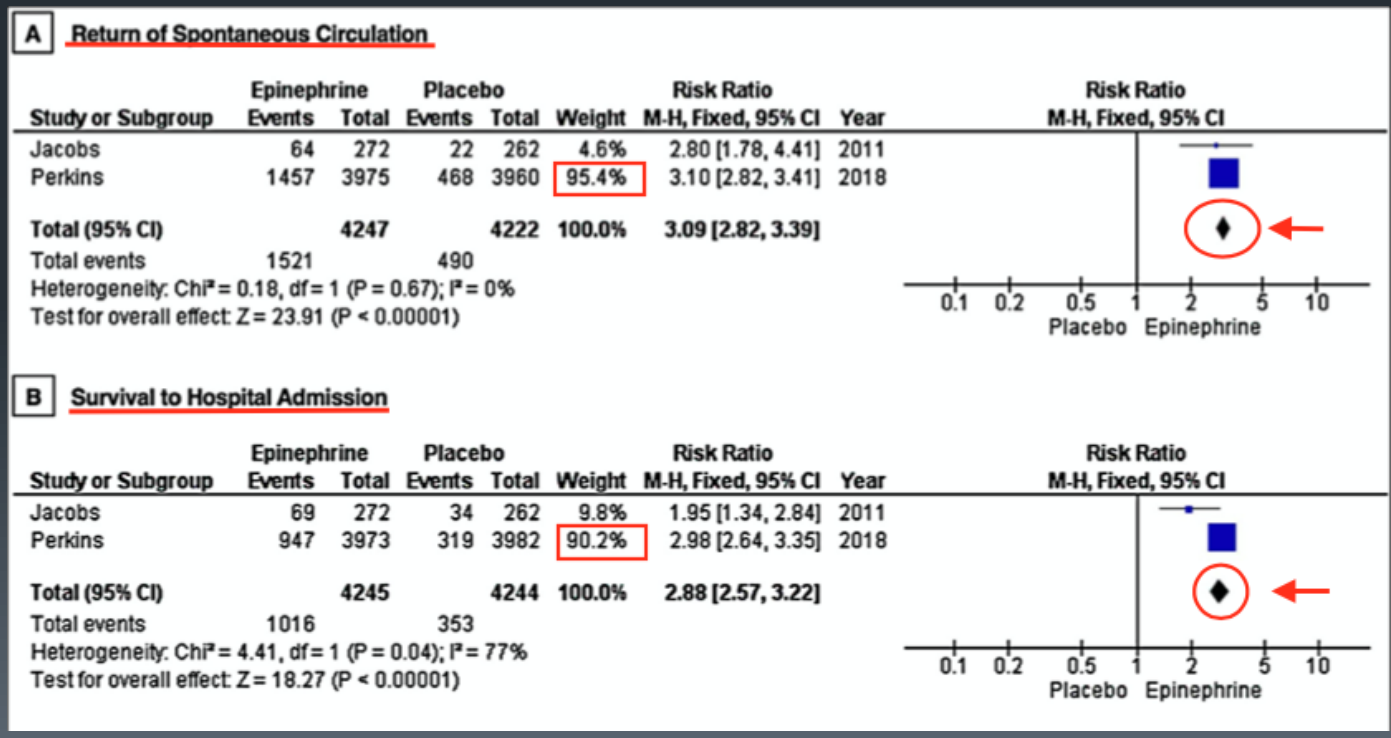
- Evidence

- Epinephrine vs placebo

x2 RCTs

PACA

PARAMEDIC2



Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

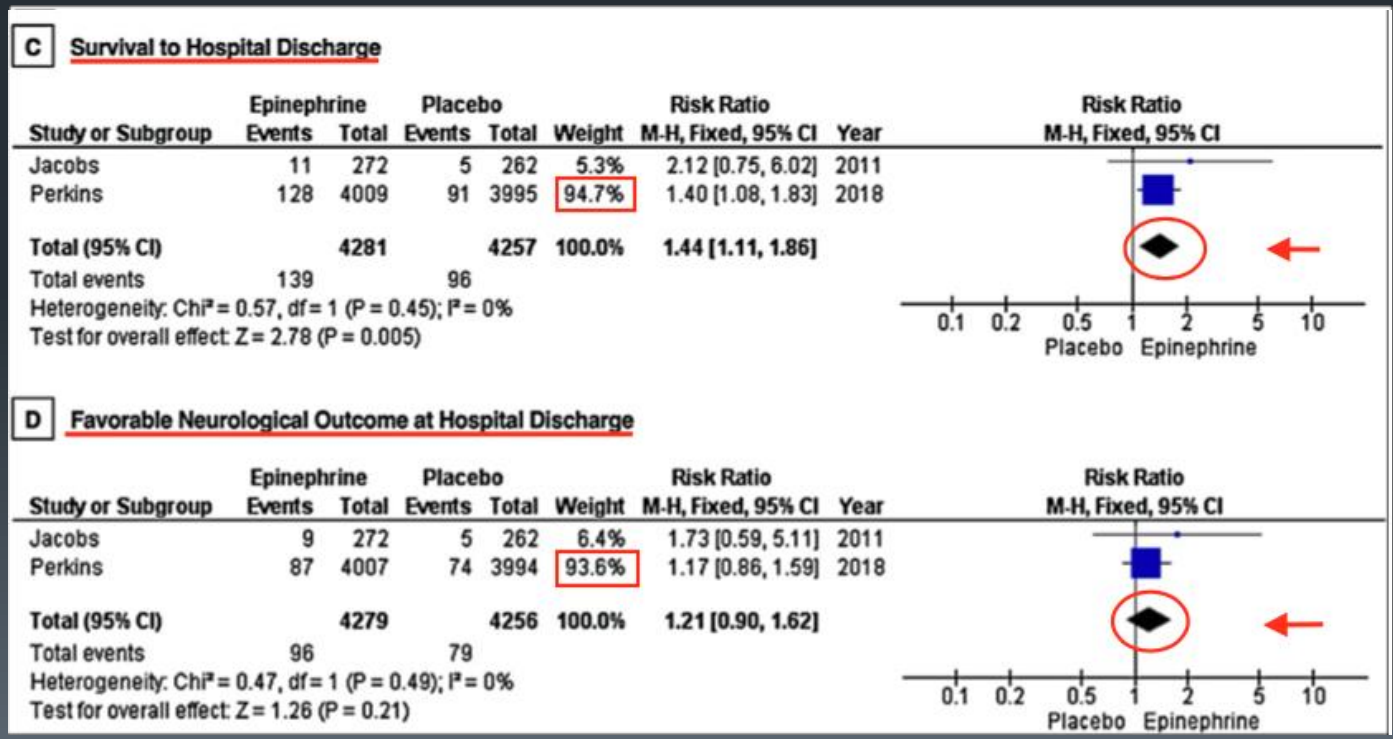
- Evidence

