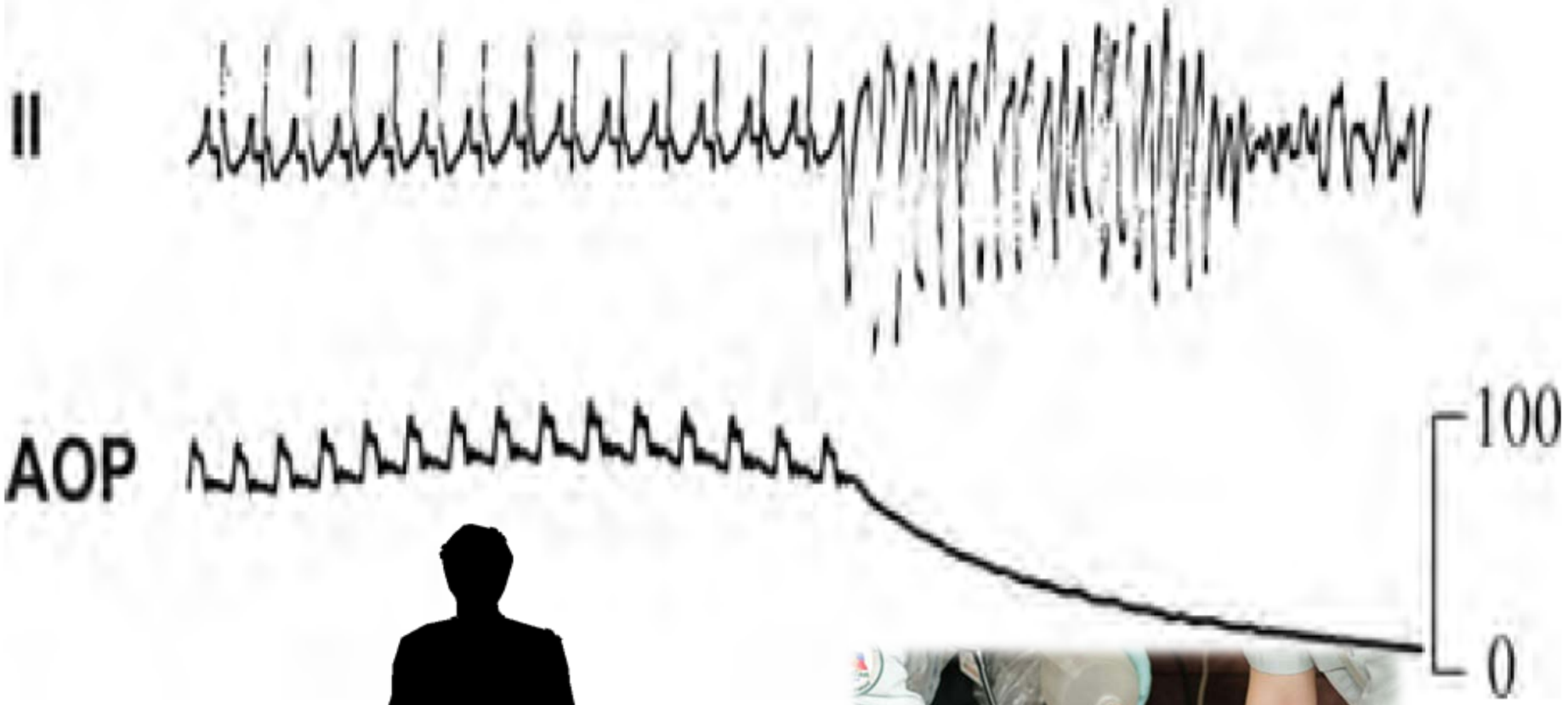
Epinephrine in Cardiac Arrest
Effective, Harmful or Indifferent?

Peter J. Kudenchuk, MD, FAHA
Professor of Medicine
University of Washington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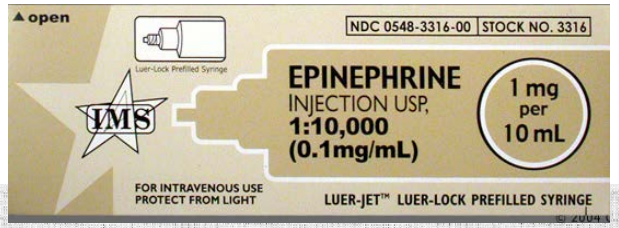
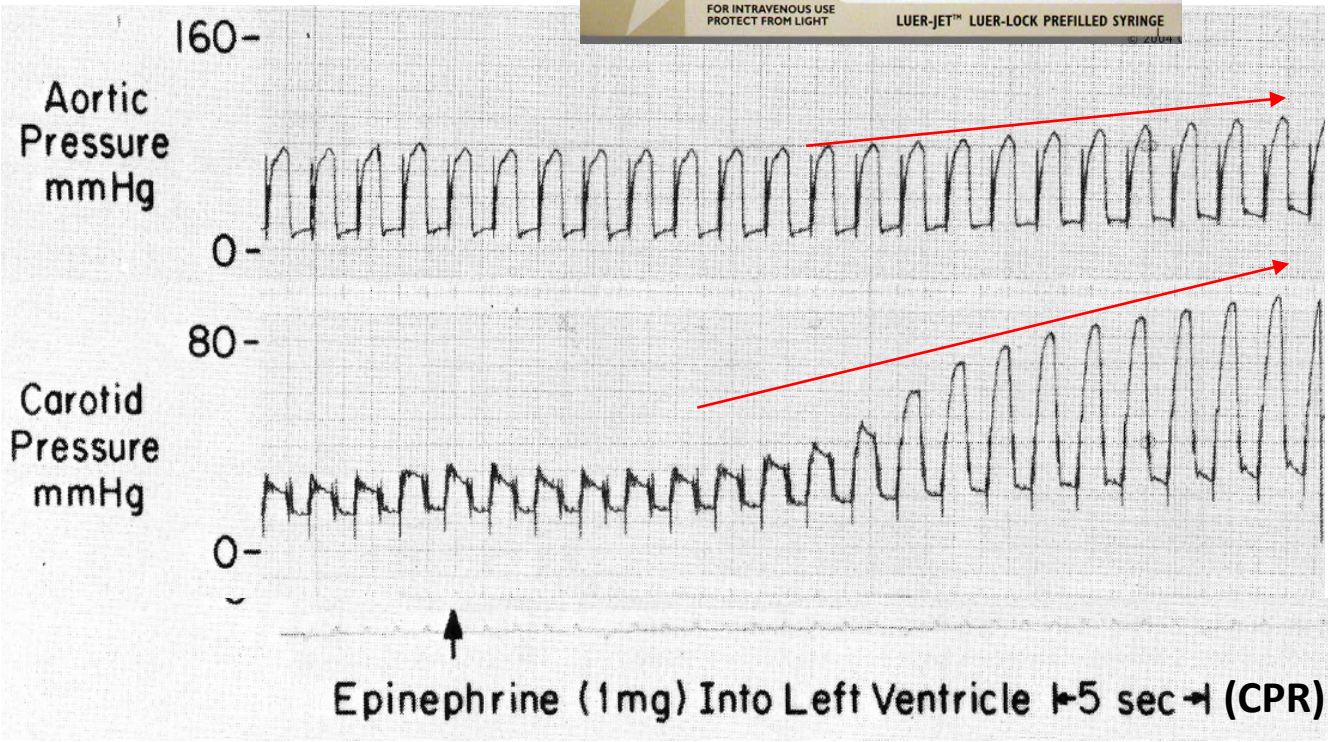
Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs

JOHN R. MICHAEL, M.D., ALAN D. GUERCI, M.D., RAYMOND C. KOEHLER, PH.D., AN-YUN SHI, M.D., JOSHUA TSITLIK, PH.D., NISHA CHANDRA, M.D., ERNEST NIEDERMEYER, M.D., MARK C. ROGERS, M.D., RICHARD J. TRAYSTMAN, PH.D., AND MYRON L. WEISFELDT, M.D.





α

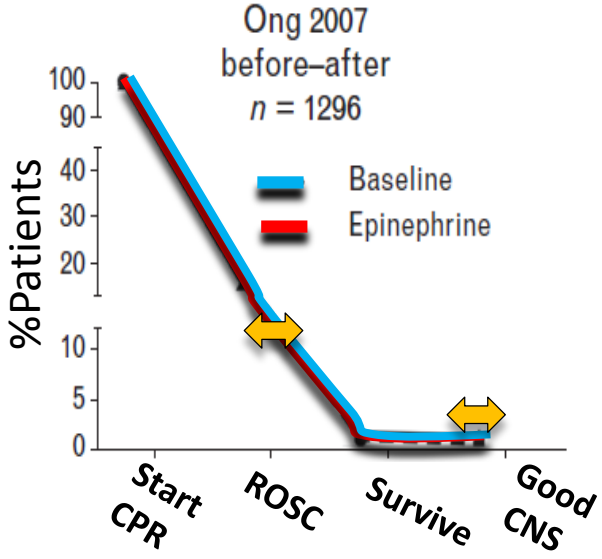
- Vasoconstriction peripheral vascular beds
- ↑cerebral & myocardial perfusion pressures

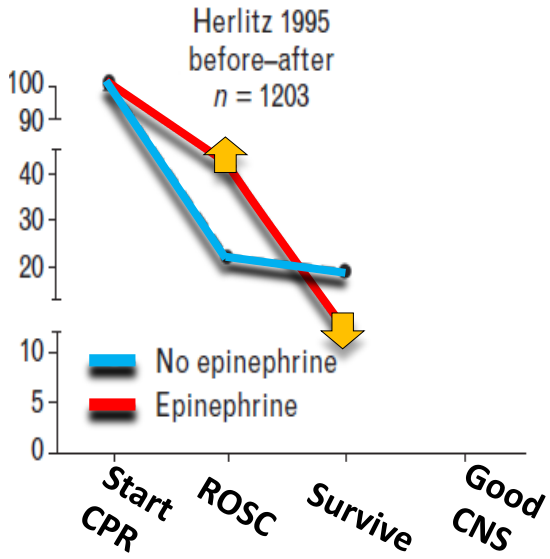
β

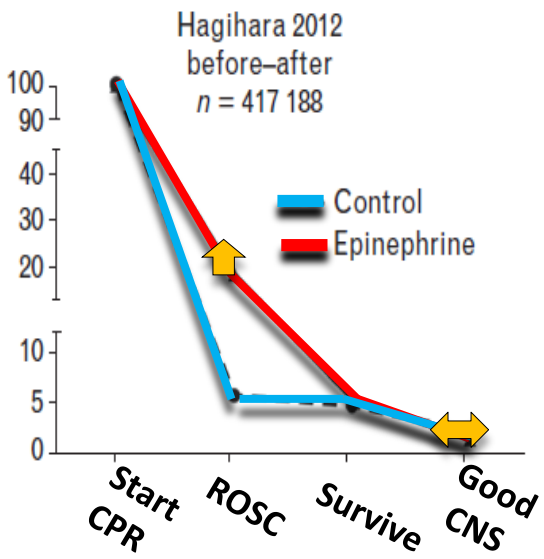
- Accelerate HR
- Improve conduction & contraction

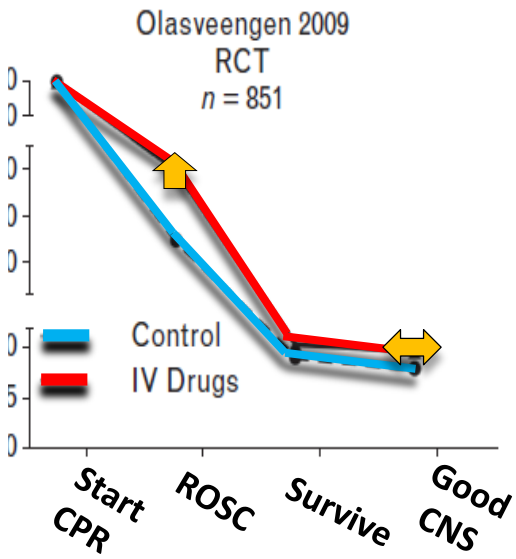
Michael JR et al. Circulation 1984;4:822-835

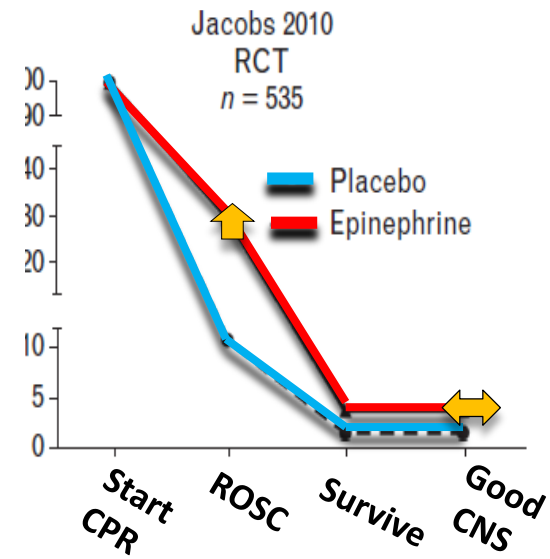
Epinephrine vs No Epinephrine in Cardiac Arrest

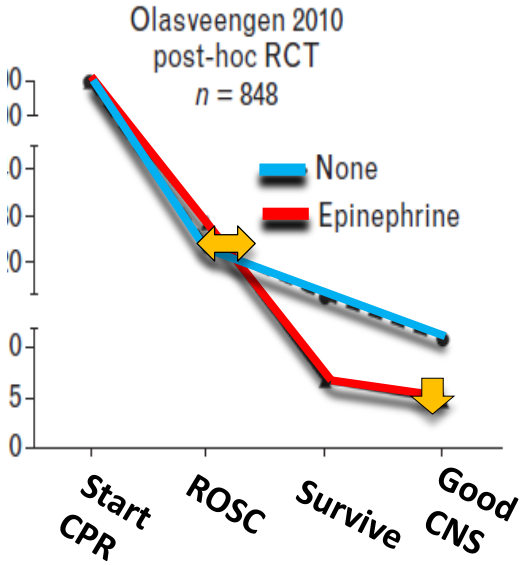










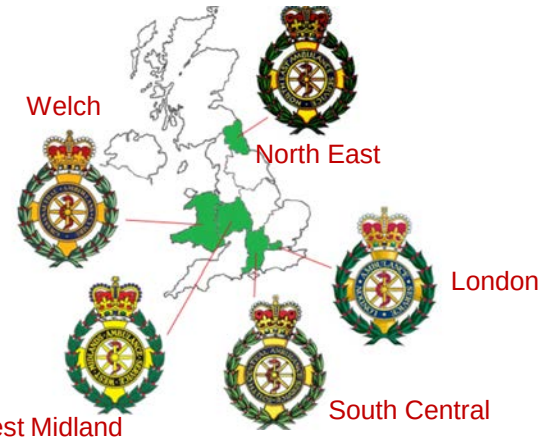


Callaway CW. Curr Opin Cardiol 2013;28:36-42 . Resuscitation 2006;71:369-78

PARAMEDIC2

The Adrenaline Trial

University of Surrey · Warwick Medical School · NHS National Institute for Health Research



Should adrenaline be used when someone's heart stops?

