

# The evidence for the use of vasoactive agent in critically ill patients

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UNSW





### The Nobel Prize in Physiology or Medicine 1936

"for their discoveries relating to chemical transmission of nerve impulses"



Sir Henry Hallett Dale



Otto Loewi



### The Nobel Prize in Physiology or Medicine 1950

"for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"



Edward Calvin Kendall



Tadeus Reichstein



Philip Showalter Hench



### The Nobel Prize in Physiology or Medicine 1970

"for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation"



Sir Bernard Katz



Ulf von Euler



Julius Axelrod



### The Nobel Prize in Physiology or Medicine 1994

"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"



Alfred G. Gilman



Martin Rodbell

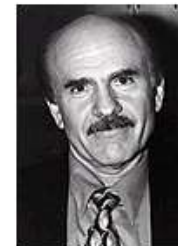


### The Nobel Prize in Physiology or Medicine 1998

"for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system"



Robert F. Furchgott

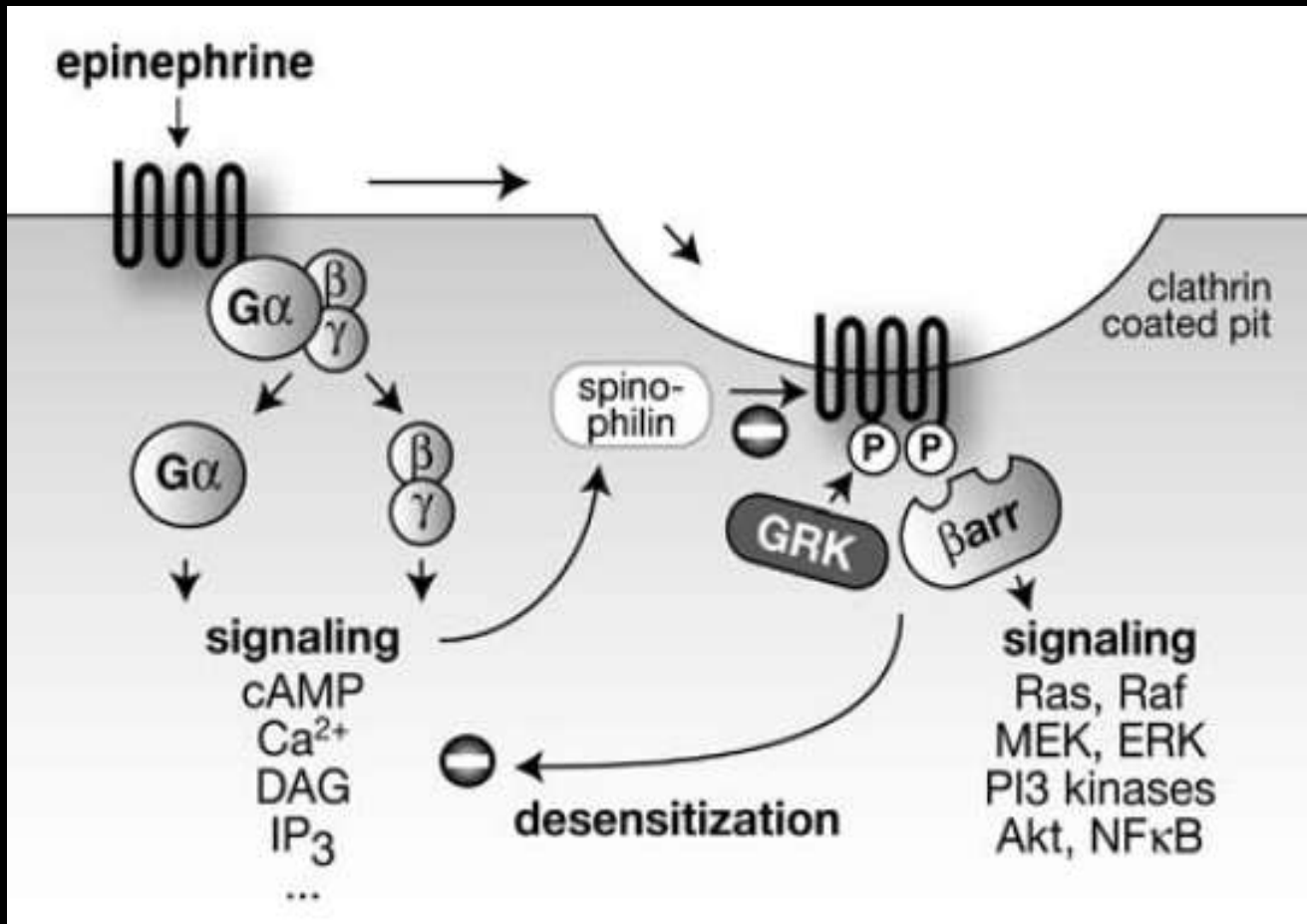


Louis J. Ignarro

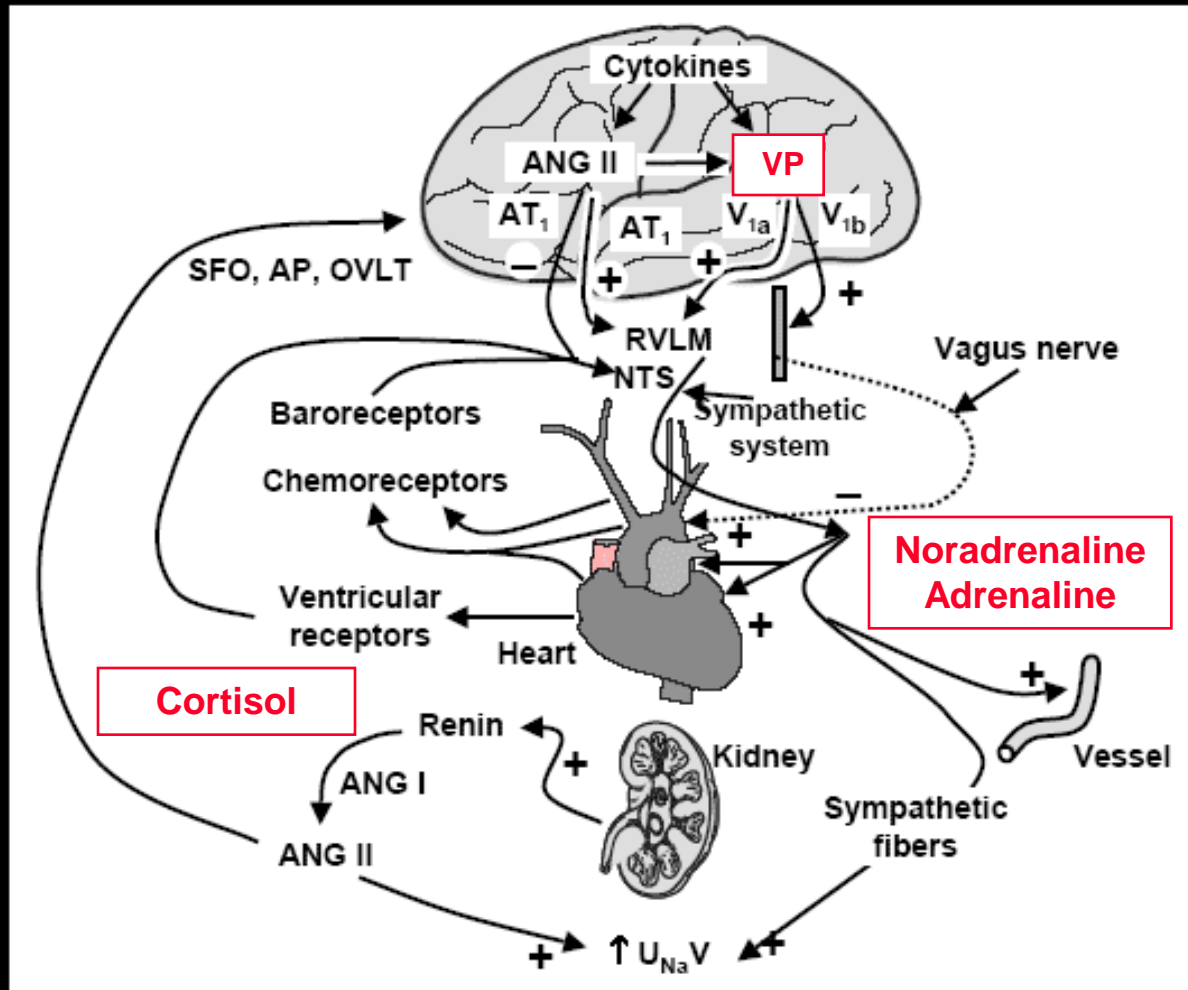


Ferid Murad

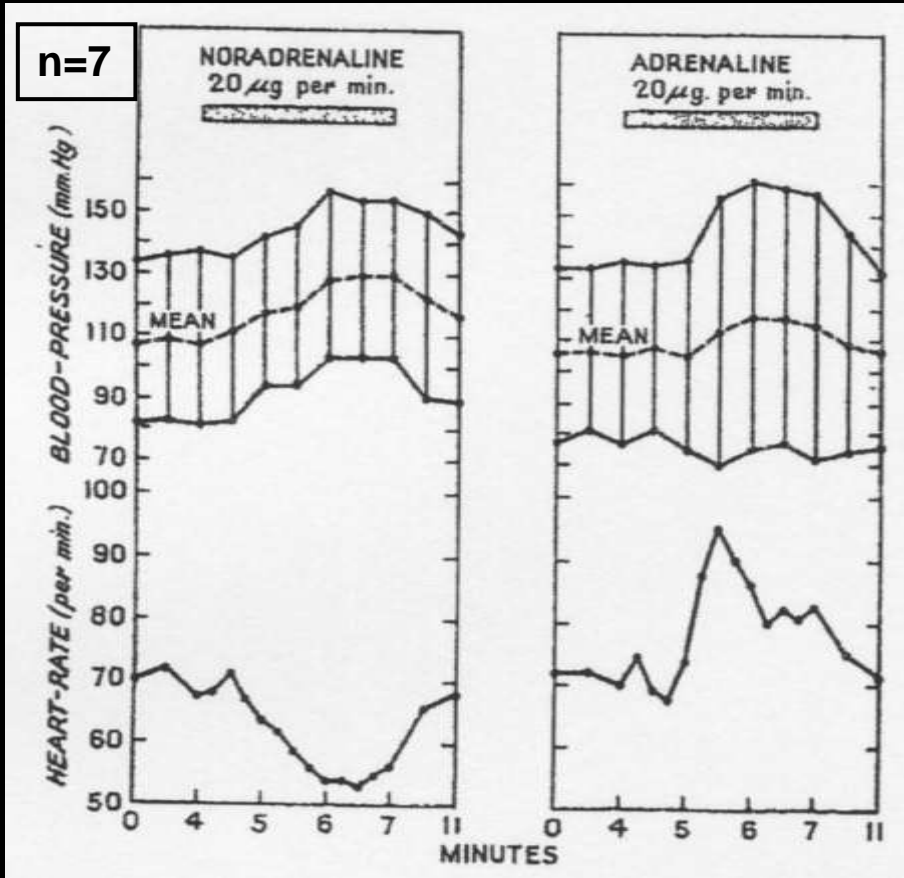
# Neurohormonal vasoregulation



# Neurohormonal vasoregulation



# Human studies



	EPINEPH- RINE	NOREPINEPH- RINE
<i>Cardiac</i>		
Heart rate	+	- †
Stroke volume	++	++
Cardiac output	+++	0,-
Arrhythmias	++++	++++
Coronary blood flow	++	++
<i>Blood Pressure</i>		
Systolic arterial	+++	+++
Mean arterial	+	++
Diastolic arterial	+0,-	++
Mean pulmonary	++	++
<i>Peripheral Circulation</i>		
Total peripheral resistance	-	++
Cerebral blood flow	+	0,-
Muscle blood flow	+++	0,-