- Epinephrine vs placebo

x2 RCTs

PACA

PARAMEDIC2



Resuscitation 139 (2019) 106-121

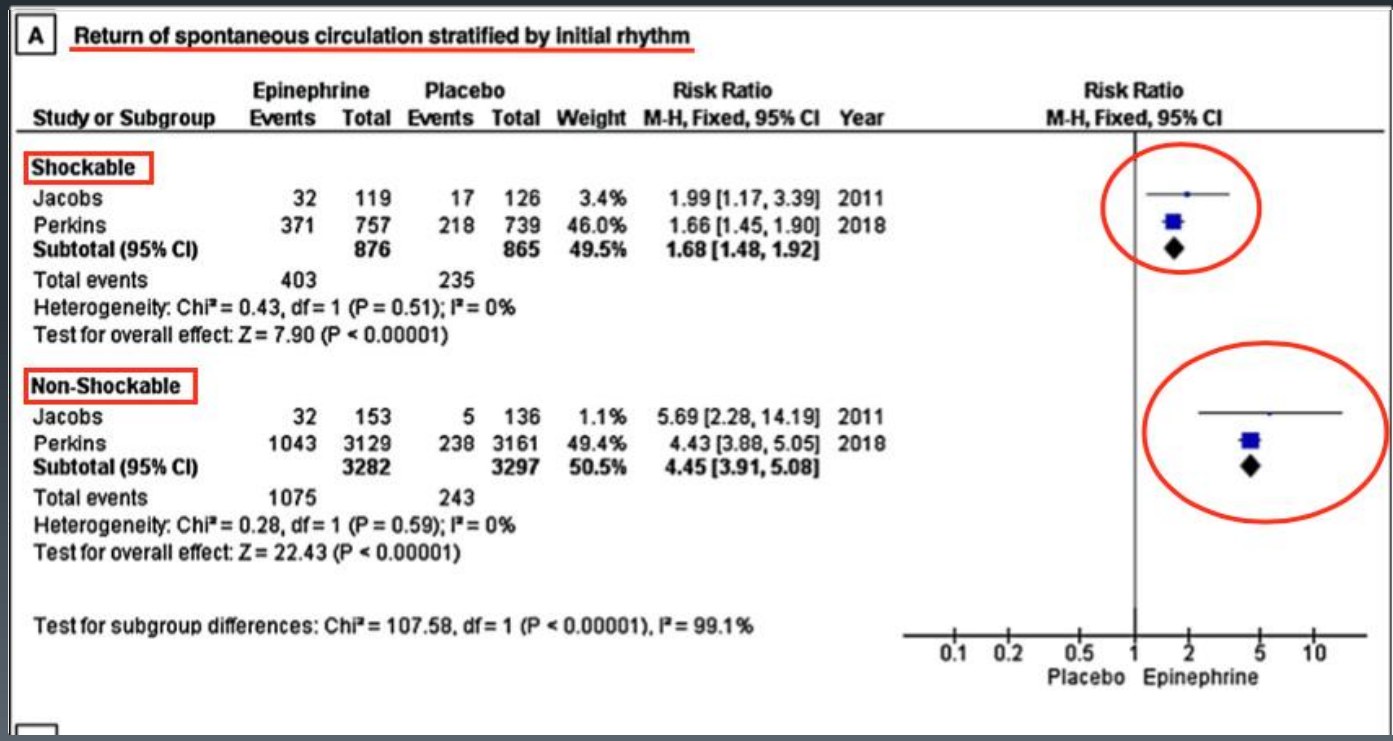
Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- Epinephrine vs placebo

