Cracking the Code: Controversies in ACLS Pharmacotherapy

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Mentor:

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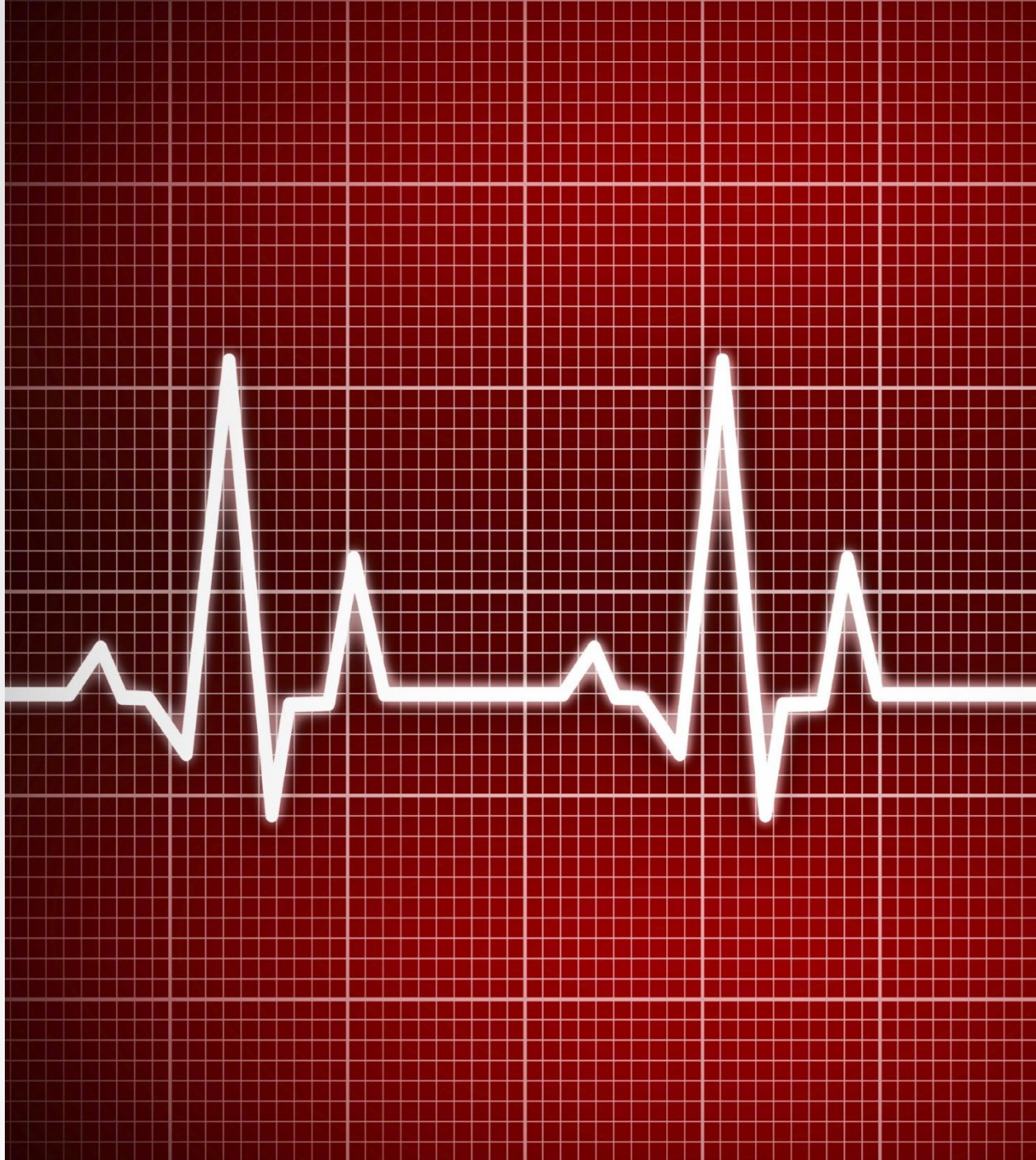


Disclosures

- **Sam Markle has no relevant financial relationships with ineligible companies to disclose**

Objectives

- After this presentation, pharmacists will be able to:

I. Describe the utility of common interventions in ACLS

II. Review the evidence supporting epinephrine in ACLS

III. Discuss the controversial role of vasopressin and VSE in cardiac arrest

IV. Compare outcomes between amiodarone and lidocaine in shockable arrest

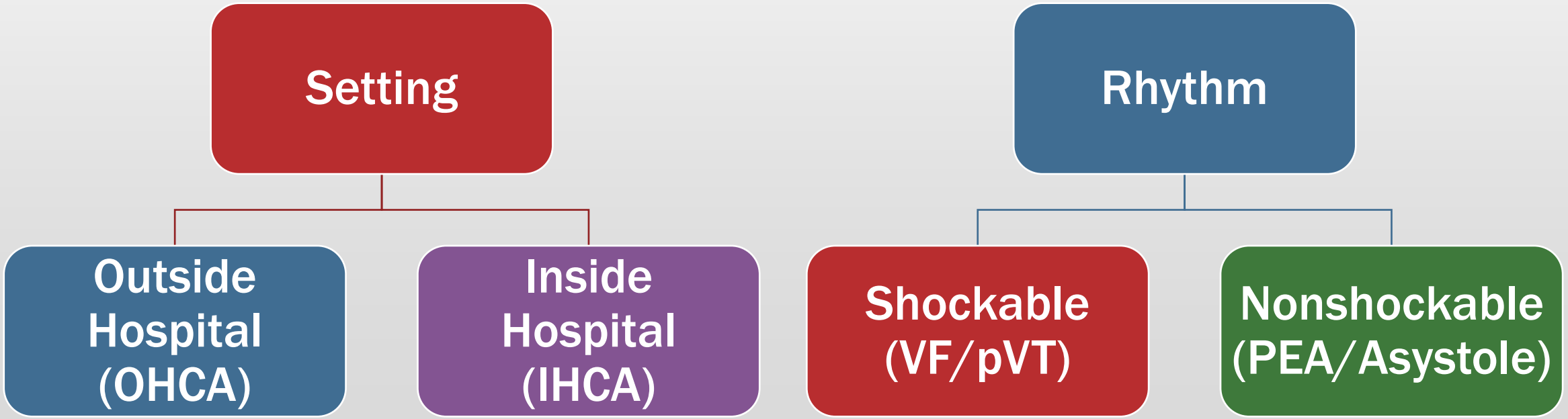
Abbreviations

- OHCA – Outside Hospital Cardiac Arrest
- IHCA – Inside Hospital Cardiac Arrest
- VF – Ventricular Fibrillation
- pVT – Pulseless Ventricular Tachycardia
- PEA – Pulseless Electrical Activity
- CPR – Cardiopulmonary Resuscitation
- BLS – Basic Life Support
- ACLS – Advanced Cardiac Life Support

Cardiac Arrest Background

- Defined as the cessation of mechanical cardiac activity, confirmed by the absence of signs of circulation

- Generally categorized according to two major classifications:



Tsao et al. *Circulation*. 2022.

Cardiac Arrest Epidemiology

- Patient outcomes are generally poor

Group	OHCA		IHCA	
	Survival to Discharge	Favorable Neurologic Outcome	Survival to Discharge	Favorable Neurologic Outcome
All patients	9.0%	7.0%	23.3%	17.8%
Initial Rhythm				
VF/pVT	25.6%	22.6%	49%	-
PEA/Asystole	5.5%	3.9%	10.5%	-

Tsao et al. *Circulation*. 2022.

Cardiac Arrest Management

Advanced Cardiac Life Support (ACLS)

