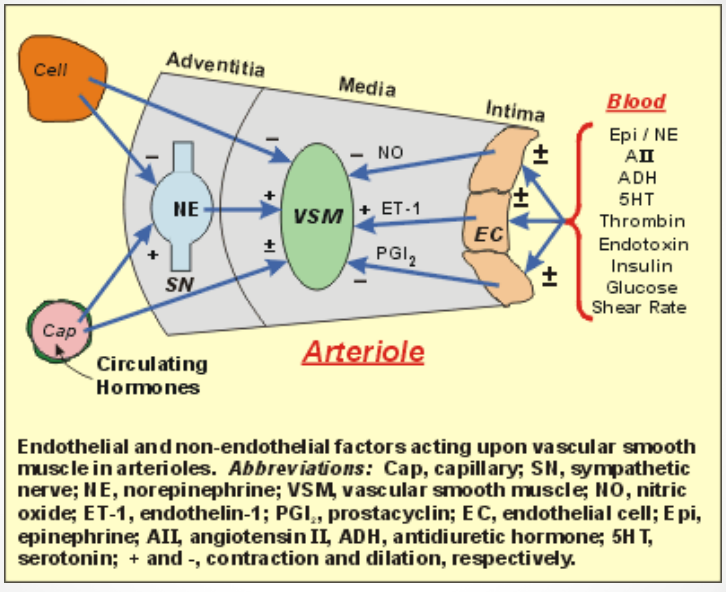
Vasopressor Therapy for Sepsis

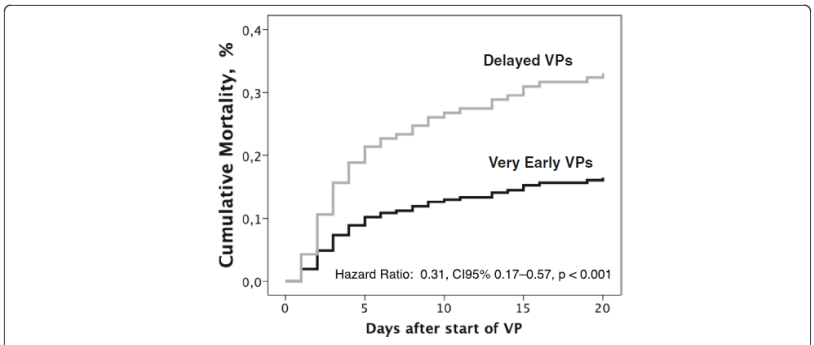
Djillali Annane, MD, PhD
General ICU, Raymond Poincaré Hospital, AP-HP, University of Versailles SQY, Garches, France



Endothelial and non-endothelial factors acting upon vascular smooth muscle in arterioles. *Abbreviations:* Cap, capillary; SN, sympathetic nerve; NE, norepinephrine; VSM, vascular smooth muscle; NO, nitric oxide; ET-1, endothelin-1; PGI_2, prostacyclin; EC, endothelial cell; Epi, epinephrine; AII, angiotensin II, ADH, antidiuretic hormone; 5HT, serotonin; + and -, contraction and dilation, respectively.

Klabunde ebook

Timing



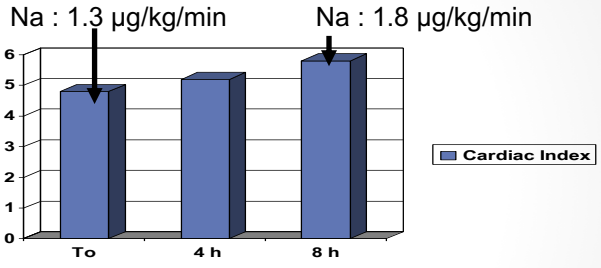
VE-VPs	93	80	78	78	76
D-VPs	93	70	63	57	56