Perkins GD et al. N Engl J Med 2018;379:711-21

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*

n=8025

- Adult nontraumatic OHCA
- All rhythms
- Ø anaphylaxis/bad asthma

PARAMEDIC2
The Adrenaline Trial

1 mg IV/IO q3-5' x 1-10

Characteristic	Epinephrine (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)
Female	1406 (35.0)	1415 (35.4)
Initial cardiac rhythm — no. (%)		
Shockable	770 (19.2)	748 (18.7)
Ventricular fibrillation	716 (17.8)	684 (17.1)
Pulseless ventricular tachycardia	25 (0.6)	20 (0.5)
Nonshockable	3149 (78.4)	3181 (79.5)
Asystole	2135 (53.2)	2194 (54.9)
Pulseless electrical activity	955 (23.8)	937 (23.4)
Bradycardia	20 (0.5)	16 (0.4)
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)
CPR performed — no. (%)		
By bystander	2382 (59.3)	2349 (58.7)
Mean drug dose (SD)	4.9 (2.5)	5.1 (2.3)
IO administration – no. (%)	1340 (33.4)	1319 (33)
CPR* compression rate/fraction %	106.8 (14.4)/76.2 (11.2)	106.5 (13.3)/78.4 (13)

*Information about EMS CPR quality limited to 1st 5 min of arrest in <5% of patients

Perkins GD et al. N Engl J Med 2018;379:711-21

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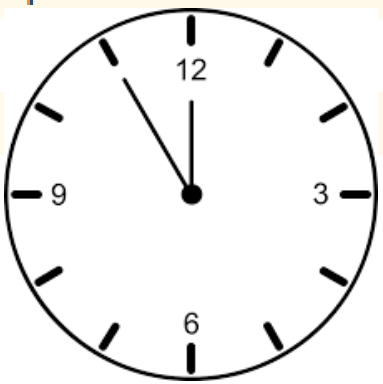
Variable	Epinephrine (N=4015)	Placebo (N=3999)
Interval between emergency call and ambulance arrival at scene		
No. of patients in analysis	4015	3999
Median (IQR) — min†	6.7 (4.3–9.7)	6.6 (4.2–9.6)
Interval between emergency call and administration of trial agent		
No. of patients in analysis	3975	3949
Median (IQR) — min†	21.5 (16.0–27.3)	21.1 (16.1–27.4)
Interval between ambulance arrival at scene and departure		
No. of patients in analysis	2039	1226
Mean — min	50.1±21.8	44.5±18.3



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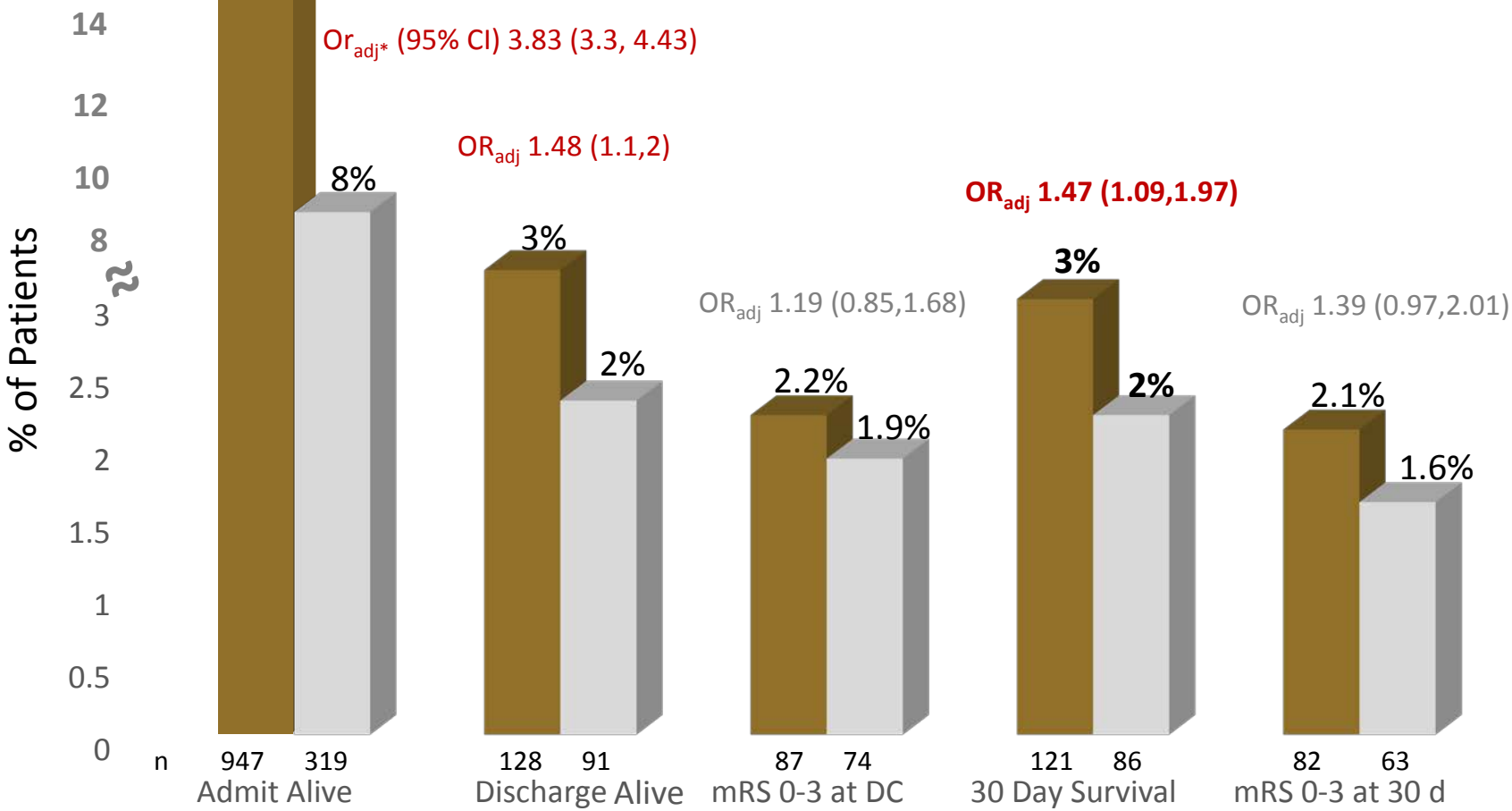
Epinephrine (n=4012)

Placebo (n=3995)



Perkins GD et al. N Engl J Med 2018;379:711-21

*Adjusted for age, sex, call to EMS arrival, EMS arrival to trial agent, arrest cause, witnessed, bystander CPR.

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

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30 day survival

Subgroup	OR (95% CI)	p (interaction)
Witness		0.32
None	2.62 (1.15, 5.96)	
Bystander	1.35 (0.95, 1.93)	
Paramedic	1.26 (0.60, 2.62)	
Bystander CPR		0.60
Bystander CPR	1.45 (1.02, 2.07)	
No Bystander CPR	1.84 (0.82, 4.17)	
Initial rhythm		0.19
Shockable rhythm	1.32 (0.95, 1.86)	
Nonshockable rhythm	2.15 (1.13, 4.09)	
Cause of cardiac arrest		0.84
Medical cause	1.46 (1.08, 1.97)	
Non-medical cause	1.20 (0.18, 8.01)	

Perkins GD et al. N Engl J Med 2018;379:711-21

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30 day survival

Subgroup (all analyzed as continuous variables)	OR (95% CI)	p (interaction)
Age		0.13
Mean age (69.7 years old)	1.30 (0.93, 1.82)	
Emergency call to ambulance arrival at scene		0.95
Mean time (7.4 minutes)	1.46 (1.07, 2.00)	
Ambulance arrival at scene to administration of trial agent		0.84
Mean time (15.2 minutes)	1.44 (1.04, 2.01)	
Emergency call to administration of trial agent		0.85
Mean time (22.6 minutes)	1.43 (1.01, 2.01)	

Perkins GD et al. N Engl J Med 2018;379:711-21

Functional Outcome at Hospital Discharge - All Enrolled Patients

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*

Epinephrine (n=4007) Placebo (n=3994)

% of All Enrolled Patients

100 2 1.5 1 0.5 0

"Good" outcome

"Bad" outcome

	0	1	2	3	0-3	4	5	4-5	6
	0.3%	0.4%	0.6%	0.9%	2.2%	0.3%	0.7%	1%	97%
	0.4%	0.3%	0.5%	1.9%	0.2%	0.2%	0.4%	98%	
n	12	15	17	10	23	29	35	20	87	74	12	8	27	8	39	16	3881	3904

Modified Rankin Scale at Hospital Discharge

Perkins GD et al. N Engl J Med 2018;379:711-21

The Effect of Standard- and High-Dose Epinephrine on Coronary Perfusion Pressure During Prolonged Cardiopulmonary Resuscitation

Norman A. Paradis, MD; Gerard B. Martin, MD; Jack Rosenberg, MD; Emanuel P. Rivers, MD; Mark G. Goetting, MD; Timothy J. Appleton; Marcia Feingold, PhD; Philip E. Cryer, MD; Jacobo Wortsman, MD; Richard M. Nowak, MD

n =32 cardiac arrest

8 VF
4 PEA
20 Asystole

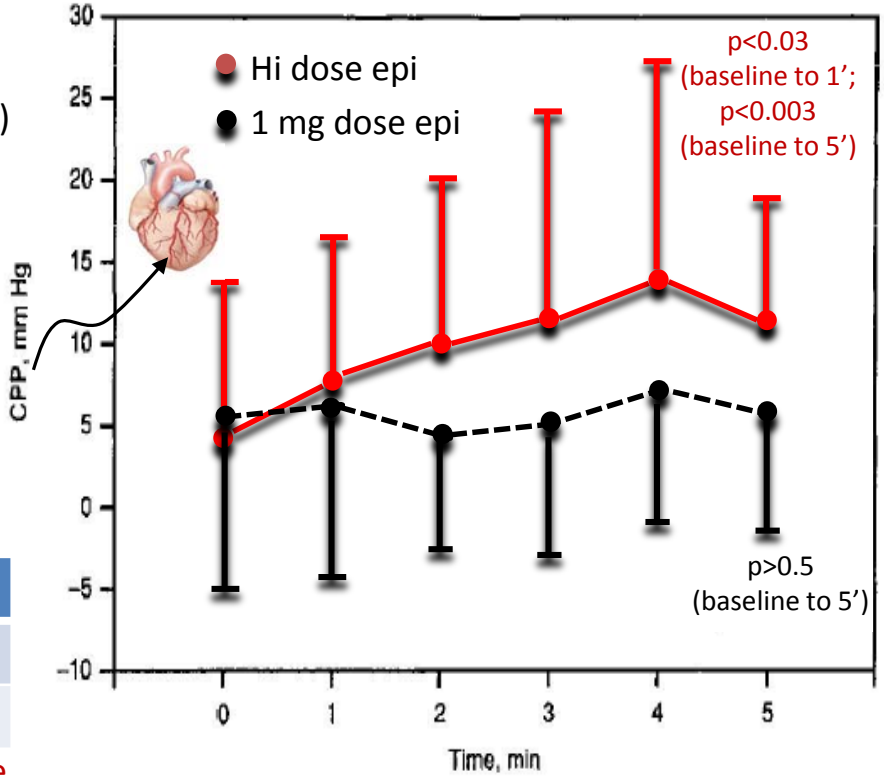
RA, Aortic catheters → **Std dose epi** **1 mg (max x 3)** → Failed Std Tx → **Hi dose epi** **0.2 mg/kg x 1**

Mean changes from Baseline Coronary Perfusion Pressures (mm Hg)

	1 min	2 min	3 min	4 min	5 min	Max
Std dose Epi	0.7 ± 6.3	0.5 ± 4.7	-0.7 ± 9	-0.6 ± 7.8	-0.6 ± 7.4	3.7 ± 5
Hi dose Epi	3.2 ± 7.6	5.3 ± 8	7.8 ± 10.8	9.1 ± 11.1	7.5 ± 7.8	11.3 ± 10
p	0.052	0.003	0.007	0.001	<0.001	<0.001

Arterial Epinephrine Concentrations (ng/mL)

	2.5 min	5 min	7.5 min
Std dose Epi	152 ± 162	95 ± 98	-
Hi dose Epi	393 ± 289*	368 ± 260*	274 ± 242



Paradis NA et al. JAMA 1991;265:1139-44.

