

Management of cardiogenic shock in acute coronary syndromes - The "Shock Team" at work

Drugs in cardiogenic shock - Which, when, how long?

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Disclosures (last 5 years)

- ▶ Speaker: Abiomed, Astra-Zeneca, Bayer, Ferrer, Maquet, Novartis, Orion-Pharma, Sanofi, Servier, Singulex
- ▶ Clinical trials: Cardiorentis, DalCor, Ferrer, Janssen, Novartis, Orion-Pharma, Singulex, Zoll
- ▶ Research grants: Novartis, Orion-Pharma, Singulex
- ▶ Royalties: No

PATIENT WITH AHF

Bedside assessment to identify haemodynamic profile

CONGESTION?

YES (95% of AHF patients)

"Wet"

NO (5% of AHF patients)

"Dry"

POOR PERFUSION?

NO

"Wet" & "Warm"

YES

"Wet" & "Cold"

NO

"Dry" & "Warm"

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Definitions of Terms Used in Cardiogenic Shock Diagnosis	
Term	Definition
Symptoms/signs of congestion (left-sided)	Orthopnoea, paroxysmal nocturnal dyspnoea, pulmonary rales (bilateral), peripheral oedema (bilateral).
Symptoms/signs of congestion (right-sided)	Jugular venous dilatation, peripheral oedema, congested hepatpmegaly, hepatojugular reflux, ascites, symptoms of gut congestionsymptoms of gut congestion.
Symptoms/signs of hypoperfusion	Clinical: cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. Laboratory measures: metabolic acidosis, elevated serum lactate, elevated serum creatinine. Hypoperfusion is not synonymous with hypotension, but often hypoperfusion is accompanied by hypotension.
Hypotension	Systolic BP <90 mmHg
Hypoxaemia	Arterial PaO2 <80 mmHg (<10,67 kPa)
Acidosis	pH <7.35
Elevated blood lactate	>2 mmol/L
Oliguria Urine output	<0.5 mL/kg/h

“Wet” & “Cold”

Systolic blood pressure <90 mmHg?

YES

- Inotropic agent
- Consider vasopressor in refractory cases
- Diuretic (when perfusion corrected)
- Consider mechanical circulatory support if no response to drugs

NO

- Vasodilators
- Diuretics
- Consider inotropic agent in refractory cases

What Do The ESC Guidelines Say?

Recommendations for inotropic and agents and vasopressors in patients with cardiogenic shock

Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.

IIb

C

An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.

IIb

C

Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.

III

A

556, 557

What Do The ESC Guidelines Say?

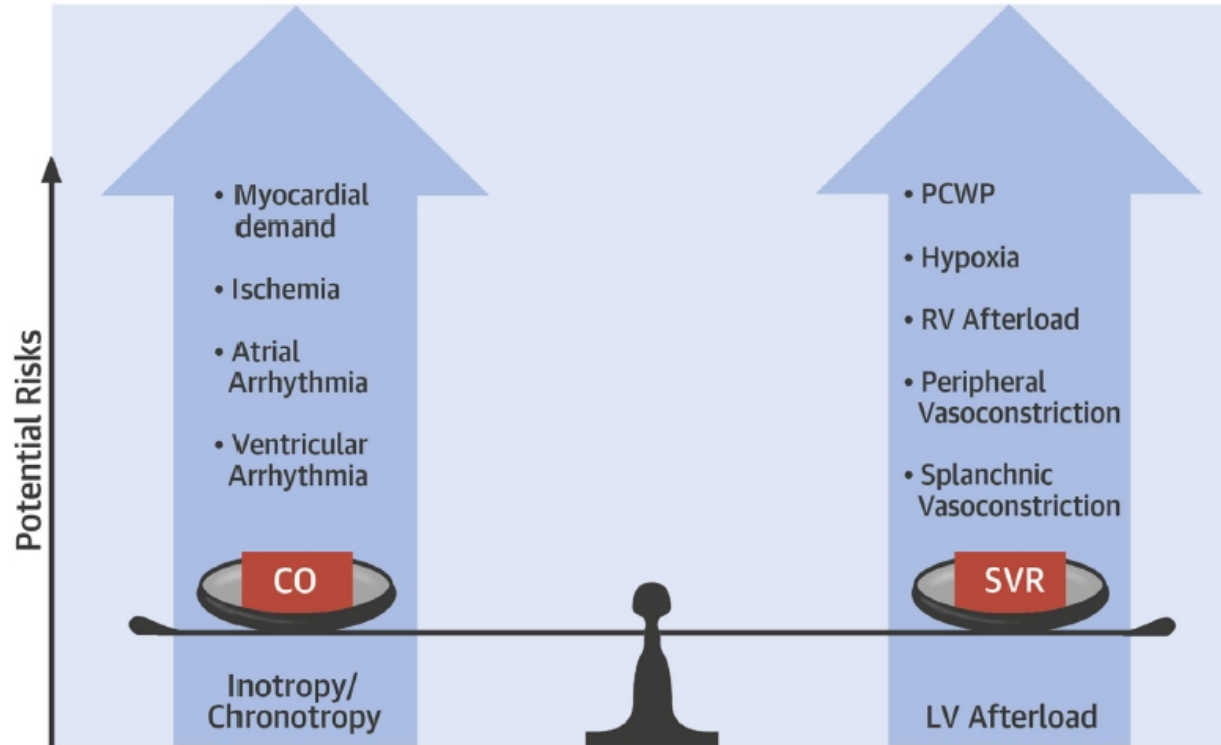
Recommendations for inotropic and agents and vasopressors in patients with cardiogenic shock

A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.	IIb	B	558
It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension.	I	C	540, 559 -563
In such cases intra-arterial blood pressure measurement may be considered.	IIb	C	

Currently Available Inotropes and Vasopressors

Drug	Mechanism	Effect
Dobutamine	β_1 (and β_2) receptor	Inotropic, chronotropic, mild vasodilatation
Dopamine	D_{1-2} (0.5 to 3 $\mu\text{g/kg/min}$), β_1 (3-10 $\mu\text{g/kg/min}$) and α_1 (>10 $\mu\text{g/kg/min}$) receptors	Dose dependent (inotropic, chronotropic, vasoconstriction)
Milrinone	Phosphodiesterase 3 inhibitor	Inotropic, vasodilatation
Levosimendan	Ca^{2+} sensitizer, ATP-dependent K^+ channels	Inotropic, vasodilatation
Noradrenaline	α_1 (mild β_1)	Vasoconstriction
Adrenaline	α_1 , β_1 and β_2	Inotropic (low dose), vasoconstriction (higher doses)