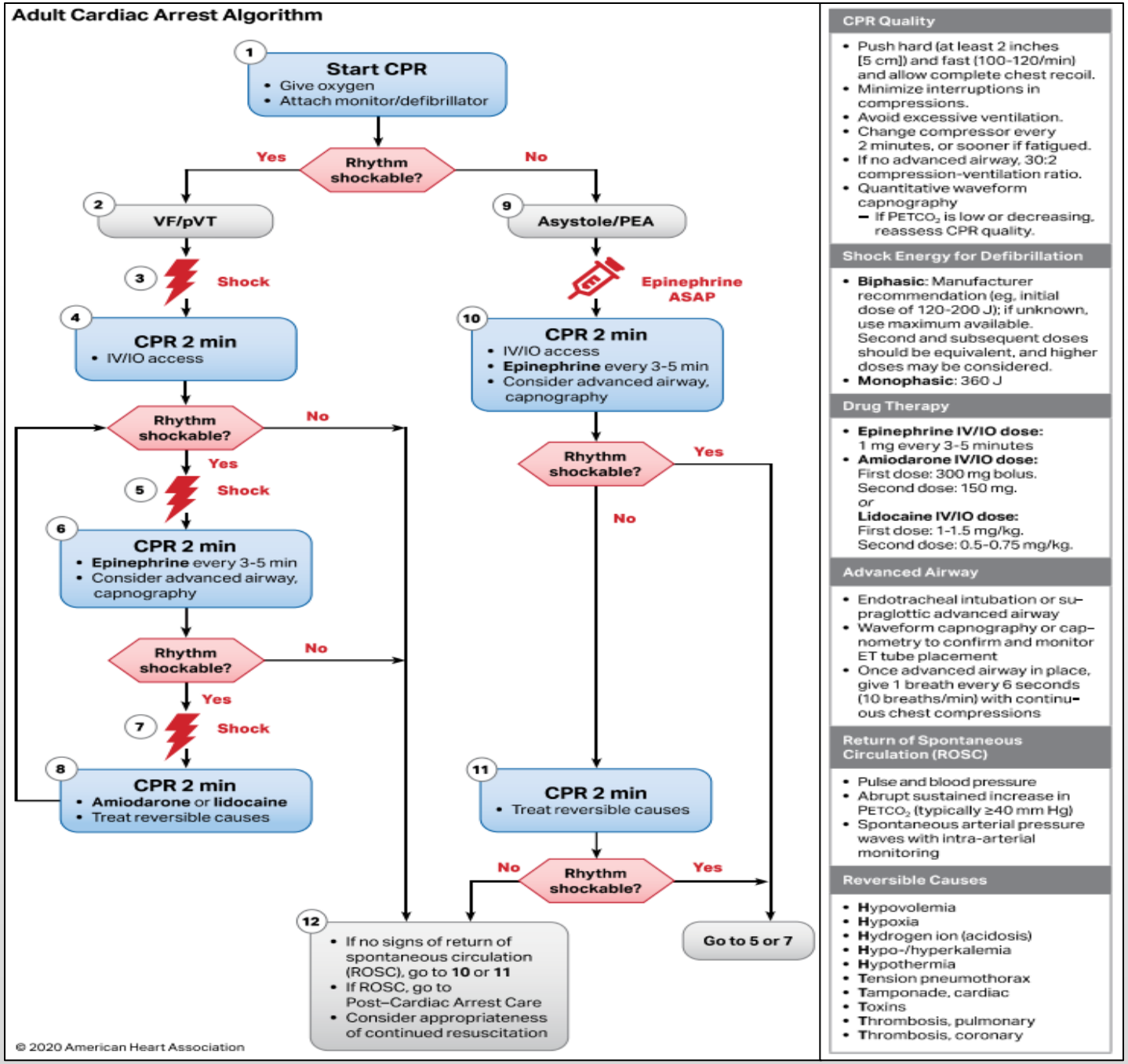
Basic Life Support

- High-Quality CPR
- Defibrillation

+

- Treatment of Underlying Causes
- Advanced Airway Management
- Pharmacotherapy

Stiell et al. *NEJM*. 2004.
Panchal et al. *Circulation*. 2020. Sanghavi et al. *JAMA Int Med*. 2015.



Advanced Cardiac Life Support (ACLS)

Panchal et al. *Circulation*. 2020.

Pharmacotherapy in ACLS

Rationale:

Assist in the restoration of cardiac activity and improve favorable outcomes

Standard Medications

- Epinephrine
- Amiodarone
- Lidocaine

Optional Medications

- Alteplase
- Calcium chloride
- Dextrose
- Insulin
- Sodium bicarbonate
- Steroids
- Vasopressin

Panchal et al. *Circulation*. 2020.

Question I

- Which of the following ACLS interventions are associated with improvement in neurologic outcomes at hospital discharge (select all that apply)?

A. Chest compressions

B. Early defibrillation

C. Epinephrine

D. Antiarrhythmic drugs

Outcomes in Cardiac Arrest Literature

Return of Spontaneous Circulation (ROSC)

Survival to Hospital Admission

Survival to Hospital Discharge

Survival with Favorable Neurologic Outcome

Pharmacotherapy Overview

Epinephrine

Vasopressin

Vasopressin, Steroids + Epinephrine (VSE)

Antiarrhythmic Drugs

Epinephrine

Epinephrine Pharmacotherapy

Mechanism of action:

- Combined α + β adrenergic agonist

Rationale for Use:

- α-adrenergic agonism leads to arterial vasoconstriction
  - Augments coronary perfusion -> improved ROSC
  - Increases cerebral perfusion -> better neurological outcomes
- β-adrenergic agonism may improve contractility

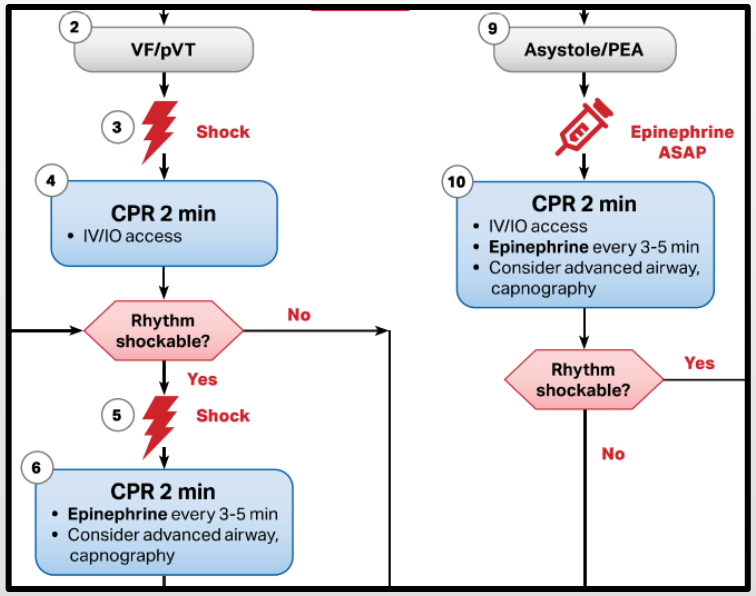
Jacobs et al. *Resuscitation.* 2011.
Ristagno et al. *Crit Care Med.* 2009.
Perkins et al. *NEJM.* 2018.

Role in Therapy

2020 AHA Guidelines

1	B-R	1. We recommend that epinephrine be administered for patients in cardiac arrest.
2a	B-R	2. Based on the protocols used in clinical trials, it is reasonable to administer epinephrine 1 mg every 3 to 5 min for cardiac arrest.
2a	C-LD	3. With respect to timing, for cardiac arrest with a nonshockable rhythm, it is reasonable to administer epinephrine as soon as feasible.
2b	C-LD	4. With respect to timing, for cardiac arrest with a shockable rhythm, it may be reasonable to administer epinephrine after initial defibrillation attempts have failed.

2020 ACLS Algorithm



2021 ERC Guidelines = Same recommendations, but wait until after 3rd shock in pVT/VF

Dose

1 mg IV (IO) every 3-5 min or with every other pulse check

Panchal et al. *Circulation*. 2020.
Soar et al. *Resuscitation*. 2021.

Adverse Effects of Epinephrine

Adverse Effects

- β-adrenergic stimulation
  - Enhanced arrhythmia risk
  - Increased myocardial oxygen demand
- Decreased microcirculatory cerebral blood flow in animal models

Jacobs et al. *Resuscitation.* 2011.
Ristagno et al. *Crit Care Med.* 2009.
Perkins et al. *NEJM.* 2018.

Controversies

- **Utility in cardiac arrest due to ventricular arrhythmias**
  - Does improvement in perfusion outweigh arrhythmia risk?
- **Timing of drug administration**
  - Would earlier administration = better outcomes?
- **Optimal dose**
  - Will higher dosing lead to greater efficacy?
- **Effect on overall patient outcomes**
  - What clinically important outcomes are improved with epinephrine?

Holmberg et al. *Resuscitation*. 2019.

PACA (2011)

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]

- **Single-center, double-blind RCT**
- **N = 534**
- **<u>Population</u>: OHCA**

- **Trial Characteristics:**
  - No information on timing of drug administration
  - Initial rhythm = VF/pVT in 45.8%, PEA in 30.1%, and Asystole in 24.1%

Jacobs et al. *Resuscitation*. 2011.

