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The Pharmacologic Approach to Cardiac Arrest:
A Focus on Vasopressors

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Grady Health System

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Objectives

- Discuss epidemiology, pathophysiology, and treatment for cardiac arrest
- Describe positive and negative effects of epinephrine during advanced cardiac life support and post-return of spontaneous circulation
- Analyze the evidence for epinephrine use in cardiac arrest

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Disclosure

- The following individuals have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation:
- Writer/Presenter:
  - Jimmy L. Pruitt III, PharmD

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Objectives

- Discuss the Epidemiology, Pathophysiology, And Vascular Management For Of Out Of Hospital Cardiac Arrest (OHCA)
- Describe the Positive And Negative Effects Of Epinephrine During Advanced Cardiac Life Support and Post-return Of Spontaneous Circulation
- List the evidence for epinephrine use in cardiac arrest
- Identify the interventions for (OHCA)

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Abbreviations

- CPC: Cerebral performance category
- CPR: Cardiopulmonary resuscitation
- EMS: Emergency medical services
- EPI: Epinephrine
- ICU: Intensive care unit
- IHCA: In-hospital cardiac arrest
- OHCA: Out-of-hospital cardiac arrest
- mRS: modified Rankin Scale
- NE: Norepinephrine
- PEA: Pulseless electrical activity
- PE: Phenylephrine
- SCD: Sudden cardiac death
- SVR: Systemic vascular resistance
- TTM: Targeted temperature management
- VASO: Vasopressin
- VF: Ventricular fibrillation
- VT: Ventricular tachycardia

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"I was overwhelmed by my lack of understanding of what was happening and baffled over the inefficiency of treatment. The cold sweaty skin and the pallor, the fading pulse, the high pulse rate, the sunken eyes and dilated pupils fixed themselves in my memory."
George W. Crile 1906

Soto-Ruiz KM. Resuscitation. 2009 Jan;80(1):6-8.

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EPIDEMIOLOGY

- **Incidence of OHCA:**
  - 356,461 in 2017
    - Adults: 347,322
    - Children: 7,037
- **Initial Shockable Rhythm:**
  - 18.7%
- **OHCA Survivor to Discharge (overall):**
  - 10.4%
- **Survival with Good Functional Status:**
  - 8.4%

Benjamin EM, et al. Heart Disease and Stroke Statistics—2019 Update. Circulation. 2019;139:00.

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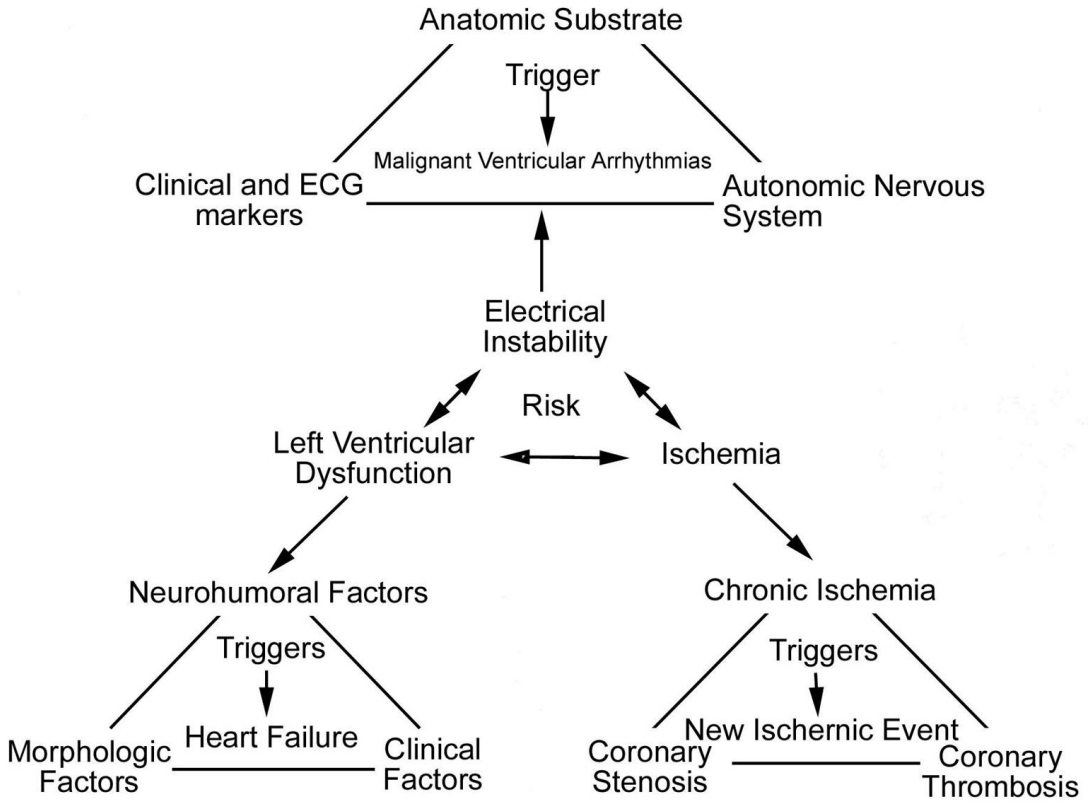
Pathophysiology



Interplay of various risk factors that can lead to SCD

https://emedicine.medscape.com/article/151907-overview

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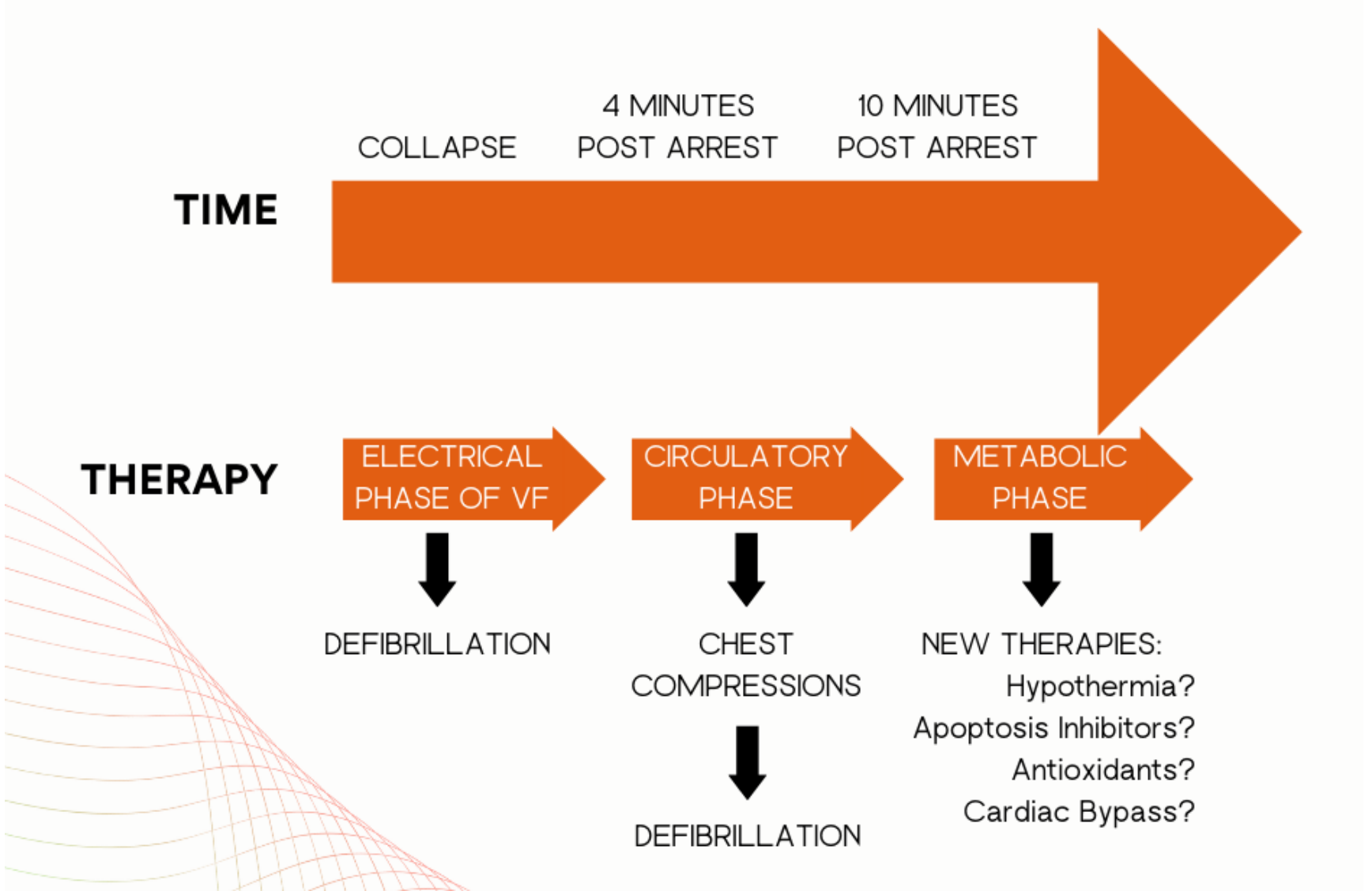
Phases of Cardiac Arrest



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Etiology

- Cardiac
- Hypothermia
- Myocardial pump failure
- Massive hemorrhage
- Respiratory failure
- Electrolyte derangement
- Drug toxicity/overdose

Benjamin EM, et al. Heart Disease and Stroke Statistics—2019 Update. Circulation. 2019;139:00.