Cutaneous blood flow	--	--
Renal blood flow	-	-
Splanchnic blood flow	+++	0,+
<i>Metabolic Effects</i>		
Oxygen consumption	++	0,+
Blood glucose	+++	0,+
Blood lactic acid	+++	0,+
Eosinopenic response	+	0
<i>Central Nervous System</i>		
Respiration	+	+
Subjective sensations	+	+

\* 0.1 to 0.4 µg/kg/min  
 + = increase; 0 = no change; -- = decrease; † = after atropine.

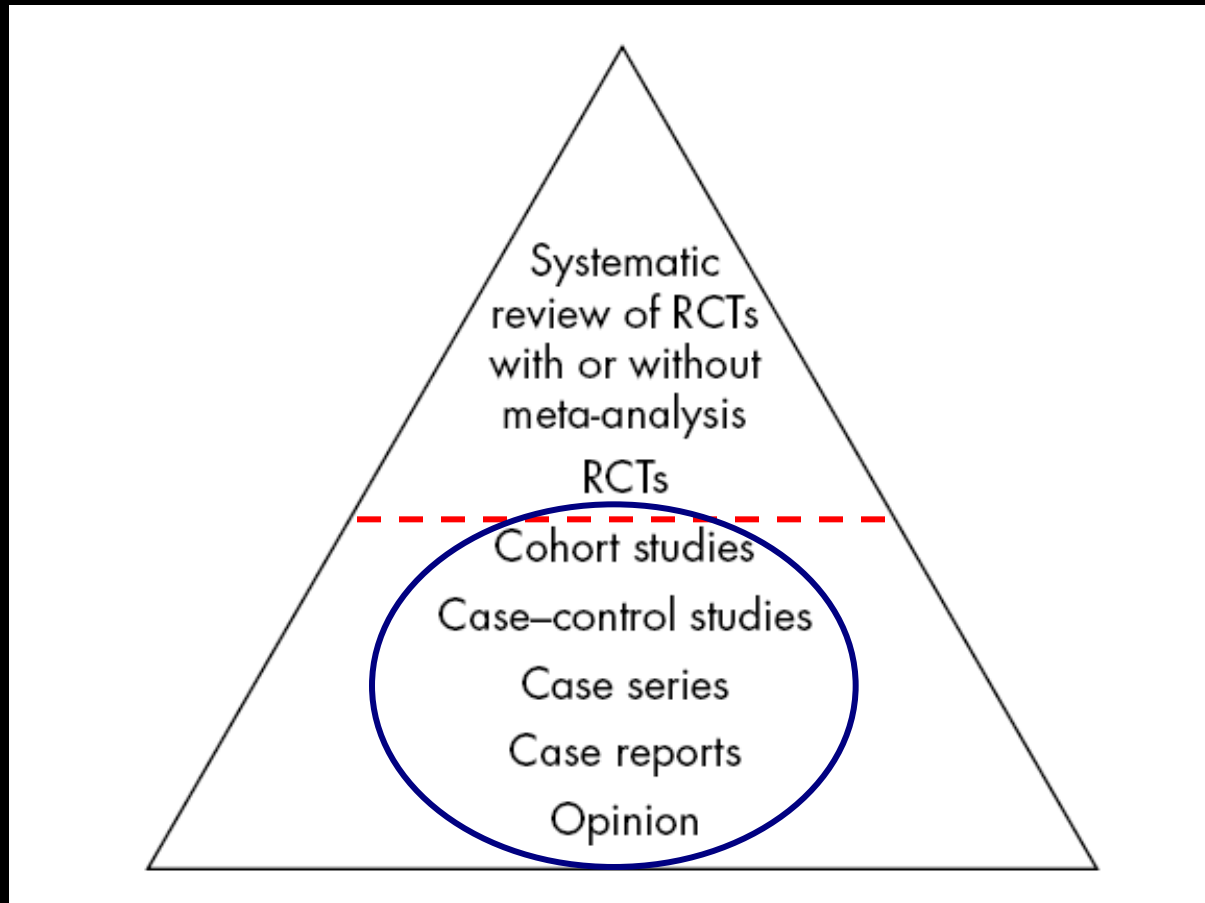
# What the textbooks say .....

**Table 1. Summary of catecholamine specificity and actions via adrenergic receptors**

Catecholamine	Receptor activity	Site of action	Effect
Epinephrine	Alpha <sub>1/2</sub> +++	Vascular smooth muscle	Vasoconstriction
	Beta <sub>1</sub> +++	Heart	Tachycardia/^ contractility
	Beta <sub>2</sub> ++	Vascular smooth muscle	Vasodilation
Norepinephrine	Alpha <sub>1</sub> +++	Vascular smooth muscle	Vasoconstriction
	Alpha <sub>2</sub> ++	Vascular smooth muscle	Vasoconstriction
	Beta <sub>1</sub> ++	Heart	Tachycardia/^ contractility
Dopamine	Alpha <sub>1/2</sub> +++	Vascular smooth muscle	Vasoconstriction
	Beta <sub>1</sub> +++	Heart	Tachycardia/^ contractility
	Beta <sub>2</sub> ++	Vascular smooth muscle	Vasodilation
Dobutamine	Alpha <sub>1/2</sub> +	Vascular smooth muscle	Vasoconstriction
	Beta <sub>1</sub> +++	Heart	Tachycardia/^ contractility
	Beta <sub>2</sub> ++	Vascular smooth muscle	Vasodilation
Dopexamine	Beta <sub>1</sub> +	Heart	Tachycardia/^ contractility
	Beta <sub>2</sub> +++	Vascular smooth muscle	Vasodilation
Phenylephrine	Alpha <sub>1</sub> +++	Vascular smooth muscle	Vasoconstriction

+ Mild receptor activation; ++ moderate receptor activation; +++ strong receptor activation.