*p=0.001 vs std dose

High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis

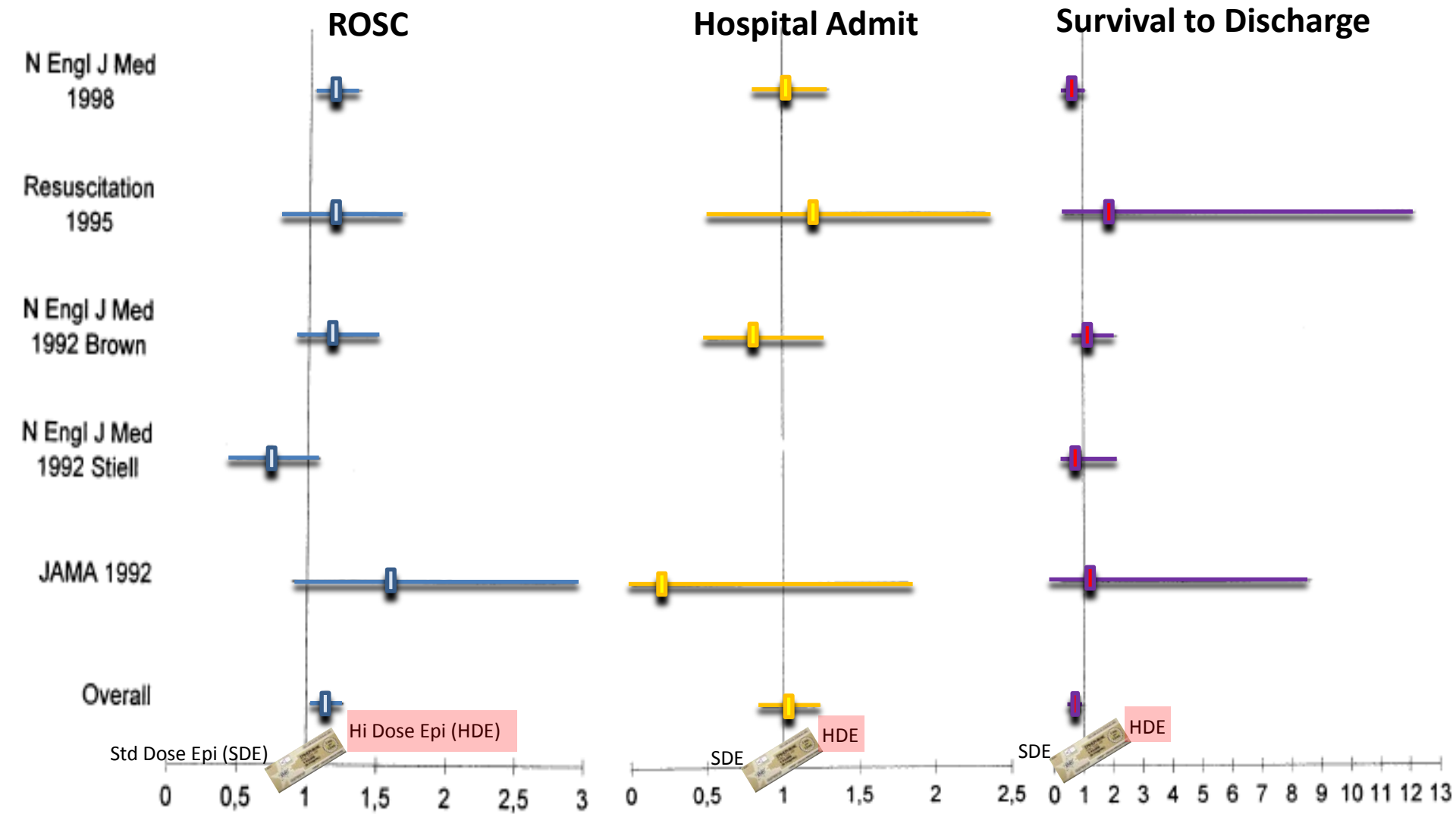
C. Vandycke *, P. Martens

Authors	Journal	Years and principal location of study	Study design	number of subjects	Dose
Gueugniaud et al.	N. Engl. J. Med.	1994–1996, France and Belgium	Randomized, prospective, multi-centred, out of hospital, double blind	Experimental dose, 1677	5 mg
				Standard dose, 1650	1 mg
Choux et al.	Resuscitation	1991–1992, Lyon (France)	Randomized, prospective, out-of hospital, double blind	Experimental dose, 271	5 mg
				Standard dose, 265	1 mg
Brown et al.	N. Engl. J. Med.	1989–1990, Houston, OH, Wisconsin, Washington, Virginia, NY	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 648	0.2 mg/kg
				Standard dose, 632	0.02 mg/kg
Stiell et al.	N. Engl. J. Med.	1989–1992, Canada	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 317	7 mg
				Standard dose, 333	1 mg
Callaham et al.	J. Am. Med. Assoc.	1990–1992, San Francisco	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 286	15 mg

Vandycke C et al. Resuscitaton 2000;45:161-5.

High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis

C. Vandycke *, P. Martens

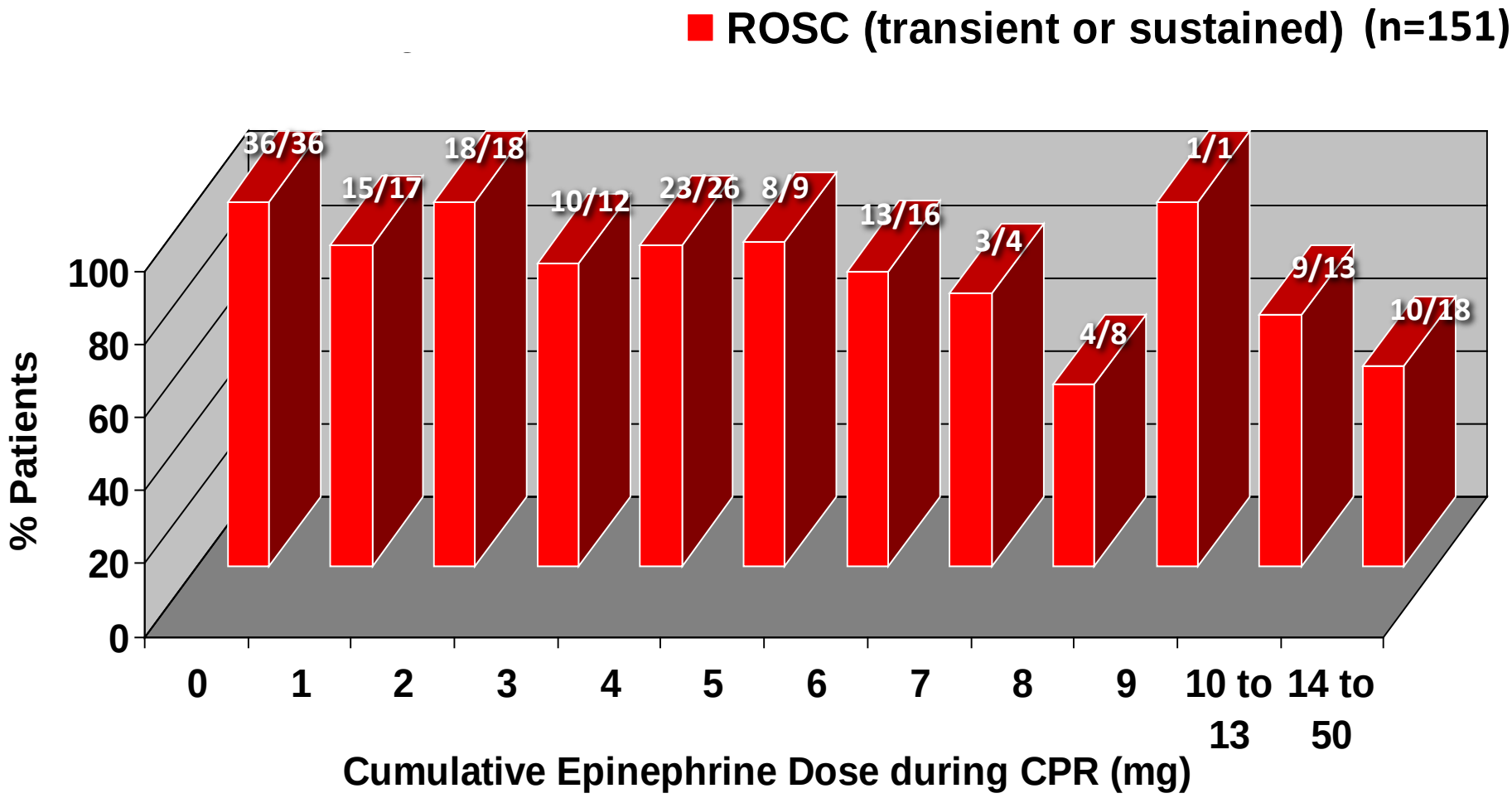


Vandycke C et al. Resuscitaton 2000;45:161-5.

Cumulative Epinephrine Dose during Cardiopulmonary Resuscitation and Neurologic Outcome

Wilhelm Behringer, MD; Harald Kittler, MD; Fritz Sterz, MD; Hans Domanovits, MD; Waltraud Schoerkhuber, MD; Michael Holzer, MD; Marcus Müllner, MD; and Anton N. Laggner, MD

n= 178 observational study witnessed, nontraumatic VF OHCA



Behringer W et al. Ann Intern Med 1998;129:450-456

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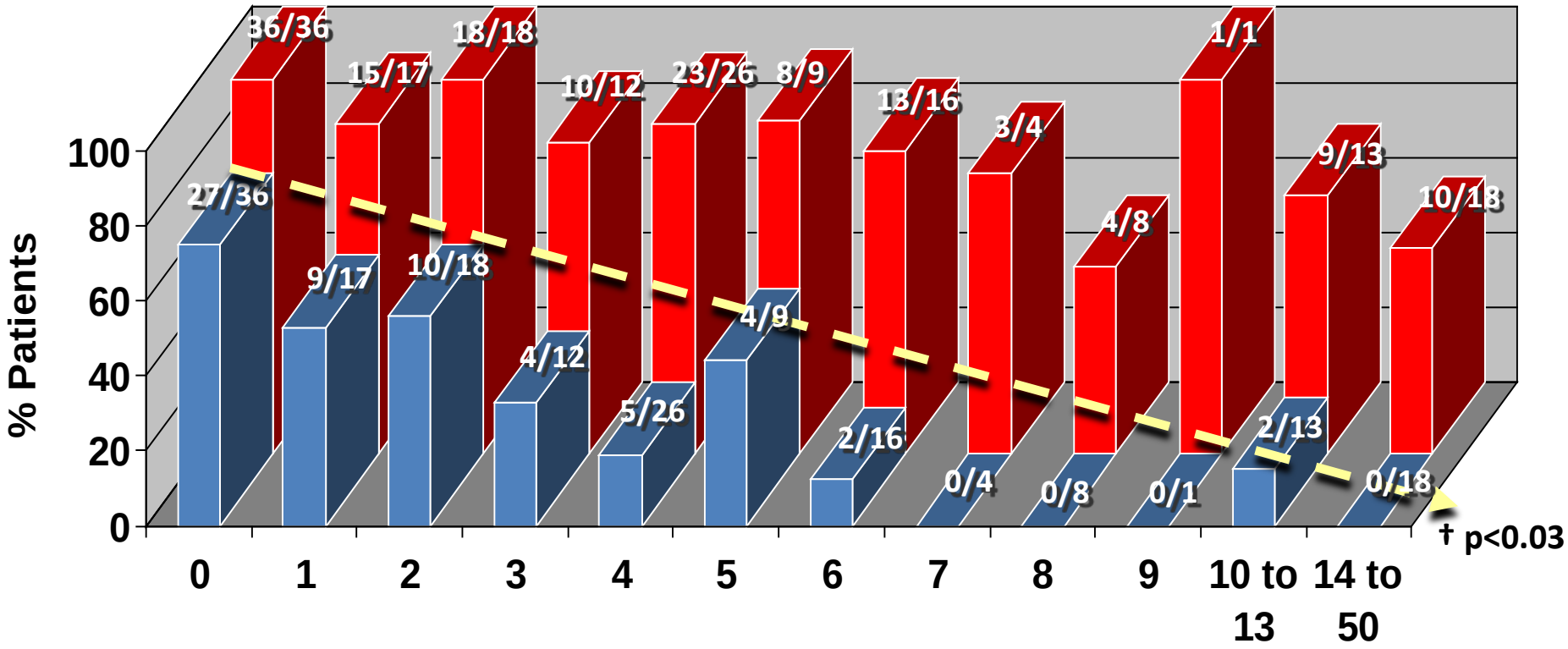
n= 178 observational study witnessed, nontraumatic VF OHCA

Good neurologic outcome* **ROSC (transient or sustained)**

* conscious, alert with slight-moderate disability



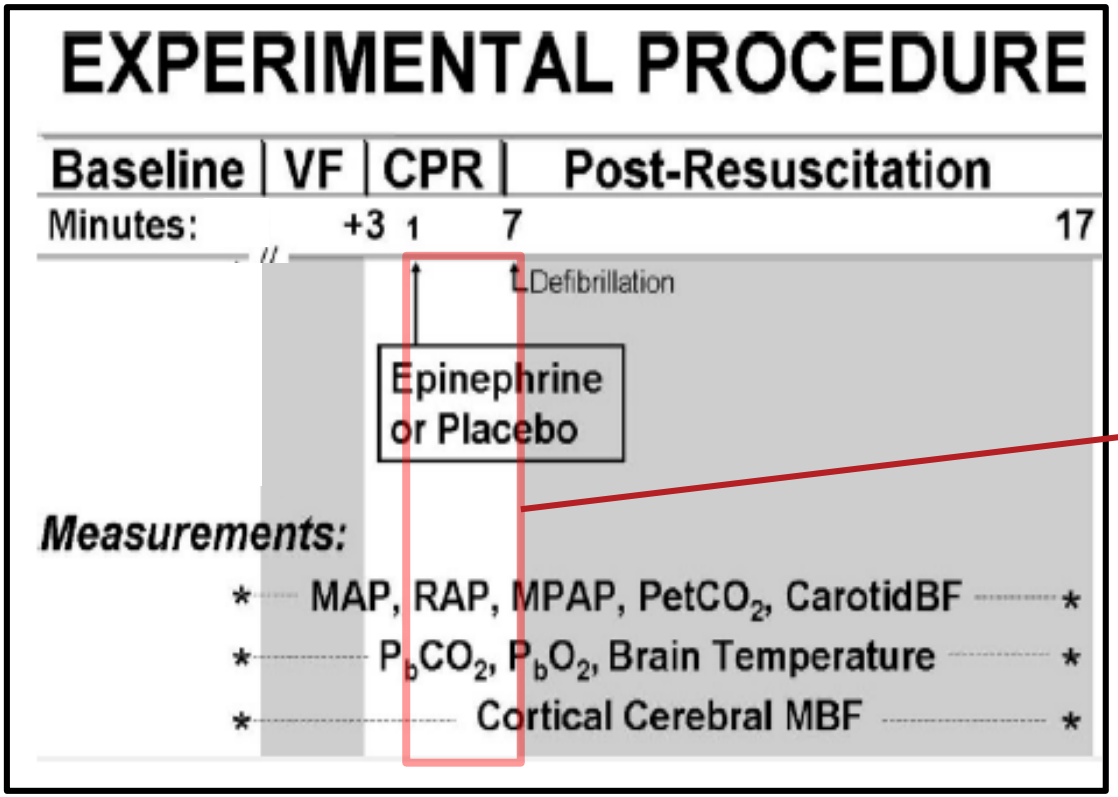
† multivariate logistic regression corrected for: age, sex, body mass, bystander CPR, location of arrest, time to BLS/ALS, time to ROSC or death