PACA (2011) - Results

Epinephrine led to:

- ↑ ROSC pre-hospital (23.5% vs. 8.4%, p < 0.001)
- ↑ Survival to hospital admission (25.4% vs. 13.0%, p < 0.001)
- ↔ Survival to hospital discharge (4.0% vs. 1.9%)
- ↔ Favorable neurologic function in survivors (81.8% vs. 100%, p = 0.31)

9/11 5/5

ROSC

Non-Shockable – OR 6.9

Shockable – OR 2.4

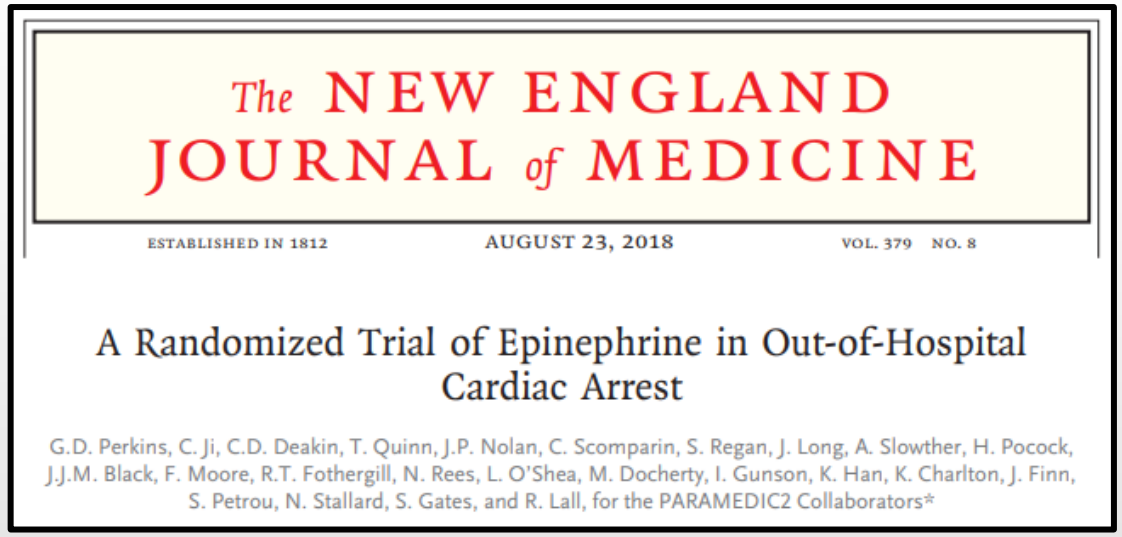
Survival to Admission

Non-Shockable – OR 2.5

Shockable – OR 2.2

Jacobs et al. *Resuscitation*. 2011.

PARAMEDIC2 (2018)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 23, 2018 VOL. 379 NO. 8

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*

- Multicenter, double-blind RCT
- N = 8014
- Population: OHCA

- **Trial Characteristics:**
  - Median time to drug administration = 21 min from EMS call
  - 79% of patients had non-shockable rhythm (53% asystole)

Perkins et al. *NEJM.* 2018.

PARAMEDIC2 (2018) - Results

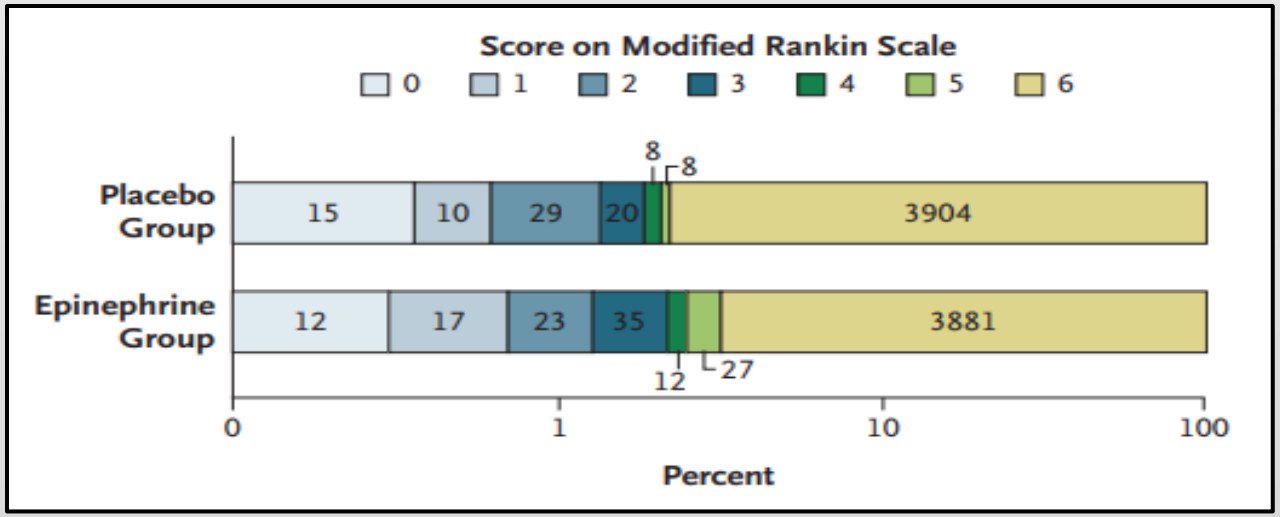
	Outcome	Epinephrine	Placebo	Odds Ratio (95% CI)
↑	Survival at 30 days	3.2%	2.4%	1.47 (1.09 to 1.97)
↑	Pre-Hospital ROSC	36.3%	11.7%	–
↑	Survival to Hospital Admission	23.8%	8.0%	3.83 (3.30 to 4.43)
↑	Survival to Hospital Discharge	3.2%	2.3%	1.48 (1.10 to 2.00)
↔	Survival with Favorable Neurologic Outcome	2.2%	1.9%	1.19 (0.85 to 1.68)

Perkins et al. *NEJM.* 2018.

PARAMEDIC2 (2018) – Results II

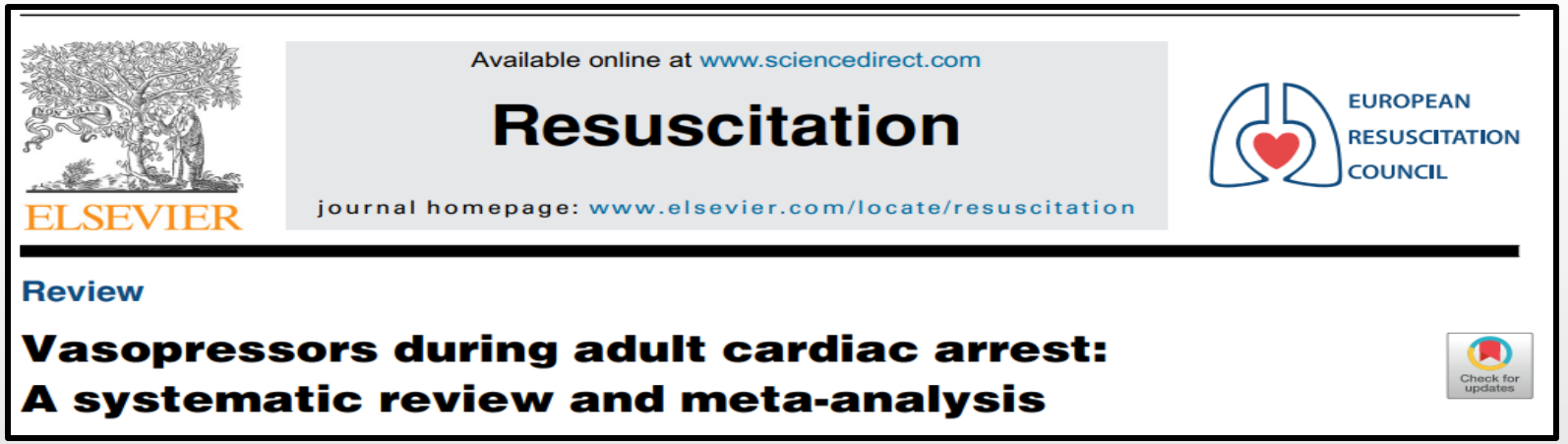
➢Subgroup Analysis:

Subgroup	Survival at 30 days: Placebo	Survival at 30 days: Epinephrine	OR (95% CI)	p (interaction)
Initial rhythm				0.15
Shockable rhythm	79/745 (11%)	99/767 (13%)	1.25 (0.91, 1.71)	
Nonshockable rhythm	14/3180 (0.4%)	29/3149 (0.9%)	2.10 (1.11, 3.98)	



Perkins et al. *NEJM.* 2018.

Holmberg et al. (2019)



- Systematic Review and Meta-Analysis
- **Inclusion**: Age ≥ 18, RCT or non-randomized trial or observational study
- **Exclusion**: VSE studies, studies on epinephrine dose comparisons

Holmberg et al. *Resuscitation*. 2019.

Holmberg et al. (2019) - Epinephrine

- **Comparison**: Epinephrine vs. Placebo
- **Studies**: 2 RCTs (N = 8469)

Epinephrine:

- **Subgroup Analysis**:
  - Non-shockable Rhythms - ↑ ROSC + Survival to Hospital Discharge
  - Shockable Rhythms - ↑ ROSC only

- Earlier administration associated with improved rates of ROSC

Holmberg et al. *Resuscitation*. 2019.