Stratified by Initial rhythm

1) ROSC
2) Survival to hospital discharge



Resuscitation 139 (2019) 106-121

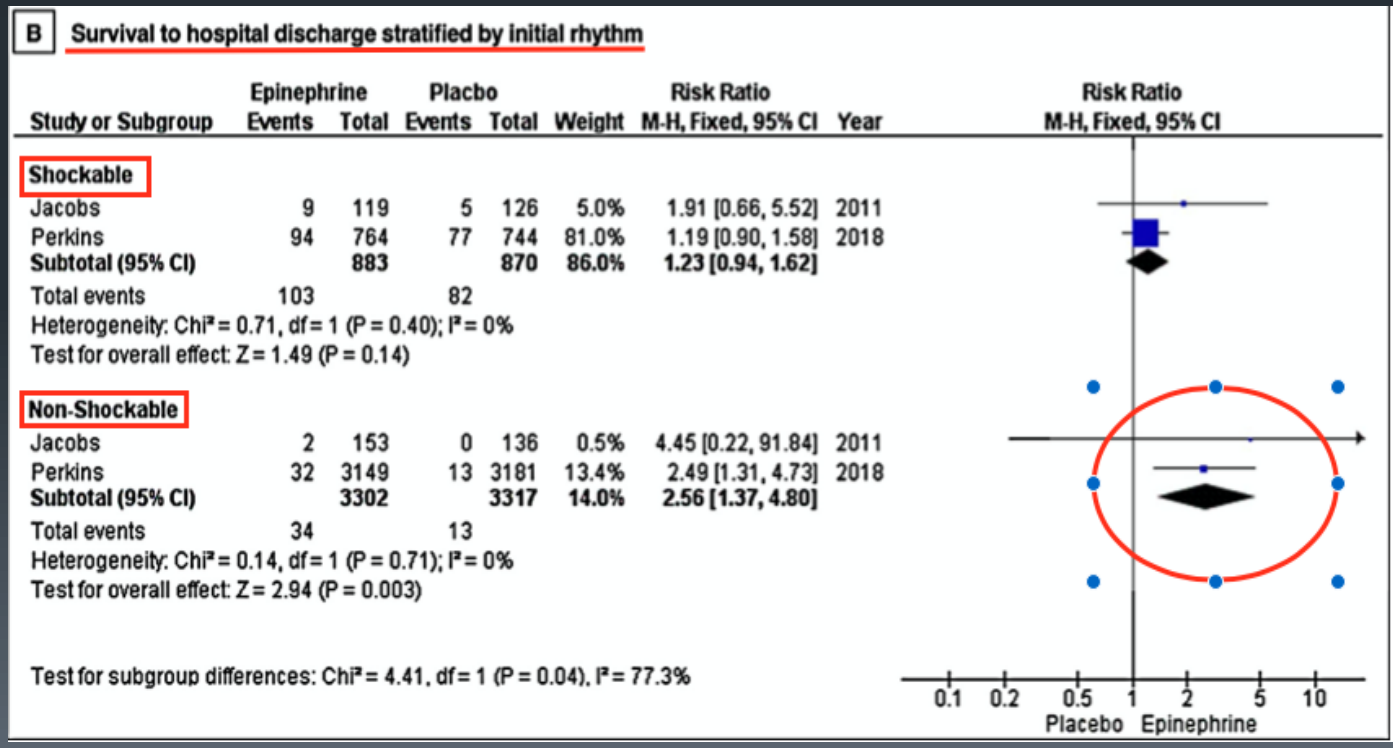
Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- Epinephrine vs placebo