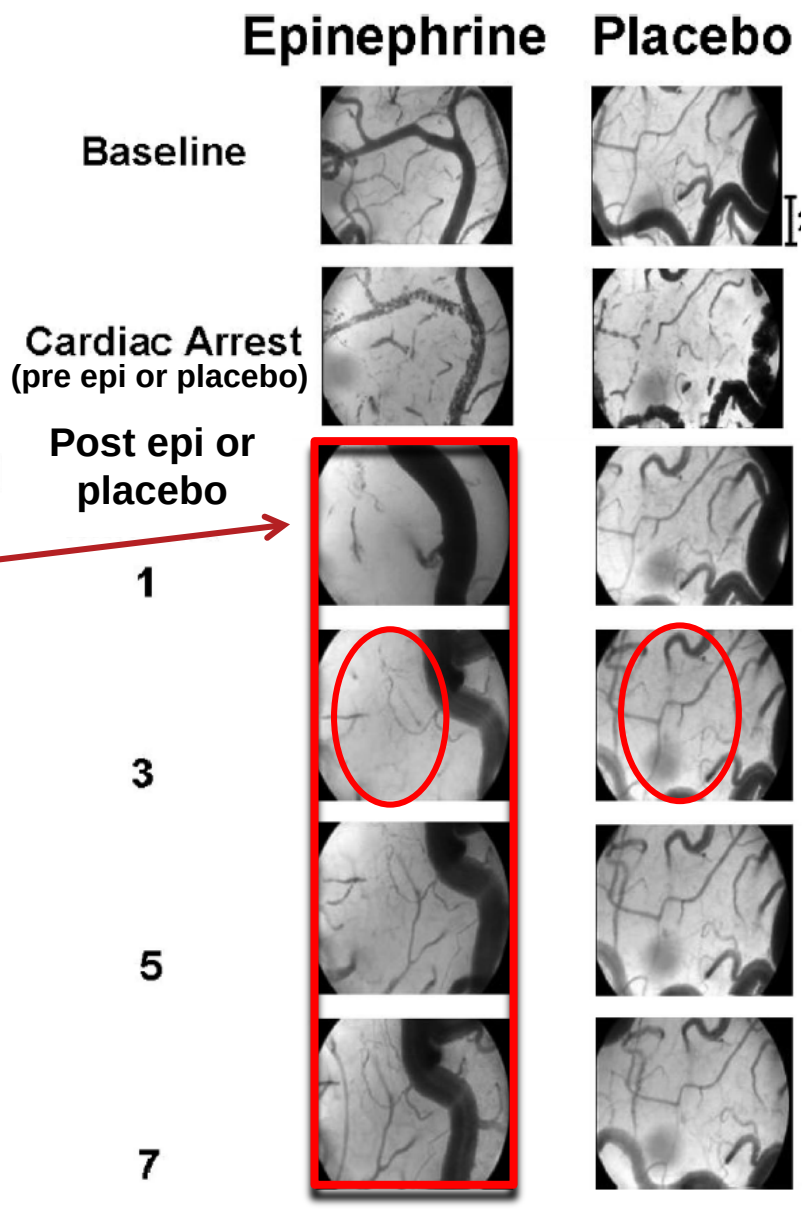
Behringer W et al. Ann Intern Med 1998;129:450-456

Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation*

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

n=20 pigs



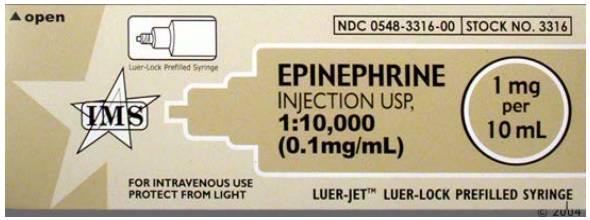


Epinephrine may produce increases in large vessel perfusion/flow but decrease cerebral blood flow, increasing severity of cerebral ischemia during CPR and post ROSC

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

Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes☆

Cameron A. Fisk[a], Michele Olsufka[b], Lihua Yin[c], Andrew M. McCoy[c], Andrew J. Latimer[c], Charles Maynard[d], Graham Nichol[e], Jonathan Larsen[f], Leonard A. Cobb[b], Michael R. Sayre[c,f,*]



Full dose Epi

Traditional Epinephrine Protocol
5/5/2006 – 9/30/2012

1 mg at 4 minutes resuscitation

→ 1 mg q 8 min shockable rhythms

→ 1 mg q 2 min nonshockable rhythms

Half-dose Epi

Low (Half-Dose) Epinephrine Protocol
10/1/2012 –> present

0.5 mg at 4 & 8 minutes resuscitation

→ 0.5 mg q 8 min shockable rhythms

→ 0.5 mg q 2 min nonshockable rhythms

Fisk CA et al. Resuscitation 2018;124:43-8

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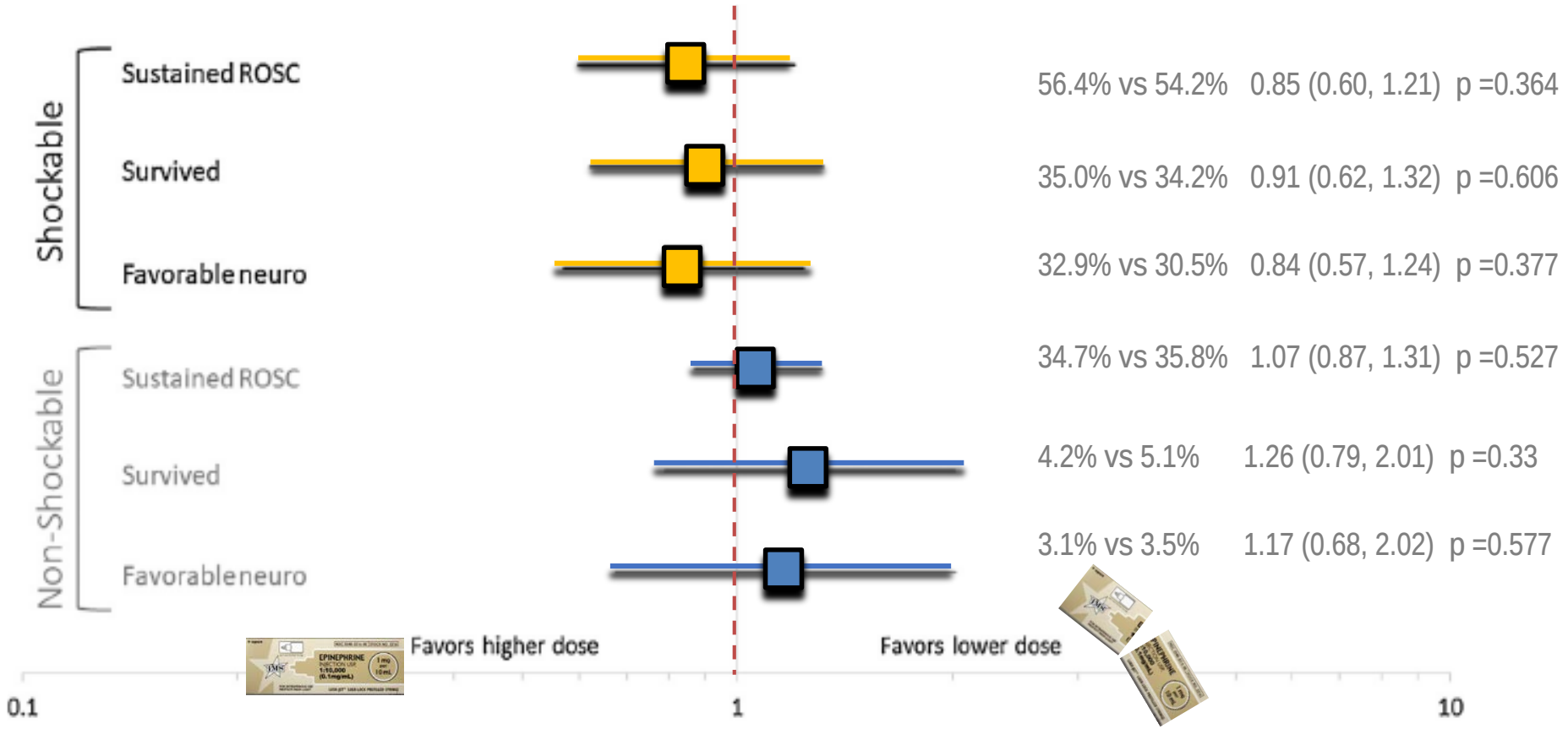
Full vs Low (Half-)Dose Epi Outcomes

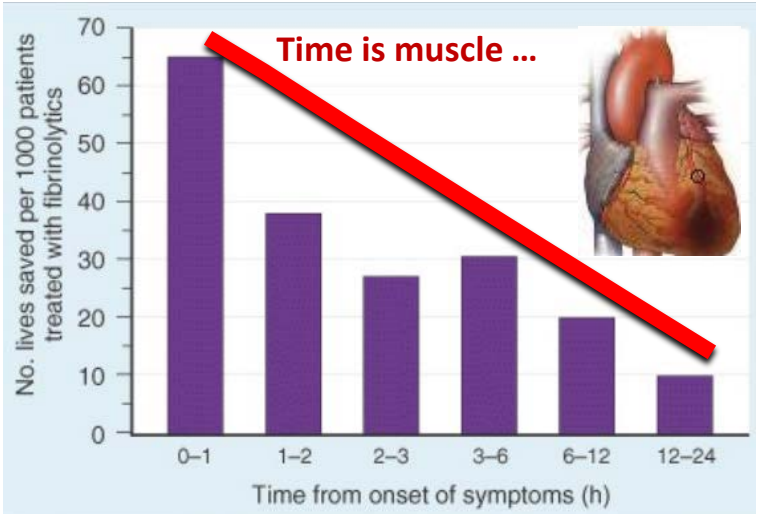


*Adj for age, sex, witnessed status, bystander CPR, call-to-patient interval; & time from ALS to epi 4/2011-12/2015

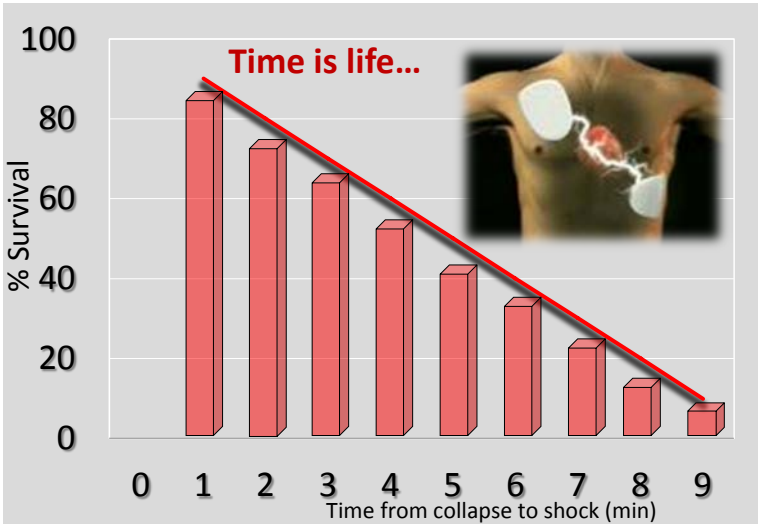
Fisk CA et al. Resuscitation 2018;124:43-8