Timing of Epinephrine - OHCA

- Okubo et al. (2021)
  - Every **1-minute delay** from EMS arrival to epinephrine administration associated with

Non-Shockable	Shockable
↓ RR of Survival by 4.4%	↓ RR of Survival by 5.5%
↓ RR of Favorable Neurologic Outcome by 7.1%	↓ RR of Favorable Neurologic Outcome by 6.4%

Andersen et al. *BMJ.* 2016.
Donnino et al. *BMJ.* 2014. Okubo et al. *JAMA Netw Open.* 2021.

Timing of Epinephrine - IHCA

Donnino et al. (2014) – Non-Shockable

- Stepwise ↓ in survival with **prolonged** time to epinephrine administration ($p < 0.001$)

Early = Better

Andersen et al. (2016) - Shockable

- ↓ survival when epinephrine given within 2 minutes of first defibrillation – OR 0.70 [0.59 to 0.82]

Early = Worse

Donnino et al. *BMJ*. 2014.
Andersen et al. *BMJ*. 2016.

Epinephrine Dose

3: No Benefit	B-R	6. High-dose epinephrine is not recommended for routine use in cardiac arrest.

Study	Population	Comparison	Survival with CPC 1 or 2	Survival to Discharge	Survival to Admission	ROSC
Callaham et al. (1992)	OHCA N = 816	HDE (15 mg) vs. SDE (1 mg)	- (p = 0.10)	- (p = 0.37)	+ (p = 0.02)	+ (p = 0.01)
Brown et al. (1992)	OHCA N = 1280	HDE (0.2 mg/kg) vs. SDE (0.02 mg/kg)	N/A	- (p = 0.98)	- (NR)	- (NR)
Stiell et al. (1992)	All CA N = 650	HDE (7 mg) vs. SDE (1 mg)	- (p = 0.24)	- (p = 0.38)	N/A	- (p = 0.12)
Choux et al. (1995)	OHCA N = 536	HDE (5 mg) vs. SDE (1 mg)	N/A	N/A	- (NR)	- (NR)
Sherman et al. (1997)	All CA N = 140	HDE (0.1 mg/kg) vs. SDE (0.01 mg/kg)	- (NR)	- (NR)	N/A	- (p = 0.25)
Gueugniaud et al. (1998)	OHCA N = 3327	HDE (5 mg) vs. SDE (1 mg)	- (p = 0.40)	- (p = 0.78)	+ (p = 0.05)	+ (p = 0.02)

Callaham et al. *JAMA*. 1992. Brown et al. *NEJM*. 1992. Stiell et al. *NEJM*. 1992. Choux et al. *Resuscitation*. 1995. Sherman et al. *Pharmacotherapy*. 1997. Gueugniaud et al. *NEJM*. 1998.

Epinephrine Summary

Non-Shockable	Shockable
↑ ROSC	↑ ROSC
↑ Survival to Admission	↔ Survival to Admission
↑ Survival to Discharge	↔ Survival to Discharge

↔ No impact on favorable neurologic survival

- Earlier administration may improve outcomes
- No clinical benefit with high-dose epinephrine

Holmberg et al. *Resuscitation*. 2019.

Question II

- Based on the currently available evidence, epinephrine has demonstrated improvement in all of the following except?

  A. ROSC

  B. Survival to Hospital Admission

  C. Survival to Hospital Discharge

  D. Favorable Neurologic Survival

Vasopressin

Vasopressin Pharmacotherapy

Mechanism of action:

- V1 Receptor Agonist -> arterial vasoconstriction
- Role in cardiac arrest = similar to epinephrine

Rationale for Use:

- Relative endogenous vasopressin deficiency in cardiac arrest
- Non-catecholamine vasopressor
  - Retains activity in severe acidosis
  - Avoids sympathetic adverse effects

Theorized Target Patient Population:

- Prolonged cardiac arrest with profound acidosis
- Ventricular arrhythmias

Wenzel et al. *NEJM*. 2004.
Gueugniaud et al. *NEJM*. 2008.

Role in Practice

- **Proposed Options:**
  - Alternative to epinephrine
  - Combination therapy with epinephrine
- **Guideline Recommendations:**

Vasopressin (40 units) may replace the 1st or 2nd dose of epinephrine in the treatment of cardiac arrest (Class IIb)

2005 AHA Guidelines

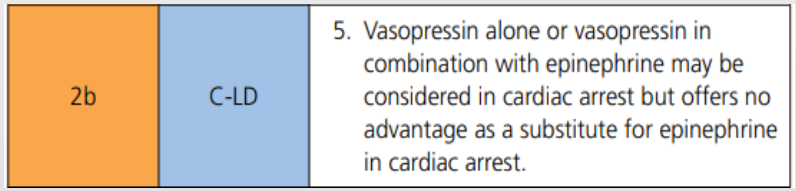
Circulation. 2005.

Vasopressin offers no advantage over epinephrine in cardiac arrest (Class IIb) or in combination with epinephrine (Class IIb)

- Removed from ACLS algorithm

2015 AHA Guidelines

Neumar et al. *Circulation*. 2010.
Link et al. *Circulation*. 2015.

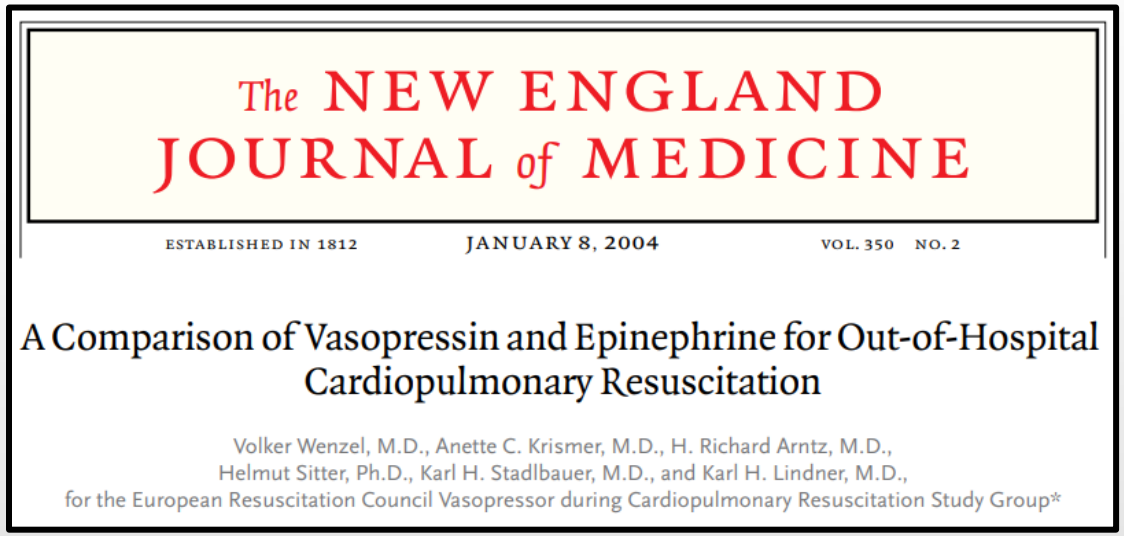


2b	C-LD	5. Vasopressin alone or vasopressin in combination with epinephrine may be considered in cardiac arrest but offers no advantage as a substitute for epinephrine in cardiac arrest.

2020 AHA Guidelines

Panchal et al. *Circulation*. 2020.
Soar et al. *Resuscitation*. 2021.

Wenzel et al. (2004)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2004 VOL. 350 NO. 2

A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation

Volker Wenzel, M.D., Anette C. Krismer, M.D., H. Richard Arntz, M.D., Helmut Sitter, Ph.D., Karl H. Stadlbauer, M.D., and Karl H. Lindner, M.D., for the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group*

- Multicenter, double-blind RCT
- N = 1186
- Population: OHCA

- **Trial Characteristics:**
  - Mean 18 minutes from arrest to drug administration
  - 45% had asystole, 40% had VF/pVT, 15% had PEA

Wenzel et al. *NEJM.* 2004.

Wenzel et al. (2004) - Results

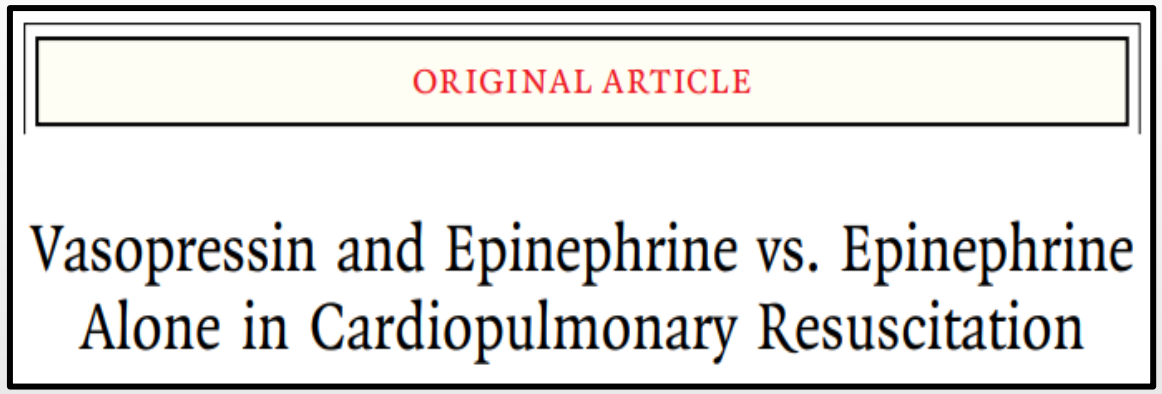
- No difference between groups for:

ROSC	Survival to Admission	Survival to Discharge	Favorable Neurologic Outcome
24.6% vs. 28.0%	36.3% vs. 31.2%	9.9% vs. 9.9%	3.23% vs. 3.45%
(p = 0.19)	(p = 0.06)	(p = 0.99)	(p = 0.99)

- No difference in outcomes between rhythm type
- ↑ survival to admission by 40% with vasopressin in <u>asystole</u>
- No harm associated with vasopressin

Wenzel et al. *NEJM.* 2004.