Stratified by Initial rhythm

1) ROSC
2) Survival to hospital discharge



Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- Meta-analysis of the two placebo-controlled trials (PACA and PARAMEDIC2) found that the effects of adrenaline on ROSC relative to placebo were greater for patients with an initially non-shockable rhythm than those with a shockable rhythms

- Similar patterns were observed for longer term survival and favourable neurological outcomes, although the differences in effects were less pronounced

Αγγειοσυσπαστικά και αναζωογόνηση

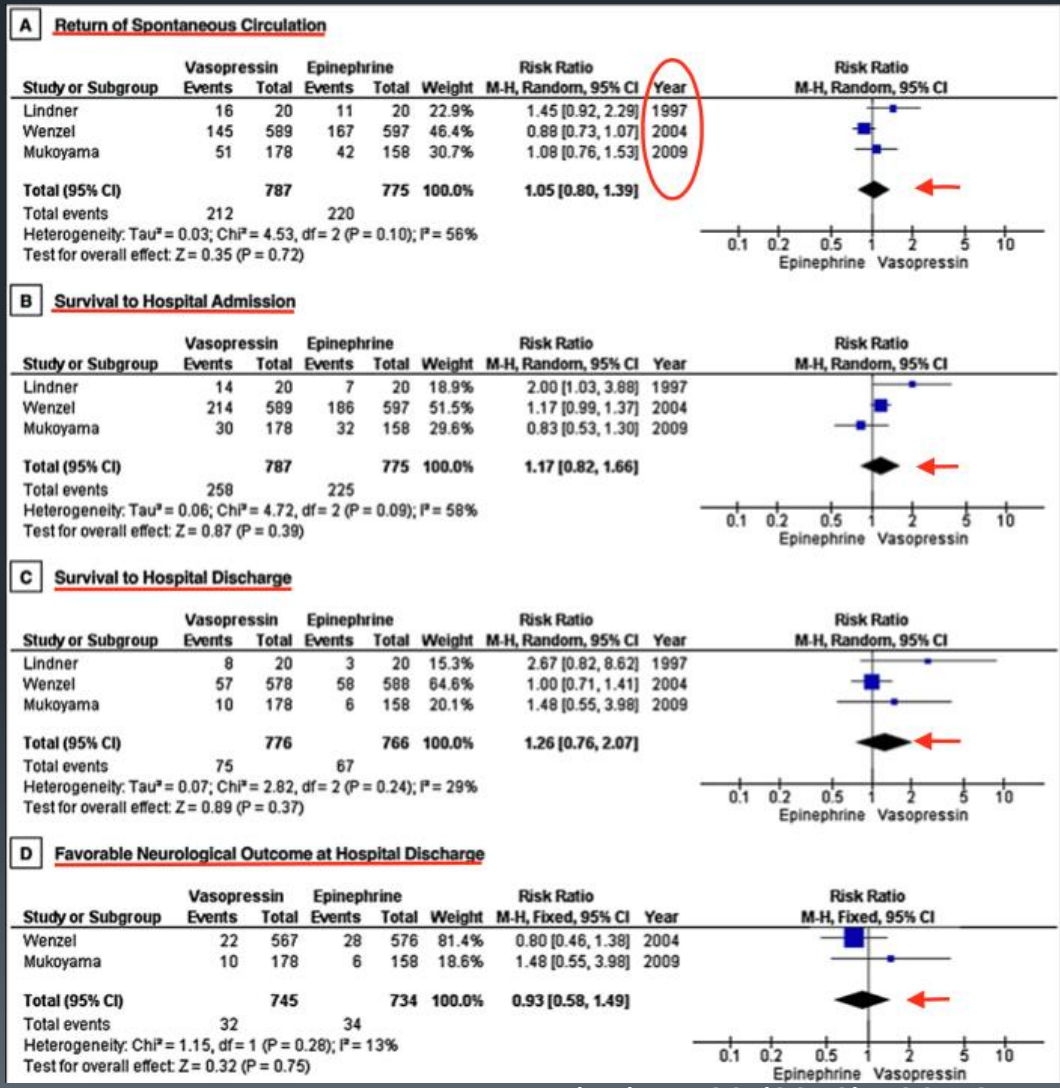
- Evidence