# What is “best” evidence?



# Synthetic catecholamines



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produkter > Dobutrex®

Dobutrex | PatientFAS5

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**elan**

## Dopexamine Dopacard®

Catécholamine de synthèse, analogue structurel de la dopamine.

# Cost

	Dose	Cost (AUD)
Adrenaline	6 mg	11
Noradrenaline	6mg	20
Dopamine	400mg	37
Dobutamine	500mg	119
Dopexamine	50mg	390
Isoprenaline	6mg	410
Milrinone	8mg	500
Levosimendan	12.5mg	1420

# Dobutamine and sepsis

	n	Dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	Endpoint	Mortality	Grade
Hayes 1994	100	5-200	DO <sub>2</sub> , VO <sub>2</sub>	34 v 54*	III
Yu 1993	67	5-20	DO <sub>2</sub> , VO <sub>2</sub>	34 v 44	III
Tuschmidt 1992	51	5 +	DO <sub>2</sub> , VO <sub>2</sub>	59 v 72%	IV
Shoemaker 1986	10	5 – 10 +	DO <sub>2</sub> , VO <sub>2</sub>	Not stated	IV
Shoemaker 1989	25	2.5-10	DO <sub>2</sub> , VO <sub>2</sub>	Not stated	IV
Shoemaker 1991	12	2.5- 10	DO <sub>2</sub> , VO <sub>2</sub>	Not stated	IV
Tell 1987	6	2.5-20	SBP, UO	50%	IV
Krachman 1994	12	5 +	DO <sub>2</sub> , VO <sub>2</sub>	100%	IV
Lejus 1991	10	5-15	PAOP, MAP	50%	IV
Jardin 1981	19	3.6-28	DO <sub>2</sub> , VO <sub>2</sub>	Not stated	IV
Vincent 1990	84	5	DO <sub>2</sub> , VO <sub>2</sub>	Not stated	IV

(11)

396

# Catecholamines and septic shock

	n	Drug	Dose	Endpoint	Grade
Duranteau 1999	12	Adr ± Nor	MAP >80	pHi	III
Joly 1999	14	Dob	7.5 µg/kg/min	pHi, CO	IV
Levy 1999	24	Dob ± Dpx	5 / 1 µg/kg/min	pHi, CO	III
Reinelt 1999	6	Phenyleph	MAP > 60	PHi	IV
Martin 1999	26	Dob ± Nor	MAP >75	CO, SVR, MAP	III
Rhodes 1999	36	Dob	10 µg/kg/min	Mortality pred	IV
Creteur 1999	36	Dob	5 + 10 µg/kg/min	pHi, CO	III
Briegel 2000	40	Dob/Nor/Adr	Shock resolution	Requirement	III
<b>(8)</b>	<b>194</b>				

# Human trials

No conclusive evidence  
Descriptive, observational, underpowered  
Variable dose ranges, selection criteria  
Variable endpoints  
Variable mortality  
“Oxygen delivery” focus  
Commercial influence  
Publication bias

Misapplication of biological principles

# Evidence-based guidelines

## Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

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Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

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## Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

# “Inotropes”

## *Initial resuscitation (first 6 hrs)*

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate  $>4$  mmol/L; do not delay pending ICU admission (1C)
- Resuscitation goals (1C)
  - CVP 8–12 mm Hg<sup>a</sup>
  - Mean arterial pressure  $\geq 65$  mm Hg
  - Urine output  $\geq 0.5$  mL·kg<sup>-1</sup>·hr<sup>-1</sup>
  - Central venous (superior vena cava) oxygen saturation  $\geq 70\%$  or mixed venous  $\geq 65\%$
- If venous oxygen saturation target is not achieved (2C)
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit of  $\geq 30\%$  and/or
  - Start dobutamine infusion, maximum  $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$

## *Inotropic therapy*

- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)

# “Vasopressors”

## *Vasopressors*

- Maintain MAP  $\geq$ 65 mm Hg (1C)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)
- Do not use low-dose dopamine for renal protection (1A)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone

Biologically plausible, but unrelated to the evidence presented

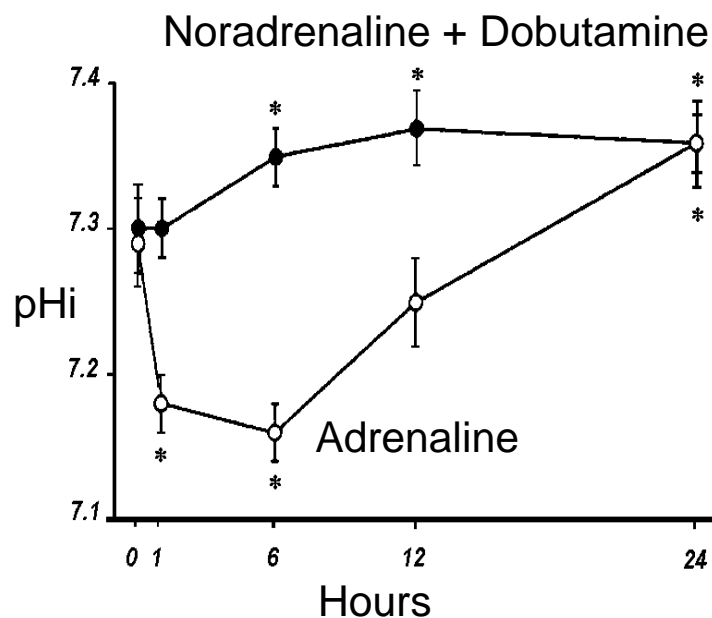
Publication bias

Intervention bias

Regional bias

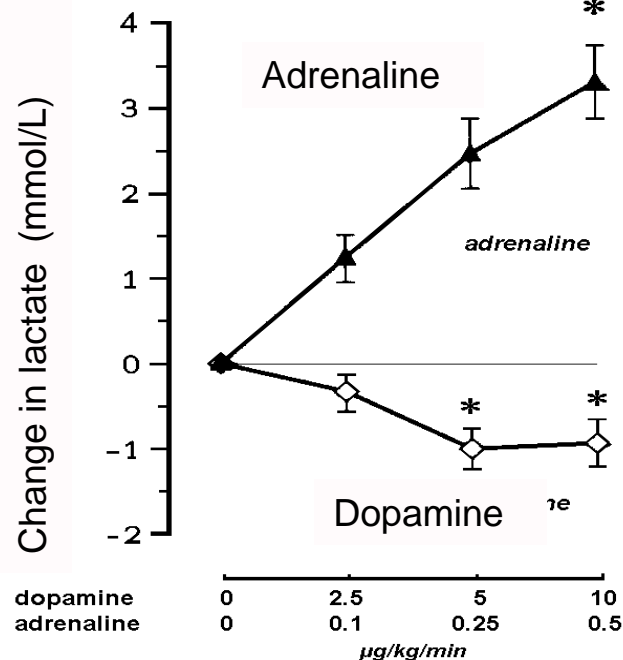
Adrenaline gets a “bad” wrap

# Adrenaline "toxicity"?



Splanchnic ischaemia

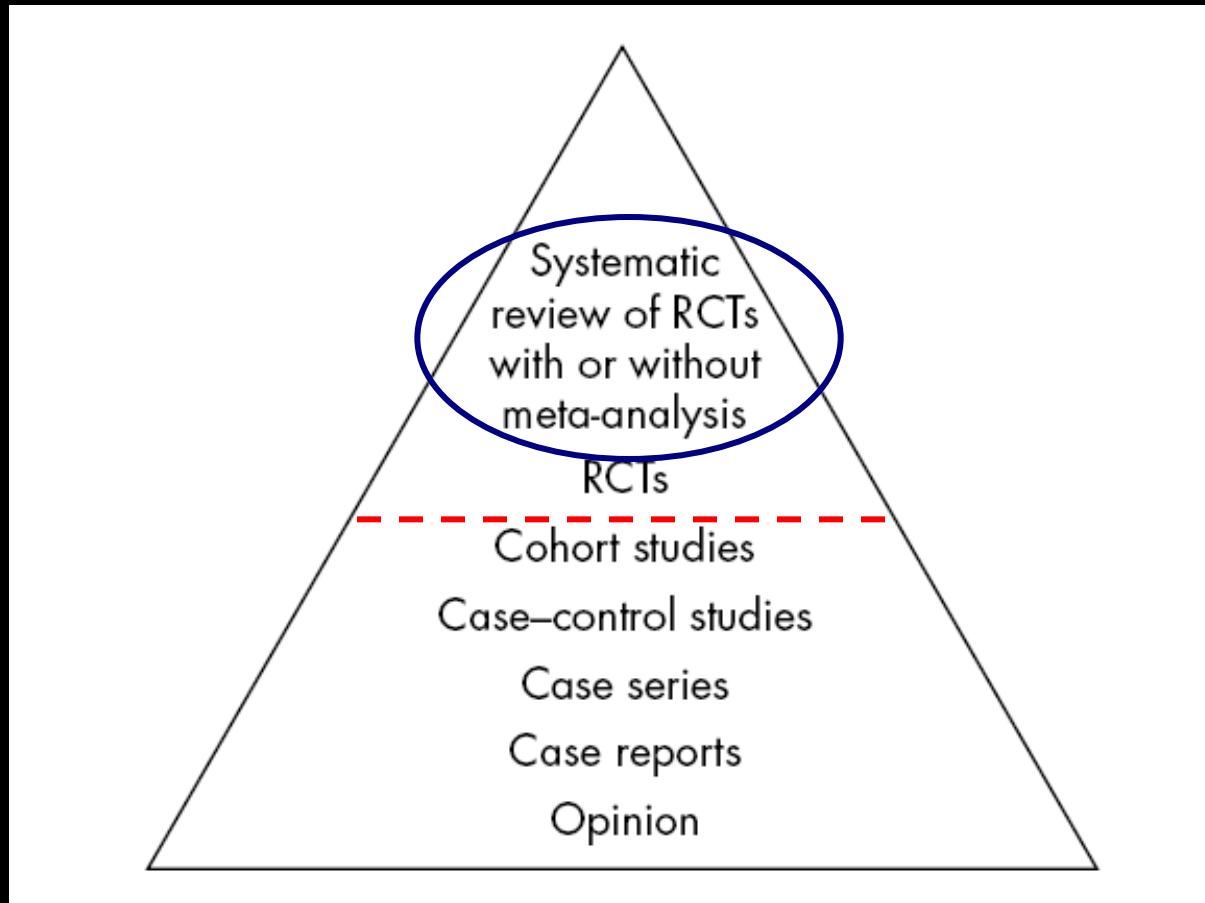
Levy: ICM 1997



Lactic acidosis

Day: Lancet 1996

# What is “best” evidence?



WHAT HAVE YOU  
LEARNT FROM  
THE COCHRANE  
COLLABORATION?

LIFE IS  
FULL OF  
TRIALS



# Vasopressors for shock (Review)

Müllner M, Urbanek B, Havel C, Losert H, Waechter F, Gamper G



**THE COCHRANE  
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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 1

<http://www.thecochranelibrary.com>

# Systematic review

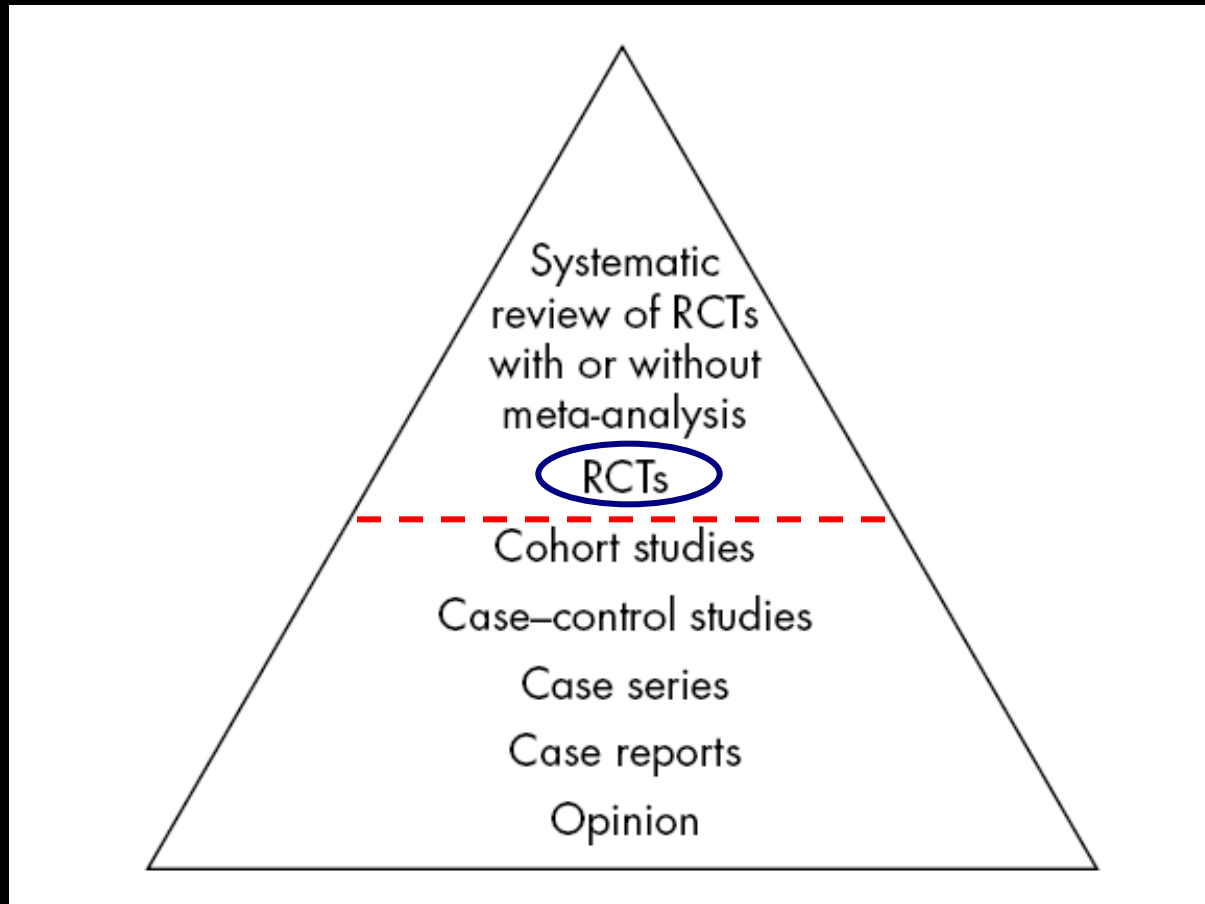
<b>Intervention</b>	<b>n</b>	<b>RR</b>	<b>95%CI</b>
NOR + DOB vs ADR	52	0.98	0.57 to 1.67
NOR vs DOP	62	0.88	0.57 to 1.36
VSP vs placebo	58	1.04	0.06 to 19.33

**114/172**

## Authors' conclusions

The current available evidence is not suited to inform clinical practice. We were unable to determine whether a particular vasopressor is superior to other agents in the treatment of states of shock.

# What is “best” evidence?





John A. Myburgh  
Alisa Higgins  
Alina Jovanovska  
Jeffrey Lipman  
Naresh Ramakrishnan  
John Santamaria  
the CAT Study investigators