Risks of Inotropes and Vasopressors in CS



The “Ideal” Cathecolamine

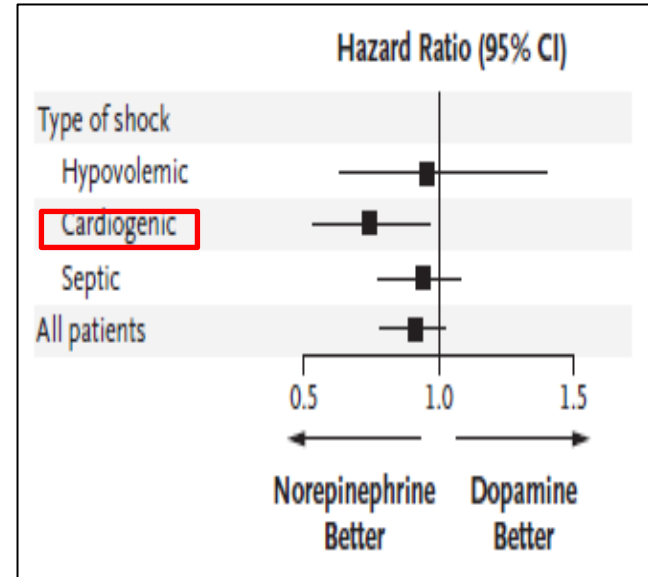
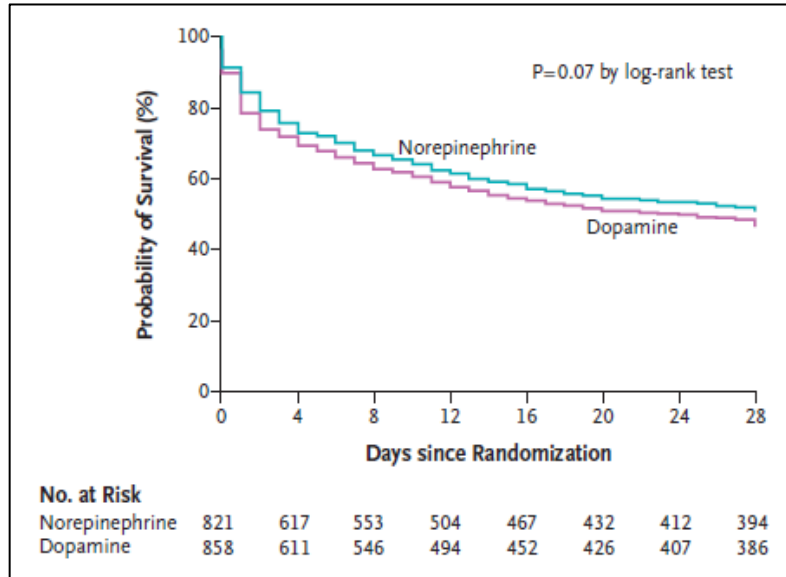
- ▶ Pharmaceutically: non-toxic, stable preparation, compatible with other drugs, peripherally deliverable, easy titration (on-off effect), steady effect (no tachyphylaxis), metabolized independent of liver and renal function
- ▶ Pharmacodynamic properties: increases contractility, increases mean arterial pressure, maintenance of diastolic blood pressure, increases cardiac output, improves regional perfusion, no increase in myocardial oxygen consumption, no tachycardia, non-arrhythmogenic, suitable in pregnancy and paediatric populations
- ▶ Beneficial effect on hard clinical end-points (save lives) and cost effective

Current Use of Inotropes and Vasopressors: CardShock Study

Vasoactive	All (n=220)	ACS (n=178)	non-ACS (n=42)	p
Vasopressors				
Noradrenaline	75%	76%	69%	NS
Adrenaline	21%	23%	14%	NS
Dopamine	26%	29%	12%	0.03
Vasopressin/Terlipressin	4%	5%	-	NS
Simultaneous vasopressors	30%	33%	14%	0.02
Inotropes				
Dobutamine	49%	51%	43%	NS
Levosimendan	24%	22%	31%	NS
PDE3i	4%	4%	5%	NS
Simultaneous vasopressor and inotrope	55%	56%	50%	NS

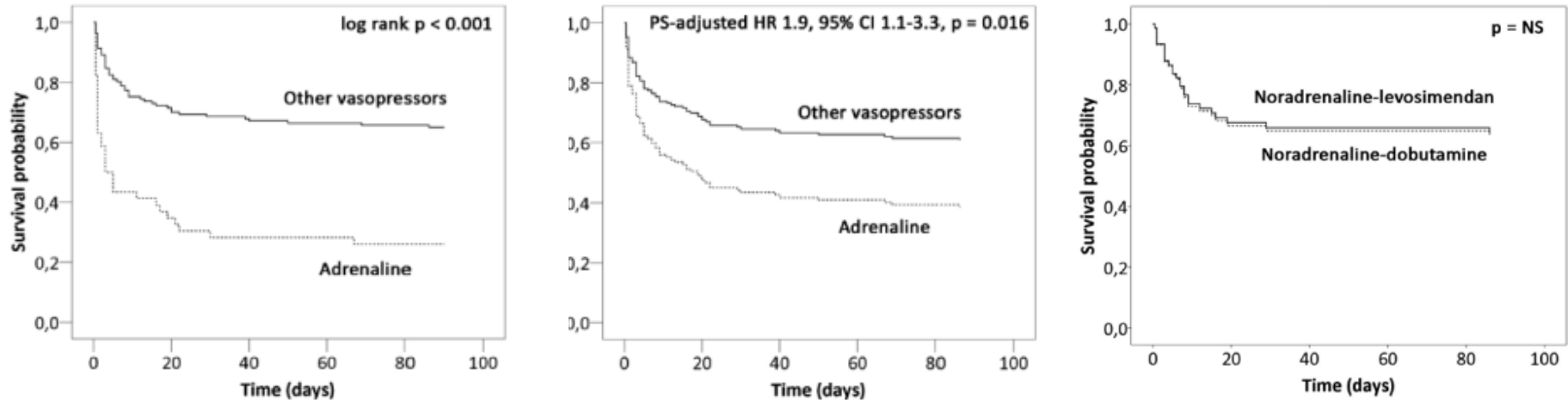
Noradrenaline

Comparison of norepinephrine and dopamine in the treatment of shock (SOAP-II trial)