- ILCOR upgrading the strength of recommendation to strong recommendation in favour of the use of adrenaline during CPR (strong recommendation, low to moderate certainty of evidence)

- The Task Force placed a very high value on the apparent life-preserving benefit of adrenaline, even if the absolute effect size is likely to be small and the effect on survival with favourable neurological outcome is uncertain

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence
- Epinephrine vs Vasopressin

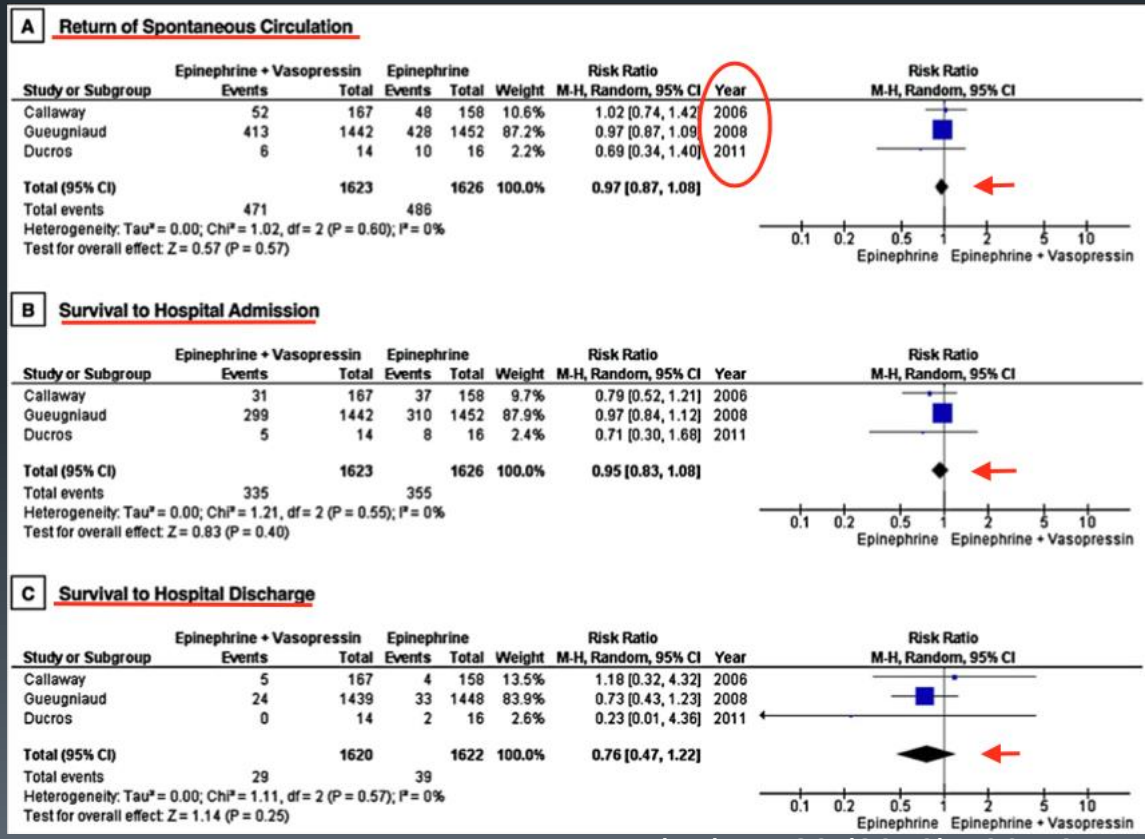


Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

- Evidence

- Epinephrine vs Vasopressin and Epinephrine



Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

- Questions (timing, dose)