## A comparison of epinephrine and norepinephrine in critically ill patients

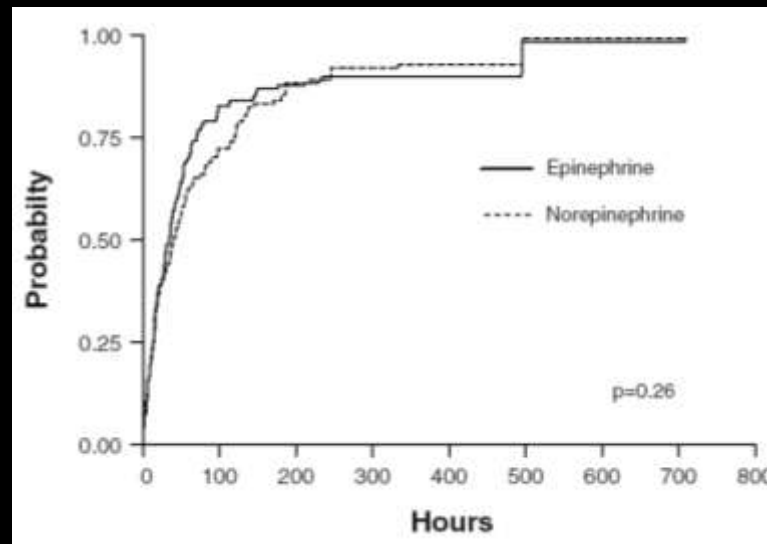
2004-2006

Relative effectiveness blinded MC RCT

n=280

Primary outcome: Clinician-prescribed target MAP > 24 hours

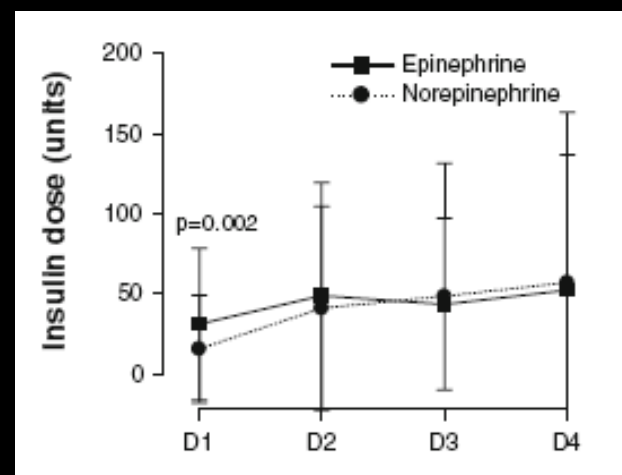
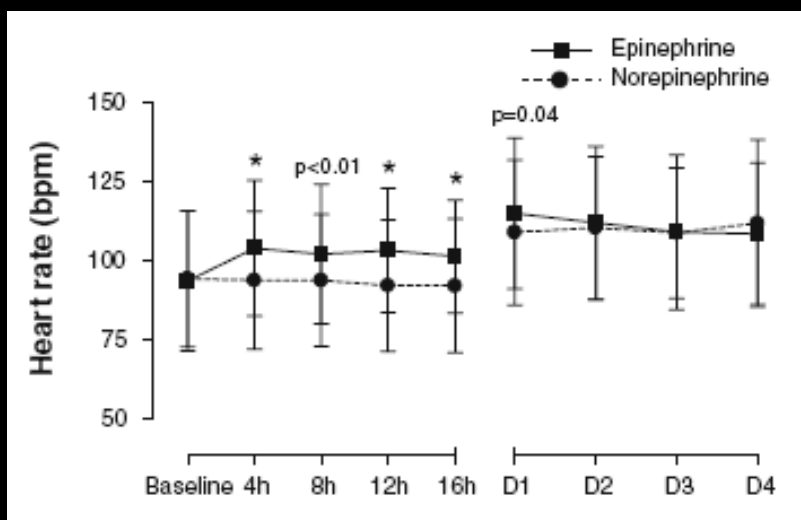
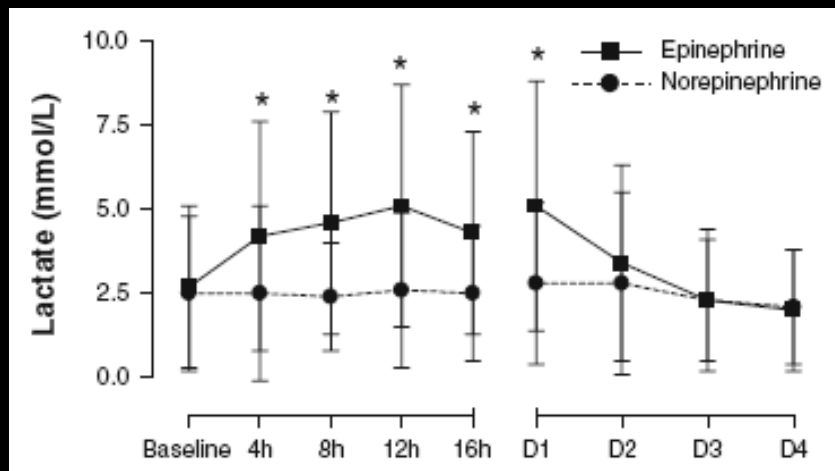
All patients	Epinephrine	Norepinephrine	Hazard ratio	95% CI	P
Time to achievement of MAP goal (h)	35.1 (13.8–70.4)	40.0 (14.5–120)	0.88	0.69–1.12	0.26
Day 28 mortality	31/138 (22.5)	36/138 (26.1)	0.86	0.57–1.31	0.48
Day 90 mortality	41/135 (30.4)	46/134 (34.3)	0.88	0.63–1.25	0.49

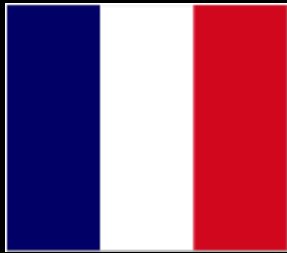




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the CAT Study investigators

# A comparison of epinephrine and norepinephrine in critically ill patients





# Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

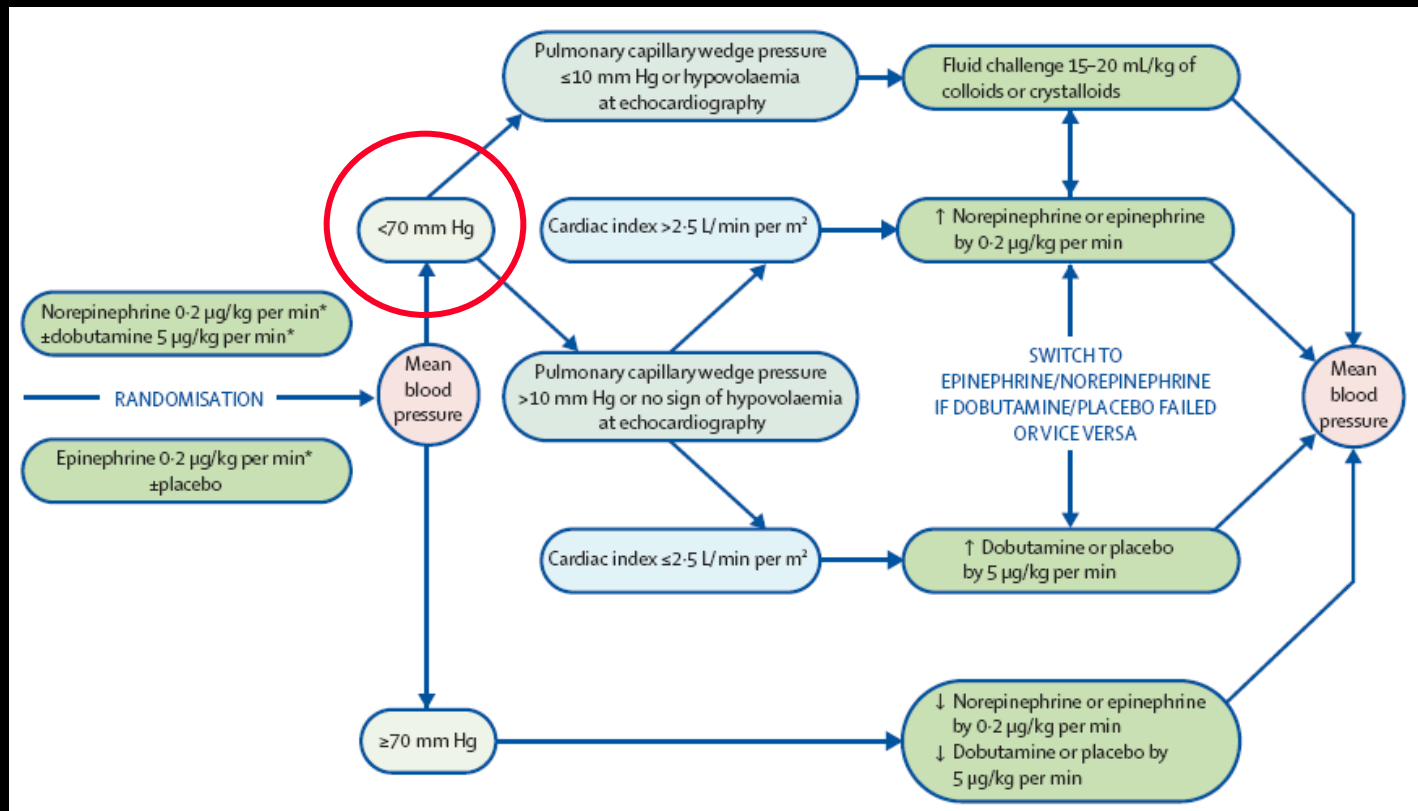
Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group\*