Gueugniaud et al. (2008)


ORIGINAL ARTICLE

Vasopressin and Epinephrine vs. Epinephrine Alone in Cardiopulmonary Resuscitation

- Multicenter, double-blind RCT
- N = 2894
- Population: OHCA

- **Trial Characteristics:**
  - Majority of patients (83%) had asystole
  - Mean 21-22 minutes from collapse to first drug administration

Gueugniaud et al. *NEJM*. 2008.

Gueugniaud et al. (2008) - Results

Table 2. Survival Data for the 2894 Patients in the Intention-to-Treat Population.*

End Point	Combination Treatment (N=1442)	Epinephrine Only (N=1452)	Relative Risk of Death (95% CI)	P Value
Survival to hospital admission — no. (%)	299 (20.7)	310 (21.3)	1.01 (0.97–1.05)	0.69
Survival to return of spontaneous circulation — no. (%)	413 (28.6)	428 (29.5)	1.01 (0.97–1.06)	0.62
Survival to hospital discharge — no./total no. (%)	24/1439 (1.7)	33/1448 (2.3)	1.01 (1.00–1.02)	0.24
1-Year survival — no./total no. (%)	18/1437 (1.3)	30/1447 (2.1)	1.01 (1.00–1.02)	0.09
Good neurologic recovery at hospital discharge — no./total no. (%)†	9/24 (37.5)	17/33 (51.5)	1.29 (0.81–2.06)	0.29

- Post-hoc analysis demonstrated ↓ survival to hospital discharge with combination therapy in patients with initial PEA (0% vs. 5.8%, p = 0.02)

Gueugniaud et al. *NEJM*. 2008.

Holmberg et al. (2019) - Vasopressin

- **Comparison**: Vasopressin vs. Epinephrine
- **Studies**:
  - Vasopressin vs. Epinephrine - 3 RCTs (N = 1562)
  - Combination Therapy vs. Epinephrine Alone – 3 RCTs (N = 3249)

Vasopressin vs. Epinephrine

No difference in any outcomes between groups

Combination vs. Epinephrine

No difference in any outcomes between groups

Holmberg et al. *Resuscitation*. 2019.

Vasopressin Summary

- No difference in outcomes with vasopressin vs. epinephrine
- No suggestion for harm with vasopressin

Personal Conclusion:

- Vasopressin offers no benefit over epinephrine and use cannot be routinely recommended
- Vasopressin may still have niche in profound acidosis or VF/pVT arrest

Question III

- Which of the following statements accurately represents the current evidence for the use of vasopressin in cardiac arrest?

A. Vasopressin alone improves survival to discharge vs. epinephrine

B. Vasopressin + epinephrine is superior to epinephrine alone

C. Vasopressin is more effective in PEA than epinephrine

D. Vasopressin does not improve outcomes vs. epinephrine

Vasopressin, Steroids and Epinephrine (VSE)

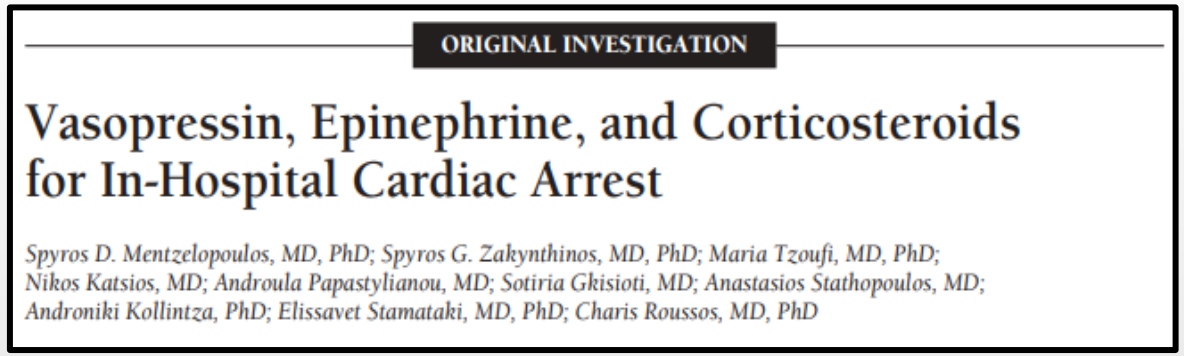
VSE Pharmacotherapy

- **Rationale for use:**
  - Epinephrine + Vasopressin -> arterial vasoconstriction
  - Corticosteroids
    - Enhances myocardial contractility
    - Reversal of relative adrenal insufficiency
    - Attenuation of systemic inflammatory response
    - Potentiation of vasopressor activity

Several small studies have demonstrated improved ROSC and survival in patients treated with steroids during and after cardiac arrest

Prigent et al. *Crit Care*. 2004. Tsai et al. *Int J Cardiology*. 2016. Liu et al. *J Int Med Res.* 2020.
Ito et al. *Resuscitation.* 2004. Tsai et al. *Am J Emerg Med*. 2007. Tsai et al. *Crit Care Med.* 2019. Andersen et al. *JAMA*. 2021.

Mentzelopoulos et al. (2009)



ORIGINAL INVESTIGATION

Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest

Spyros D. Mentzelopoulos, MD, PhD; Spyros G. Zakynthinos, MD, PhD; Maria Tzoufi, MD, PhD; Nikos Katsios, MD; Androula Papastylianou, MD; Sotiria Gkisioti, MD; Anastasios Stathopoulos, MD; Androniki Kollintza, PhD; Elissavet Stamataki, MD, PhD; Charis Roussos, MD, PhD

- Single-center, double-blind RCT
- N = 100
- Population: IHCA

- **Trial Characteristics:**
  - Initial rhythm was asystole in 62%, PEA in 23%, and VF/pVT in 15%
  - Mean time to ACLS was 1 min

Mentzelopoulos et al. *Arch Intern Med*. 2009.

Mentzelopoulos et al. (2009) - Results

VSE led to:

- ↑ ROSC (81% vs. 52%, p = 0.003)
- ↑ Survival to hospital discharge (18.8% vs. 3.8%, p = 0.02)
- ↑ More rapid attainment of ROSC

- Patients with post-resuscitation shock had ↑ survival with steroids
  - 29.6% vs. 0%, p = 0.02

Mentzelopoulos et al. *Arch Intern Med*. 2009.

Mentzelopoulos et al. (2013)

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest

A Randomized Clinical Trial

- Multicenter, double-blind RCT
- N = 268
- Population: IHCA

- **Trial Characteristics:**
  - Initial rhythm was asystole in 65-70%, PEA 15-20%, and pVT/VF in 17%
  - Time to ACLS was ~2 min

Mentzelopoulos et al. *JAMA*. 2013.

Mentzelopoulos et al. (2013) - Results

VSE led to:

- ↑ ROSC (83.9% vs. 65.9%, p = 0.005)
- ↑ Survival to hospital discharge with Favorable Neurological Outcome (13.9% vs. 5.1%, p = 0.02)
- ↓ Duration of ACLS (13 vs. 19 min, p = 0.01)

➢ Validates prior study with larger population and neurologic outcomes

Mentzelopoulos et al. *JAMA*. 2013.

VAM-IHCA (2021)


Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest

A Randomized Clinical Trial

- Multicenter, double-blind RCT
- N = 501
- Population: IHCA

- **Trial Characteristics:**
  - Majority of patients had non-shockable rhythm (90%)
  - Mean duration to trial drug was ~8 min

Andersen et al. *JAMA*. 2021.