Αγγειοσυσπαστικά και αναζωογόνηση

- Questions (dose)

High-dose epinephrine (>0.2mg/kg) vs Standard dose (1mg)

- Reviewed in detail by the previous ILCOR-commissioned systematic review and no new studies since that review were identified

1) We suggest against the routine use of HDE in cardiac arrest (weak recommendation, low-quality evidence)

2) HDE improves short-term outcomes but note that the low-quality evidence failed to show an improvement in the critical outcomes of survival and neurologic outcome

- These HDE studies were published in the 1990s*

Circulation. 2015;132:S84–S145

Αγγειοσυσπαστικά και αναζωογόνηση

- Questions (dose)

- A retrospective review of 3151 OHCA patients receiving one or more doses of adrenaline during CPR.

- A significant inverse relationship was found between increasing cumulative doses of adrenaline and survival both to hospital discharge and one year post-arrest

- **No survivors amongst patients requiring more than 10 doses of adrenaline**

Resuscitation. 2019 May;138:316-321

Αγγειοσυσπαστικά και αναζωογόνηση

- Questions (dose)

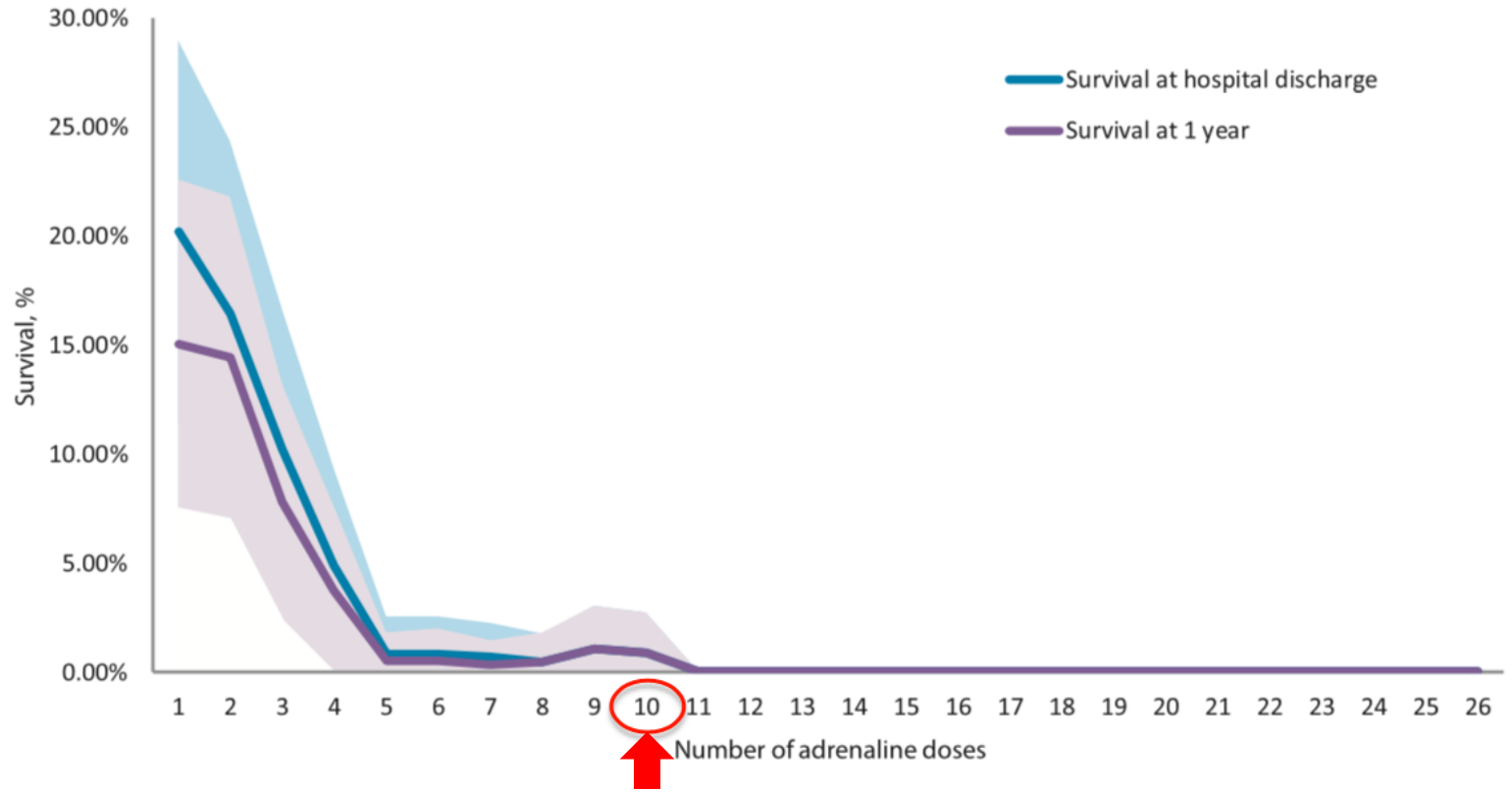


Fig. 2 – Relationship between the number of adrenaline doses and percentage survival to hospital discharge and survival to 1-year post-arrest. Shaded regions represent 95% confidence interval. 33 unknown outcomes were excluded from analysis.

Resuscitation. 2019 May;138:316-321

Αγγειοσυσπαστικά και αναζωογόνηση

- Questions (timing)

- In terms of timing of epinephrine administration, we identified 16 observational studies

- All of these studies found higher rates of ROSC when epinephrine was administered early, although the critical risk of bias across all studies again limits interpretation of these results.

- Differences in survival to hospital discharge and favorable neurologic outcome were additionally limited by very low event rates and inconsistent results between studies

Resuscitation 139 (2019) 106-121

Αγγειοσυσπαστικά και αναζωογόνηση

- 2021 Guidelines

RESUSCITATION 161 (2021) 115 –151

Available online at www.sciencedirect.com

Resuscitation

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

ELSEVIER

EUROPEAN RESUSCITATION COUNCIL

European Resuscitation Council Guidelines 2021: Adult advanced life support