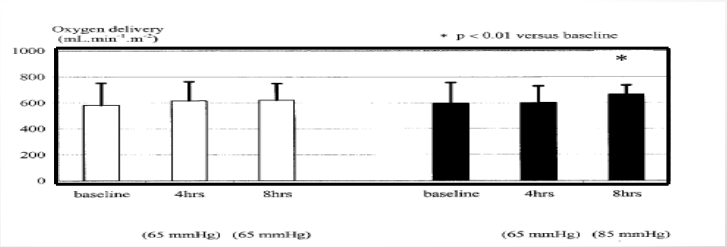
Fig. 2 Cox proportional hazard model for risk of death at day 28 for very early- (VE-VPs) and delayed-vasopressor support (D-VPs). The Cox proportional hazards model was adjusted by SOFA score at day 1, the presence of hyperlactatemia (septic shock according to Sepsis 3.0 definition), delay time of antibiotic administration, and the net fluid balance at 24 h. Very early VPs, vasopressor support initiated before or within the next hour of the first fluid resuscitation (FRLoad). Delayed VPs, vasopressor support initiated > 1 h of the first fluid resuscitation (FRLoad). VPs, start of vasopressor support

Ospina Tascon CC 2020

Increasing mean arterial pressure in patients with septic shock: Effects on oxygen variables and renal function*

Aurélie Bourgoin, MD; Marc Leone, MD; Anne Delmas, MD; Franck Garnier, MD; Jacques Albanèse, MD; Claude Martin, MD, FCCM





High versus Low BP Target in Septic Shock

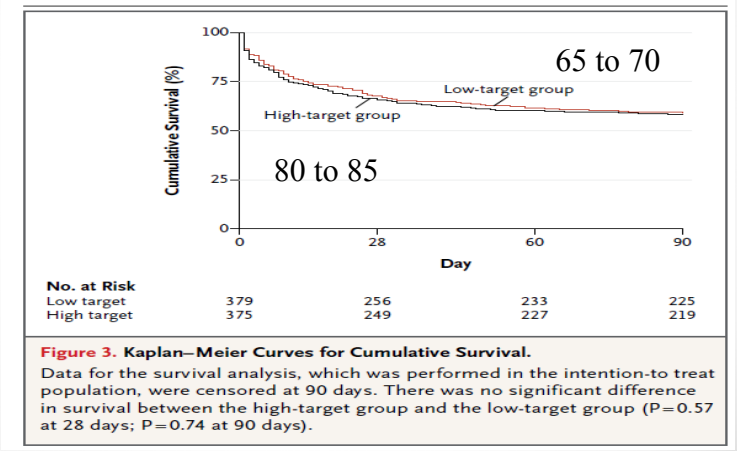


Figure 3. Kaplan–Meier Curves for Cumulative Survival.
Data for the survival analysis, which was performed in the intention-to treat population, were censored at 90 days. There was no significant difference in survival between the high-target group and the low-target group (P=0.57 at 28 days; P=0.74 at 90 days).

Asfar NEJM 2014

Targeting microcirculation?

JAMA Network

QUESTION Does a resuscitation strategy targeting normalization of capillary refill time, compared with targeting serum lactate levels, reduce mortality in patients with septic shock?

CONCLUSION This randomized clinical trial of adults with septic shock found that use of a peripheral perfusion-targeted resuscitation strategy, compared with targeting serum lactate, did not significantly reduce mortality.

POPULATION

198 Men 226 Women

Adults in the ICU with septic shock

Mean age: 63 years

LOCATIONS

28 ICUs in 5 countries in South America

INTERVENTION

424 Patients randomized

212 **Peripheral perfusion group**
Resuscitation protocol of normalizing capillary refill time (measured in seconds)

212 **Lactate group**
Resuscitation protocol of normalizing or decreasing lactate levels (>20% per 2 hours)

PRIMARY OUTCOME

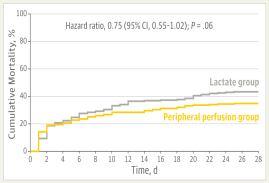
All-cause mortality at 28 days

FINDINGS

All-cause mortality at 28 days

Peripheral perfusion group 34.9% (74 patients died)

Lactate group 43.4% (92 patients died)



No significant risk difference between groups:
-8.5% (95% CI, -18.2% to 1.2%),

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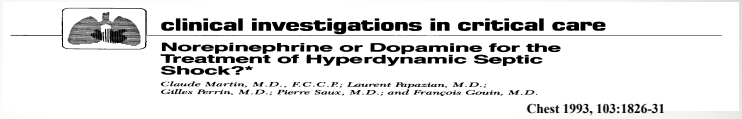
Hernández G, Ospina-Tascón GA, Petri Damiani L, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial [published February 17, 2019]. *JAMA*. doi:10.1001/jama.2019.0071

Select a vasopressor & inotrope

Dopamine or Noradrenaline ?



clinical investigations in critical care

Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?*

Claude Martin, M.D., F.C.C.P.; Laurent Papazian, M.D.; Gilles Perrin, M.D.; Pierre Saux, M.D.; and François Gouin, M.D.