1999-2004

Blinded MC RCT

n=330

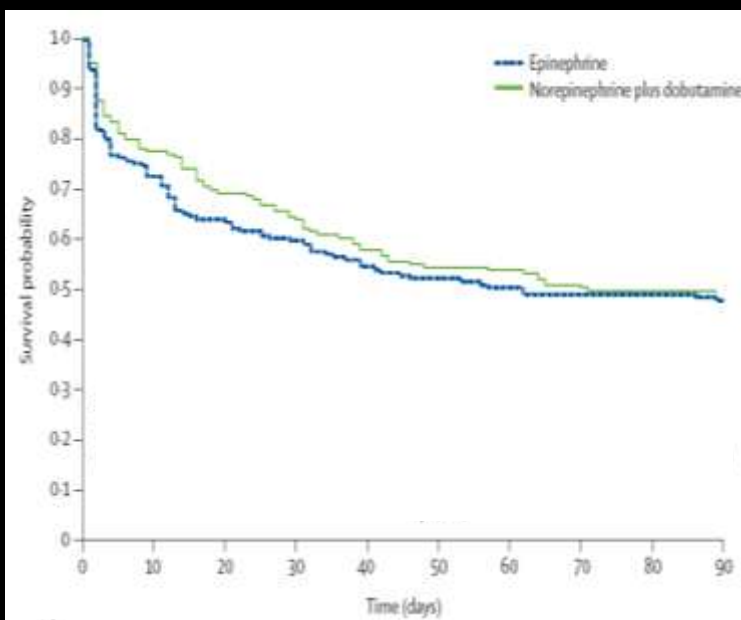
Primary outcome: D28 mortality



# Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group\*

	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)	p
At day 7	40 (25%)	34 (20%)	0.30
At day 14	56 (35%)	44 (26%)	0.08
At day 28	64 (40%)	58 (34%)	0.31
At discharge from intensive care	75 (47%)	75 (44%)	0.69
At discharge from hospital	84 (52%)	82 (49%)	0.51
At day 90	84 (52%)	85 (50%)	0.73



**No difference in secondary outcome measures:**

Haemodynamic endpoints

Dose of drug(s)

Organ failure resolution

ICU LOS

**Epinephrine associated with lactic acidosis**



# Comparison of Dopamine and Norepinephrine in the Treatment of Shock

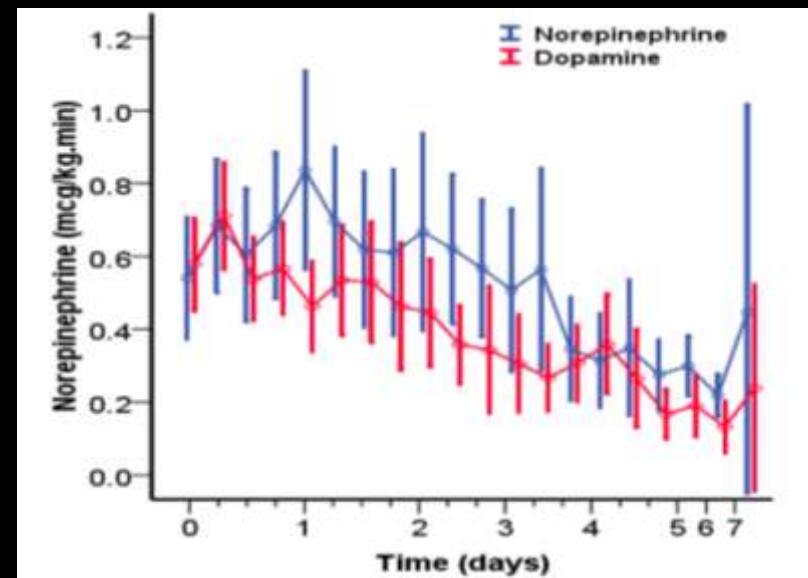
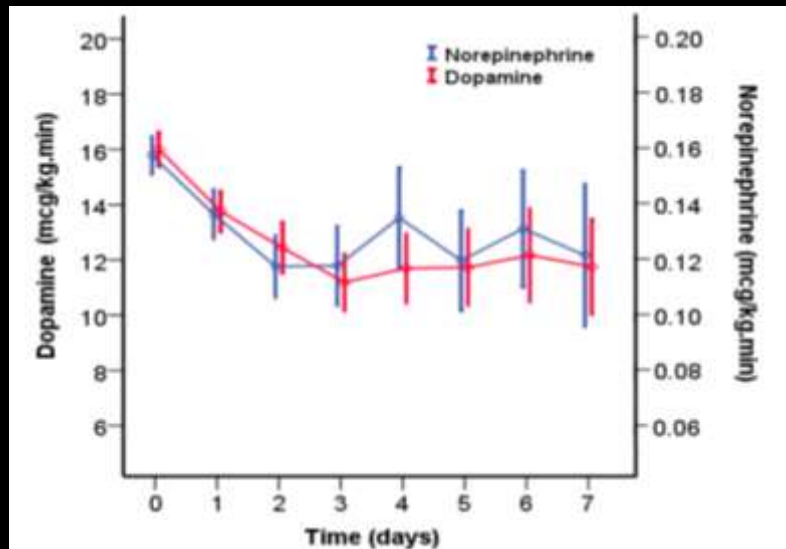
Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators\*

2003-2007

Blinded M RCT

n=1679

Primary outcome: 28d mortality  
15% RRR from 40% mortality



**Trial drug**

Dopamine n=858

Norepinephrine n=821

**Open label norepinephrine:**

20µg/kg/min dopamine – 18.3%

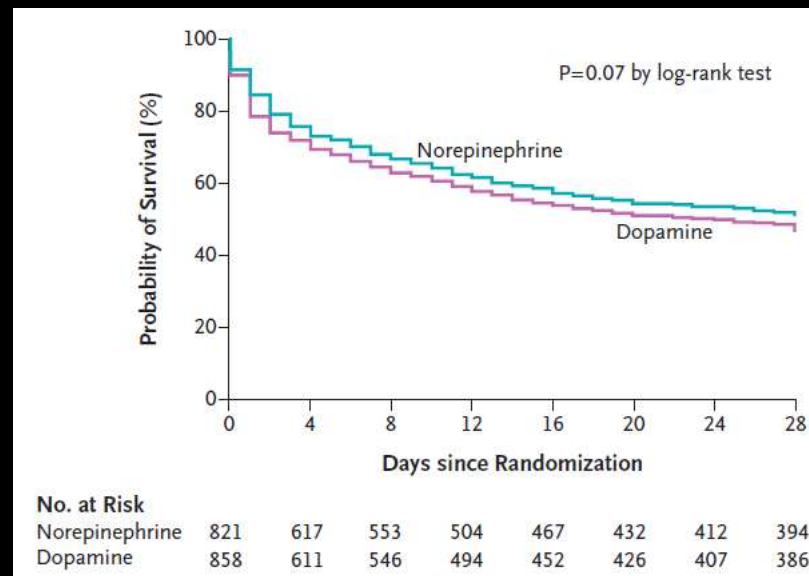
0.19 µg/kg/min norepinephrine – 13.0%



# Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators\*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI) <sup>†</sup>	P Value
	<i>percent mortality</i>			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34



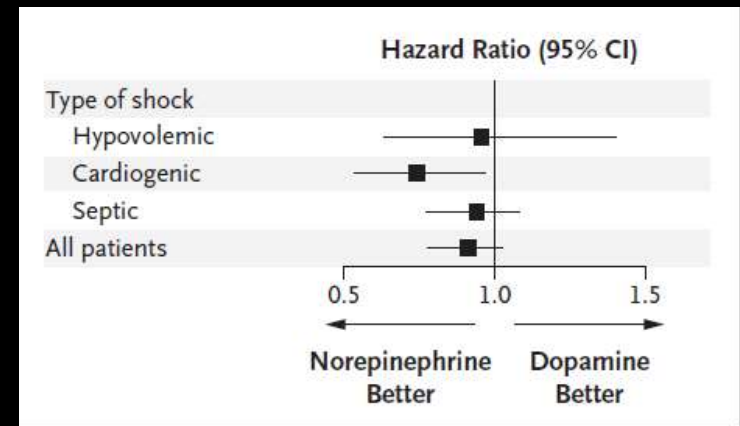


# Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	
Myocardial infarction — no. (%)	19 (2.2)	25 (3.0)	0.29
New infectious episode			0.69
No. of episodes			
Median	1	1	
Interquartile range	0–1	0–1	
Patients with at least one episode — no. (%)	674 (78.6)	619 (75.4)	0.35
Skin ischemia — no. (%)	56 (6.5)	34 (4.1)	0.09
Mild‡	46 (5.4)	28 (3.4)	
Severe‡	10 (1.2)	6 (0.7)	
Arterial occlusion — no. (%)§	23 (2.7)	20 (2.4)	0.12
Arms or fingers	5 (0.6)	1 (0.1)	
Legs	7 (0.8)	13 (1.6)	
Bowel	11 (1.3)	6 (0.7)	