VAM-IHCA (2021) - Results

Table 2. Outcomes According to Treatment Assignment[a]

	Vasopressin and methylprednisolone (n = 237)	Placebo (n = 264)	Difference, % (95% CI)[b]	Risk ratio (95% CI)	*P* value
Primary outcome					
Return of spontaneous circulation	100 (42)	86 (33)	9.6 (1.1 to 18.0)	1.30 (1.03 to 1.63)	.03
Secondary outcomes					
30-d Outcomes					
Survival	23 (9.7)	31 (12)	−2.0 (−7.5 to 3.5)	0.83 (0.50 to 1.37)	.48
Favorable neurologic outcome (CPC 1-2)[c]	18 (7.6)	20 (7.6)	0.0 (−4.7 to 4.9)	1.00 (0.55 to 1.83)	>.99
Favorable neurologic outcome (mRS 0-3)[d]	11 (4.6)	19 (7.2)	−2.6 (−6.9 to 1.7)	0.64 (0.32 to 1.31)	
EQ-5D-5L[e]	62 (15)	56 (23)	6 (−4 to 17)		
EQ-5D-5L-Index[e]	45 (37)	40 (33)	5 (−14 to 24)		

Andersen et al. *JAMA*. 2021.

VSE Limitations

Mentzelopoulos Trials

- Prompt ACLS initiation (within 1-2 min)
- Single trial group in Greece
- N = 368 total

VAM-IHCA

- Slower time to drug administration
- Lack of post-arrest steroid protocolization
- Not powered for long-term outcomes

Overall

- Only studied in IHCA
- Predominantly evaluated in non-shockable rhythms
- Multi-intervention confounding effect

Mentzelopoulos et al. *Arch Intern Med*. 2009.

Mentzelopoulos et al. *JAMA*. 2013.
Andersen et al. *JAMA*. 2021.

VSE Summary

IHCA

VSE Therapy, compared to epinephrine alone:

- Consistently ↑ ROSC
- May ↑ survival and favorable neurological outcomes
  - Conflicting data
- No suggestion of harm

Discussion:

- Should we use VSE in routine clinical practice?

Mentzelopoulos et al. *Arch Intern Med*. 2009.

Mentzelopoulos et al. *JAMA*. 2013.
Andersen et al. *JAMA*. 2021.

Question IV

- Which of the following outcomes was <u>most consistently</u> demonstrated with the Vasopressin, Steroids and Epinephrine trials?

  A. ROSC

  B. Survival to Hospital Admission

  C. Survival to Hospital Discharge

  D. Favorable Neurological Outcomes

Antiarrhythmic Drugs: Amiodarone vs. Lidocaine

Antiarrhythmic Drugs in ACLS

➢Used in patients with VF/pVT refractory to defibrillation

Rationale:

- Chemical cardioversion to restore perfusing rhythm
- Lowers defibrillation threshold

Two drugs primarily used:

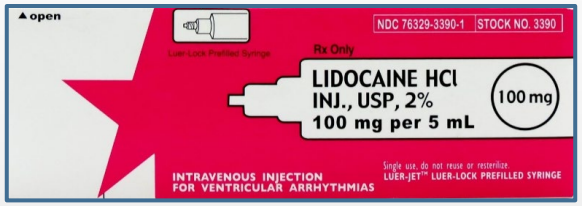
- Amiodarone
- Lidocaine

Panchal et al. *Circulation*. 2020.

Amiodarone vs. Lidocaine

Amiodarone

- **Mechanism**: Class III antiarrhythmic with effects on α/β receptors + Na/K/Ca channels
- **Dose**:
  - Initial = 300 mg
  - Repeat = 150 mg
- **Adverse Effects**:
  - Hypotension
  - Bradycardia



Lidocaine

- **Mechanism**: Class 1b antiarrhythmic (Na channel blocker)
- **Dose**:
  - Initial = 1-1.5 mg/kg
  - Repeat = 0.5-0.75 mg/kg
- **Adverse Effects**:
  - Seizures
  - Bradycardia

Fresenius Kabi. Amiodarone.
McGuff Medical. Lidocaine.
Lexicomp. Amiodarone.
Lexicomp. Lidocaine.

Guideline Recommendation History

2020 AHA Guidelines

2b	B-R	1. Amiodarone or lidocaine may be considered for VF/pVT that is unresponsive to defibrillation.

Circulation. 2005.
Neumar et al. *Circulation*. 2010.
Link et al. *Circulation*. 2015.
Panchal et al. *Circulation*. 2018.
Panchal et al. *Circulation*. 2020.
Soar et al. *Resuscitation*. 2021.

ARREST (1999)

AMIODARONE FOR RESUSCITATION AFTER OUT-OF-HOSPITAL CARDIAC ARREST DUE TO VENTRICULAR FIBRILLATION

PETER J. KUDENCHUK, M.D., LEONARD A. COBB, M.D., MICHAEL K. COPASS, M.D., RICHARD O. CUMMINS, M.D., ALIDENE M. DOHERTY, B.S.N., C.C.R.N., CAROL E. FAHRENBRUCH, M.S.P.H., ALFRED P. HALLSTROM, PH.D., WILLIAM A. MURRAY, M.D., MICHELE OLSUFKA, B.S.N., AND THOMAS WALSH, M.I.C.P.

- Multicenter, double-blind, placebo controlled RCT (N = 504)
- **Compared**:
  - Amiodarone 300 mg IV x 1 dose vs. placebo in ≥ 3 shock refractory VF/pVT OHCA
- **Results**:
  - Amiodarone ↑ survival to hospital admission (44% vs. 34%, p = 0.03)
  - No difference in survival to hospital discharge or favorable neurologic outcomes

Kudenchuk et al. *NEJM*. 1999.

ALIVE (2002)

AMIODARONE AS COMPARED WITH LIDOCAINE
FOR SHOCK-RESISTANT VENTRICULAR FIBRILLATION

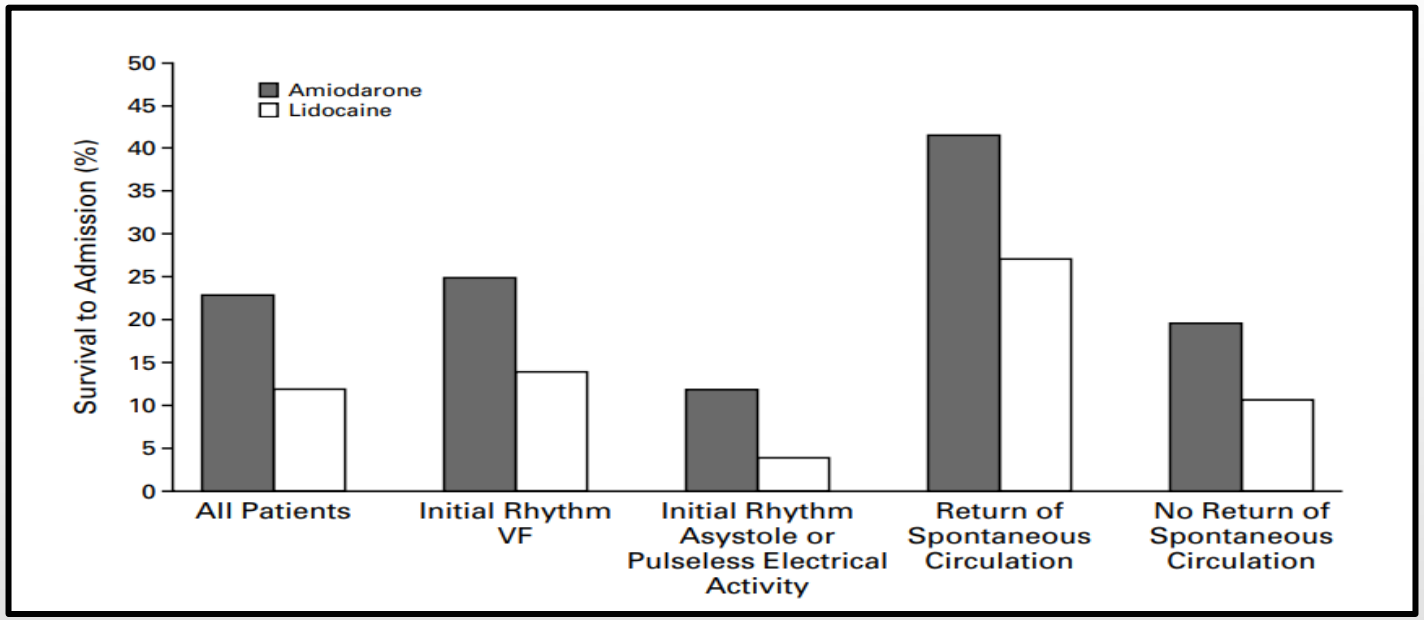
PAUL DORIAN, M.D., DAN CASS, M.D., BRIAN SCHWARTZ, M.D., RICHARD COOPER, M.D., ROBERT GELAZNIKAS, B.SC., AND AIALA BARR, PH.D.

- Multicenter, double-blind RCT
- N = 347
- Population: OHCA, ≥ 4 shocks

- **Trial Characteristics:**
  - Mean time from dispatch to drug administration = 25 minutes
  - Median 4 shocks delivered prior to study drug

Dorian et al. *NEJM.* 2002.