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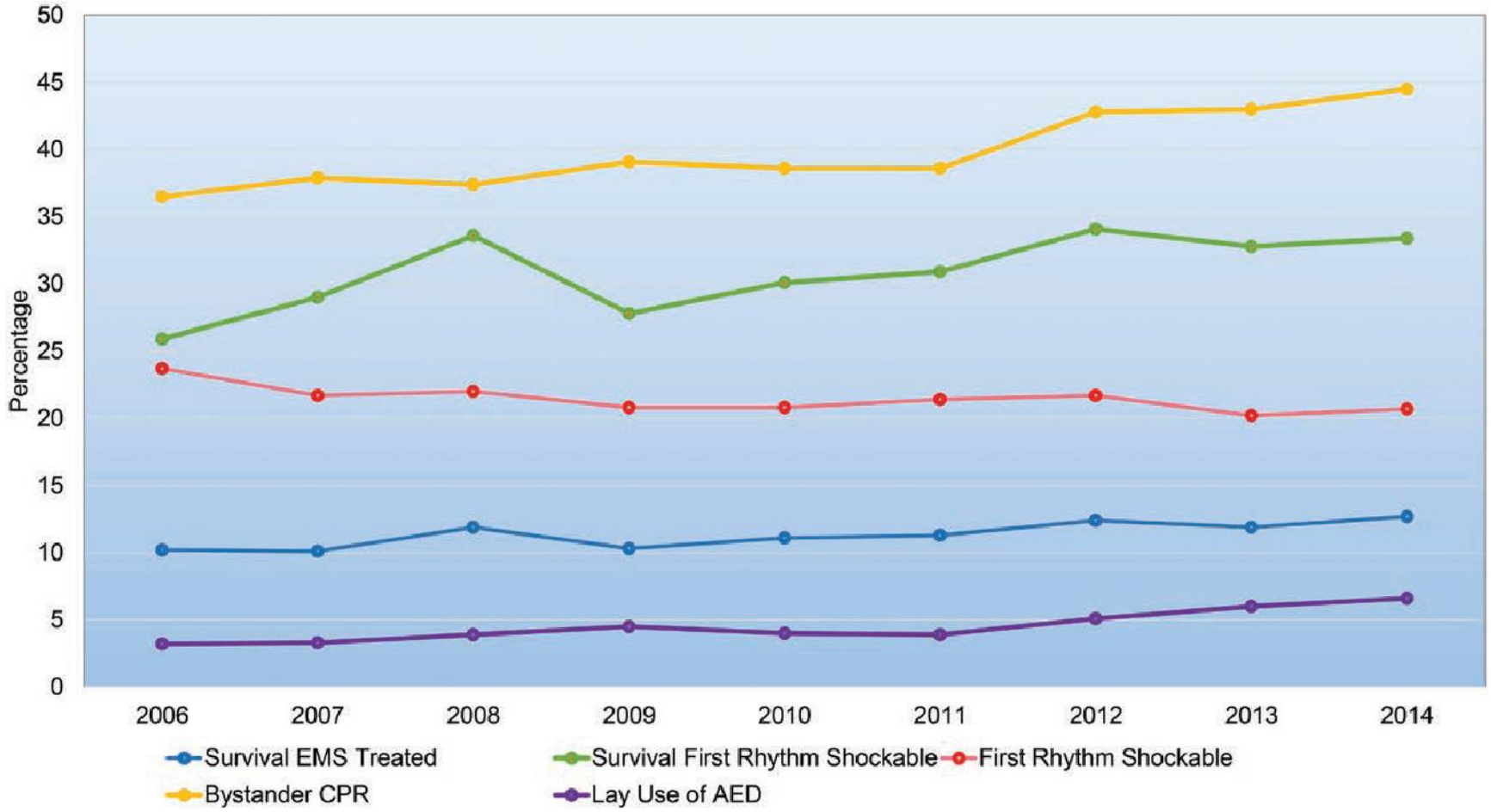
Survival Rates After OHCA



Benjamin EM, et al. Heart Disease and Stroke Statistics—2019 Update. Circulation. 2019;139:00.

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Predictors for Survival

- CPR from a bystander
- Initial shockable rhythm
- ROSC prior to hospital
- Defibrillator available at public sites

Sasson C. Circ Cardiovasc Qual Outcomes 2010;3:63-81.

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Treatment for Cardiac Arrest

Neumar RW, et al. Circulation. 2015 Nov 3;132(18 Suppl 2):S315-67.

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BLS

- High-quality cardiopulmonary resuscitation
  - Chest compressions are associated with increased survival to hospital discharge
  - Do not interrupt for vascular access, drug delivery, or advanced airway placement
- Defibrillation
- Ventilation
  - 1 breath every 6-8 seconds (10 breaths per minute)

Neumar RW, et al. Circulation. 2015 Nov 3;132(18 Suppl 2):S315-67.

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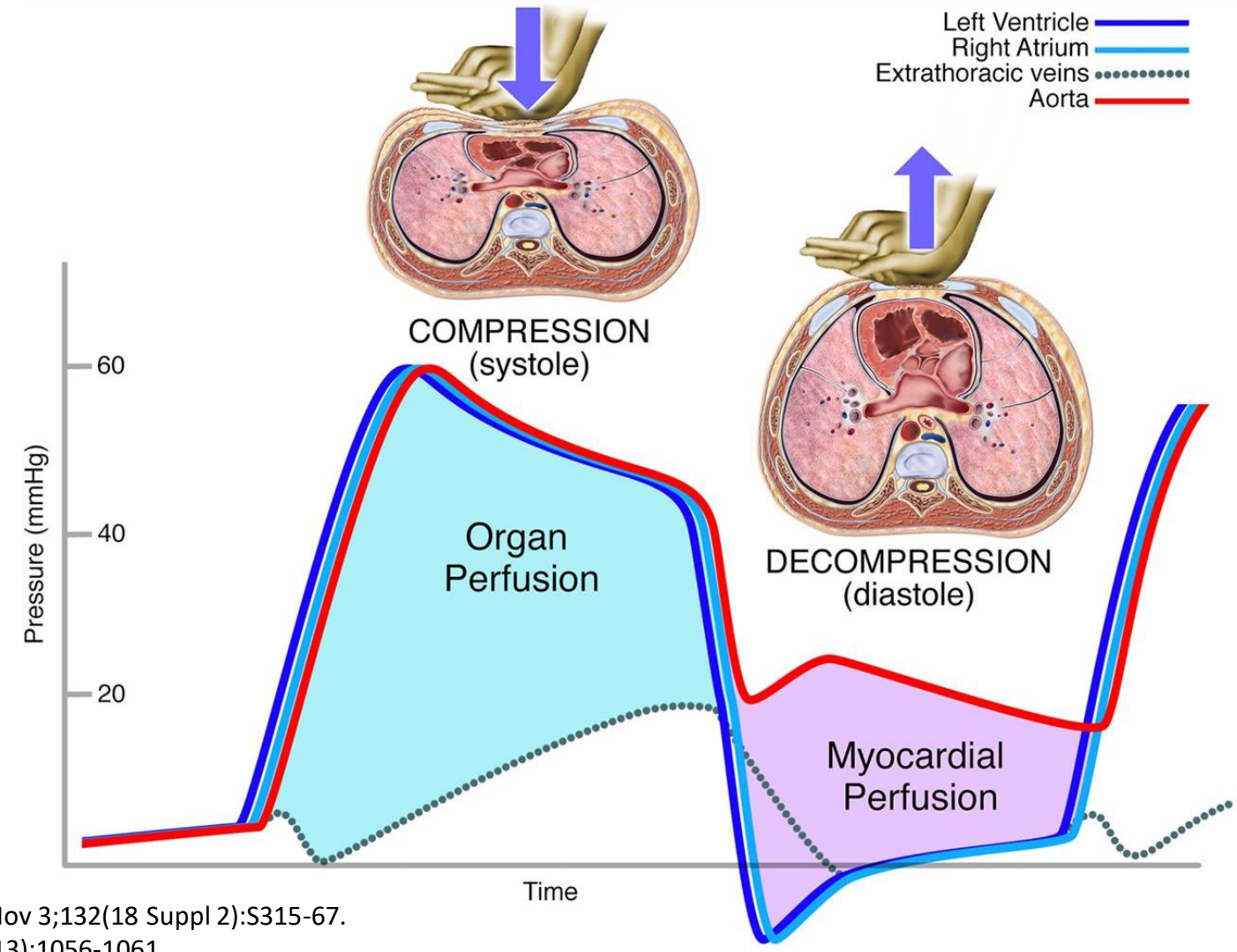
Chest Compressions



Neumar RW, et al. Circulation. 2015 Nov 3;132(18 Suppl 2):S315-67.
Harris AW, et al. Heart. 2018 Jul;104(13):1056-1061

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Chest Compressions

- How to do Compressions?
  - Push hard and fast
  - > 2 inches (5 cm) deep
  - Allow for complete chest recoil
- NNT
  - 27-36

Neumar RW, et al. Circulation. 2015 Nov 3;132(18 Suppl 2):S315-67
http://www.wetpaint.com/greys-anatomy-cpr-depiction-1440439/.

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Defibrillation

- Only for shockable rhythms
- Associated with increase in survival
  - NNT
    - 4

- Biphasic preferred method
  - Energy (J) depends on device
  - Monophasic: 360 J
  - Biphasic: 120-200 J

Kleinman ME et al. Circulation 2015; 132 (18 Suppl 2): S414 – 25.

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2018 ACLS Algorithm

- **Monophasic:** 360 J

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

-OR-

Lidocaine IV/IO dose: First dose: 1-1.5 mg/kg. Second dose: 0.5-0.75 mg/kg.

Advanced Airway

Kleinman ME et al. Circulation 2015; 132 (18 Suppl 2): S414 – 25.

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Vasopressors

- Purpose
  - ↑coronary perfusion pressure = ↑ chance of ROSC
    - CPP< 15 mmHg = ↓ ROSC

- Agents
  - Epinephrine
  - Phenylephrine
  - Norepinephrine
  - Vasopressin

Kleinman ME et al. Circulation 2015; 132 (18 Suppl 2): S414 – 25.

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Vasopressor Activity Chart

Agent	A_1	B_1	B_2	DA	V1 + V2
Dopamine	+++	++++	++	++++	-
Epinephrine	++++	++++	+++	-	-
Norepinephrine	+++++	+++	++	-	-
Phenylephrine	+++++	-	-	-	-
Vasopressin	-	-	-		+++++
Dobutamine	+	++++	++	-	-
Isoproterenol	-	+++++	+++++		

Attaran RR, Ewy GA. Epinephrine in resuscitation: Curse or cure?. *Future Cardiol* 2010; 6(4):473-82.

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Vasopressors in OHCA

Author, Year	Design	Dosing	Outcome
Eilfvast,1985	RCT Human n=65	EPI 0.5 mg vs PE 1 mg	**No difference** in successful resuscitation, bradycardia, or HTN
Lindner, 1989	Cohort Animal n=21	DOPA 2.5 mg/kg Vs EPI 45 mcg/kg Vs placebo	**EPI ↑ ROSC** in asphyxial arrest **DOPA ↑ ROSC** in VF arrest
Callaham, 1992	RCT Human n=816	EPI 15 mg Vs EPI 1 mg Vs NE 11 mg	**↑ ROSC** with EPI 15 mg, hospital discharge compared to EPI 1mg **↑ ROSC** with NE 11 compared to EPI 1mg
Gueugniaud, 2008	RCT Human n=2894	EPI 1 mg + VASO 40 units Vs EPI 1 mg	**No difference** in hospital admission, ROSC, hospital discharge, 1 year mortality, and good neurological recover at discharge

Attaran RR, Ewy GA. Epinephrine in resuscitation: Curse or cure?. *Future Cardiol* 2010; 6(4):473-82.

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EPI Dose

Author	Design	Dose	Outcome
Brown, 1992	RCT n =1280	EPI 0.02 mg/kg (SDA) EPI 0.2 mg/kg (HDA)	**No difference** in ROSC, Hospital admission, discharge from hospital
Choux, 1995	RCT n = 536	EPI 1 mg (SDA) EPI 5 mg (HDA)	**No difference** in ROSC, Hospital admission, discharge from hospital, neurological function
Fisk, 2018	Observational n=2255	EPI 1 mg EPI 0.5 mg	**No difference** in ROSC, discharge from hospital, neurological function
Gueugniaud, 1998	RCT n = 3327	EPI 1 mg (SDA) EPI 5 mg (HDA)	EPI 5 mg ↑ **ROSC** , ↑ hospital discharge compared to EPI 1 mg No Difference in hospital discharge and neurological function
Stiell, 1992	RCT n = 335	EPI 1 mg (SDA) EPI 7 mg (HDA)	**No difference** in 1 hr survival, hospital discharge, or neurological function

Lin S. Resuscitation. 2014 Jun;85(6):732-40.