Jasmeet Soar[a,], Bernd W. Böttiger[b], Pierre Carli[c], Keith Couper[d], Charles D. Deakin[e], Therese Djärv[f], Carsten Lott[g], Theresa Olasveengen[h], Peter Paal[i], Tommaso Pellis[j], Gavin D. Perkins[k], Claudio Sandroni[l,m], Jerry P. Nolan[n]*

[a] *Southmead Hospital, North Bristol NHS Trust, Bristol, UK*
[b] *Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Cologne, Cologne, Germany*
[c] *SAMU de Paris, Centre Hospitalier Universitaire Necker Enfants Malades, Assistance Publique Hôpitaux de Paris, and Université Paris Descartes, Paris, France*
[d] *Critical Care Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; Warwick Medical School, University of Warwick, Coventry,UK*
[e] *University Hospital Southampton NHS Foundation Trust, Southampton, UK; South Central Ambulance Service NHS Foundation Trust, Otterbourne,UK*
[f] *Dept of Acute and Reparative Medicine, Karolinska University Hospital, Stockholm, Sweden, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden*
[g] *Department of Anesthesiology, University Medical Center, Johannes Gutenberg-Universitaet Mainz, Germany*
[h] *Department of Anesthesiology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Norway*
[i] *Department of Anaesthesiology and Intensive Care Medicine, Hospitallers Brothers Hospital, Paracelsus Medical University, Salzburg, Austria*
[j] *Department of Anaesthesia and Intensive Care, Azienda Sanitaria Friuli Occidentale, Italy*
[k] *University of Warwick, Warwick Medical School and University Hospitals Birmingham NHS Foundation Trust, Coventry, UK*
[l] *Department of Intensive Care, Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy*
[m] *Institute of Anaesthesiology and Intensive Care Medicine, Università Cattolica del Sacro Cuore, Rome, Italy*
[n] *University of Warwick, Warwick Medical School, Coventry, CV4 7AL; Royal United Hospital, Bath, UK*

Abstract

These European Resuscitation Council Advanced Life Support guidelines, are based on the 2020 International Consensus on Cardiopulmonary Resuscitation Science with Treatment Recommendations. This section provides guidelines on the prevention of and ALS treatments for both in-hospital cardiac arrest and out-of-hospital cardiac arrest.