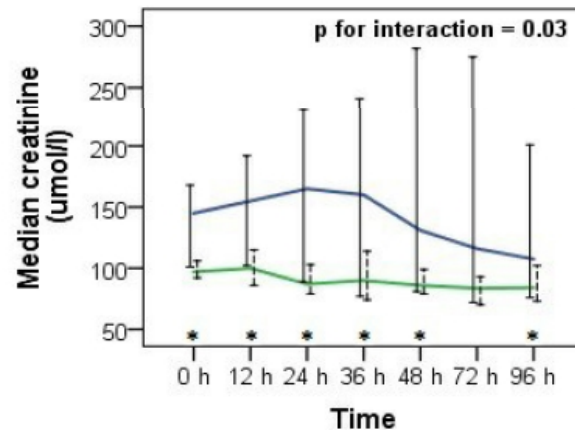
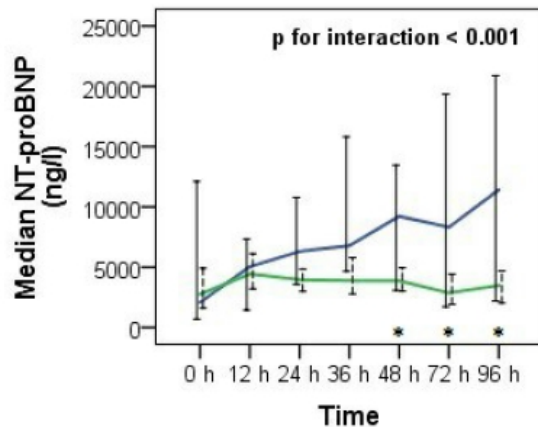
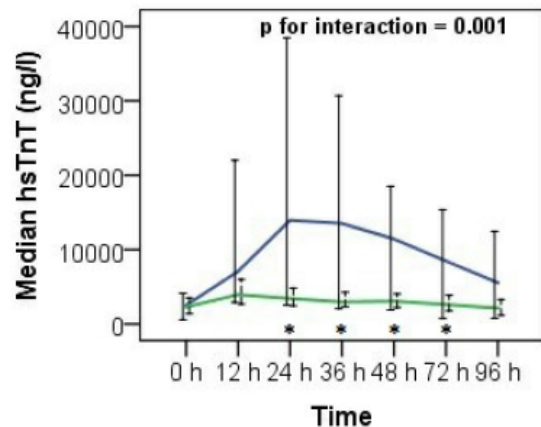
Adrenaline Independent Predictor of Mortality

Survival curves for use of adrenaline



Propensity score: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, hypertension, renal insufficiency), acute coronary syndrome as the etiology of cardiogenic shock, resuscitation prior to inclusion and initial presentation (confusion, blood lactate, creatinine, systolic blood pressure, sinus rhythm, and left ventricular ejection fraction).