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Epinephrine Pros

- $Alpha_1$
  - Arterial vasoconstriction
  - Venous vasoconstriction
  - Coronary vasoconstriction
- $Alpha_2$
  - Venous vasoconstriction

- ↑ SVR = ↑ CPP + ↑ oxygen delivery

https://www.vectorstock.com/royalty-free-vector/thumbs-up-emoticon-vector-9701163

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Epinephrine Cons

- $Alpha_1$
  - ↑ Cerebral constriction
- $Beta_1 + Beta_2$
  - ↑ Inotropy
  - ↑ Oxygen demand
  - ↑ Recurrent VF
  - ↑ Clotting

Attaran RR, et al. *Future Cardiol* 2010; 6(4):473-82.
https://www.emojirequest.com/r/ThumbsDownEmoji

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Objectives

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- Review the interventions for post-arrest care

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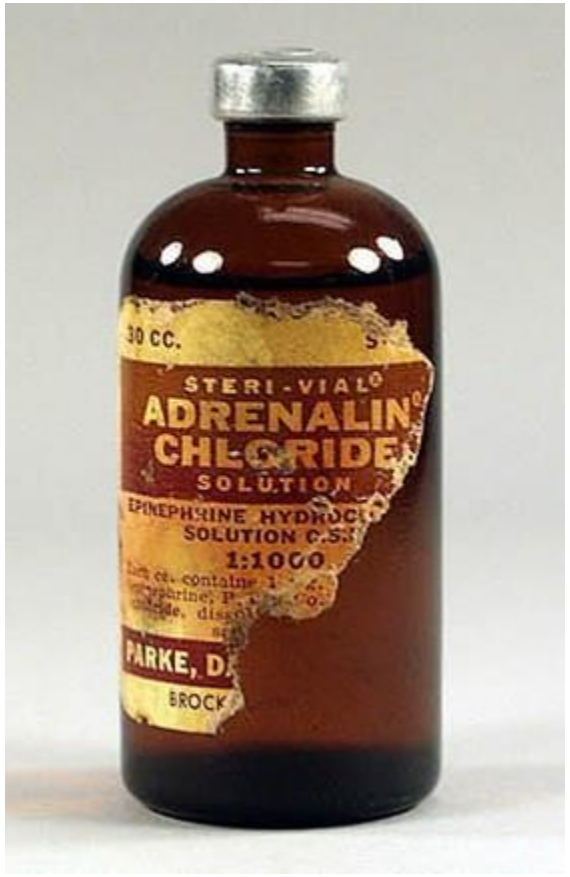

"Crile recorded the animal's last heart beat and respiration and after 15 min he injected adrenaline with salt solution into the carotid arteries and performed chest compressions. Less than 3 min later, the dog was as alive as he had been a half hour before." - 1906

Soto-Ruiz KM. Resuscitation. 2009 Jan;80(1):6-8.
https://mhc.andornot.com/en/list?q=%2Brepository%3APharmacy&p=2&ps=20&sort=title_sort%20asc

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Primary Outcomes That Matter!

Short Term Outcomes

- ROSC
- Survival to hospital admission
- 24 hour survival

Long Term Outcomes

- Survival to hospital discharge
- Long term survival (30-60 days)
- Good neurological outcomes
  - CPC 1 or 2
  - mRS <3

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EPI Evidence

Author	Year	Design	Outcome (EPI vs Comparator)
Holmberg et al.	2002	Observational	↑ Mortality
Stiell et al. (OPALS)	2004	Observational	↑ ROSC ↔neurological intact survival
Ong et al.	2007	Observational	↔ neurological intact survival
Olasveengen et al.	2009	RCT	↑ ROSC ↔/↑* neurological intact survival
Jacobs et al.	2011	RCT	↑ ROSC ↔ neurological intact survival
Hagihara et al.	2012	Observational	↑ ROSC ↓ neurological intact survival
Nakahara et al.	2013	Observational	↔ neurological intact survival or Mortality
Dumas et al.	2014	Observational	↓ Neuro intact survival
Sanghavi et al.	2015	Observational	↑ Mortality ↓ Neuro intact survival
Perkins, 2018 (PARAMEDIC-2)	2018	RCT	??

* Post Hoc analysis

ORIGINAL ARTICLE

Advanced Cardiac Life Support in Out-of-Hospital Cardiac Arrest

Ian G. Stiell, M.D., George A. Wells, Ph.D., Brian Field, A.C.P., M.B.A., Daniel W. Spaite, M.D., Lisa P. Nesbitt, M.H.A., Valerie J. De Maio, M.D., Graham Nichol, M.D., M.P.H., Donna Cousineau, B.Sc.N., Josée Blackburn, B.Sc., Doug Munkley, M.D., Lorraine Luinstra-Toohey, B.Sc.N., M.H.A.,

Objective

- Determine effect of EPI on survival to hospital discharge in OHCA

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

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Methods

Design	• "Before–After" observational trial
Funding	• The Ontario Ministry of Health and Long-Term Care
Setting	• EMS with 11 base hospitals throughout Ontario
Population	• 5638 OHCA patients

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

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Methods

Primary Outcome

- Survival to hospital discharge

Secondary Outcome

- Pre-hospital ROSC (ROSC in the field for greater 30s)
- Admission to hospital
- Survivors' cerebral performance category, level 1
- Survivors' Health Utility Index, Mark III, at one year

Statistics

- Sample size required 2213 patients per group
- Alpha 0.05 (two tailed) and power of 80%
- Pearson's chi-square and t-test (or Mann–Whitney) for categorical and continuous data respectively

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

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Intervention

Patients

- >16 years old in out-of-hospital cardiac arrest

Intervention

- EMS delivered ACLS

Comparison

- EMS delivered BLS

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

Baseline Characteristics

	Rapid-Defibrillation Phase	Advanced-Life-Support Phase
Age (mean, years) ± SD	68.9±14.4	69.3±14.6
Male, n (%)	936 (67.3)	2823 (66.5)
Arrest witnessed by bystander, n (%)	649 (46.7)	1737 (40.9)
Arrest witnessed by EMS personnel, n (%)	119 (8.6)	411 (9.7)
Initial cardiac rhythm — no./total no. (%)		
- Ventricular fibrillation or tachycardia	480/1357 (34.5)	1339/4094 (31.5)
- Pulseless electrical activity	350/1357 (25.8)	1036/4094 (25.3)
- Asystole	527/1357 (38.8)	1719/4094 (42.0)
CPR by bystander, n (%)	220 (15.8)	612 (14.4)
CPR by first responder, n (%)	470 (33.8)	1679 (39.5)
First responder preceded EMS to scene, n (%)	1161/1258 (92.3)	3576/3817 (93.7)
Defibrillator to scene in ≤8 min, n (%)	401/1214 (33.0)	1454/3655 (39.8)
IV medications administered — no. (%)		
-Epinephrine	-	3583 (95.8)
-Atropine	-	3267 (87.3)
-Lidocaine	-	882 (23.6)
-Dopamine	-	105 (2.8)
-Bicarbonate	-	92 (2.5)

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Outcomes			
	Rapid-Defibrillation Phase (n=1391)	Advanced-Life-Support Phase (n=4247)	P Value
Primary Outcome			
Survival to hospital discharge, No.(%)	69 (5.0)	217 (5.1)	0.83
Secondary Outcomes			
Return of spontaneous circulation, No.(%)	180 (12.9)		<0.001
Admission to hospital, No.(%)	152 (10.9)	621 (14.6)	<0.001
Survivors' cerebral performance category, level 1, No.(%)	54 (78.3)	145 (66.8)	0.73
Survivors' Health Utility Index, Mark III, at one year, Median	0.84	0.79	0.67

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

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Author's Conclusion

In conclusion, systematic introduction of ACLS programs to an EMS system that had previously optimized its rapid-defibrillation program did not decrease mortality or morbidity associated with cardiac arrest.

Stiell IG. N Engl J Med. 2004 Aug 12;351(7):647-56.

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Strengths & Limitations

Strengths

- Before and After Design
- Patient centered outcome

Limitations

- Observational
- Did not isolate EPI
- Confounders not adjusted for

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

Akihito Hagihara, DMSc, MPH
Manabu Hasegawa, MD
Takeru Abe, MA
Takashi Nagata, MD
Yoshifumi Wakata, MD
Shogo Miyazaki, PhD

C ion for out-of-hospital cardiac arrest (OHCA). However, the effectiveness of epinephrine use before hospital arrival has not been established.

Objective To evaluate the association between epinephrine use before hospital arrival and short- and long-term mortality in patients with cardiac arrest.

Design, Setting, and Participants Prospective, nonrandomized, observational propensity analysis of data from 417 188 OHCAs occurring in 2005-2008 in Japan in which

Objective

- To evaluate the association between epinephrine use before hospital arrival and short and long term mortality in cardiac arrest

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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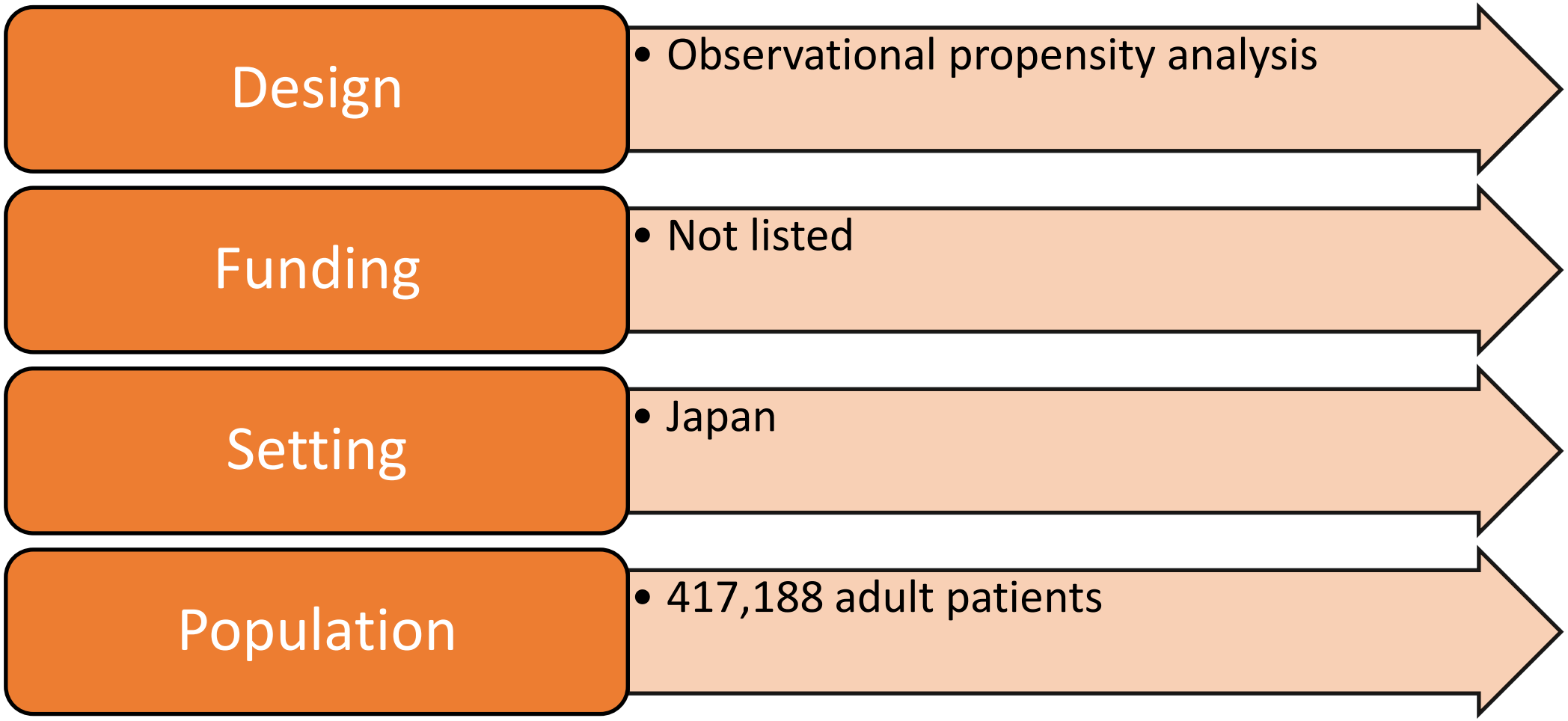
Methods



Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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Methods

Primary Outcome

- pROSC
- One-month survival
- One-month survival with favorable CPC of 1-2
- Survival with no, mild, or moderate neurological disability

Statistics

- 2-sided at the 5% level
- Propensity score to control potential confounding and selection bias
- Estimated actual 1-month survival rate of 5.4% in the intravenous epinephrine group and 4.7% in the no epinephrine group
- 15,030 samples for each group provided a power level of 92.0%

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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Intervention

Patients

- Adult Japanese patients in OHCA

Intervention

- Epinephrine

Comparison

- No Epinephrine

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

Baseline Characteristics

	EPI (n = 13,401)	No EPI (n = 13,401)
	Mean (%)	Mean (%)
Age, mean (SD), y	72.43 (15.5)	72.40 (15.7)
Male	8480 (63.3)	8427 (62.9)
Bystander eyewitness	5854 (43.7)	5918 (44.2)
Family member bystander eyewitness	4519 (33.7)	4533 (33.8)
Origin of cardiac arrest • Cardiac • Noncardiac	 8039 (60.0) 5362 (40.0)	 7984 (59.6) 5417 (40.4)
Bystander chest compression	5854 (43.7)	5918 (44.2)
Life support by EMS personnel • Physician present in ambulance • Advanced life support performed by physician	13, 316 (99.4) 811 (6.1) 2122 (15.8)	13 308 (99.3) 873 (6.5) 2233 (16.7)
Time from call to arrival at scene, mean (SD), min **Time from call to arrival at hospital, mean (SD), min**	7.50 (4.0) 37.92 (13.2)	7.47 (4.0) 37.66 (18.3)
First documented rhythm • VF/pVT • PEA/asystole	 1758 (13.1) 11 643 (86.9)	 1781 (13.3) 11 620 (86.7)
Defibrillation by EMS personnel	2610 (19.5)	2602 (19.4)
Use of advanced life support devices	10 294 (76.8)	10 290 (76.8)
Insertion of intravenous line	12 868 (96.0)	12 865 (96.0)

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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EPI vs No-EPI

Outcomes	OR (95% CI)			
Unconditional Logistic Regression Analyses				
	ROSC	1-month survival	CPC 1-2	OPC 1-2
Unadjusted	3.75 (3.59-3.91)	1.15 (1.07-1.23)	0.61 (0.53-0.70)	0.63 (0.55-0.73)
Adjusted for selected variables	3.06 (2.93-3.21)	0.43 (0.39-0.46)	0.21 (0.18-0.24)	0.22 (0.19-0.25)
Adjusted for all covariates	2.36 (2.22-2.50)	0.46 (0.42-0.51)	0.31 (0.26-0.36)	0.32 (0.27-0.38)

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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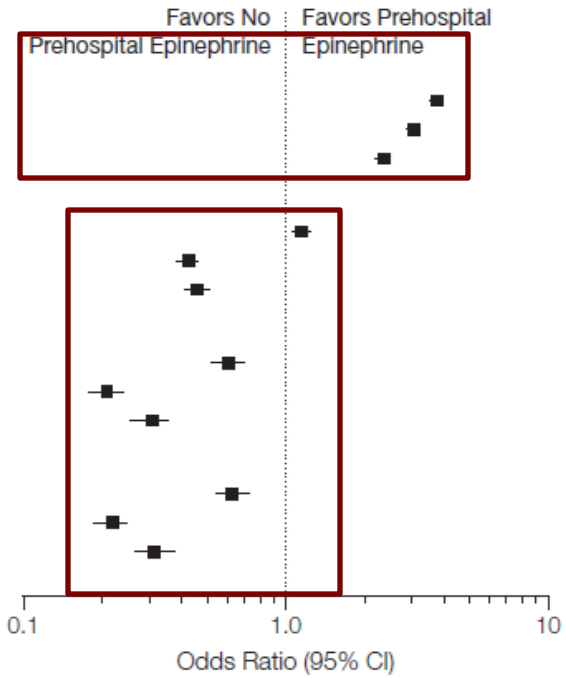
Figure 2. Results of Unconditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome		Odds Ratio (95% CI)
		Epinephrine	No Epinephrine	
ROSC				
Unadjusted	417 155	2786 (18.5)	23 042 (5.7)	3.75 (3.59-3.91)
Adjusted for selected variables[a]	412 078	2692 (18.6)	22 804 (5.7)	3.06 (2.93-3.21)
Adjusted for all covariates[b]	391 046	2556 (18.6)	21 629 (5.7)	2.36 (2.22-2.50)
1-Month survival				
Unadjusted	417 186	805 (5.4)	18 906 (4.7)	1.15 (1.07-1.23)
Adjusted for selected variables[a]	412 078	772 (5.3)	18 637 (4.7)	0.43 (0.39-0.46)
Adjusted for all covariates[b]	391 046	733 (5.3)	17 677 (4.7)	0.46 (0.42-0.51)
CPC 1 or 2				
Unadjusted	417 187	205 (1.4)	8903 (2.2)	0.61 (0.53-0.70)
Adjusted for selected variables[a]	412 078	197 (1.4)	8781 (2.2)	0.21 (0.18-0.24)
Adjusted for all covariates[b]	391 046	187 (1.4)	8329 (2.2)	0.31 (0.26-0.36)
OPC 1 or 2				
Unadjusted	417 187	211 (1.4)	8831 (2.2)	0.63 (0.55-0.73)
Adjusted for selected variables[a]	412 078	202 (1.4)	8710 (2.2)	0.22 (0.19-0.25)
Adjusted for all covariates[b]	391 046	192 (1.4)	37 732 (2.2)	0.32 (0.27-0.38)



Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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Outcomes	OR (95% CI)			
Conditional Logistic Regression Analysis				
	ROSC	1-month survival	CPC 1-2	OPC 1-2
Unadjusted	1.91 (1.78-2.05)	0.71 (0.64-0.79)	0.41 (0.34-0.49)	0.43 (0.36-0.51)
Adjusted for propensity	2.01 (1.83-2.21)	0.71 (0.62-0.81)	0.41 (0.33-0.52)	0.43 (0.34-0.54)
Adjusted for propensity and selected variables	2.24 (2.03-2.48)	0.60 (0.49-0.74)	0.40 (0.26-0.63)	0.43 (0.28-0.66)
Adjusted for propensity and all covariates	2.51 (2.24-2.80)	0.54 (0.43-0.68)	0.21 (0.10-0.44)	0.23 (0.11-0.45)

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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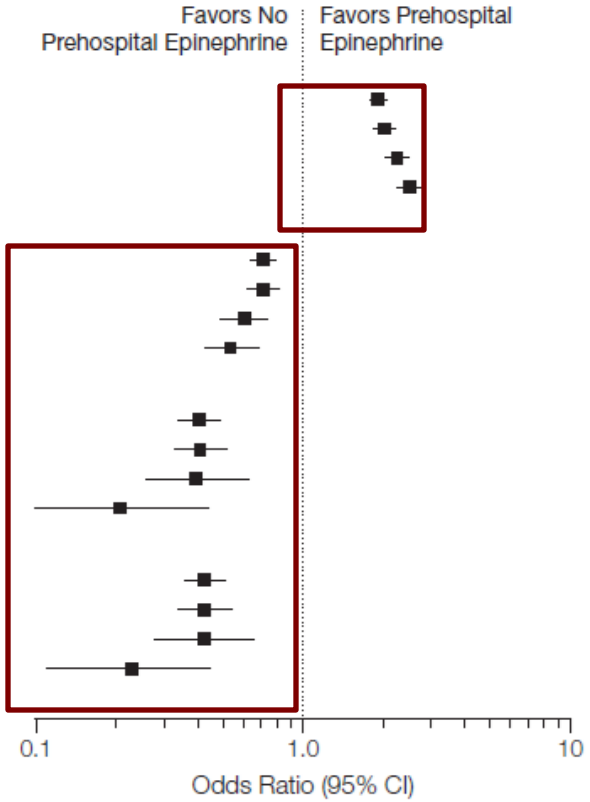
Figure 3. Results of Conditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome		Odds Ratio (95% CI)
		Epinephrine	No Epinephrine	
ROSC	26 802	2446 (18.3)	1400 (10.5)	
Unadjusted				1.91 (1.78-2.05)
Adjusted for propensity				2.01 (1.83-2.21)
Adjusted for propensity and selected variables[a]				2.24 (2.03-2.48)
Adjusted for all covariates[b]				2.51 (2.24-2.80)
1-Month survival	26 802	687 (5.1)	944 (7.0)	
Unadjusted				0.71 (0.64-0.79)
Adjusted for propensity				0.71 (0.62-0.81)
Adjusted for propensity and selected variables[a]				0.60 (0.49-0.74)
Adjusted for all covariates[b]				0.54 (0.43-0.68)
CPC 1 or 2	26 802	173 (1.3)	413 (3.1)	
Unadjusted				0.41 (0.34-0.49)
Adjusted for propensity				0.41 (0.33-0.52)
Adjusted for propensity and selected variables[a]				0.40 (0.26-0.63)
Adjusted for all covariates[b]				0.21 (0.10-0.44)
OPC 1 or 2	26 802	178 (1.3)	410 (3.1)	
Unadjusted				0.43 (0.36-0.51)
Adjusted for propensity				0.43 (0.34-0.54)
Adjusted for propensity and selected variables[a]				0.43 (0.28-0.66)
Adjusted for all covariates[b]				0.23 (0.11-0.45)



Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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Author's Conclusion

Among patients with OHCA in Japan, use of prehospital epinephrine was significantly associated with increased chance of return of spontaneous circulation before hospital arrival but decreased chance of survival and good functional outcomes 1 month after the event.

Hagihara A. JAMA. 2012 Mar 21;307(11):1161-8.

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Strengths & Limitations

Strengths

- Large sample
- Assessed EPI
- Patient centered outcome

Limitations

- Observational
- Survivalship bias
- Uncontrolled confounders
- CPR quality and time to EPI administration not assessed

Published in final edited form as:
JAMA Intern Med. 2015 February 1; 175(2): 196–204. doi:10.1001/jamainternmed.2014.5420.

Outcomes After Out-of-Hospital Cardiac Arrest Treated by Basic vs Advanced Life Support

Prachi Sanghavi, BS, **Anupam B. Jena, MD, PhD**, **Joseph P. Newhouse, PhD**, and **Alan M. Zaslavsky, PhD**

Objective

- To compare the effects of BLS and ACLS on outcomes after out-of-hospital cardiac arrest.