Time-Dependence of Acute Cardiovascular Interventions

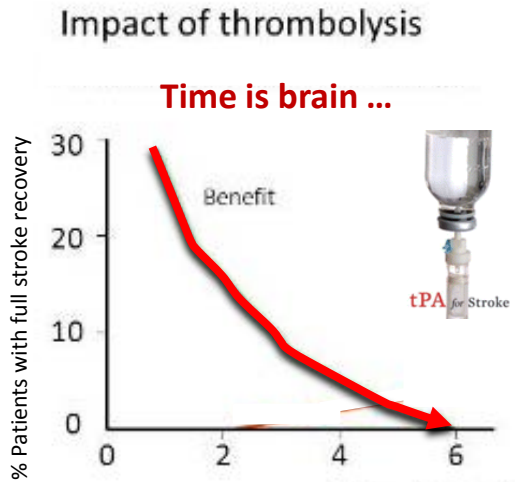
Time-to-thrombolysis in acute MI



Time-to-shock in witnessed VF

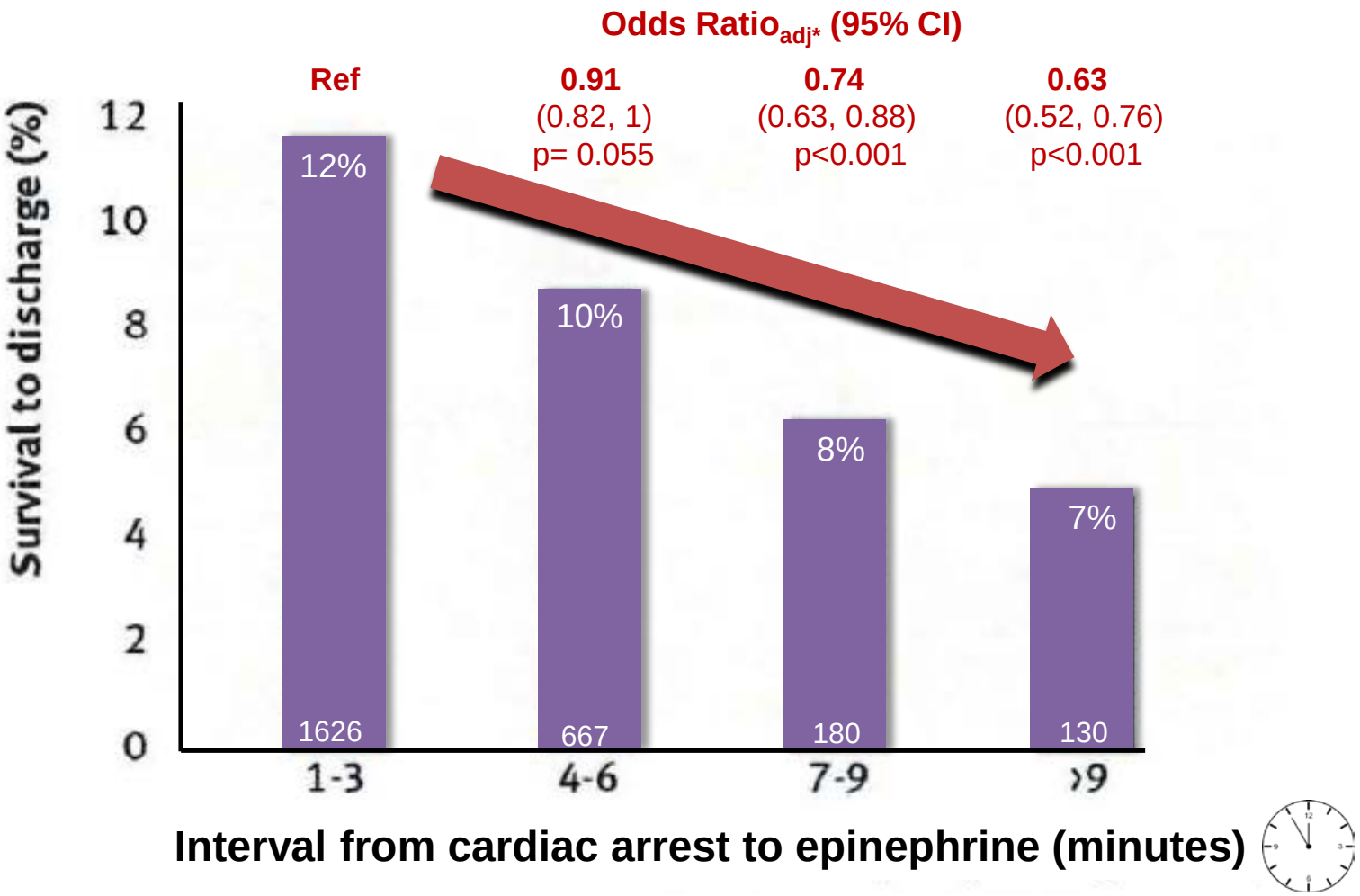


Time-to-thrombolysis in Stroke



Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry

n= 25,095 adults with in-hospital cardiac arrest from asystole or PEA



Donnino MW et al. BMJ 2014;348:g3028

PARAMEDIC2

The Adrenaline Trial

Time Interval *Median (IQR)	Epinephrine n=4015	Placebo n=3999
Call to ambulance arrival, min*	6.7 (4.3-9.7)	6.6 (4.2-9.6)
Call to drug, min*	**21.5 (16-27.3)**	**21.1 (16.1-27.4)**
On-scene time, min; mean±SD	50.1 ± 21.8	44.5 ± 18.3

Time to Epinephrine Administration and Survival from Non-Shockable Out-of-Hospital Cardiac Arrest Among Children and Adults

Matthew Hansen, MD, MCR[1]; Robert H. Schmicker, MS[2]; Craig D. Newgard, MD, MPH[1]; Brian Grunau, MD, MHSc[3]; Frank Scheuermeyer, MD, MHSc[4]; Sheldon Cheskes, MD[5]; Veer Vithalani, MD[6]; Fuad Alnaji, MD, FRCPC[7]; Thomas Rea, MD, MPH[8]; Ahamed H. Idris, MD[9]; Heather Herren, RN, MPH[2]; Jamie Hutchison, MD[10]; Mike Austin, MD[11]; Debra Egan, MPH[12]; Mohamud Daya, MD, MS[1]; For the Resuscitation Outcomes Consortium Investigators

OHCA 2011-2015

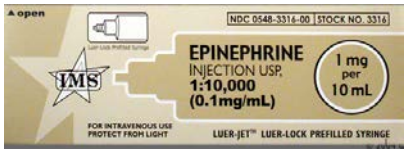
- All ages
- All nonshockable rhythms
- Time 1st EMS → epi

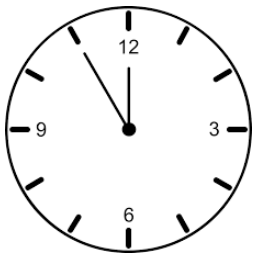
Excluded:

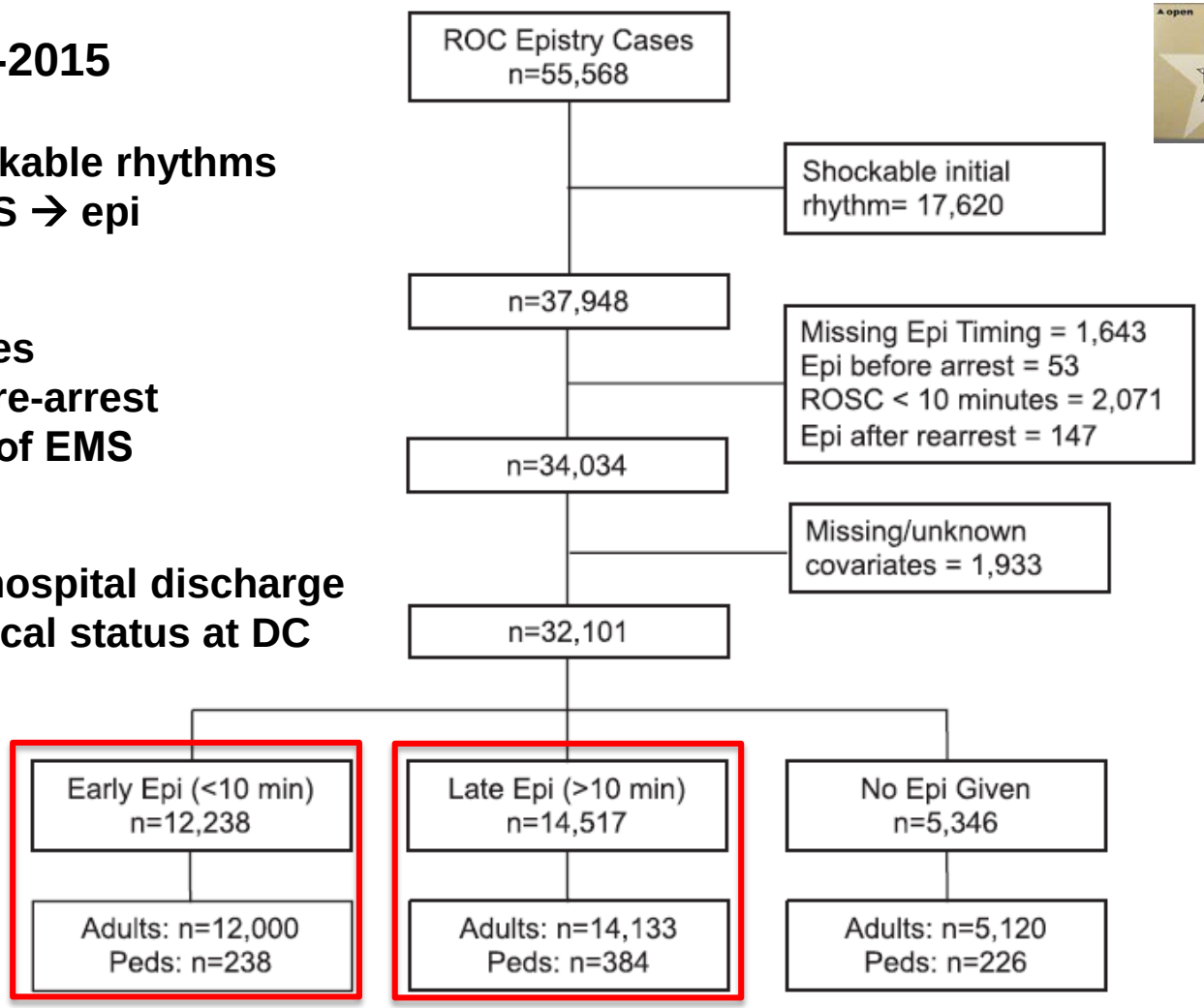
- Missing times
- 1st epi post re-arrest
- ROSC ≤ 10' of EMS

Outcome

- 1º Survival hospital discharge
- 2º Neurological status at DC







Hansen M et al. Circulation 2018;137:2032-40.

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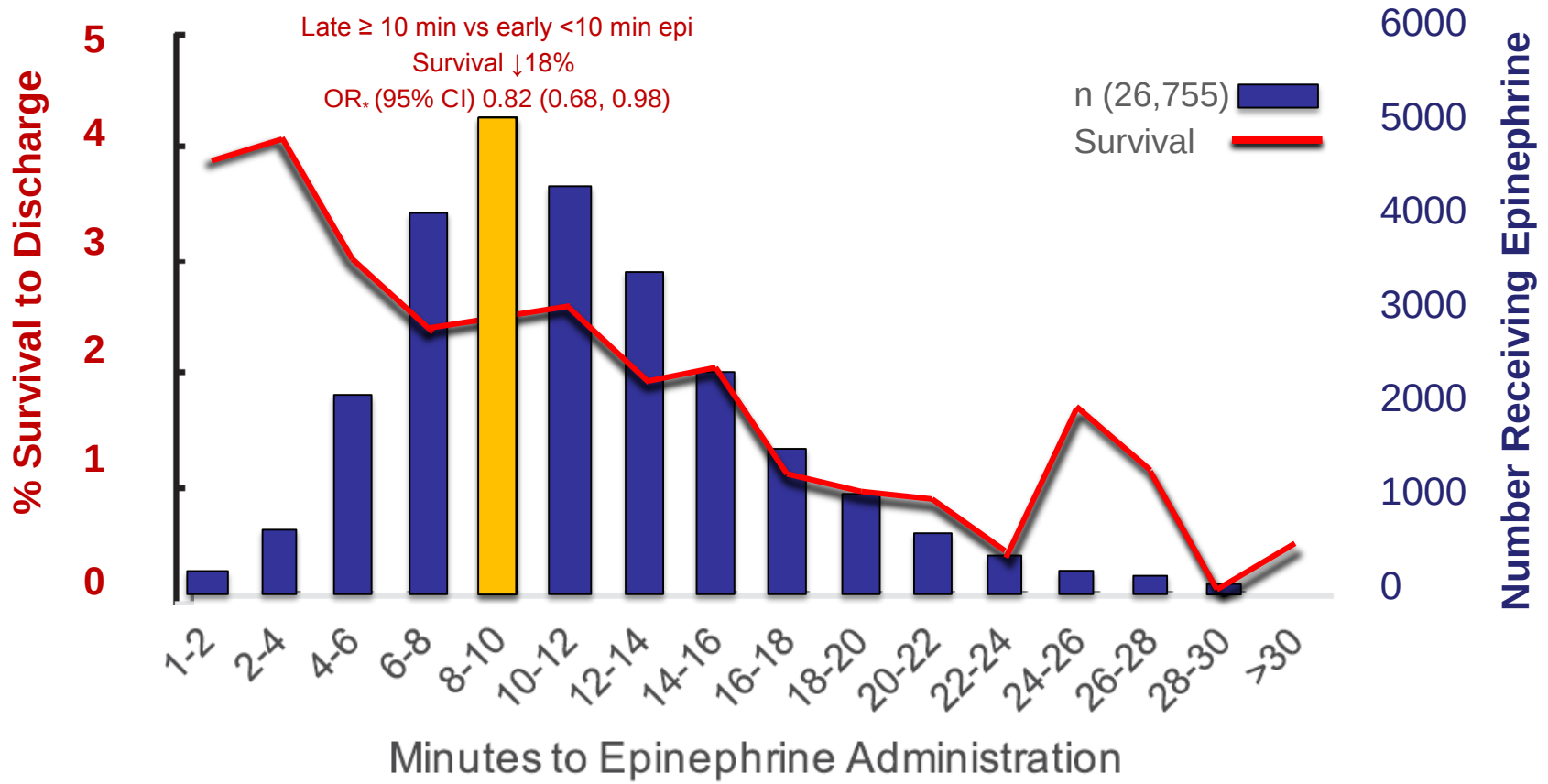


*Adj for gender, age, witnessed status, bystander CPR, initial rhythm, 911 to EMS, successful vasc access, ETT, location, etiology, ROC site

Hansen M et al. Circulation 2018;137:2032-40.

PARAMEDIC2

The Adrenaline Trial

How v

Should adrenaline be used when someone's heart stops?