Adrenaline Use Related to Deterioration in Cardiac and Renal Biomarkers in CS

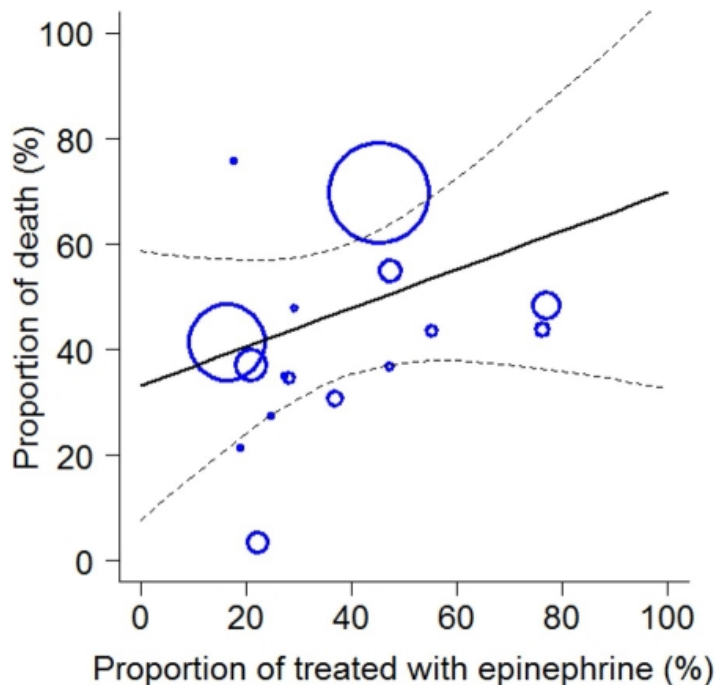


— adrenaline
— other vasopressors

* p < 0.05 for pairwise comparison

Epinephrine and Short-term Survival in CS

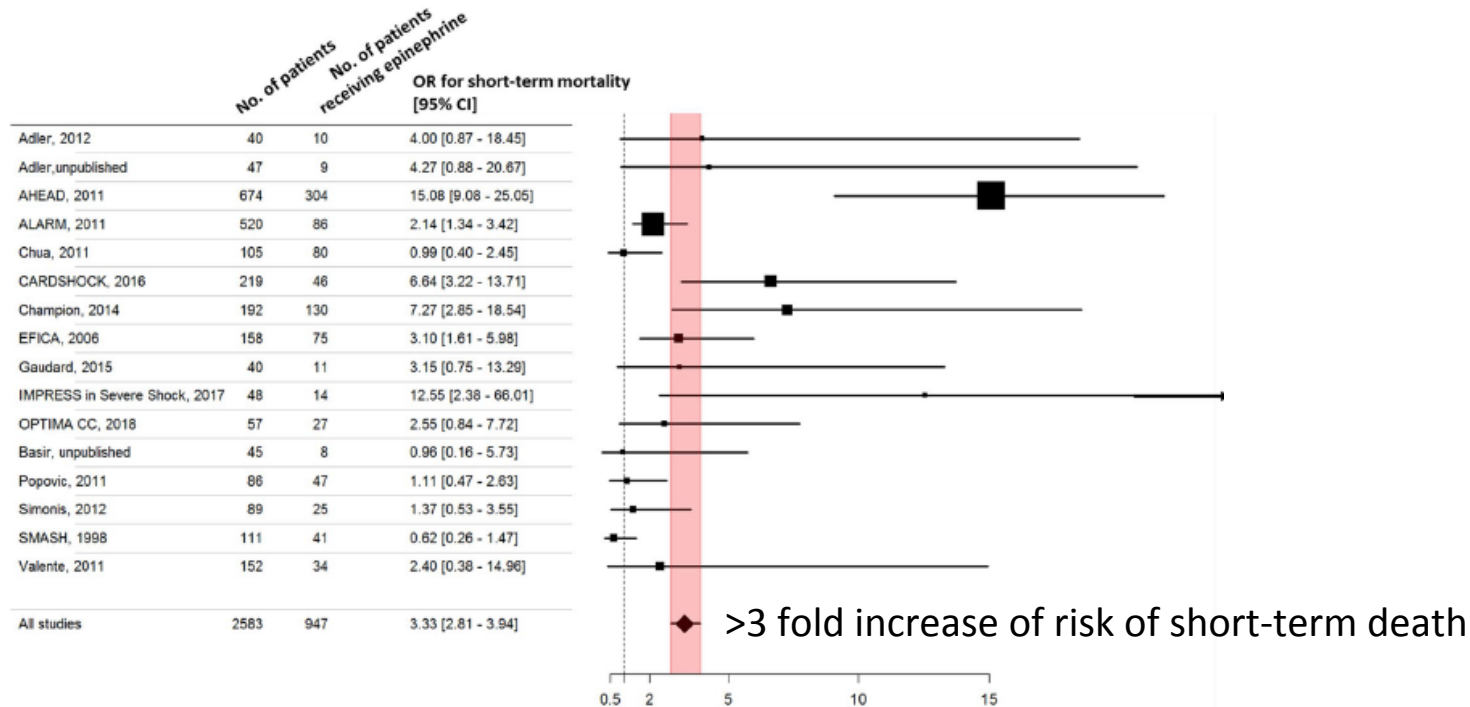
Meta-analysis of individual patient data from 16 studies (n 2583)



- Epinephrine frequently used: 37% (17-76%)
- Increased use corresponds with higher mortality

Epinephrine and Short-term Survival in CS

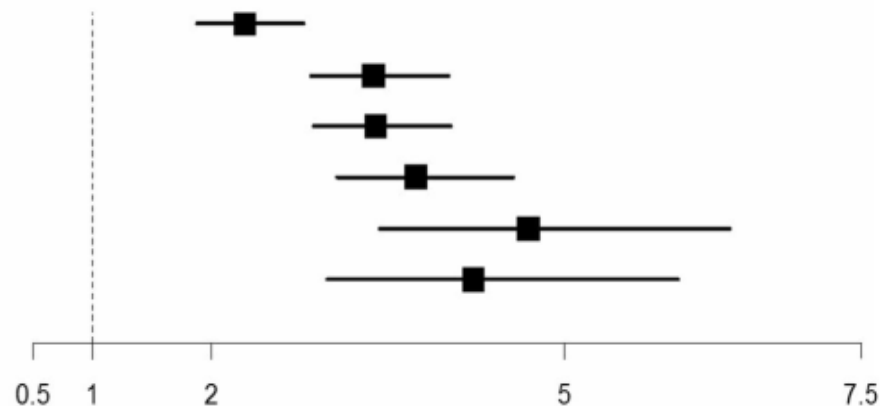
Meta-analysis of individual patient data from 16 studies (n 2583)



Epinephrine and Short-term Survival in CS

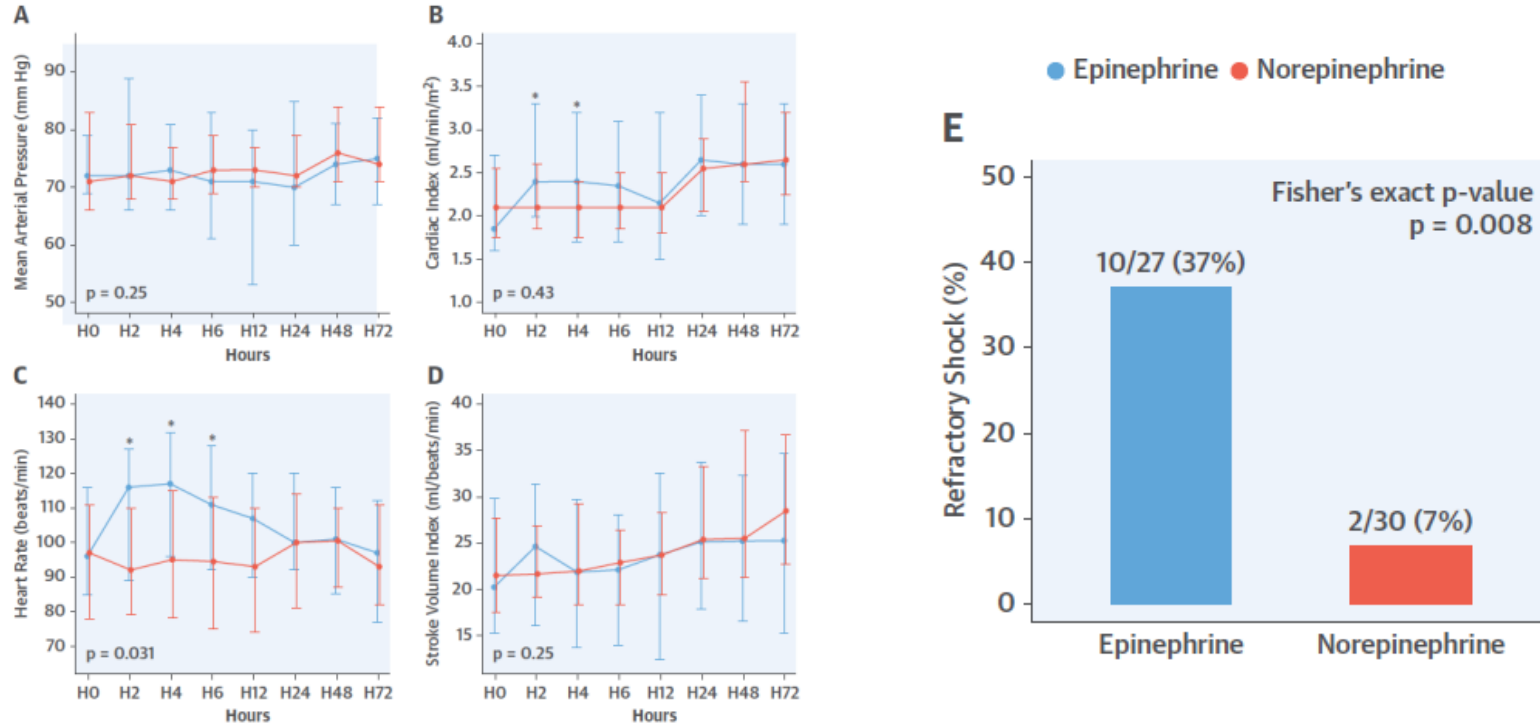
Meta-analysis of individual patient data from 16 studies (n 2583)