Chest 1993, 103:1826-31

32 patients randomized to: either dopamine (up to 25 µg/kg) **or norepi** (up to 5 µg/kg)

Objective : to reach and maintain mean BP > 80 mmHg over 6 hours

Dopa (n=16)

success (n=5)

10 to 25 µg/kg/min

increase in urine output
decrease in lactate

failure (n=11)

25 µg/kg/min

Norepi (n=16)

success (n=15)

1.5±1.2 µg/kg/min

increase in urine output
decrease in lactate

failure (n=1)

5 µg/kg/min

N=10

Dopa + Norepi (25 µg/kg/min +1.7±1.8 µg/kg/min)

increase in urine output
and decrease in lactate

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
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

* Data were available for 1656 patients in the intensive care unit, in the hospital, and at 28 days; for 1443 patients at 6 months; and for 1036 patients at 12 months.
† Odds ratios for death are for the comparison of the dopamine group with the norepinephrine group.

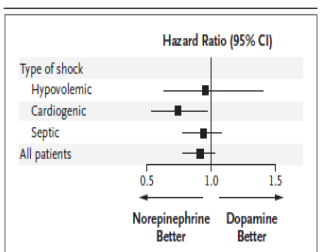


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.
A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

De Backer et al NEJM 2010

Norepinephrine versus Dopamine

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Dopamine compared with norepinephrine for hypotensive shock

Patient or population: hypotensive shock
Settings: critical care units
Intervention: dopamine
Comparison: norepinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Norepinephrine	Dopamine				
Total mortality[a]	Moderate[b]		RR 1.07 (0.99 to 1.16)[c]	1400 (6 RCTs)	⊕⊕⊕⊕ HIGH[d,e]	
	380 per 1000	407 per 1000 (376 to 441)				
Arrhythmia < BR/> follow-up: range 28 days	Moderate[f,g]		RR 2.33 (1.45 to 3.85)	1931 (2 RCTs)	⊕⊕⊕⊕ HIGH[h]	
	76 per 1000	177 per 1000 (110 to 293)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

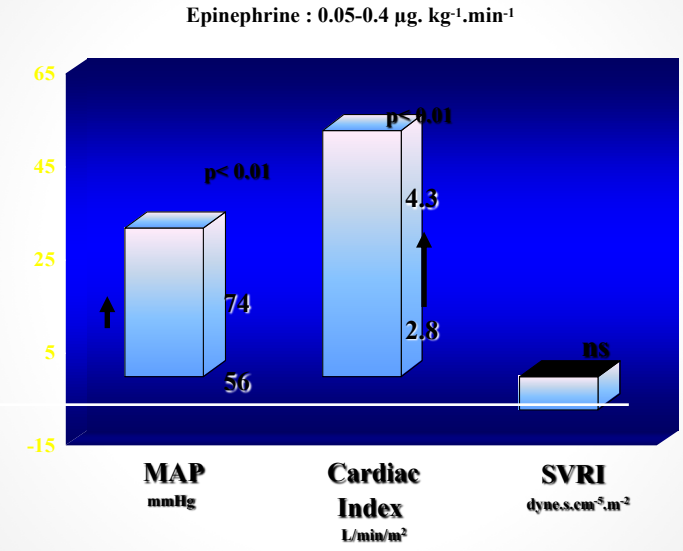
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] The largest study reported 12-month mortality, one study reported 28-day mortality and one hospital mortality. For the remaining 3 studies, the time point of mortality assessment was undetermined. A sensitivity analysis indicates no influence on effects by differences in mortality definition