Access	Epinephrine n=4015	Placebo n=3999
Intravenous (IV)	2739 (68.2%)	2763 (69.1%)
Intraosseous (IO)	1340 (33.4%)	1319 (33%)
Unknown	76 (1.9%)	66 (1.7%)

Intraosseous compared to intravenous drug resuscitation in out-of-hospital cardiac arrest☆

Bryan A. Feinstein[a], Benjamin A. Stubbs[b], Tom Rea[c], Peter J. Kudenchuk[d,*]

n=1800 EMS-Tx Adults OHCA 2012-2014

Known …
- Initial rhythm
- Arrest etiology
- Vascular access

Disclaimers
- IV always initial attempt
- IO secondary option
- IO invariably tibial

Total with IV access
n = 1525

Total with IO access
n = 275

Primary study cohort

n = 504
Unknown vascular access times

n = 55
Unknown vascular access times

IV cases with known vascular access times included in sensitivity analysis
n = 1021
16.3±6 min*

IO cases with known vascular access times included in sensitivity analysis
n = 220
18.4±6.8 min*

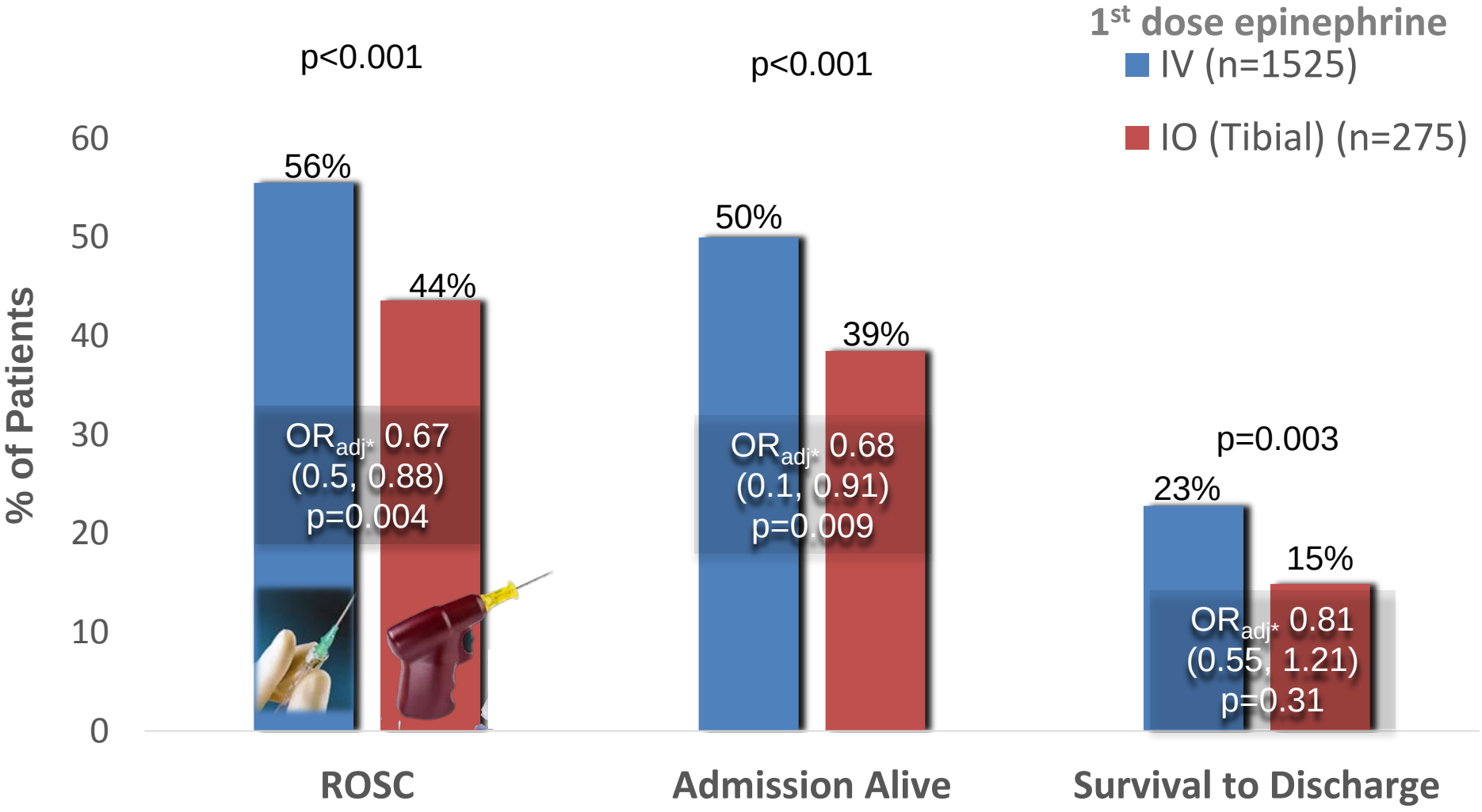
Sensitivity analysis cohort

Feinstein BA et al. Resuscitation 2017;117:91-6.

*p<0.001

Intraosseous compared to intravenous drug resuscitation in out-of-hospital cardiac arrest☆ n=1800

Bryan A. Feinstein[a], Benjamin A. Stubbs[b], Tom Rea[c], Peter J. Kudenchuk[d,*]

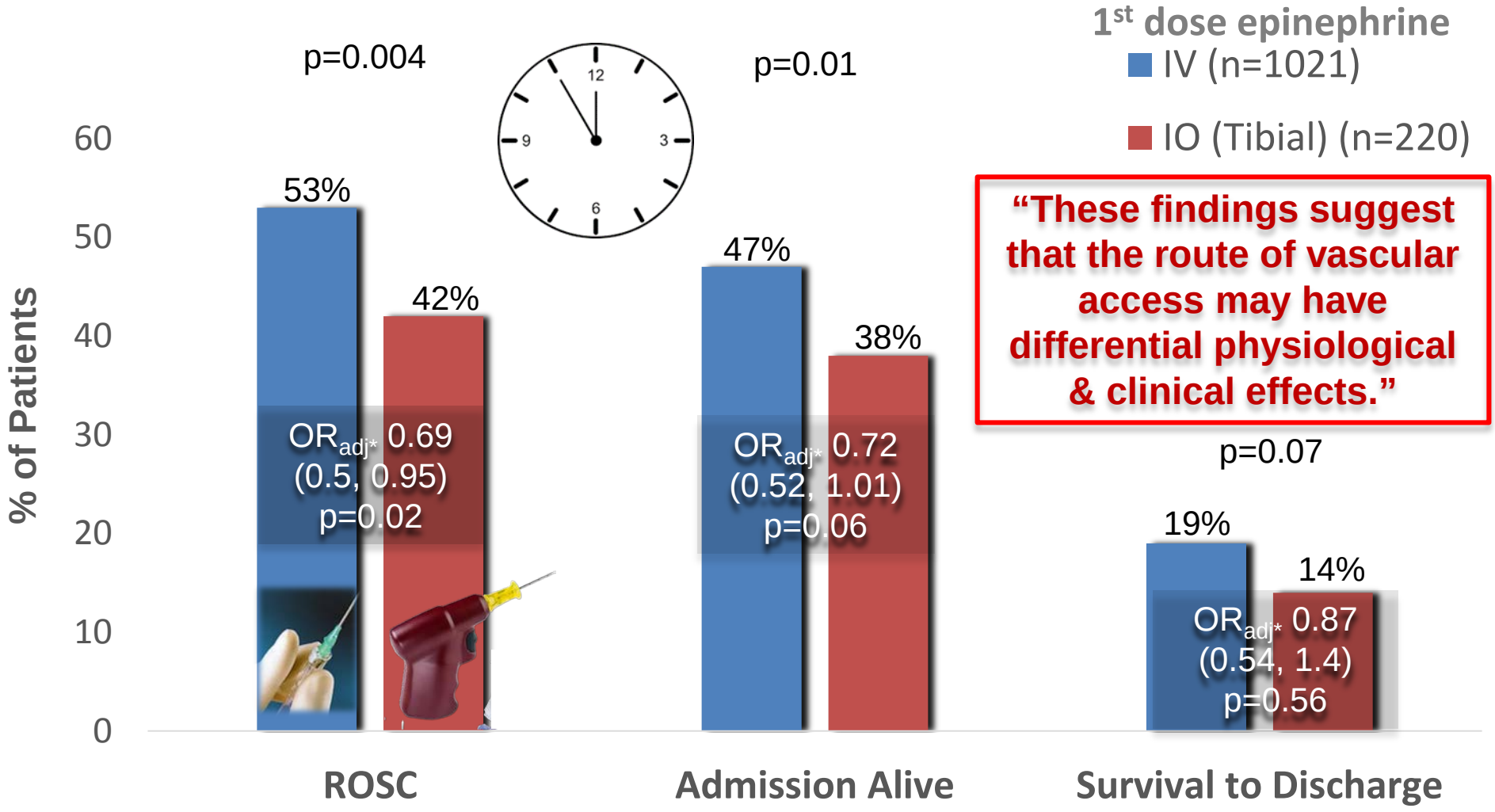


Feinstein BA et al. Resuscitation 2017;117:91-6.

*Adjusted for Utstein data elements related to outcome: arrest etiology, age, gender, initial rhythm, witnessed status, bystander CPR, arrest location, EMS response interval

Intraosseous compared to intravenous drug resuscitation in out-of-hospital cardiac arrest☆ n=1241 with known access interval

Bryan A. Feinstein[a], Benjamin A. Stubbs[b], Tom Rea[c], Peter J. Kudenchuk[d,*]



"These findings suggest that the route of vascular access may have differential physiological & clinical effects."

Feinstein BA et al. Resuscitation 2017;117:91-6.

*Adj for arrest etiology, age, gender, initial rhythm, witnessed, bystander CPR, location, IO vs IV, **vascular access interval**

Intraosseous Vascular Access Is Associated With Lower Survival and Neurologic Recovery Among Patients With Out-of-Hospital Cardiac Arrest

Takahisa Kawano, MD, PhD*; Brian Grunau, MD, MHSc; Frank X. Scheuermeyer, MD, MHSc; Koichiro Gibo, MD, MMSc; Christopher B. Fordyce, MD, MHS; Steve Lin, MD, MSc; Robert Stenstrom, MD, PhD; Robert Schlamp, MEd; Sandra Jenneson, MD; Jim Christenson, MD

From June 2007 to November 2009

Total number of EMS treated patients with OHCA
n = 17,445

(Exclusion n = 4,290)

• Patients aged 17 and less	25
• No vascular access	2,923
• Patients who had both IO and IV accesses	244
• Patients with IV whom EMS failed to get IO access	61
• Patients with IO whom EMS failed to get IV access	311
• Patients who EMS tried only IV access but failed	654
• Patients who EMS tried only IO access but failed	4
• Verbal or written Do Not Resuscitation order	68

Eligible patients n = 13,155 (75.4%)

IO access	n =	660 (5.0 %)
IV access	n =	12,495 (95.0 %)

IO vs IV as 1st and only vascular access

Kawano T et al. Ann Emerg Med 2018;71:588-96

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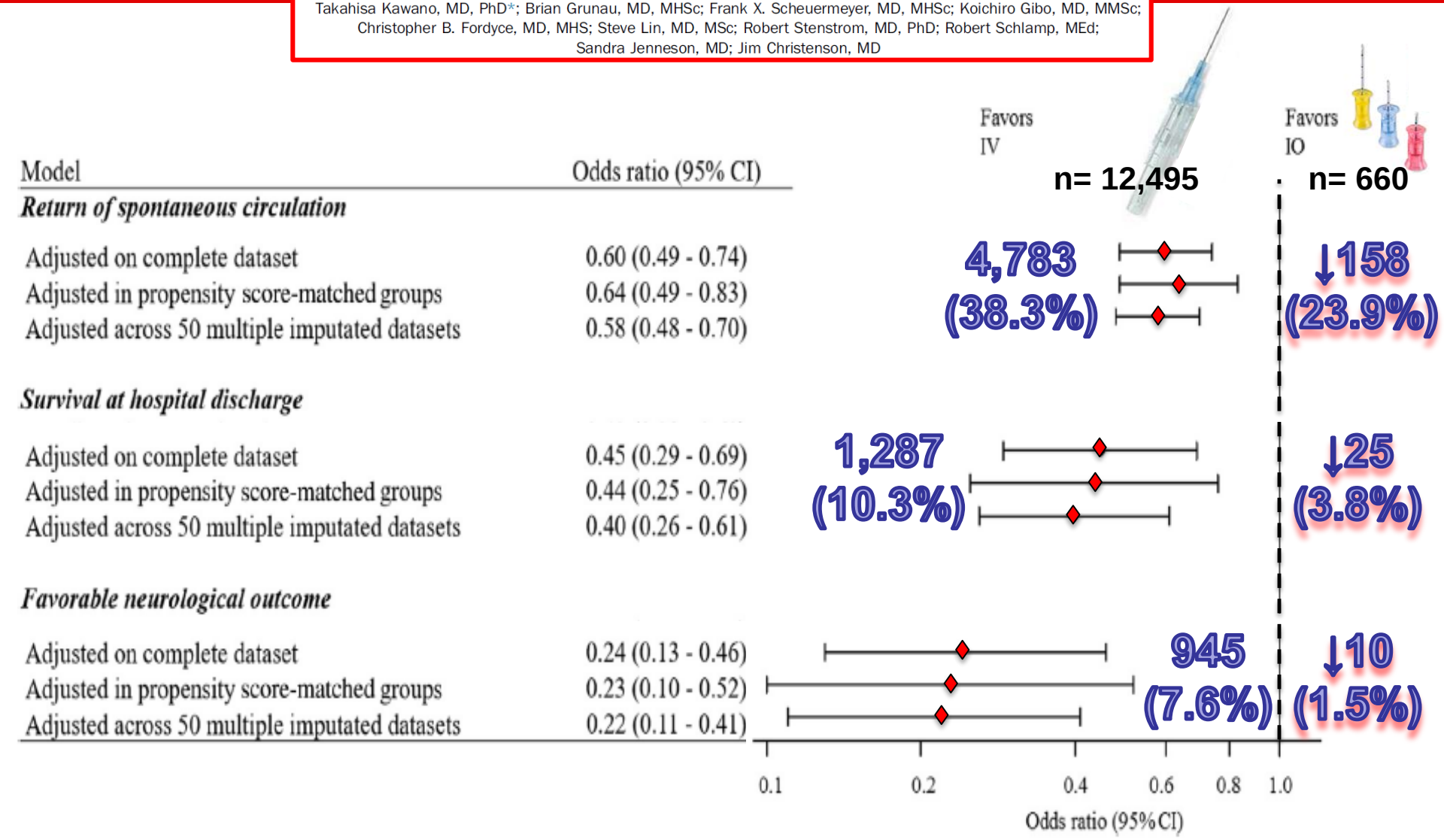


*Adjusted for age, sex, initial rhythm, witnessed status, bystander CPR, location, AED use, time of call→EMS, clustering study region

Kawano T et al. Ann Emerg Med 2018;71:588-96

PARAMEDIC2

The Adrenaline Trial

"Information about EMS CPR quality was limited to first 5 min of arrest in <5% of patients …"

CPR Parameter (1st 5 minutes)	Epinephrine n=149	Placebo n=137
Compression rate, mean/min (SD)	106.8 (14.4)	106.5 (13.3)
Compression fraction, mean (SD)	76.2% (11.2)	78.4% (13)

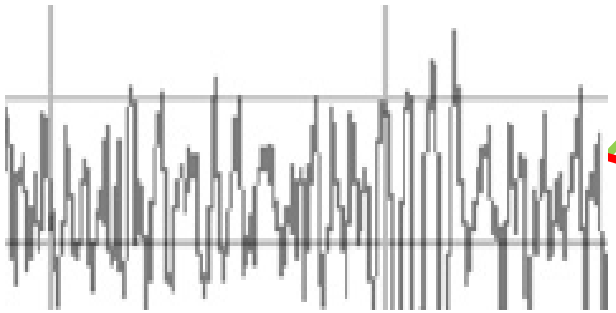
Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs☆

Morten Pytte[a,b,*], Jo Kramer-Johansen[b,c], Joar Eilevstjønn[d], Morten Eriksen[b], Tævje A. Strømme[b], Kristin Godang[e], Lars Wik[b,f], Petter Andreas Steen[a], Kjetil Sunde[a,b]

"We hypothesized that drug delivery & drug effect depend on the quality of CPR."