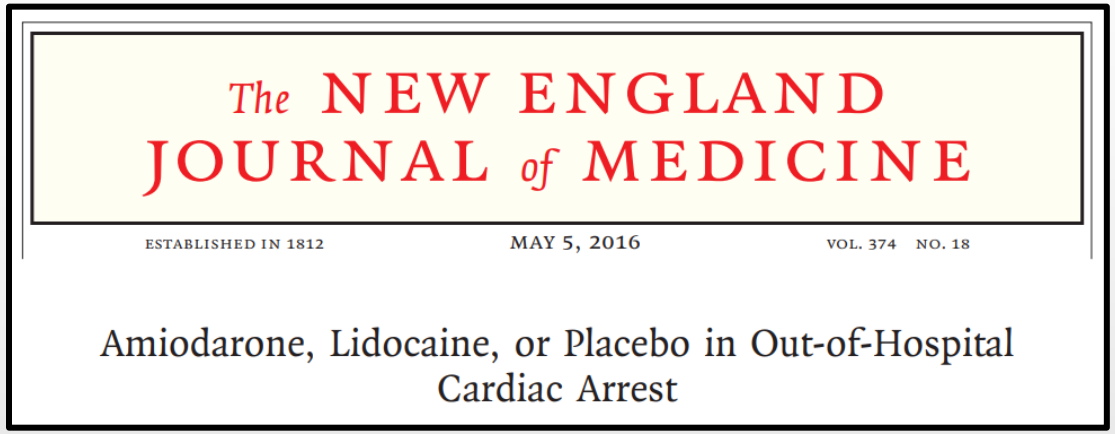
ALIVE (2002) - Results



- Amiodarone ↑ survival to hospital admission vs. lidocaine (22.8% vs. 12.0%, p = 0.009)
- Odds of survival ↓ by 12% for every minute delay between dispatch and drug admin
- No difference in survival to hospital discharge (5% vs. 3%, p = 0.34)

Dorian et al. *NEJM.* 2002.

ROC-ALPS (2016)



- Multicenter, double-blind RCT
- N = 3026
- Population: OHCA, ≥ 1 shocks

- **Trial Characteristics:**
  - Mean 19.3 minutes from dispatch to drug administration
  - Median 3 shocks administered prior to study drug

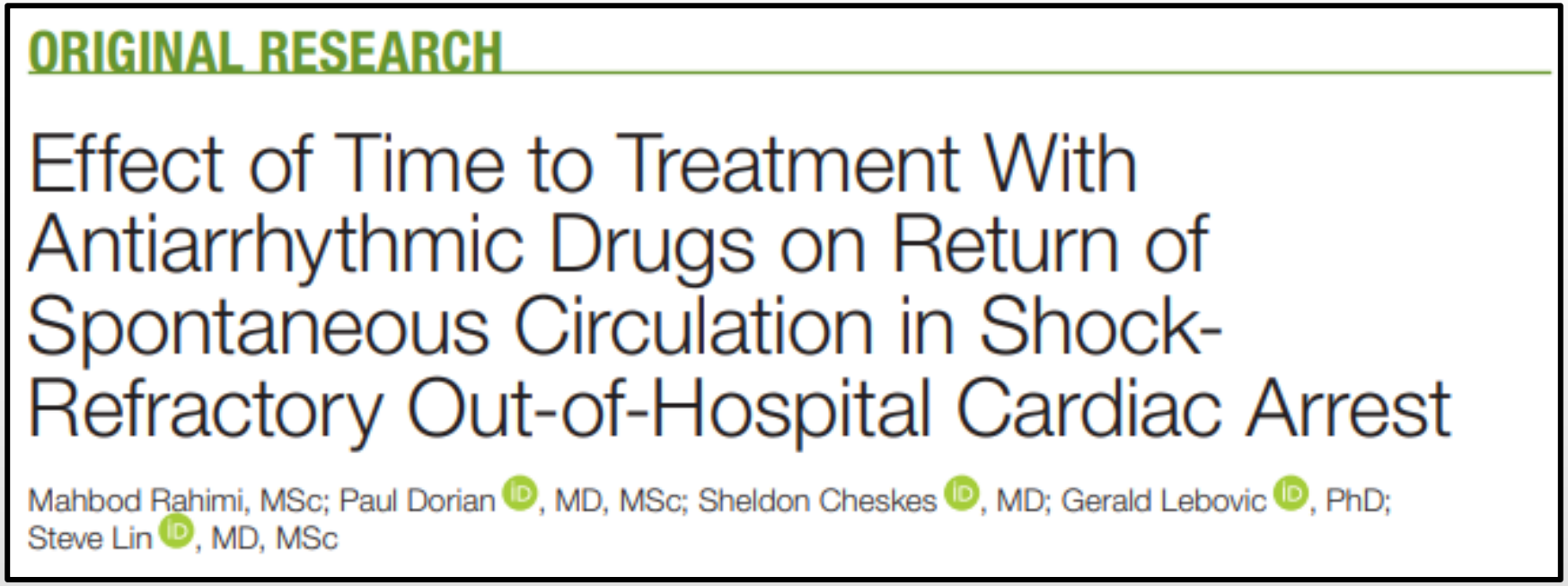
Kudenchuk et al. *NEJM.* 2016.

ROC-ALPS (2016) - Results

Outcome	Amiodarone (N=974)	Lidocaine (N=993)	Placebo (N=1059)	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
Primary outcome: survival to discharge — no./total no. (%)†	237/970 (24.4)	233/985 (23.7)	222/1056 (21.0)	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
Secondary outcome: modified Rankin score ≤3 — no./total no. (%)‡	182/967 (18.8)	172/984 (17.5)	175/1055 (16.6)	2.2 (–1.1 to 5.6)	0.19	0.9 (–2.4 to 4.2)	0.59	1.3 (–2.1 to 4.8)	0.44
Mechanistic (exploratory) outcomes									
Return of spontaneous circulation at ED arrival — no./total no. (%)	350/974 (35.9)	396/992 (39.9)	366/1059 (34.6)	1.4 (–2.8 to 5.5)	0.52	5.4 (1.2 to 9.5)	0.01	–4.0 (–8.3 to 0.3)	0.07
Admitted to hospital — no. (%)	445 (45.7)	467 (47.0)	420 (39.7)	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

Kudenchuk et al. *NEJM.* 2016.

Rahimi et al. (2022)



ORIGINAL RESEARCH

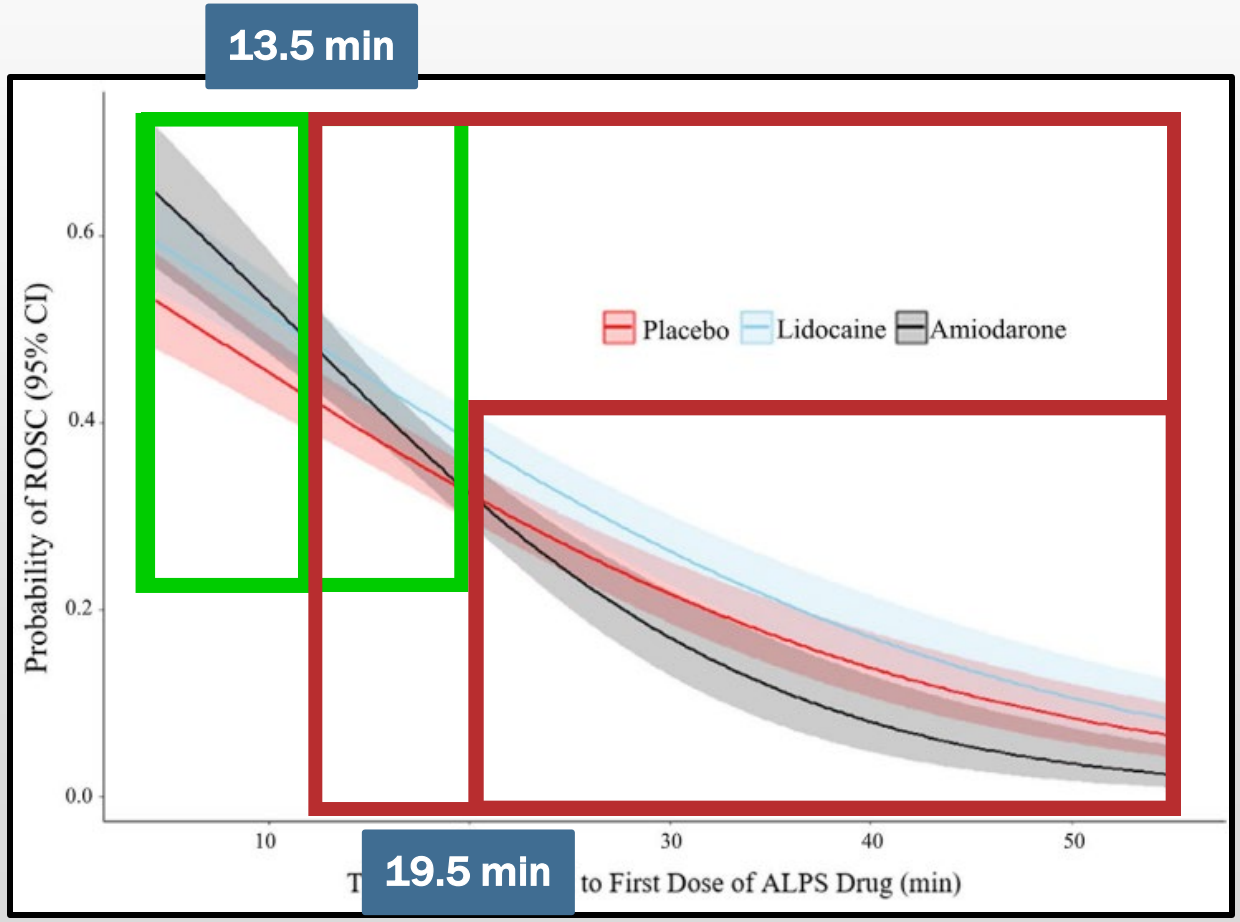
Effect of Time to Treatment With Antiarrhythmic Drugs on Return of Spontaneous Circulation in Shock-Refractory Out-of-Hospital Cardiac Arrest