Αγγειοσυσπαστικά και αναζωογόνηση

- 2021 Guidelines

➢ <u>Vascular access</u>

i. Attempt IV access first to enable drug delivery in adults in cardiac arrest

ii. Consider intraosseous access if attempts at IV access are unsuccessful or not feasible

RESUSCITATION 161 (2021) 115 -151

Αγγειοσυσπαστικά και αναζωογόνηση

- 2021 Guidelines

➢ Vasopressor drugs

I. Give adrenaline 1 mg IV (IO) as soon as possible for adult patients in cardiac arrest with a non-shockable rhythm

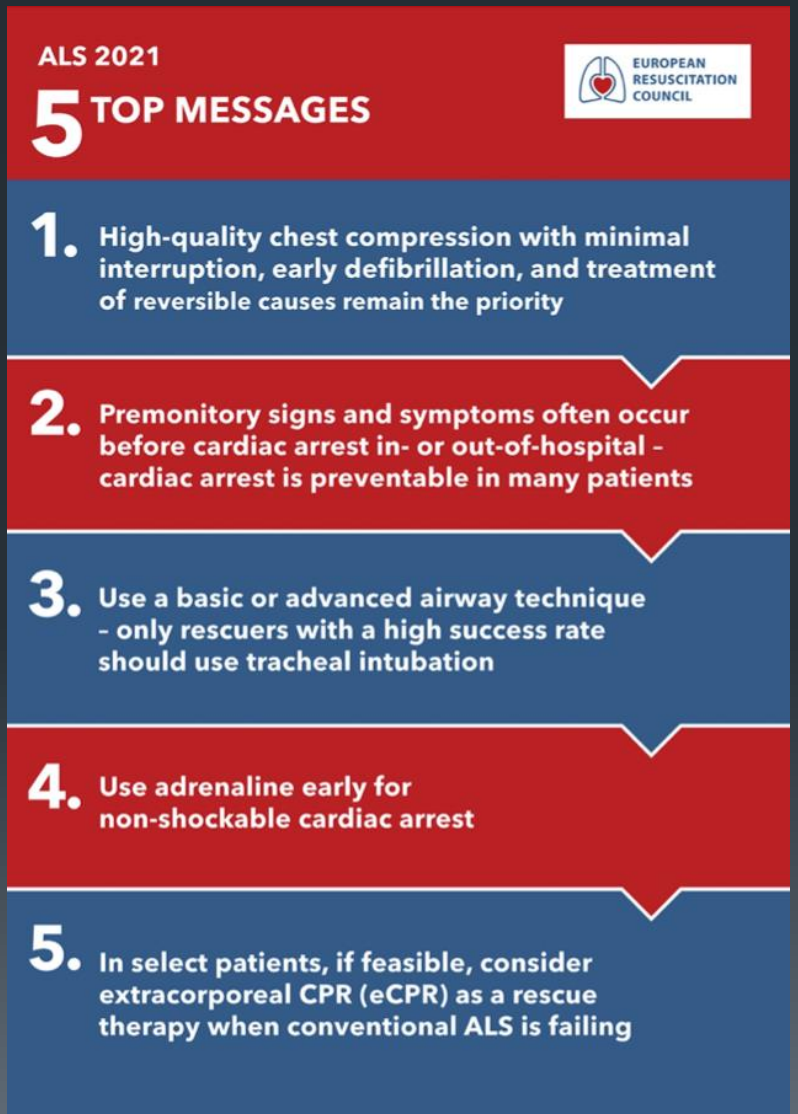
II. Give adrenaline 1 mg IV (IO) after the 3rd* shock for adult patients in cardiac arrest with a shockable rhythm

III. Repeat adrenaline 1 mg IV (IO) every 3-5 min whilst ALS continues

RESUSCITATION 161 (2021) 115 -151

Αγγειοσυσπαστικά και αναζωογόνηση

- 2021 Guidelines



Αγγειοσυσπαστικά και αναζωογόνηση