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Methods

Design	• Observational cohort study
Funding	• Agency for Healthcare Research and Quality and NIH
Setting	• Non-rural counties within the USA
Population	• Medicare beneficiaries experiencing out-of-hospital cardiac arrest

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Methods

Primary Outcome

- Survival to hospital discharge, 30 days, and 90 days

Secondary Outcome

- Neurological performance (CPC)
- Medical spending

Statistics

- Propensity score regression
- 2-sided at the 5% level
- Kaplan-Meier survival curves were prepared from the weighted observations

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Intervention

Patients

- Medicare beneficiaries from non-rural areas in OHCA

Intervention

- ACLS-trained providers

Comparison

- BLS-trained providers

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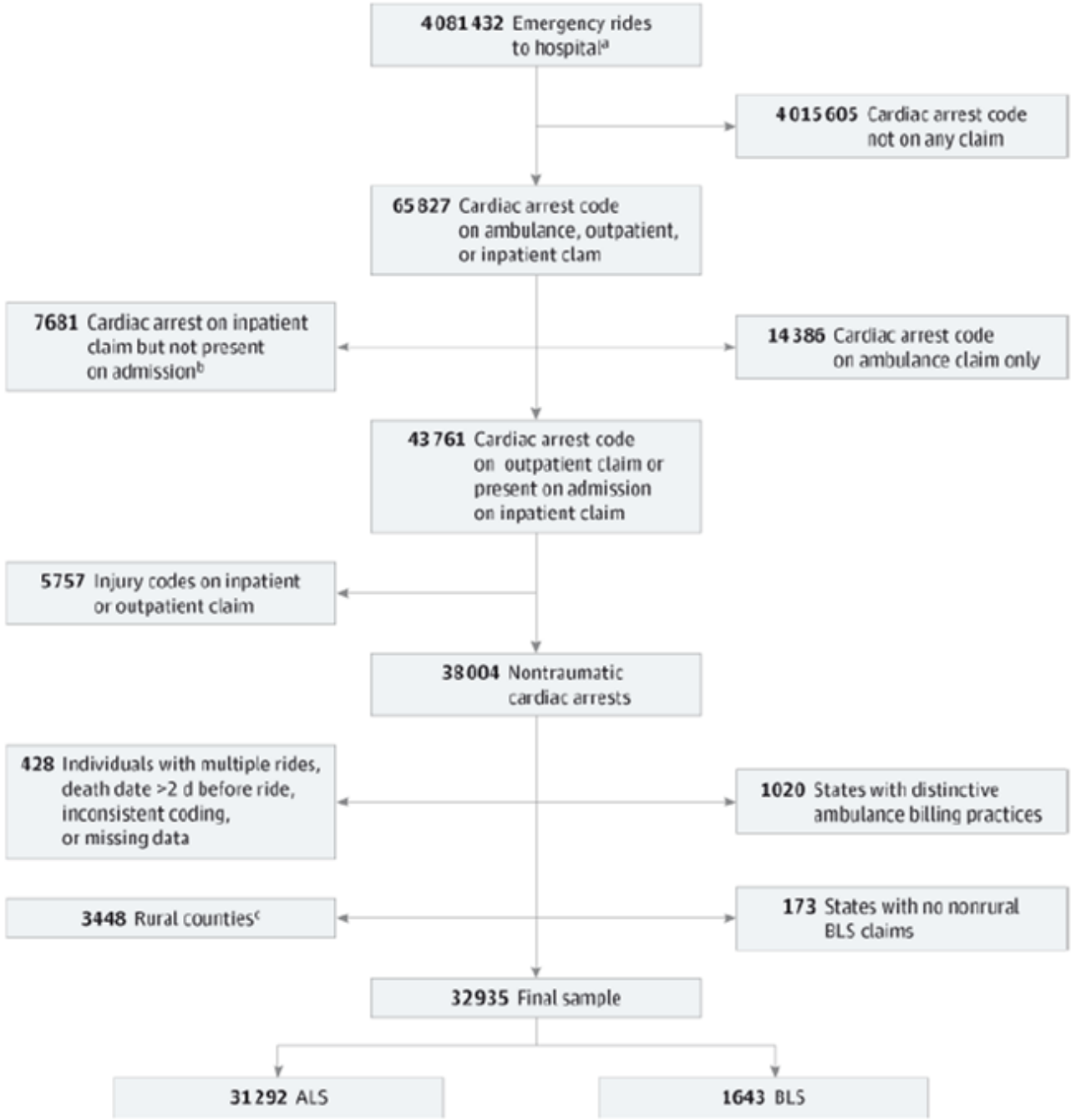


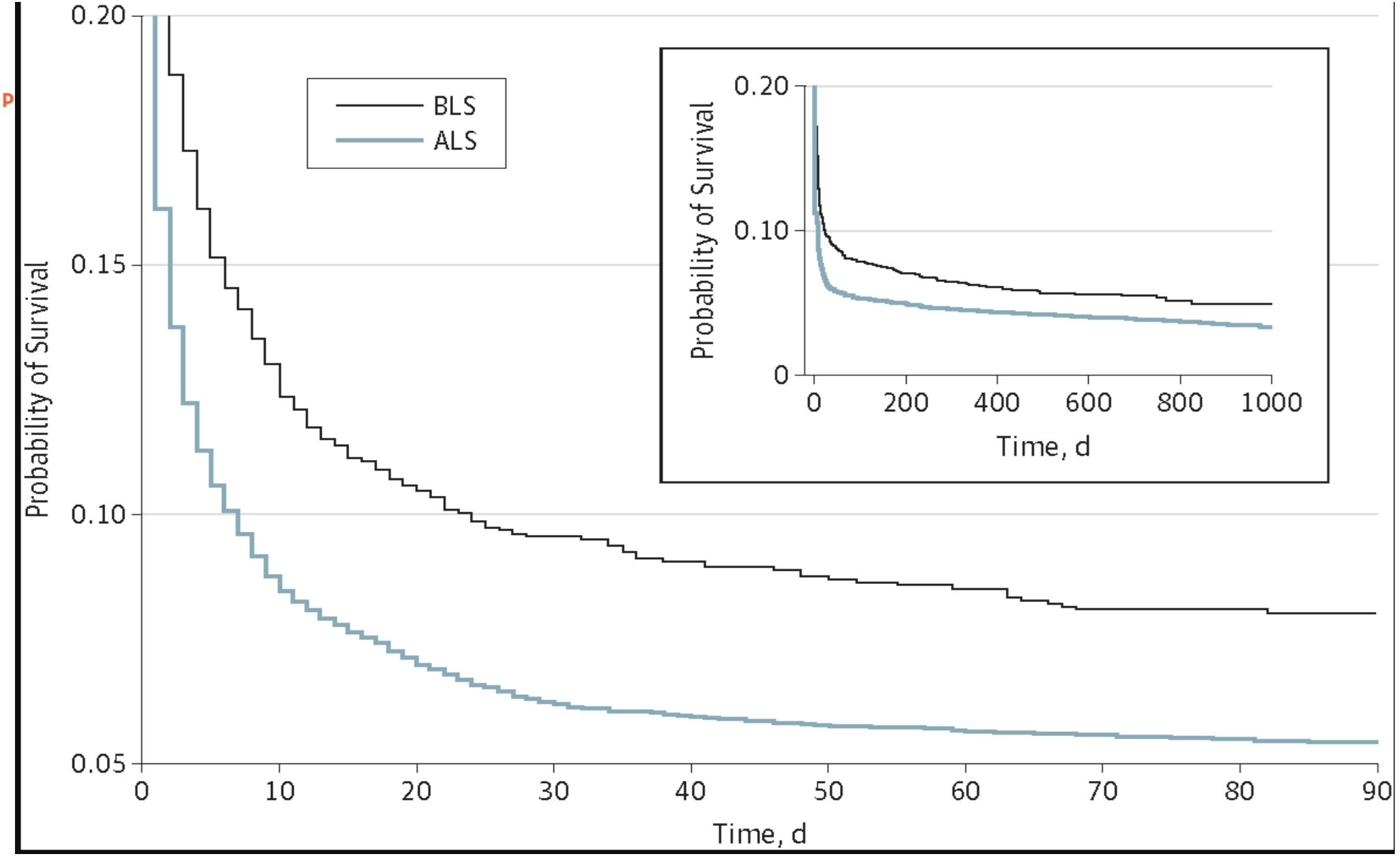
Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

Baseline Characteristics			
	BLS (n = 1643)	ALS (n = 31,292)	P value
Age (years)	77	75	<0.001
Female (%)	52	46	<0.001
Ambulance mileage, mean, km	8.7	9.5	0.002
Pickup location, %			
-Residence	55	65	0.05
-Skilled nursing facility	27	14	0.06
-Scene	14	17	
-Non–skilled nursing facility nursing home	5	4	
Comorbidity score, mean	5.5	4.8	<0.001
Past Medical History			
-Acute myocardial infarction	13	14	0.17
-Atrial fibrillation	30	29	0.25
-Chronic kidney disease	53	48	<0.001
-Heart failure	66	62	0.01
-Diabetes mellitus	58	53	<0.001
-Ischemic heart disease	75	72	<0.001
-Stroke or transient ischemic attack	32	27	<0.001

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

Outcomes			
	BLS % (95% CI)	ACLS % (95% CI)	Ratio (95 %CI)
Primary Outcome			
Unadjusted Outcomes			
-Survival to hospital discharge	13.1 (11.5-14.8)	9.6 (9.3-9.9)	1.4 (1.2-1.5)
-Survival to 30 d	9.6 (8.1-11)	6.5 (6.2-6.8)	1.5 (1.2-1.7)
-Survival to 90 d	8.0 (6.7–9.3)	5.8 (5.5-6.1)	1.4 (1.2-1.6)
Adjusted Outcomes			
-Survival to hospital discharge	13.1 (11.5-14.8)	9.2 (8.7-9.7)	1.4 (1.2-1.6)
-Survival to 30 d	9.6 (8.1-11)	6.2 (5.8-6.6)	1.5 (1.3-1.8)
-Survival to 90 d	8.0 (6.7–9.3)	5.4 (5.0-5.8)	1.5 (1.2-1.8)
-Survival to 1 yr	6.2 (4.9-7.6)	4.4 (4.0-4.8)	1.4 (1.1-1.8)
-Survival to 2 yr	6.8 (4.8-8.9)	3.9 (3.3-4.5)	1.7 (1.2-2.4)
Secondary Outcomes			
Poor neurological performance	6.1 (5.0–7.3)	9.7 (9.1-10.2)	0.6 (0.5–0.8)
Admission to hospital	25.4 (23.3-27.5)	20.5 (19.8-21.2)	1.2 (1.1–1.4)
1-y Medical spending for all beneficiaries	$ 11,875	$ 9097	1.3 (1.1-1.6)

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.



Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Author's Conclusion

Our study calls into question the widespread assumption that advanced prehospital care improves outcomes of out-of-hospital cardiac arrest relative to care following the principles of BLS, including rapid transport and basic interventions such as effective chest compressions, bag valve mask ventilation, and automated external defibrillation.