	No. of analyzed patients	OR for short-term mortality [95% CI]
AHEAD excluded	1909	2.29 [1.88 - 2.78]
OPTIMA CC excluded	2526	3.38 [2.85 - 4.01]
Published cohorts only	2491	3.40 [2.87 - 4.03]
Cluster effect	2583	3.74 [3.07 - 4.56]
Fully adjusted *	1227	4.68 [3.43 - 6.39]
PS-matched	676	4.22 [2.99 - 5.96]



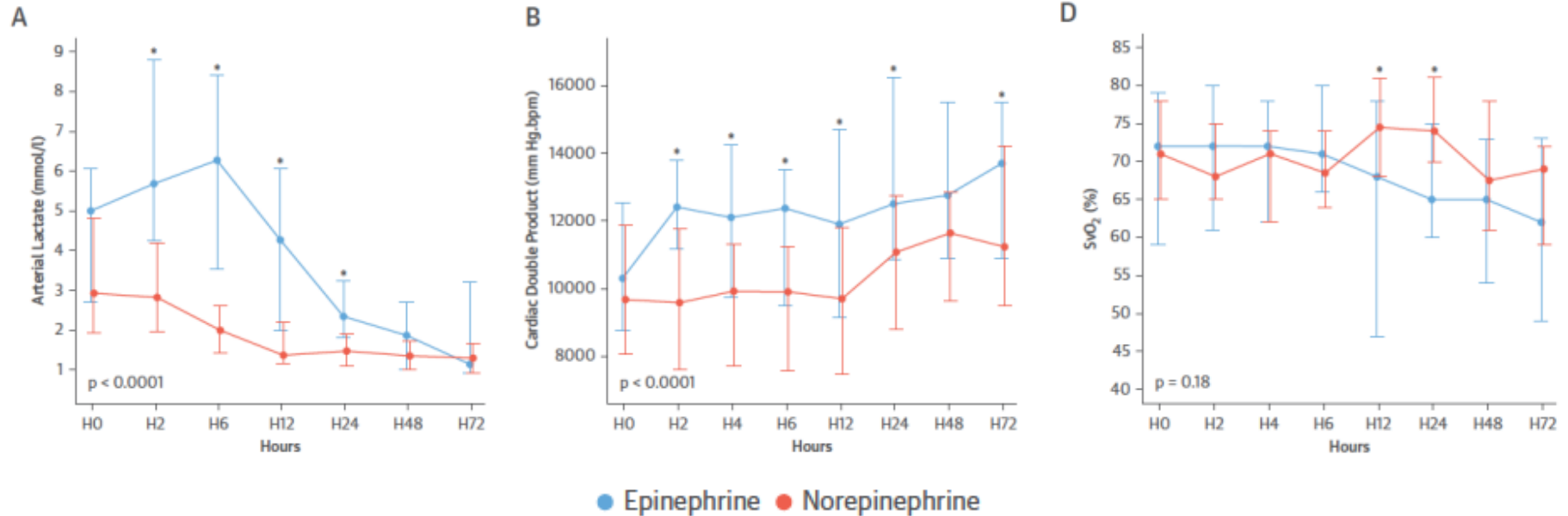
* age, gender, ischaemic heart disease, eGFR, LVF

Epinephrine vs Norepinephrine in AMI Related CS



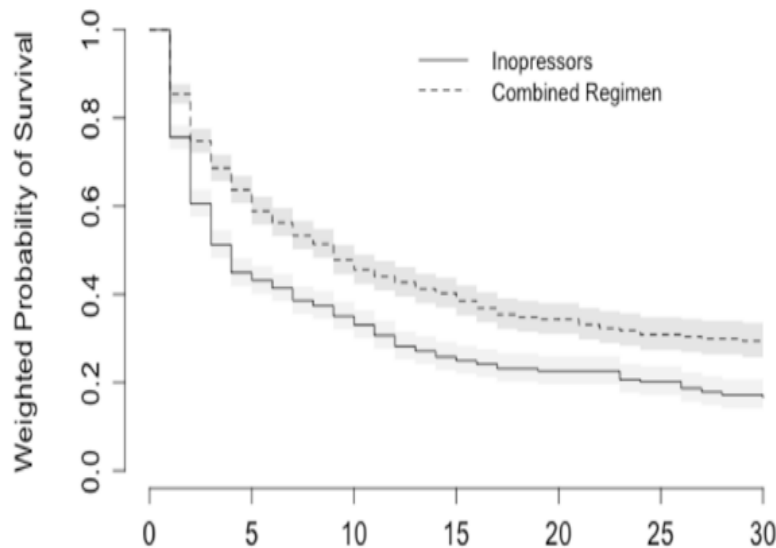
Epinephrine vs Norepinephrine in AMI Related CS