Mahbod Rahimi, MSc; Paul Dorian, MD, MSc; Sheldon Cheskes, MD; Gerald Lebovic, PhD; Steve Lin, MD, MSc

- Secondary analysis of ROC-ALPS trial (N = 2994)
- Analyzed data to determine impact of time to drug administration on efficacy

Rahimi et al. *JAHA.* 2022.

Rahimi et al. (2022) - Results



- ROSC with time to drug administration
- Lidocaine ROSC regardless of intervention timing (OR 1.29)

Amiodarone:

- ROSC with early administration
- ROSC with late administration
  - Inflection point:
    - 13.5 min (vs. lidocaine)
    - 19.5 min (vs. placebo)

Rahimi et al. *JAHA.* 2022.

Antiarrhythmic Drugs Summary

Conclusions from literature:

- Amiodarone and Lidocaine likely result in similar outcomes in VF/pVT arrest
  - Older data suggests better outcomes with amiodarone
  - Modern data suggests lidocaine might be superior
- Earlier antiarrhythmic drug administration may improve outcomes

Personal conclusions:

- Either amiodarone or lidocaine are reasonable options in ACLS
  - Early in ACLS (< 15 min), both drugs are similar
  - Late in ACLS (> 15 min), lidocaine is preferred + amiodarone may be harmful
- Consider earlier drug administration in shockable algorithm

Question V

- Which of the following statements most accurately describes the data comparing lidocaine and amiodarone in ACLS?

A. Amiodarone improves neurologically favorable survival

B. Lidocaine is superior in improving survival to hospital discharge

C. Lidocaine may be more effective if given late in cardiac arrest

D. Amiodarone is associated with worse outcomes if given early

Conclusion

Areas of Uncertainty

Influence of Pharmacotherapy Timing

Optimal Dosing and Duration of Medications

Heterogeneity of Cardiac Arrest Phenotypes

- OHCA vs. IHCA
- Shockable vs. PEA vs. Asystole
- Etiology of Cardiac Arrest

Optimal Outcomes in Cardiac Arrest

Return of Spontaneous Circulation (ROSC)

Survival to Hospital Admission

Survival to Hospital Discharge

Survival with Favorable Neurologic Outcome

Summary of Evidence

Controversy	Evidence	Recommendation
Epinephrine	↑ ROSC ↑ Survival to Admission ↑ Survival to Discharge	1 | B-R | 1. We recommend that epinephrine be administered for patients in cardiac arrest.
Vasopressin	↔ vs. epinephrine ↔ in combination	2b | C-LD | 5. Vasopressin alone or vasopressin in combination with epinephrine may be considered in cardiac arrest but offers no advantage as a substitute for epinephrine in cardiac arrest.
VSE	↑ ROSC vs. epinephrine May ↑ Survival to Discharge and Favorable Neurologic outcomes	2b | C-LD | 2. For patients with OHCA, use of steroids during CPR is of uncertain benefit. **Insufficient evidence to make recommendation on VSE**
Amiodarone vs. Lidocaine	Both ↑ survival to admission ↔ in Survival to Discharge or Favorable Neurologic Outcomes	2b | B-R | 1. Amiodarone or lidocaine may be considered for VF/pVT that is unresponsive to defibrillation.

Questions?

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H's + T's

H's	T's
Hypoxia	Toxins
Hypovolemia	Thrombosis (Myocardial Infarction)
Hypothermia	Thrombosis (Pulmonary Embolism)
Hyper/Hypokalemia	Tension Pneumothorax
Hydrogen ion excess (Acidosis)	Tamponade (Cardiac)
Hypoglycemia	

Panchal et al. *Circulation*. 2020.

Limitations of Cardiac Arrest Research

Ethical Considerations

- Comparisons with standard of care vs. placebo
- Difficulties with informed consent

Challenges in Study Design

- Impossible to control for all aspects of care

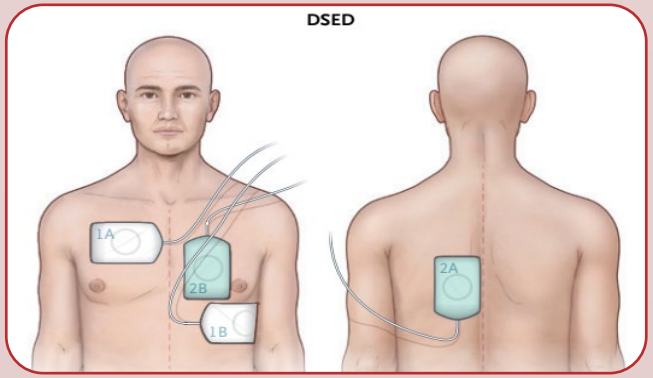
Confounders with Observational Research

- Especially prevalent in OHCA literature

Refractory VF

- Defined as VF unresponsive to ≥ 3-5 defibrillations + epinephrine + antiarrhythmic drug administration

Options



Double Sequential Defibrillation (DSD)

Esmolol

Cheskes et al. *NEJM*. 2022.
Henry Schein. Esmolol.

Double Sequential Defibrillation

- Use of second set of defibrillator pads to administer two sequential shocks in rapid succession
- Rationale for Use:
  - Enhanced energy delivery
  - Change in defibrillation vector
  - First shock may potentiate efficacy of second defibrillation
- Early case series and animal models demonstrated efficacy in terminating cardiac arrest

Cortez et al. *Resuscitation*. 2016.
Cheskes et al. *NEJM*. 2022.

DOSE-VF (2022)

- Multicenter RCT (N = 405)
- Compared DSD vs. vector change vs. standard defibrillation

Table 3. Primary and Secondary Outcomes.

Outcome	Standard Defibrillation (N=136)	VC Defibrillation (N=144)	DSED (N=125)	Adjusted Relative Risk (95% CI)*	
				DSED vs. Standard	VC vs. Standard
	number of patients/total number (percent)				
Survival to hospital discharge†	18/135 (13.3)	31/143 (21.7)	38/125 (30.4)	2.21 (1.33–3.67)	1.71 (1.01–2.88)
Termination of ventricular fibrillation	92/136 (67.6)	115/144 (79.9)	105/125 (84.0)	1.25 (1.09–1.44)	1.18 (1.03–1.36)
ROSC	36/136 (26.5)	51/144 (35.4)	58/125 (46.4)	1.72 (1.22–2.42)	1.39 (0.97–1.99)
Modified Rankin scale score ≤2†‡	15/134 (11.2)	23/142 (16.2)	34/124 (27.4)	2.21 (1.26–3.88)	1.48 (0.81–2.71)

Cheskes et al. *NEJM*. 2022.

Esmolol

- **Rationale for Use:**
  - Ultra short-acting β-1 antagonist -> blunts catecholamine-mediated electrical activity
  - May reduce arrhythmogenicity, lower the defibrillation threshold, decrease myocardial oxygen demand, and improve maintenance of normal rhythm

- **Evidence:**
  - **Driver et al. (2014)** – Case series (N = 6 esmolol, 19 control)
    - Demonstrated ↑ ROSC, survival to hospital admission, and favorable neurologic outcomes in patients treated with esmolol vs. control
  - **Lee et al. (2016)** – Retrospective cohort (N = 16 esmolol, 25 control)
    - Esmolol ↑ ROSC and survival to hospital admission (56% vs. 16%, p = 0.007)
    - No difference in survival to 30 days or favorable neurologic outcomes

Driver et al. *Resuscitation*. 2014.
Lee et al. *Resuscitation*. 2016.