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Strengths & Limitations

Strengths

- Large sample size
- Relevant outcomes

Limitations

- Observational data
- CPR quality and time to EPI administration not assessed
- Did not isolate EPI
- Confounders not adjusted for

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Contents lists available at ScienceDirect

Resuscitation

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

Clinical paper

Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial☆

Ian G. Jacobs[a,c,*], Judith C. Finn[a,c], George A. Jelinek[b], Harry F. Oxer[c], Peter L. Thompson[d,e]

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[b] Department of Medicine, University of Melbourne (St Vincents Hospital), Victoria Parade, Fitzroy, 3065 Melbourne, Australia
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[d] School of Medicine and Population Health, University of Western Australia, Western Australia, Australia
[e] Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, 6009 Western Australia, Australia

Objective

- To determine the effect of adrenaline on patient survival to hospital discharge in out of hospital cardiac arrest

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

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Methods

Design	• Randomized double blind placebo-controlled
Funding	• National Health and Medical Research Council
Setting	• EMS covering Western Australia
Population	• 534 OHCA patients

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

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Methods

Primary Outcome

- Survival to hospital discharge

Secondary Outcome

- Pre-hospital ROSC (ROSC in the field for greater 30s)
- CPC at hospital discharge

Statistics

- Sample size required 2213 patients per group
- Alpha 0.05 (two tailed) and power of 80%
- Pearson's chi-square and t-test (or Mann–Whitney) for categorical and continuous data respectively

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

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Intervention

Patients

- >18 years old in out-of-hospital cardiac arrest

Intervention

- IV Epinephrine 1 mg

Comparison

- Placebo (sodium chloride 0.9%)

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

Baseline Characteristics			
	Placebo (n = 262)	Adrenaline (n = 272)	P value
Age (years), mean (SD)	64.9 (17.4)	64.3 (17.5)	0.69
Male, n (%)	196(74.8)	193(71.0)	0.33
Cardiac etiology: n (%)	242 (92.4)	246 (90.4)	0.43
Cardiac arrest witnessed: n (%) -Bystander -Paramedic	 138 (52.7) 14 (5.3)	 120 (44.1) 26 (9.6)	 0.05 0.06
Bystander CPR, n (%)	129 (49.2)	144 (52.9)	0.39
Initial cardiac arrest rhythm: n (%) -VF/VT -PEA -Asystole	 126 (48.1) 70 (26.7) 66 (25.2)	 119 (43.8) 91 (33.5) 62 (22.8)	0.24
EMS response interval (min): mean (SD)	10.2 (7.3)	10.1 (5.5)	0.76
Airway management: n (%) **-Tracheal intubation** **-Laryngeal mask airway**	 198 (75.6) 61 (23.3)	 192 (70.6) 66 (24.3)	 0.19 0.79
Volume of trial drug (ml): median (IQR)	5.0 (3.0–8.0)	5.0 (3.0–7.0)	0.13
Volume of IV fluids administered (ml): median (IQR)	500 (237–700)	500 (200–700)	0.28
Transported to hospital: n (%)	215 (82.1)	241 (88.6)	0.03

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Outcomes			
	Placebo (n = 262)	Adrenaline (n = 272)	P Value
Primary Outcome			
Survival to hospital discharge, No.(%)	5 (1.9)	11 (4.0)	0.15
Secondary Outcomes			
Return of spontaneous circulation, No.(%)	22 (8.4)	64 (23.5)	<0.001
Admission to hospital, No.(%)	34 (13.0)	69 (25.4)	<0.001
CPC 1 or 2, No.(%)	5 (100)	9 (81.8)	0.31

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

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Author's Conclusion

Patients receiving adrenaline during cardiac arrest had no statistically significant improvement in the primary outcome of survival to hospital discharge although there was a significantly improved likelihood of achieving ROSC.

Jacobs IG et al. Resuscitation 2011; 82:1138-43.

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Strengths & Limitations

Strengths

- RCT
- Assessed EPI
- Patient centered outcome

Limitations

- Sample size
- CPR quality and time to EPI administration not assessed

PHA

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*

Objective

- In adult patients that present to paramedics with out-of-hospital arrest in the field, does acute cardiac life support performed with epinephrine as compared to placebo lead to improved survival and neurological outcome.

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Methods

Design

- Multicenter, double-blind, randomized trial

Funding

- Health Technology Assessment Programme of the U.K National Institute for Health Research

Setting

- Five National Health Service ambulance services in the United Kingdom

Duration

- December 2014 through October 2017

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Methods

Primary Outcome

- Survival at 30 days

Secondary Outcome

- Survival until hospital admission
- Median length of stay in ICU (IQR) — days
- Median length of hospital stay
- Survival until hospital discharge
- Favorable neurologic outcome at hospital discharge
- Survival at 3 mo
- Favorable neurologic outcome at 3 mo

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Methods

Statistics

- 8000 patients would provide the best threshold to balance precision and practicality.
- Data and safety monitoring committee performed interim reviews every 3 months
- Intention-to-treat population
- Bayesian analysis for the primary outcome and for survival with a favorable neurologic outcome

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Intervention

Patients

- Adult patients with OHCA receiving ACLS provided by trial-trained paramedics

Intervention

- IV epinephrine 1mg q3 – 5min + standard care

Comparison

- IV 0.9% normal saline bolus + standard care

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Time Intervals That Matter

	EPI (n = 4015)	Placebo (n = 3999)
Interval between emergency call and EMS arrival		
• Median (IQR) — min	6.7 (4.3–9.7)	6.6 (4.2–9.6)
Interval between emergency call and admin of trial agent		
• Median (IQR) — min	21.5 (16.0–27.3)	21.1 (16.1–27.4)
Interval between ambulance arrival at scene and departure		
• Mean — min	50.1±21.8	44.5±18.3
Interval between ambulance departure from scene and hospital arrival		
• Mean — min	12.9±9.8	12.4±8.9
Median interval between initiation of advanced life support and cessation (IQR) — min	47.5 (35.1–64.0)	43.1 (33.5–56.1)
Return of spontaneous circulation — no. (%)		
• Yes	1457 (36.3)	468 (11.7)
• No	2518 (62.7)	3492 (87.3)
• Missing data	40 (1.0)	39 (1.0)
Transportation of patient to hospital — no. (%)		
• Yes	2041 (50.8)	1227 (30.7)
• No	1974 (49.2)	2772 (69.3)

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Baseline Characteristics

	EPI (n = 4015)	Placebo (n = 3999)
Mean age ±SD — yr	69.7±16.6	69.8±16.4
Sex — no. (%)		
• Male	2609 (65.0)	2584 (64.6)
Initial cardiac rhythm — no. (%)		
• Shockable	770 (19.2)	748 (18.7)
• Nonshockable	3149 (78.4)	3181 (79.5)
Cause of cardiac arrest — no. (%)		
• Medical cause	3656 (91.1)	3691 (92.3)
• Traumatic cause	66 (1.6)	57 (1.4)
• Drug overdose	74 (1.8)	72 (1.8)
• Asphyxia	117 (2.9)	81 (2.0)
• Other	102 (2.6)	180 (4.5)
Witness of cardiac arrest — no. (%)		
• None	1498 (37.3)	1505 (37.6)
• Paramedic	452 (11.3)	470 (11.8)
• Bystander	2013 (50.1)	1967 (49.2)
• Not identified	1 (<0.1)	1 (<0.1)
• Missing data	51 (1.3)	56 (1.4)
CPR performed — no. (%)		
• By bystander	2382 (59.3)	2349 (58.7)
• By paramedic during witnessed event	452 (11.3)	470 (11.8)
• Not identified	1 (<0.1)	1 (<0.1)
• Missing data	69 (1.7)	84 (2.1)

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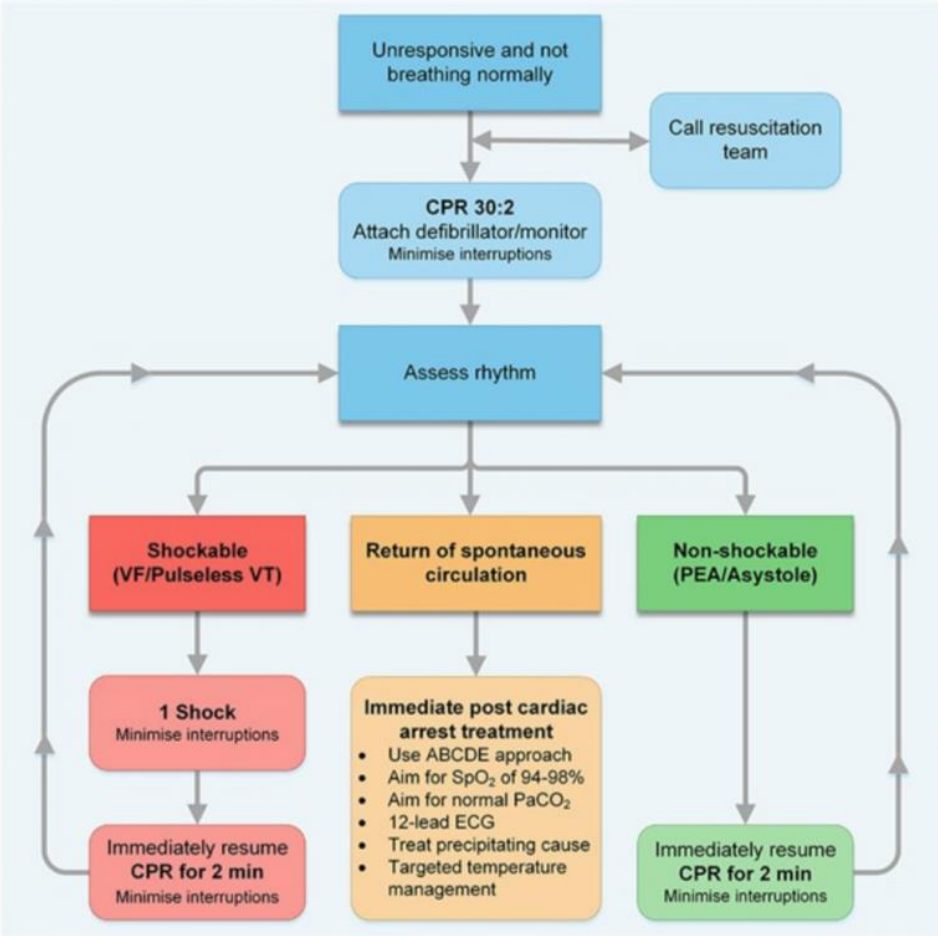
European Resuscitation Council's (ERC) Guidelines



In shockable rhythms

- Epinephrine is administered after 3 shocks

In non-shockable rhythms

- Epinephrine is administered as soon as possible

Lloyd G. Br J Hosp Med (Lond). 2015 Dec;76(12):678

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PARAMEDIC 2 Results

Primary Outcome

- <u>Survival at 30 days</u>
  - 3.2% vs. 2.4%
  - OR unadjusted 1.39 (1.06-1.82)
  - OR adjusted 1.47 (1.09-1.97)

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Outcomes				
	EPI (n = 4015)	Placebo (n = 3999)	Odds Ratio (95% CI)	
	no./total no. (%)	no./total no. (%)	Unadjusted	Adjusted
Secondary Outcomes				
Survival until hospital admission	947/3973 (23.8)	319/3982 (8.0)	3.59 (3.14–4.12)	3.83 (3.30–4.43)
Median ICU LOS • Patients who survived • Patients who died	 7.5 (3.0–15.0) 2.0 (1.0–5.0)		NA	NA
Median hospital LOS • Patients who survived • Patients who died	 21.0 (10.0–41.0) 0	 20.0 (9.0–38.0) 0	NA	NA
Survival until hospital discharge	128/4009 (3.2)	91/3995 (2.3)	1.41 (1.08–1.86)	1.48 (1.10–2.00)
Favorable neurologic outcome at hospital Discharge	87/4007 (2.2)	74/3994 (1.9)	1.18 (0.86–1.61)	1.19 (0.85–1.68)
Survival at 3 mo	121/4009 (3.0)	86/3991 (2.2)	1.41 (1.07–1.87)	1.47 (1.08–2.00)
Favorable neurologic outcome at 3 mo	82/3986 (2.1)	63/3979 (1.6)	1.31 (0.94–1.82)	1.39 (0.97–2.01)

Sanghavi P. JAMA Intern Med. 2015 Feb;175(2):196-204.