Hemodynamic, Metabolic, and Cardioenergetic Parameters

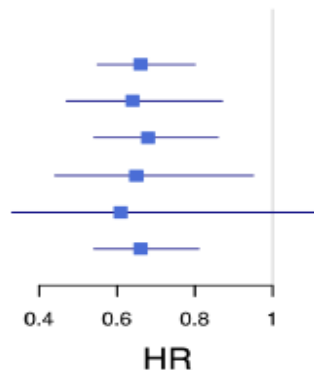


Inodilators in Cardiogenic Shock: Propensity Score Analysis

ALARM-HF, EFFICA, AHEAD Registries (988 CS patients)



	n	HR
PS Weighting	988	0.66
No ACS	374	0.64
ACS	614	0.68
ALARM-HF	297	0.65
EFICA	572	0.61
AHEAD	119	0.66



Combined Regimen **Better**

Assesment Macro & Microcirculation in CS

Macrocirculation

Parameter	Range	Invasive
HR	100 (?) bpm	NI
SBP	>90 mmHg	NI
MAP	>60-65 (?) mmHg	NI
PCWP	<18 mmHg	I
MPAP	9-17 mmHg	I
CI	2.6-4.2 L/min/m ²	I
CPO	>0.53 W	I
SVR	700-1600 dyn·s·cm ⁻⁵	I

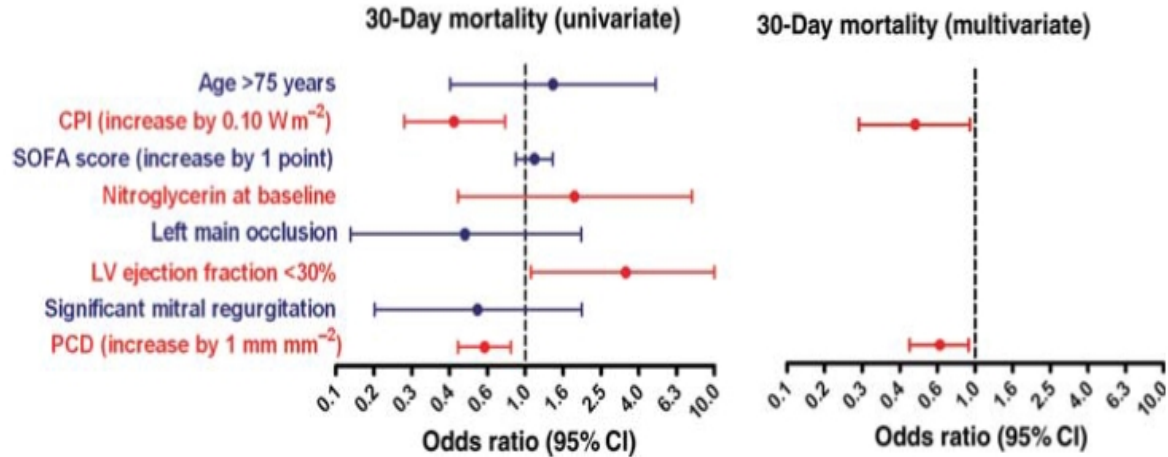
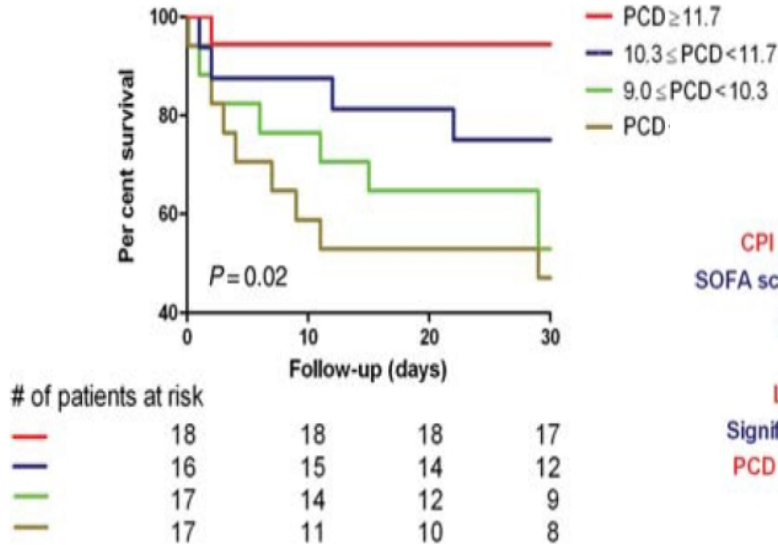
CPO: cardiac power output

Microcirculation

Parameter	Range	Invasive
Lactate	<1.8 mmol/L	NI
SvO ₂	>65%	I
Skin mottling	1-5 scale	NI
CRT	2.5-5 sec	NI
NIRS (rSO ₂)	60-75% (trend)	NI
NIRS (tSO ₂)	85% (trend)	NI
PPI	<1.4	NI
PCD	11.7 (?)	NI

CRT: capillary refill time; NIRS: near infrared spetroscopy; PPI: peripheral perfusion index; PCD: sublingual capillary perfusion

Microcirculation in Cardiogenic Shock



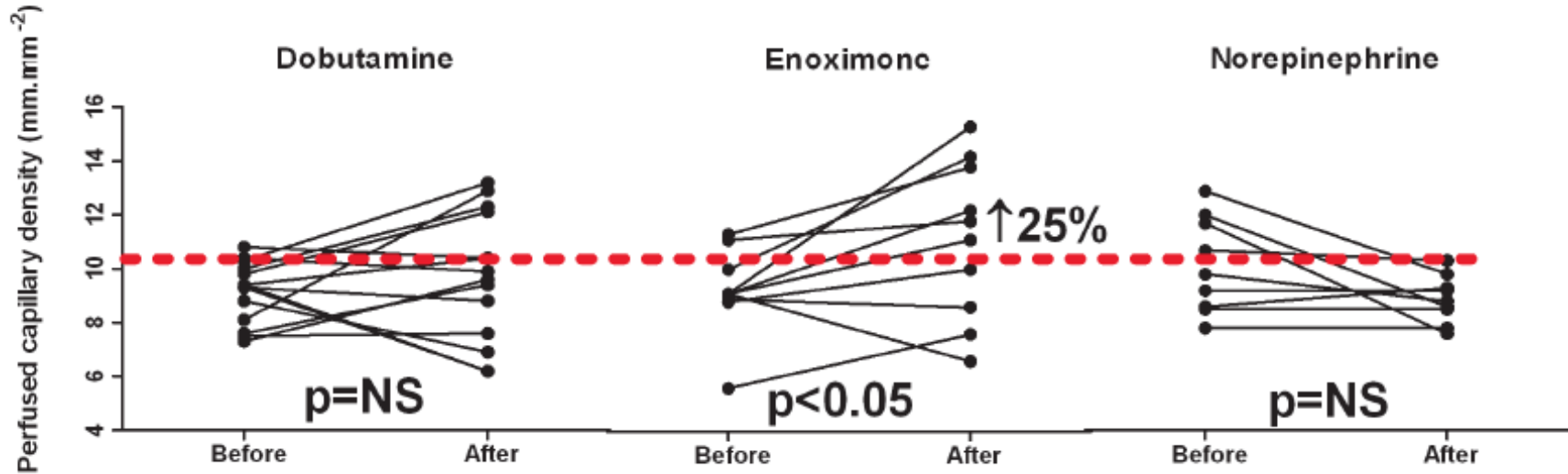
Survival stratified according to quartile of baseline sublingual PCD