17 instrumented pigs

- Aortic, RA pressure
- Central venous O_2
- Doppler cortical blood flow



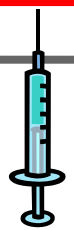
"GOOD" CPR

100cpm (50/50 duty cycle); 45 mm depth
Asynchronous Chest Compression + V @12bpm

"POOR" CPR

100 cpm; 30-38 mm depth
Interrupted CC:V = 15:2 (9" pause for ventilation)

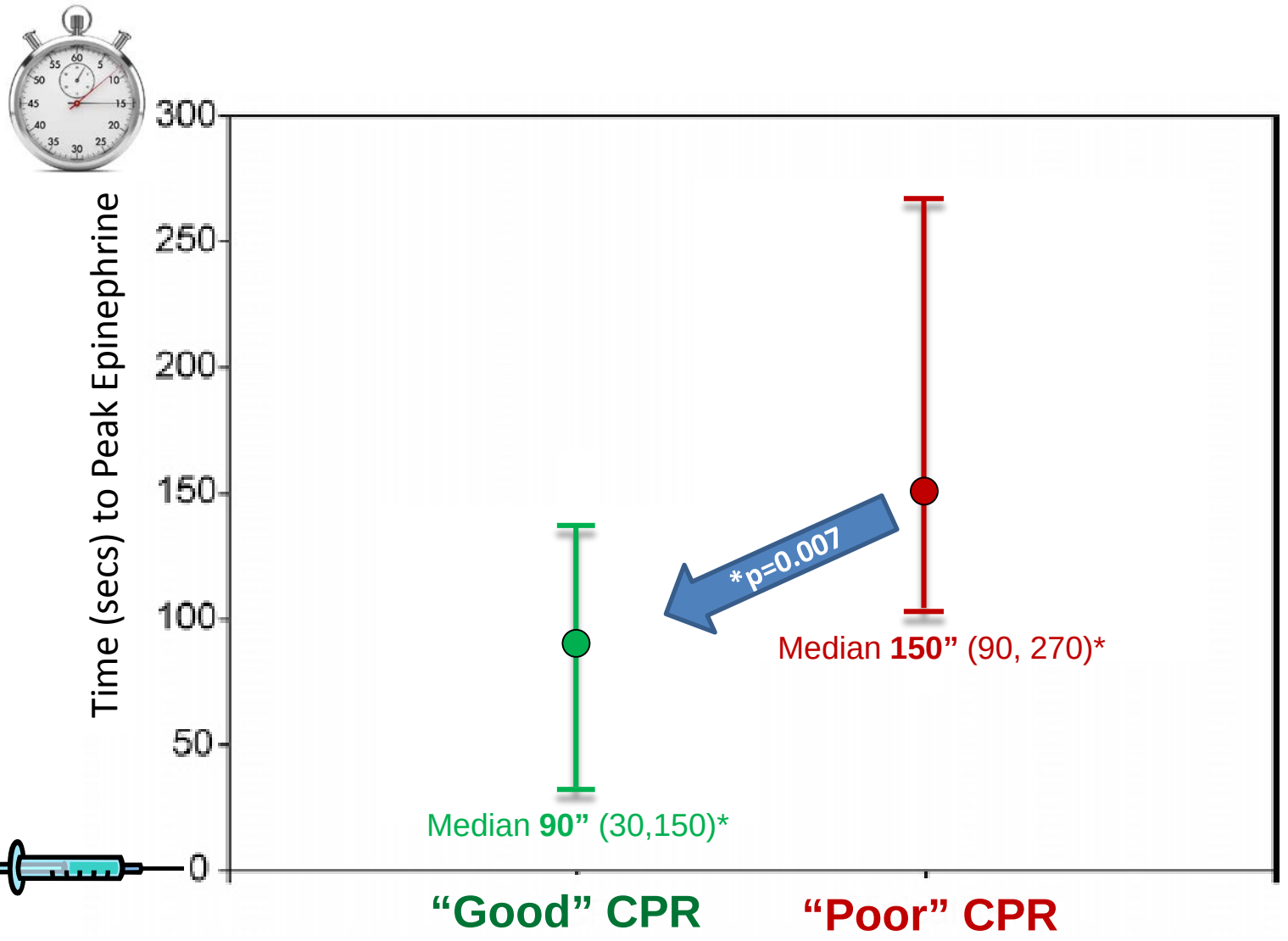
VF x 4' → "BLS" x 4' → ALS x 14'



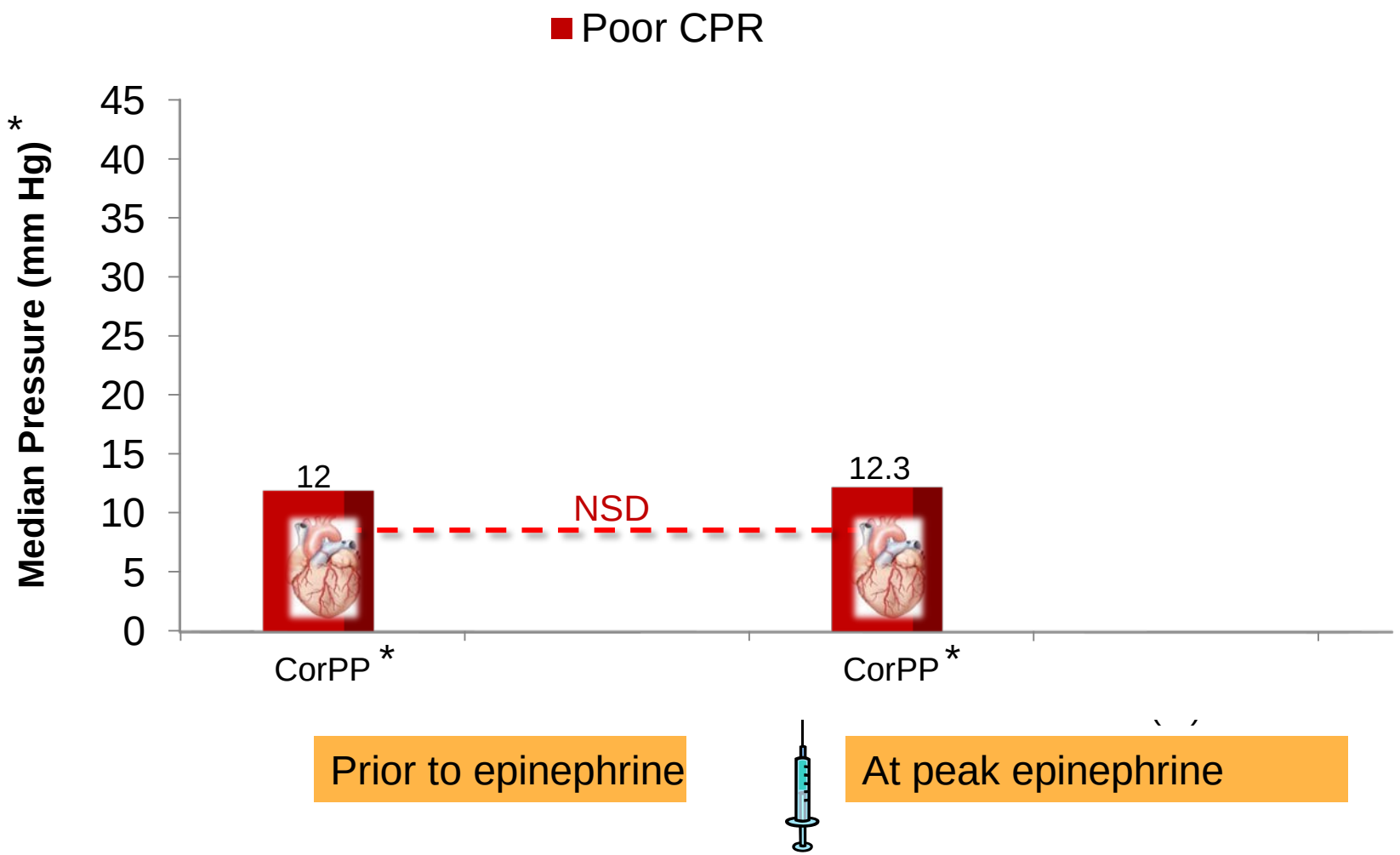
Epi 0.02mg/kg IV @ 30" into ALS (AHA std dose)

Pytte M et al. Resuscitation 2006;71:369-78

Time to Peak Epi: Good vs. Poor CPR



Effects of CPR Quality on Coronary & Cerebral Perfusion



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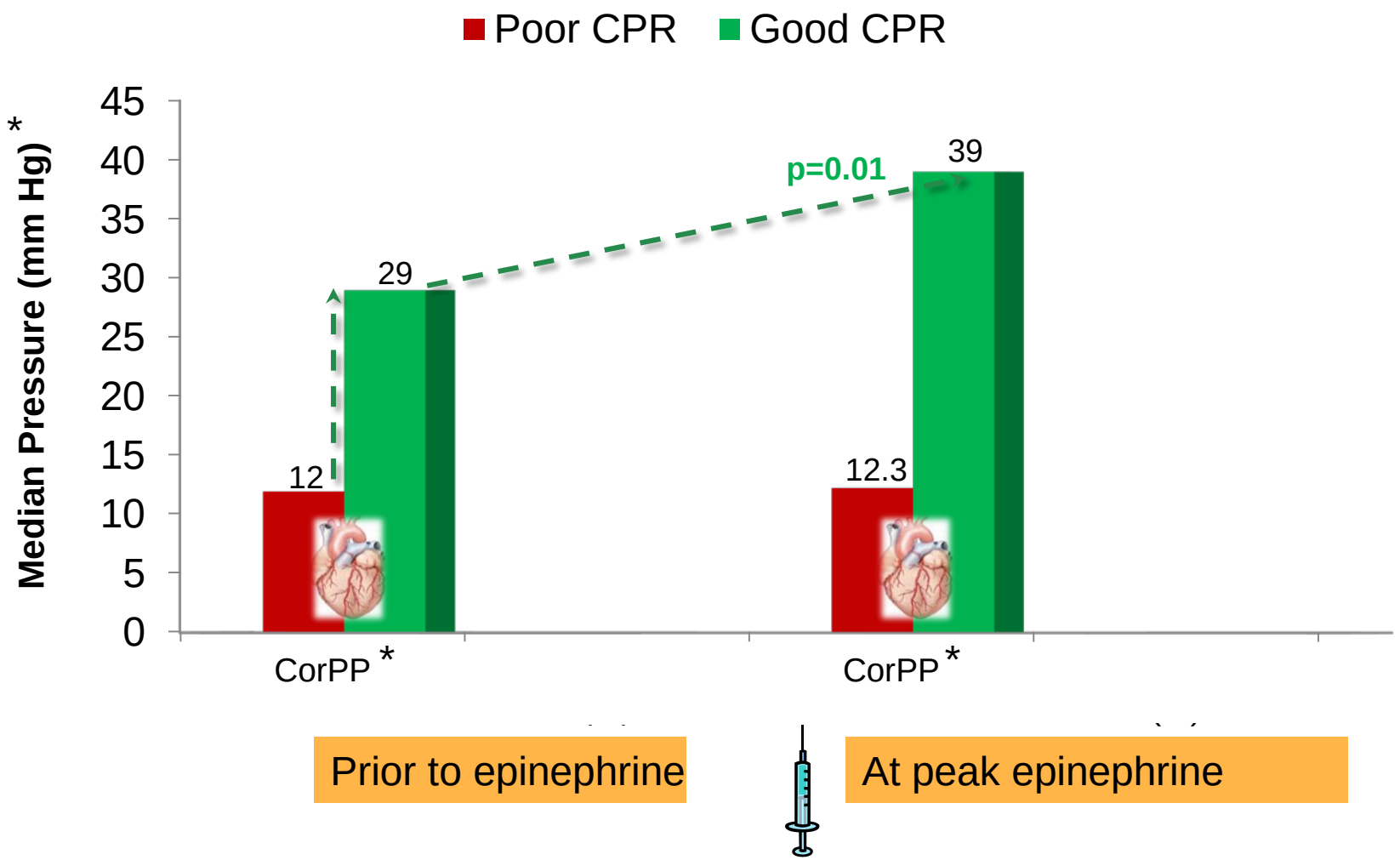