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Neurologic Impairment

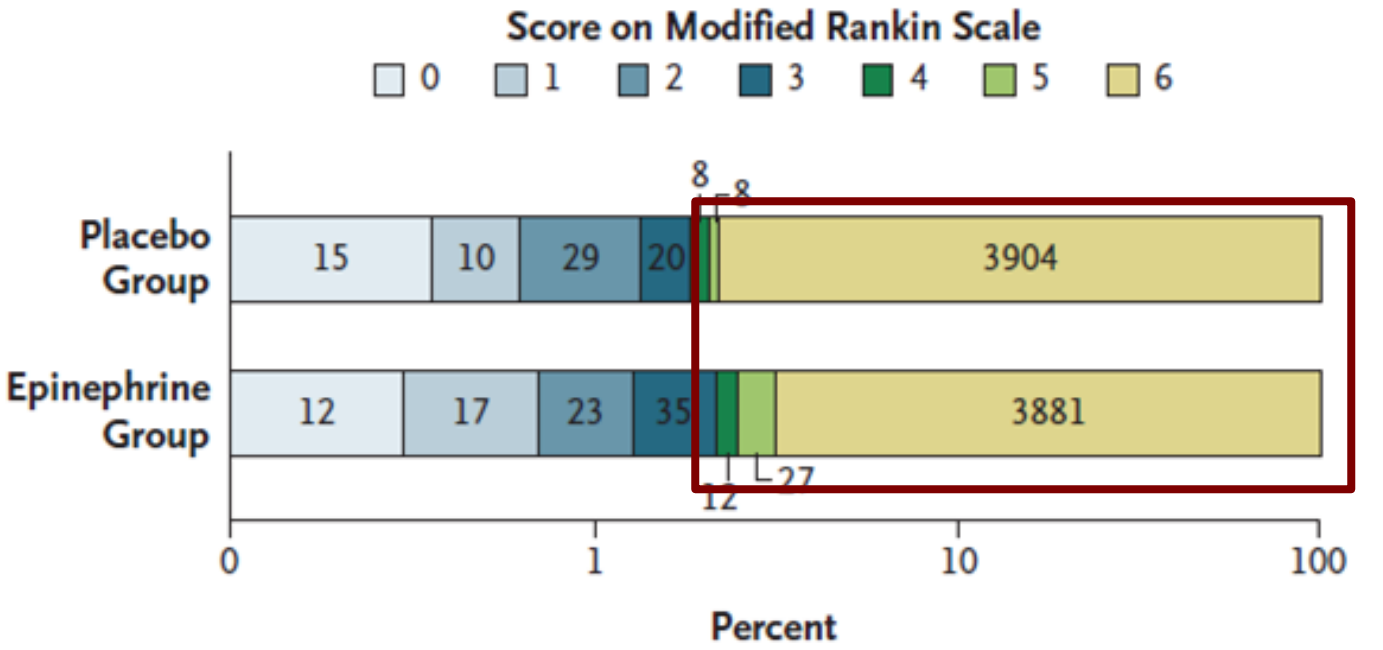

Figure 2. Survival with a Favorable Neurologic Outcome at Hospital Discharge.

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Author's Conclusion

In conclusion, in this randomized trial involving patients with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of survival at 30 days 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.

Perkins GD. N Engl J Med. 2018 Aug 23;379(8):711-721

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Strengths & Limitations

Strengths

- RCT
- Relevant outcomes
- Strong design

Limitations

- Low survival rate
- Post-arrest in-hospital management was not controlled for nor measured
- Time to drug administration was longer as compared to other trials

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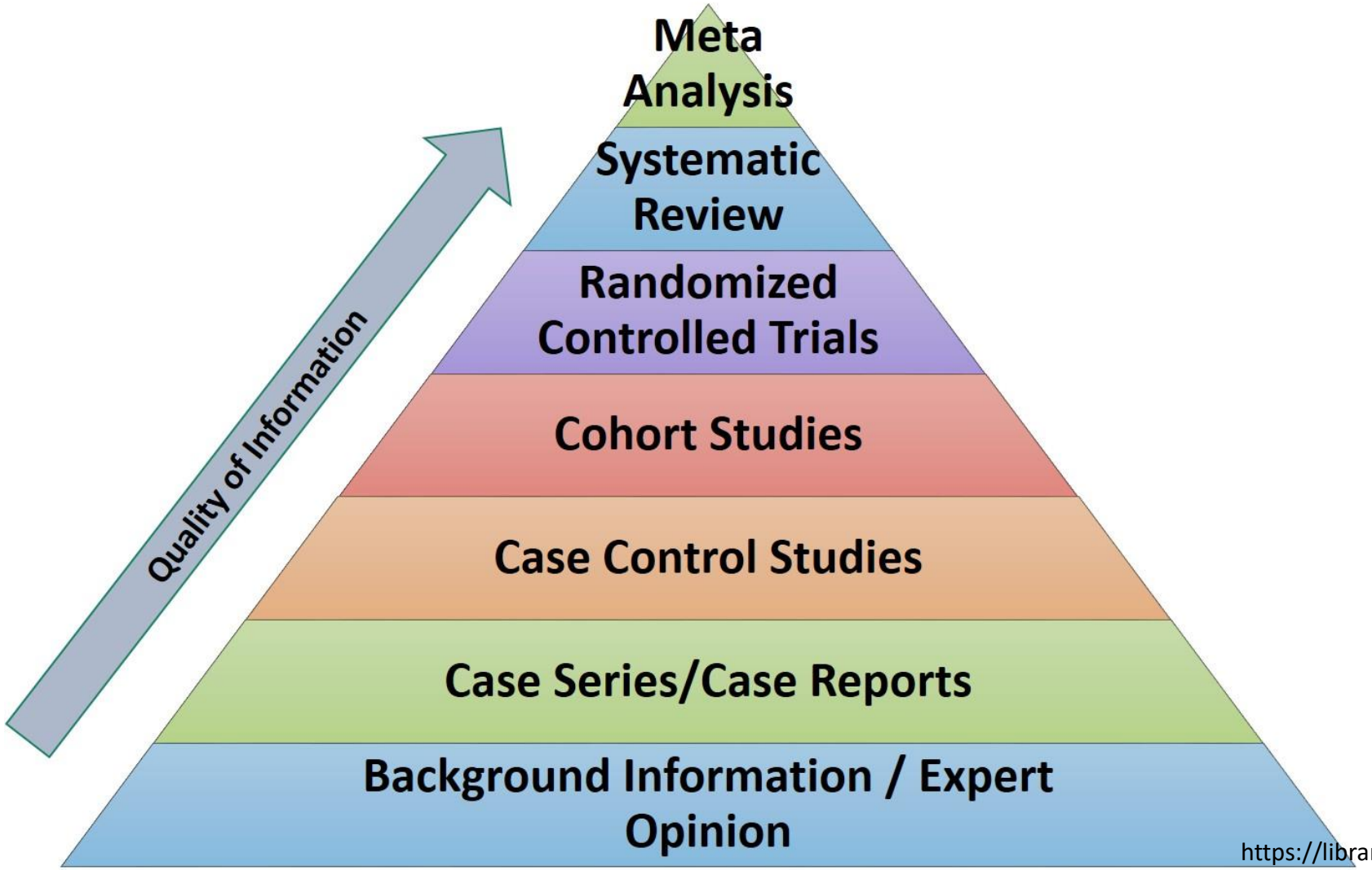
Meta Analysis on EPI in OHCA



https://library.triton.edu/c.php?g=433673&p=3720267

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

Rohit Seth Loomba, MD [a,*], Karan Nijhawan, BS [b], Saurabh Aggarwal, MD [c], Rohit Romesh Arora, MD [d]

[a] Division of Cardiology, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI
[b] Division of Medicine, Rush University Medical Center, Chicago, IL
[c] Division of Cardiology, Creighton University Medical Center, Omaha, NE
[d] Division of Cardiology, Chicago Medical School, North Chicago, IL

Comparison of survival at 1 month

Study or Subgroup	Epinephrine Events	Epinephrine Total	No epinephrine Events	No epinephrine Total	Weight	Odds Ratio M-H, Random, 95% CI
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: Tau² = 0.08; Chi² = 102.02, df = 4 (P < .00001); I² = 96%
Test for overall effect: Z = 0.19 (P = .85)

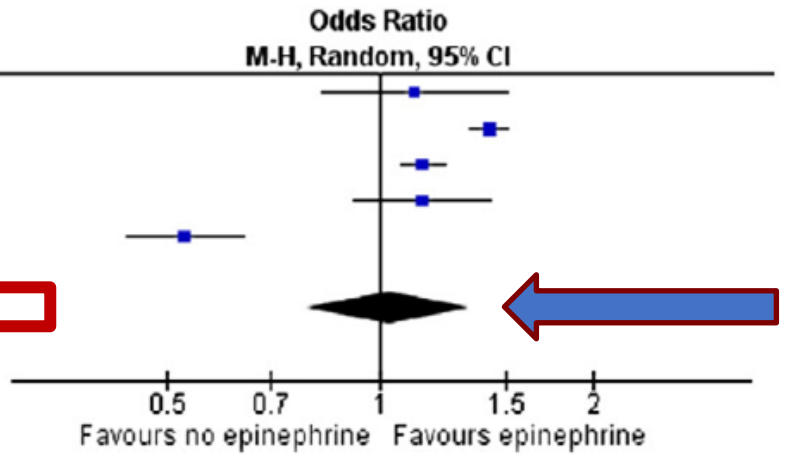

Fig. 3. Forest plot comparing survival at 1 month between those who had and had not received epinephrine.

Loomba RS. J Crit Care. 2015 Dec;30(6):1376-81.