Vasoactive Drugs in CS: Why Have We Failed?

	Dobutamine (n = 14)	Enoximone (n = 10)	Norepinephrine (n = 9)	P-value
HR, bpm	84 [59–99]	91 [78–107]	101 [84–118]	NS
MAP, mmHg	66 [60–71]	68 [62–81]	55 [51–58]	0.006
CVP, mmHg	14 [11–17]	14 [9–16]	16 [12–19]	NS
PCWP, mmHg	19 [16–25]	23 [17–25]	20 [17–27]	NS
MPAP, mmHg ^a	27 [21–33]	33 [28–37]	28 [25–39]	NS
CI, L.min ⁻¹ .m ⁻²	2.2 [1.7–2.5]	1.9 [1.7–3.2]	2.6 [1.6–3.2]	NS
SVR, dynes.sec.cm ⁻⁵	1182 [743–1502]	1057 [843–1246]	837 [555–1031]	NS
SvO ₂ , %	64 [60–68]	62 [56–71]	67 [61–70]	NS
Lactate, mmol.L ⁻¹	1.4 [1.1–4.6]	1.3 [1.1–2.9]	2.1 [1.1–2.8]	NS
Delta-T, °C	6.6 [4.5–6.9]	6.1 [4.3–7.5]	6.2 [3.7–13.9]	NS
PCD, mm.mm ⁻²	9.3 [8.0–10.1]	9.1 [8.9–10.2]	9.8 [8.6–11.9]	NS

30 CS patients (baseline parameters)

Vasoactive Drugs in CS: Why Have We Failed?



Changes in perfused capillary density for individual patients

Vasoactive Drugs in CS: Why Have We Failed?

Effects on Parameters of Macro- and Microcirculation

	Dobutamine (n = 14)	Enoximone (n = 10)	Norepinephrine (n = 9)	P-value
Δ HR, bpm	+9 [0; +16]**	+4 [-11; +9]	+1 [-15; +4]	NS
Δ MAP, mmHg	+6 [-5; +21]	+8 [+1; +14]	+17 [+13; +32]**	NS
Δ CVP, mmHg	-1 [-3; +1]	-2 [-3; -1]*	+2 [-4; +4]	NS
Δ PCWP, mmHg	-2 [-4; -1]**	-2 [-3; -1]**	+5 [-1; +7]	NS
Δ MPAP, mmHg ^a	0 [-3; +3]	-1 [-9; 0]	+4 [-1; +7]	NS
Δ CI, L.min ⁻¹ .m ⁻²	+0.8 [+0.3; +1.4]**	+0.6 [-0.1; +1.5]	0.0 [-0.5; +0.1]	0.006
Δ SVR, dynes.sec.cm ⁻⁵	-201 [-623; +220]	-119 [-491; +175]	+390 [+237; +505]*	0.03
Δ SvO ₂ , %	+6 [+2; +12]**	0 [-3; +4]	0 [-3; +6]	0.04
Δ Lactate, mmol.L ⁻¹	-0.4 [-2.5; -0.1]**	0.0 [-0.6; +0.2]	0.0 [-0.2; +0.5]	NS
Δ Delta-T, °C	-0.4 [-0.8; 0]	-1.1 [-1.9; +0.6]	0.0 [-2.2; +0.6]	NS
Δ PCD, mm.mm ⁻²	+0.6 [-0.9; +2.3]	+2.0 [+0.5; +3.4]*	-0.4 [-3.3; 0.0]	0.01

Take Home Messages

- When?
 - Only if symptoms and signs of congestion and hypoperfusion are present
 - As soon as possible
 - Treatment with inotropes frequently in combination with a vasopressor is the standard of care in patients with CS
- Which?
 - No RCT demonstrating clear clinical benefit for any drug
 - Inotrope of choice based on local expertise. Dobutamine is most frequently used
 - Accumulating evidence showing noradrenaline should be the vasopressor of choice over dopamine and adrenaline
- How long?
 - Use the lowest dose able to achieve desired targets (resolution of hypoperfusion and end organ damage) and for the shortest possible time