## Adverse events



## A priori subgroups

Septic 62.1%  
 Cardiogenic 16.7%  
 Hypovolaemic 15.6%



# Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators\*

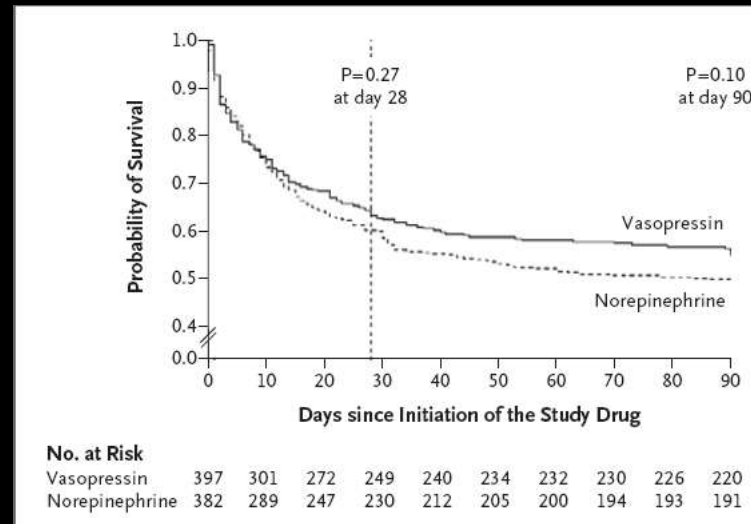
Blinded MC RCT

n=779

Primary outcome: 28d mortality

10% ARR from 60% mortality

Vasopressin (max 0.03 u/min) vs noradrenaline (5-15µg/min)

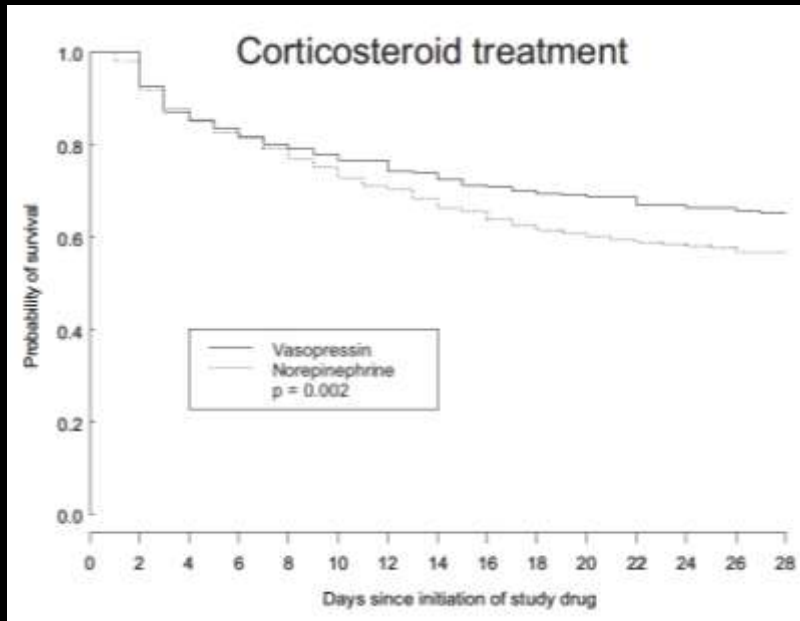


Stratum	Norepinephrine Group no./total no. (%)	Vasopressin Group no./total no. (%)	P Value†	Absolute Risk Reduction (95% CI) %	Relative Risk (95% CI)
More severe septic shock					
28-day mortality	85/200 (42.5)	88/200 (44.0)	0.76	-1.5 (-11.2 to 8.2)	1.04 (0.83 to 1.3)
90-day mortality	105/199 (52.8)	103/199 (51.8)	0.84	1.0 (-8.8 to 10.8)	0.98 (0.81 to 1.18)
Less severe septic shock					
28-day mortality	65/182 (35.7)	52/196 (26.5)	0.05	9.2 (-0.1 to 18.5)	0.74 (0.55 to 1.01)
90-day mortality	83/180 (46.1)	69/193 (35.8)	0.04	10.4 (0.4 to 20.3)	0.78 (0.61 to 0.99)

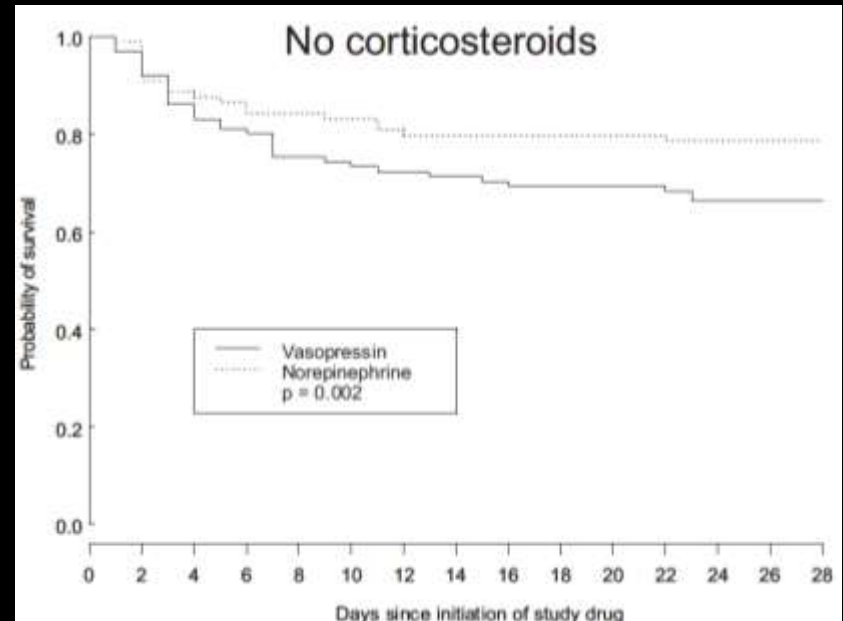


# Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock\*

James A. Russell, MD; Keith R. Walley, MD; Anthony C. Gordon, MB, BS, MD; D. James Cooper, BM, BS, MD; Paul C. Hébert, MD; Joel Singer, PhD, MD; Cheryl L. Holmes, MD; Sangeeta Mehta, MD; John T. Granton, MD; Michelle M. Storms, BScN; Deborah J. Cook, MD; Jeffrey J. Presneill, MB BS, PhD; Dieter Ayers for the Vasopressin and Septic Shock Trial (VASST) Investigators



Norepinephrine 131/293 (44.7%)  
Vasopressin 106/295 (35.9%)  
P=0.03



Norepinephrine 19/89 (21.3%)  
Vasopressin 34/101 (33.7%)  
P=0.06

## Vasopressors for hypotensive shock (Review)

Havel C, Arrich J, Losert H, Gamper G, Müllner M, Herkner H



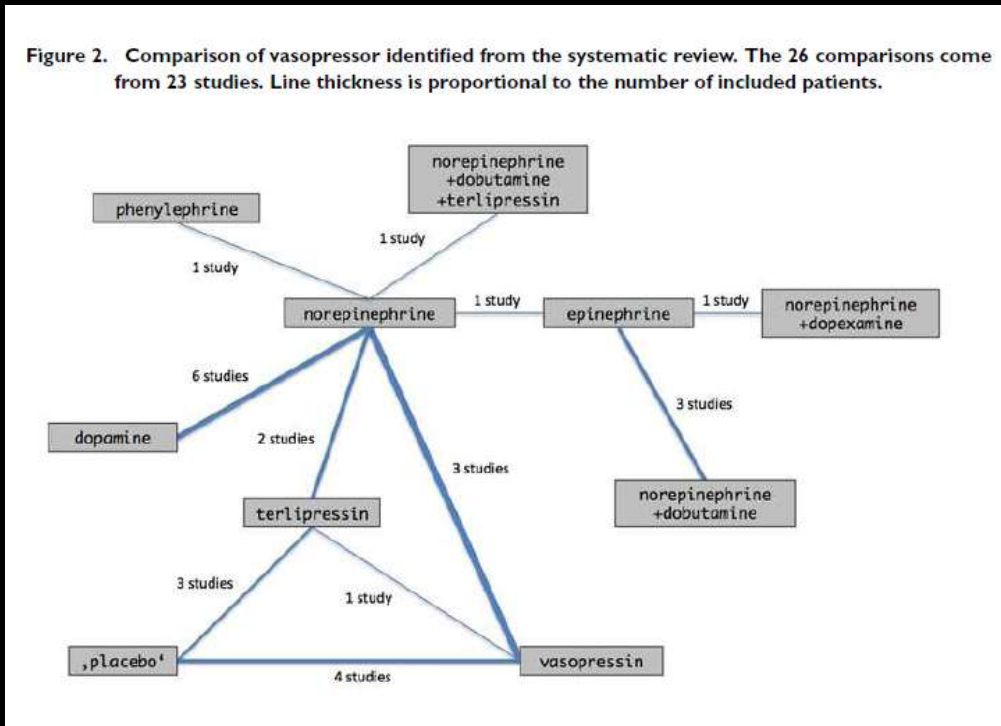
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# Updated systematic review