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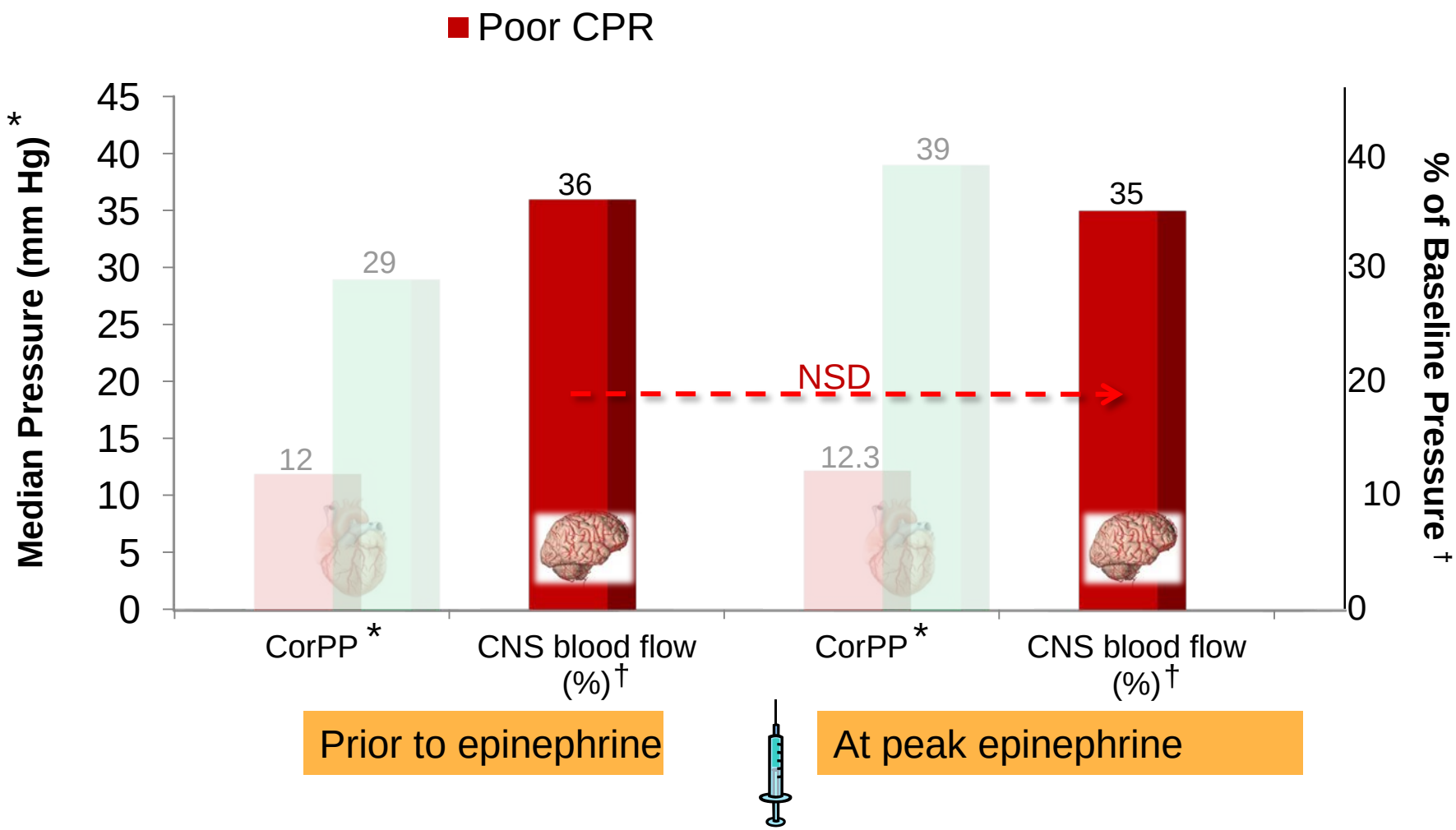

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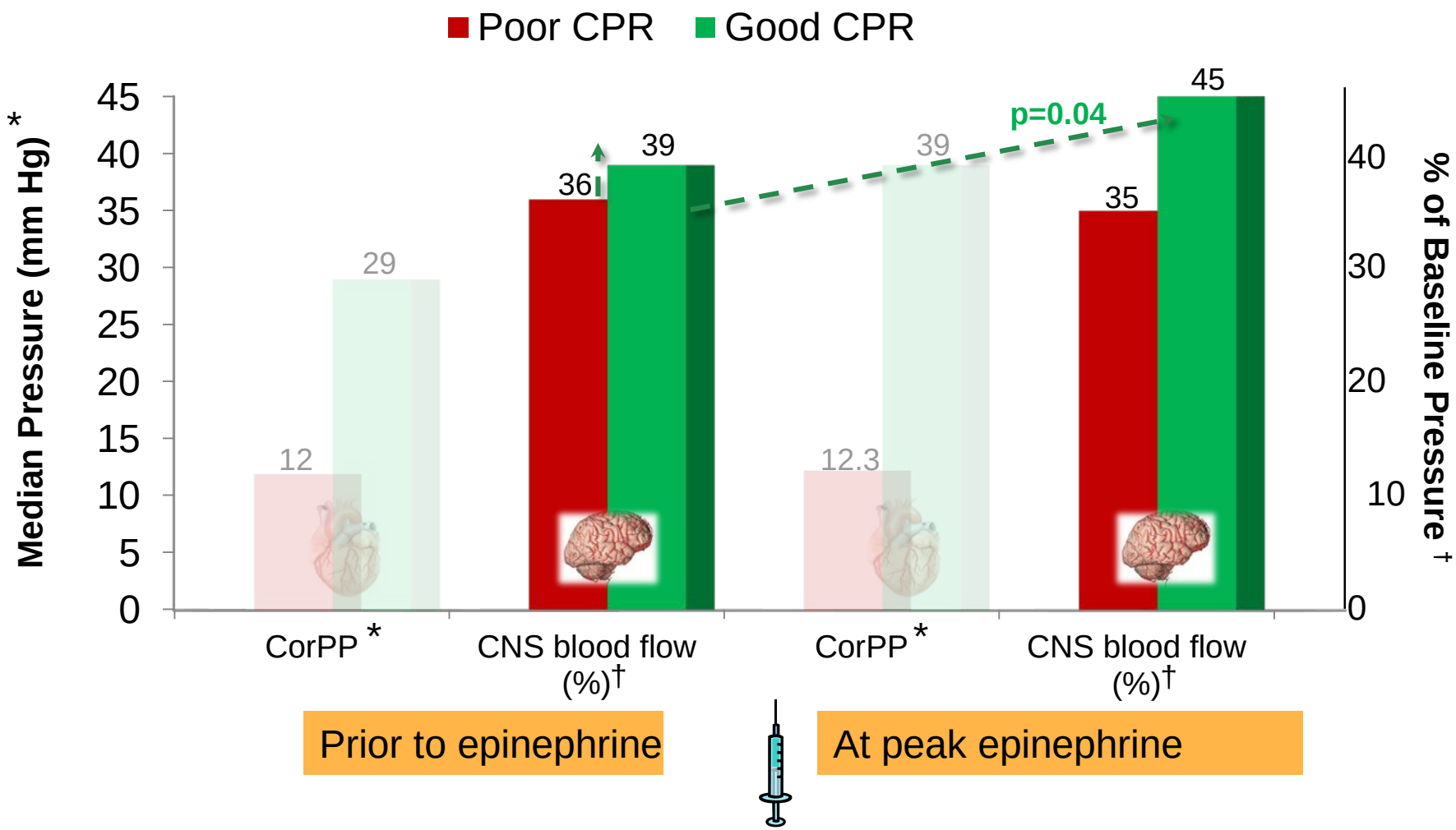

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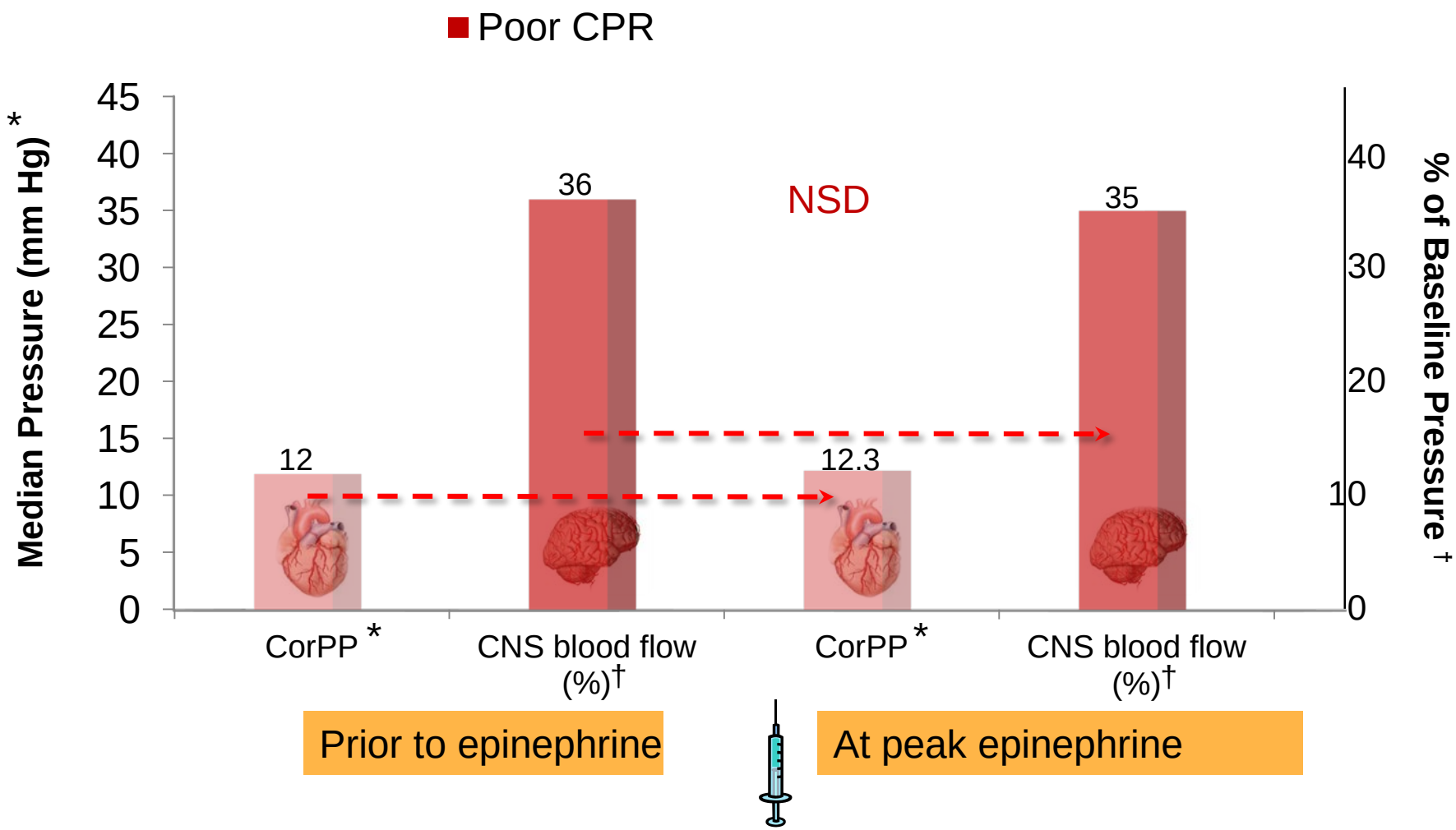

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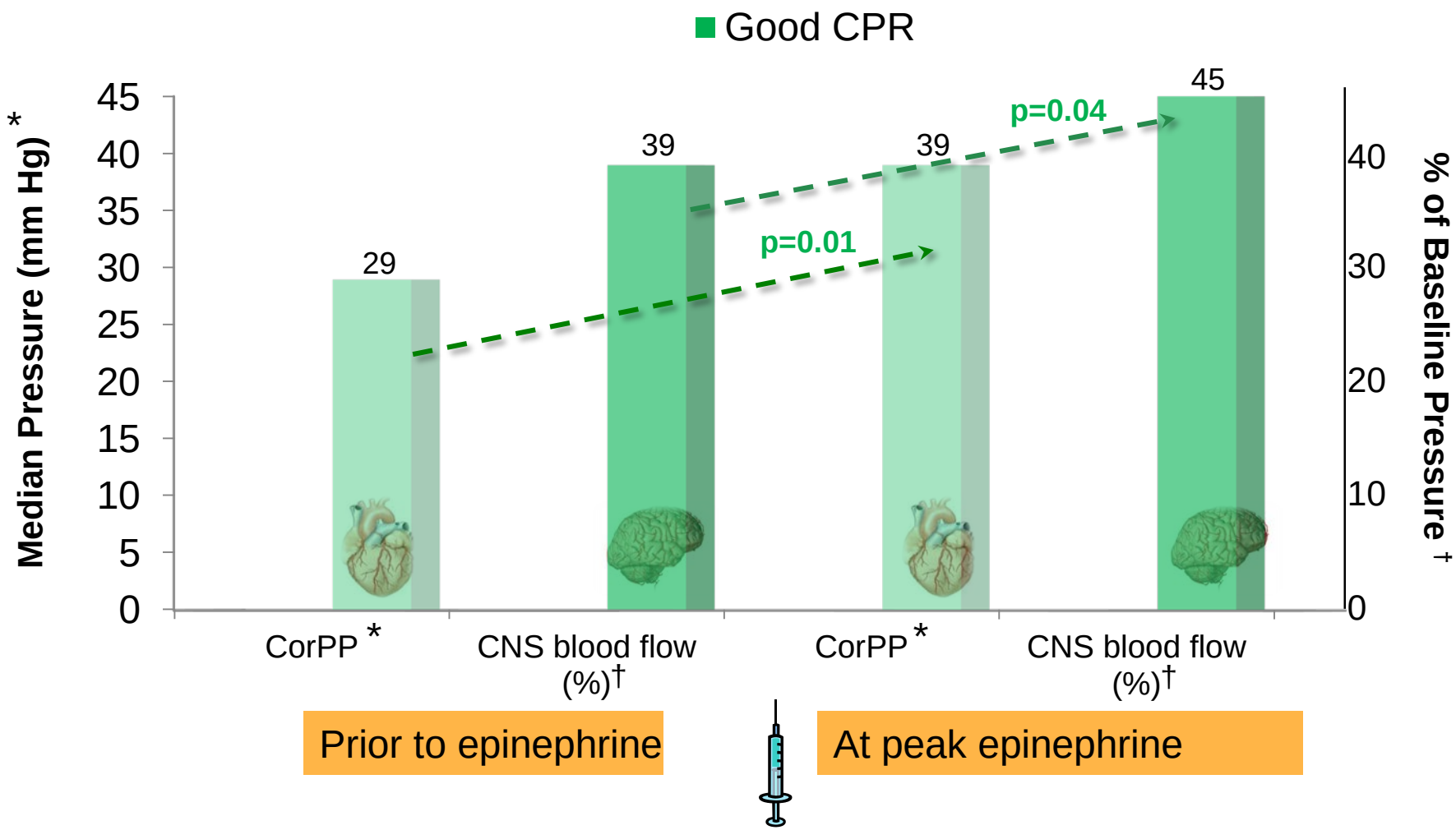

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Pharmacologic Challenges in Cardiac Arrest Resuscitation

Giving the **right** . . .

- ✓ drug
- ✓ dose
- ✓ time
- ✓ route
- ✓ way (HPCPR)