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Levosimendan: SURVIVE Trial

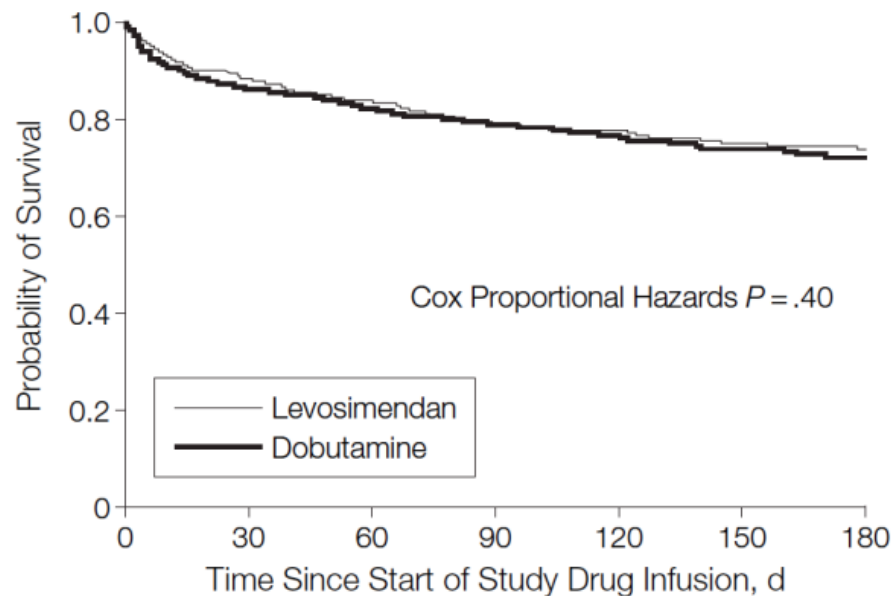
ORIGINAL CONTRIBUTION

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

- ▶ Randomized, double-blind trial comparing levosimendan versus dobutamine
- ▶ 1327 AHF patients with LVEF <30%, insufficient response to iv diuretics and: dyspnoea at rest or mechanical ventilation, oliguria, PCWP > 18 mmHg and/or CI <2.2 L/min/m²
- ▶ Very sick cardiogenic shock patients excluded

Levosimendan: SURVIVE Trial



No. at Risk					
Levosimendan	664	608	586	525	462
Dobutamine	663	596	568	519	454

Levosimendan: REVIVE Trial

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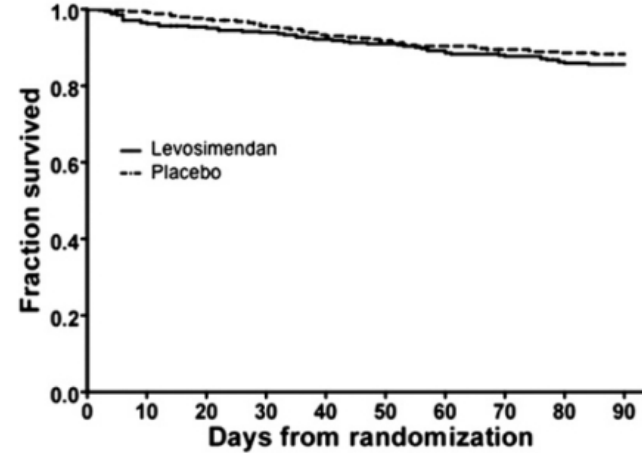
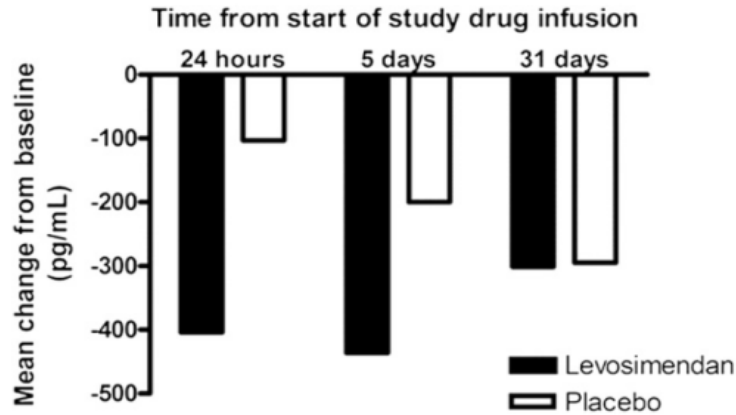
CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

Milton Packer, MD,* Wilson Colucci, MD,† Lloyd Fisher, PhD,‡ Barry M. Massie, MD,§
John R. Teerlink, MD,§ James Young, MD,|| Robert J. Padley, MD,¶ Roopal Thakkar, MD,¶
Leticia Delgado-Herrera, RPh,¶ Jeffrey Salon, MD,¶ Chris Garratt, MB, ChB,# Bidan Huang, PhD,¶
Toni Sarapohja, MSc,# for the REVIVE Heart Failure Study Group
*Dallas, Texas; Boston, Massachusetts; Seattle, Washington; San Francisco, California; Cleveland, Ohio;
Abbott Park, Illinois; and Espoo, Finland*

- ▶ Randomized, double-blind trial comparing levosimendan vs placebo (inclusion 2001-2004, published 2013)
- ▶ 600 AHF patients with LVEF <35% (CS excluded)
- ▶ Primary end-point changes in clinical status during first 5 days

Levosimendan: REVIVE Trial

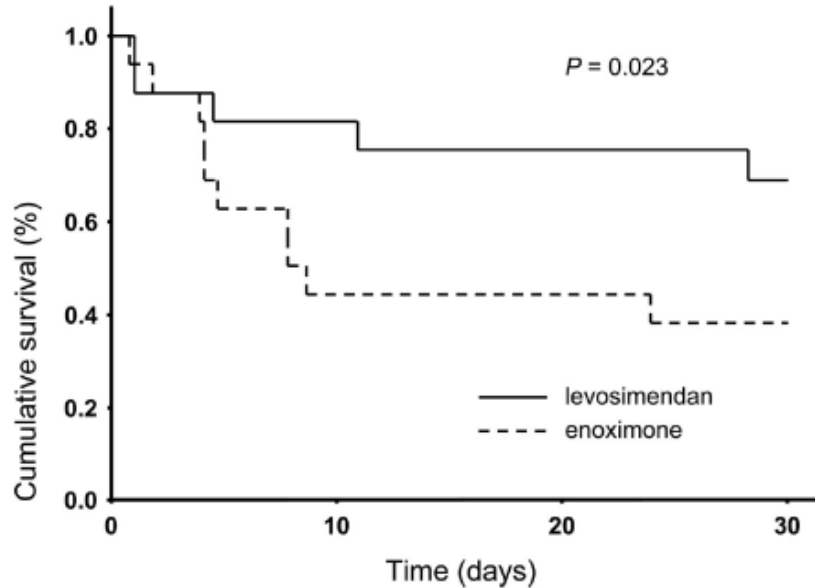


Placebo	349	344	336	328	320	313	307	303	299	295
Levosimendan	348	333	326	322	314	309	302	298	291	287

- ▶ Significant benefit in favour of levosimendan for primary end-point but increased risk of adverse cardiovascular events
- ▶ Significant drop in BNP but no effect on mortality

Levosimendan in Cardiogenic Shock

Small (32 patients), single center, open label, randomized trial



Number of deaths