Additional 17 studies identified: total 23  
 N=3212, 1629 mortality outcomes  
 Sensitivity analysis of 10 studies with low risk of bias



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Explicit in-text inclusion criteria	ITT-analysis	Adequate patient description	Identical care	Outcome description	Physicians blinded	Outcome assessors blinded?
Albanese 2005	?	?	?	?	?	?	?	?	?
Annane 2007	?	?	?	?	?	?	?	?	?
Boccardo 2003	?	?	?	?	?	?	?	?	?
Choong 2008	?	?	?	?	?	?	?	?	?
De Backer 2010	?	?	?	?	?	?	?	?	?
Dünser 2003	?	?	?	?	?	?	?	?	?
Lauzier 2006	?	?	?	?	?	?	?	?	?
Lewy 1997	?	?	?	?	?	?	?	?	?
Luckner 2006	?	?	?	?	?	?	?	?	?
Malay 1998	?	?	?	?	?	?	?	?	?
Marik 1984	?	?	?	?	?	?	?	?	?
Mathin 1993	?	?	?	?	?	?	?	?	?
Mathur 2007	?	?	?	?	?	?	?	?	?
Morelli 2008a	?	?	?	?	?	?	?	?	?
Morelli 2008b	?	?	?	?	?	?	?	?	?
Morelli 2008	?	?	?	?	?	?	?	?	?
Myburgh 2008	?	?	?	?	?	?	?	?	?
Patel 2010	?	?	?	?	?	?	?	?	?
Ruokonen 1993	?	?	?	?	?	?	?	?	?
Russell 2008	?	?	?	?	?	?	?	?	?
Seguin 2002	?	?	?	?	?	?	?	?	?
Seguin 2006	?	?	?	?	?	?	?	?	?
Yildizdas 2008	?	?	?	?	?	?	?	?	?

# Updated systematic review

In summary, there was no difference in mortality in any of the comparisons between different vasopressors or combinations. More arrhythmias were observed in patients treated with dopamine compared to norepinephrine. Norepinephrine versus dopamine, as the largest comparison in 1400 patients from six trials, yielded almost equivalence (RR 0.95, 95% confidence interval 0.87 to 1.03). Vasopressors used as add-on therapy in comparison to placebo were not effective either. These findings were consistent among the few large studies as well as in studies with different levels of within-study bias risk.

# “Vasopressors” and SSC

## *Vasopressors*

- Maintain MAP  $\geq$ 65 mm Hg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

## On current high quality evidence:

Noradrenaline is the probably vasoactive drug of choice.

Adrenaline is equieffective, with transient metabolic effects

Dopamine associated with adverse effects, particularly arrhythmia

Dobutamine has no demonstrable benefit

Vasopressin has no proven benefit in severe shock

# Non-catecholamine “inodilators”





# The SURVIVE Study

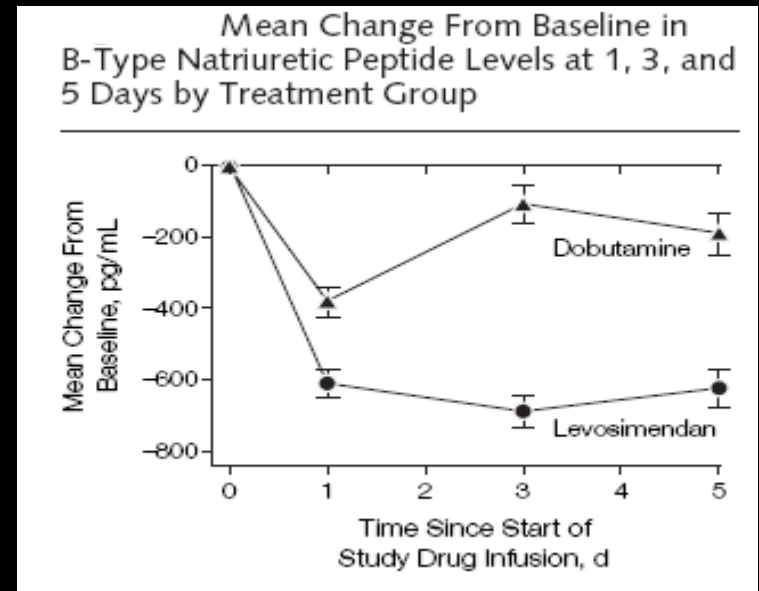
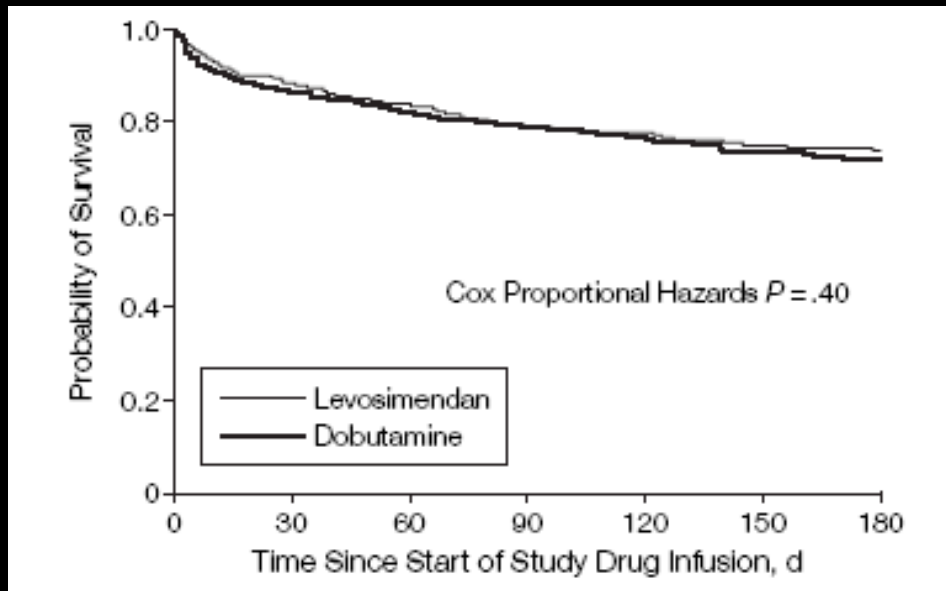
Blinded MC RCT

n=1320

Primary outcome: 180d mortality

Secondary outcome:  $\delta$ BNP

Levosimendan ( $12\mu\text{g}/\text{kg} + 0.1 \mu\text{g}/\text{kg}/\text{min}$ ) x 2 h vs dobutamine ( $5\text{-}40 \mu\text{g}/\text{kg}/\text{min}$ )



# Conclusions

An body of higher-quality, investigator-initiated trials of catecholamines on patient-centred outcomes in critically ill patients is finally emerging.

There is no evidence of superiority of any of the currently used catecholamines, used solely or in combination, over adrenaline or noradrenaline on resolution of shock, development or resolution of organ failure or mortality.

Catecholamine-sparing strategies with vasopressin and corticosteroids have an undefined, unproven role.

# Interpretation

The role of catecholamines for the treatment of shock is evolving from “rescue” therapy to “neurohormonal augmentation” therapy in vulnerable patients.

It is biologically implausible that synthetic catecholamine compounds will produce improvements in patient-centred outcomes.

Current evidence-based guidelines and bundles will need revision to accord with global considerations outside the imperative of industry.

# Adrenaline



"God's own inotrope..."

*When did you last get a notepad like this?!*

Generics Ltd. - we'll market anything!