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

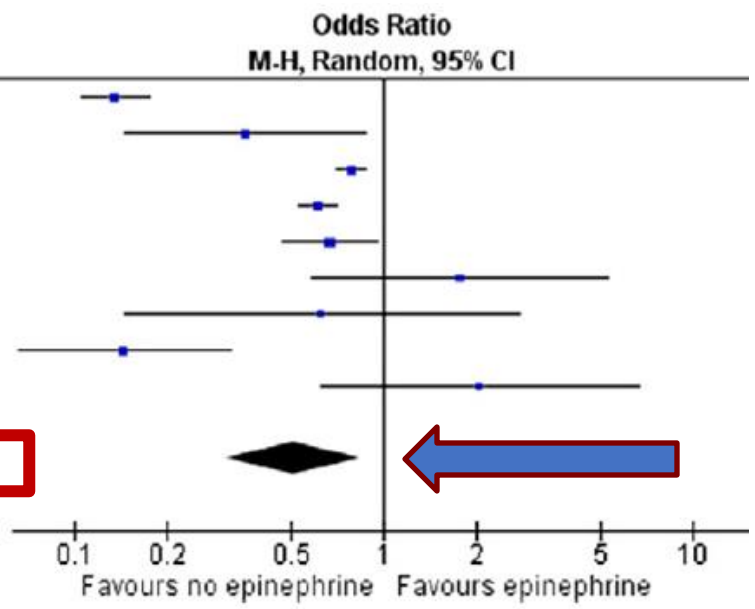
Rohit Seth Loomba, MD [a,*], Karan Nijhawan, BS [b], Saurabh Aggarwal, MD [c], Rohit Romesh Arora, MD [d]

[a] Division of Cardiology, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI
[b] Division of Medicine, Rush University Medical Center, Chicago, IL
[c] Division of Cardiology, Creighton University Medical Center, Omaha, NE
[d] Division of Cardiology, Chicago Medical School, North Chicago, IL

Comparison of neurological outcome at discharge

Study or Subgroup	Epinephrine Events	Epinephrine Total	No epinephrine Events	No epinephrine Total	Weight	Odds Ratio M-H, Random, 95% CI
Dumas et al	194	1134	255	422	14.1%	0.14 [0.11, 0.17]
Fukuda et al	5	770	113	6301	9.9%	0.36 [0.15, 0.88]
Goto et al	340	23676	3379	185901	14.5%	0.79 [0.70, 0.88]
Hagihara et al	205	15030	8903	402158	14.4%	0.61 [0.53, 0.70]
Hayashi et al	42	1013	130	2148	13.6%	0.67 [0.47, 0.96]
Jacobs et al	9	272	5	262	8.5%	1.76 [0.58, 5.32]
Machida et al	2	49	28	443	6.5%	0.63 [0.15, 2.73]
Olasveengen et al	7	367	57	481	10.6%	0.14 [0.07, 0.32]
Ong et al	9	681	4	615	8.0%	2.05 [0.63, 6.68]
Total (95% CI)		**42992**		**598731**	**100.0%**	**0.51 [0.31, 0.84]**
Total events	813		12874			

Heterogeneity: Tau² = 0.45; Chi² = 181.79, df = 8 (*P* < 00001); I² = 96%
Test for overall effect: Z = 2.64 (*P* = .008)



NNH= 83

Fig. 5. Forest plot comparing positive neurologic outcome at discharge between those who had and had not received epinephrine.

Loomba RS. J Crit Care. 2015 Dec;30(6):1376-81.

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Objectives

- Discuss epidemiology, pathophysiology, and treatment for cardiac arrest
- Describe positive and negative effects of epinephrine during advanced cardiac life support and post-return of spontaneous circulation
- Analyze evidence for epinephrine use in cardiac arrest
- Review the interventions for post-arrest care

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"When about a quarter of fluid has passed into the blood vessels, 15–30 minims of a one to one thousands adrenaline solution are injected into the vessel" – George W. Crile 1906

Soto-Ruiz KM. Resuscitation. 2009 Jan;80(1):6-8.

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TTM

- ACLS Guidelines
  - Recommend that comatose adult patients with ROSC after cardiac arrest have TTM
    - Class I, LOE B-R for VF/pVT OHCA
    - Class I, LOE C-EO for non-VF/pVT
      - Nonshockable and in-hospital cardiac arrest
  - Studies report NNT 8 for good neurological outcome

http://www.medivance.com/imagelibrary

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What About the Catheterization Suite?

- Significant disease identified in 57% of patients without acute ischemic ECG changes

- Coronary angiography increased good clinical outcome OR 2.16 (95% CI 1.12- 4.19) P < 0.02

Reynolds JC. J Intensive Care Med. 2009 May-Jun;24(3):179-86
https://www.dicardiology.com/article/5-technologies-reduce-cath-lab-radiation-exposure

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Summary of Interventions

Bystander CPR

- NNT 24-36

Defibrillation

- NNT 3

EPI

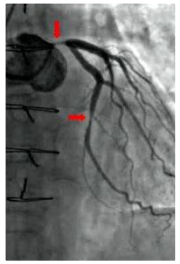
- NNT 112
- NNH 83

Vasopressin+ Steroids+ EPI

- NNT 7-17

TTM

- NNT 8



PCI

- NNT 4

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ACLS Recommendations

Standard-dose epinephrine (1 mg every 3 to 5 minutes) **may be reasonable** for patients in cardiac arrest (Class IIb, LOE B-R).

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Presenter's Opinion

EPI MAY be used to achieve ROSC

EPI has been used in OHCA since 1960s

EPI should not delay or minimize focus on therapies with proven benefit

The dose, route, timing of EPI needs further research

EPI may not be the preferred vasopressor

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Summary

EPI has been used in CPR since the 1970's despite weak and conflicting evidence

Current literature has failed to consistently find benefit from EPI in long-term outcomes (survival to hospital discharge and good neurological outcomes)

We need more trials with optimal study design and patient-centered outcomes

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Assessment Question

- What is the most common presenting rhythm in cardiac arrest?
  A. PEA/ Asystole
  B. Ventricular Fibrillation
  C. Bradycardia
  D. Supraventricular tachycardia

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Assessment Question

- What is the most common presenting rhythm in cardiac arrest?
  A. PEA/ Asystole
  B. Ventricular Fibrillation
  C. Bradycardia
  D. Supraventricular tachycardia3

- Answer: PEA/Asystole is the most common presentation of cardiac arrest

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Assessment Question

- What is the most dose of epinephrine utilized in cardiac arrest?
  A. 2 mg
  B. 1 mg
  C. 0.5 mg
  D. 10 mcg

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Assessment Question

- What is the most dose of epinephrine utilized in cardiac arrest?
  - A. 2 mg
  - **B. 1 mg**
  - C. 0.5 mg
  - D. 10 mcg

- Answer: 1 mg is the most common dose of epinephrine used in cardiac arrest

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Assessment Question

- True or False. There is a significant amount of clinical literature that reports that epinephrine increase the odds of patients being discharged with good neurological outcomes.
    A. True
    B. False

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Assessment Question

- True or False. There is a significant amount of clinical literature that reports that epinephrine increase the odds of patients being discharged with good neurological outcomes.
  A. True
  B. False

- Answer: false, epinephrine has not be consistently proven to increase the odds of discharge with good neurological outcomes.

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Assessment Question

- True or False. The PARAMEDIC 2 trial displayed a significant finding that epinephrine increase the odds of patients obtaining ROSC compared to placebo.
    A. True
    B. False

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Assessment Question

- True or False. The PARAMEDIC 2 trial displayed a significant finding that epinephrine increase the odds of patients obtaining ROSC compared to placebo.
  - **A. True**
  - B. False
  - Answer: True, epinephrine was shown to increase the odds of obtaining return of spontaneous circulation compared to placebo.

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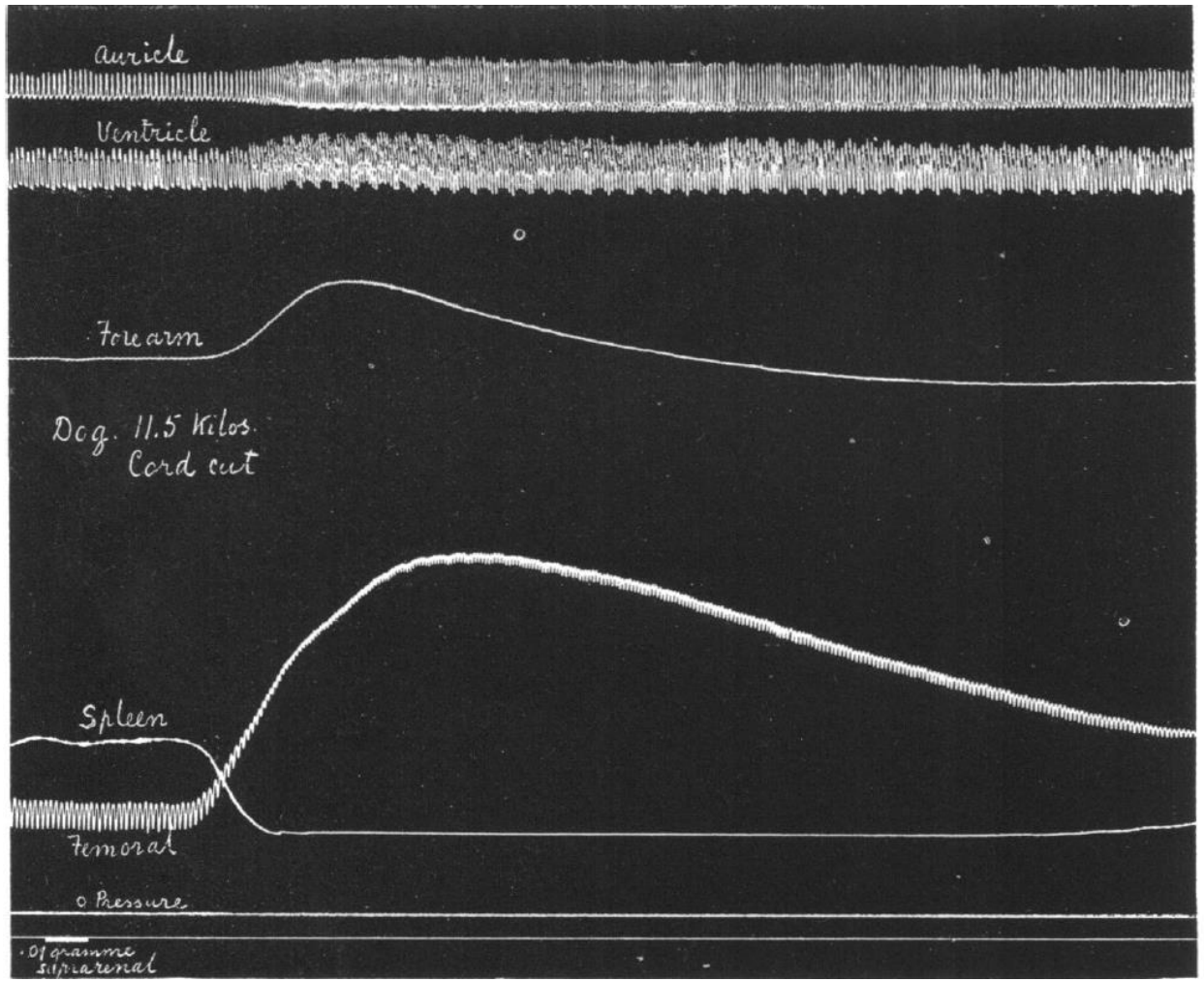

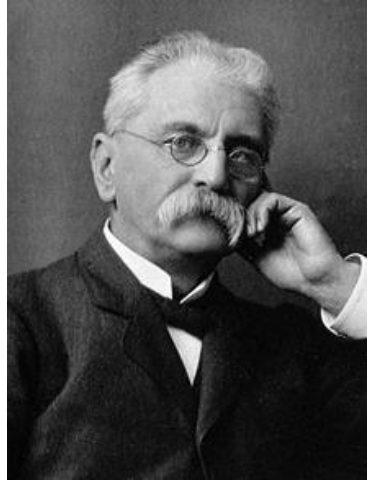

GEORGE OLIVER, M.D

Oliver et al. J Physiol. 1895 Jul 18; 18(3): 230–276..

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The Pharmacologic Approach to Cardiac Arrest:
A Focus on Vasopressors

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