Gamper Cochrane DBSR 2016

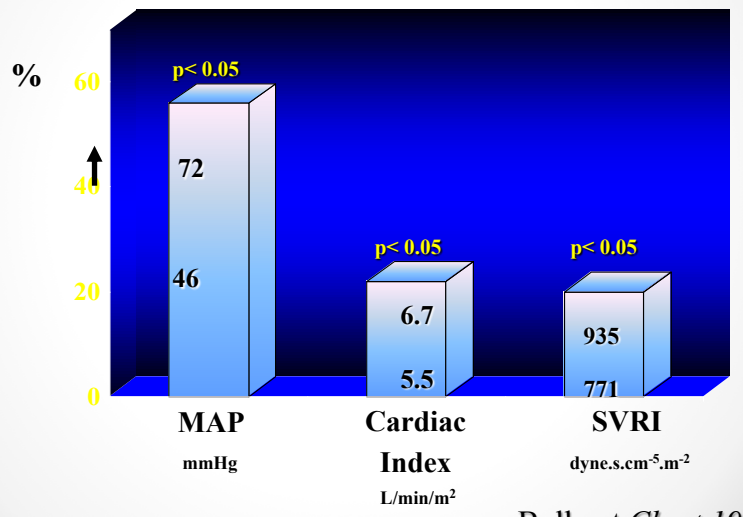
Select a vasopressor & inotrope

Noradrenaline or Adrenaline?



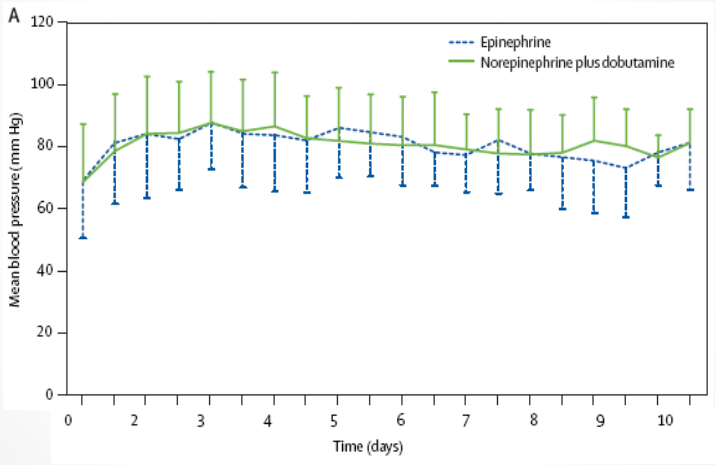
Mackenzie *ICM 1991*

epinephrine : 0.5-1 µg. kg^{-1}.min^{-1}



Bollaert *Chest 1990*

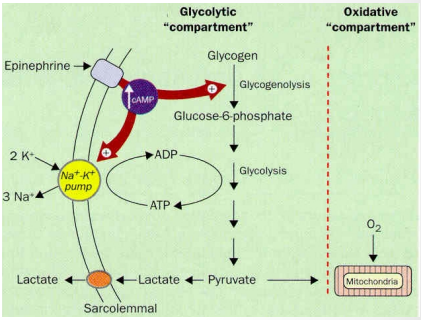
Hemodynamic Effects



Annane Lancet 2007

Aerobic production of lactate

- Epinephrine binds to muscle adrenergic β 2 receptors and raises AMP production
  - Activation of sarcolemmal Na+-K+ATPase and increases ADP level
  - Stimulation of glycogenolysis
- Epinephrine increases glycogenolysis with a net increase in pyruvate production and thus an increase in lactate concentration
- ADP increases PFK activity and thus pyruvate production



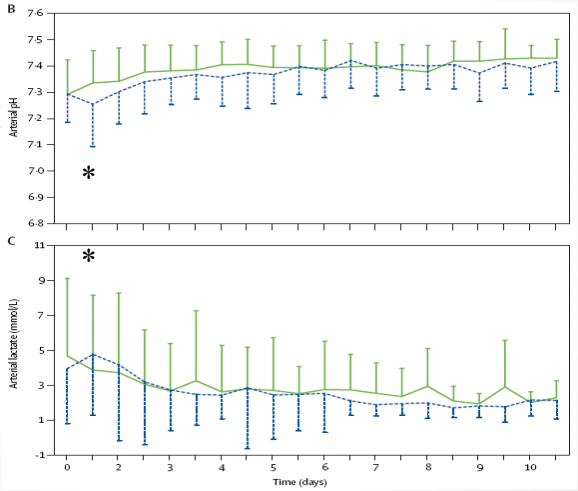
James et al, Lancet 1999

The CATS Study:

Metabolic Effects

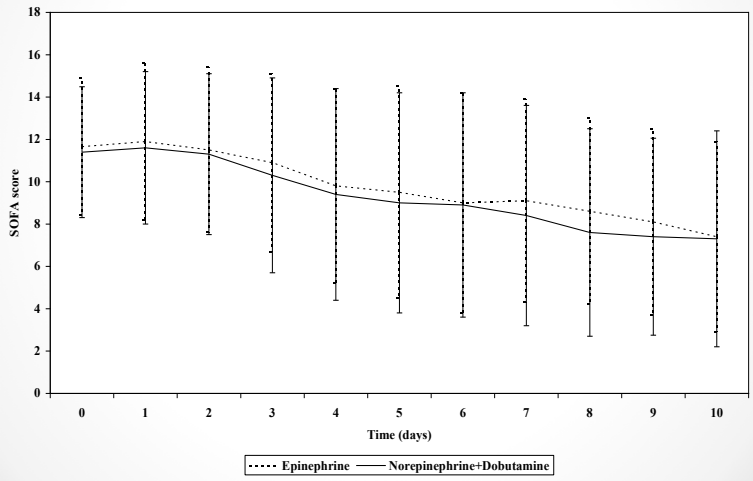
pH

Lactate



Annane Lancet 2007

Effects on Organ Dysfunction



Annane Lancet 2007

Mortality Data

	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

Data are number of deaths (%).

Table 3: All-cause mortality rates

Annane Lancet 2007

Outcomes in CAT Study

Outcome	Epinephrine	Norepinephrine	RR	95% CI	p
Resolution of shock: median (IQR) hours	**35.1 (13.8-70.4)**	**40.0 (14.5-120.0)**	**0.88**	**0.69 to 1.12**	**0.26**
Resolution of shock 48 hours: n (%)	**87 (62.6)**	**75 (54.4)**	**1.15**	**0.94 to 1.41**	**0.16**
Day 28: dead - n/N (%)	31/138 (22.5)	36/138 (26.1)	0.86	0.57 to 1.31	0.48
Day 90: dead - n/N (%)	41/135 (30.4)	46/134 (34.3)	0.88	0.63 to 1.25	0.49
Ventilated hours	161.9 ± 204.4	219.8 ± 329.1	-57	-122.5 to 7.0	0.08
ICU LOS	9.4 ± 10.7	12.1 ± 15.4	-2.8	-5.9 to 0.4	0.08

Myburgh ICM 2009

Select a vasopressor & inotrope

AVP and analogs?

	Vasopressin	Terlipressin	Selepressin
molecule	Natural hormone nonapeptide	Synthetic dodecapeptide	synthetic
receptors	V2 and at high dose V1	V1 – onw intrinsic VC & pro-drug for lysine vasopressin Selective splanchinc territory	Selective V1a

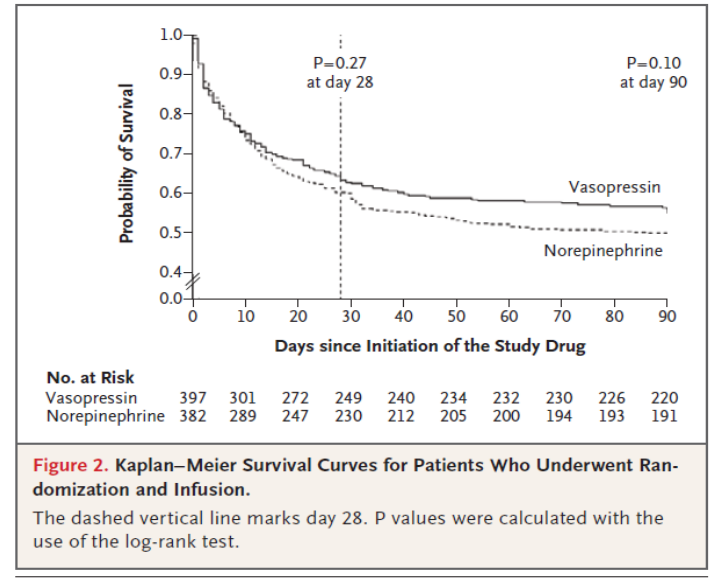


Figure 2. Kaplan–Meier Survival Curves for Patients Who Underwent Randomization and Infusion.

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

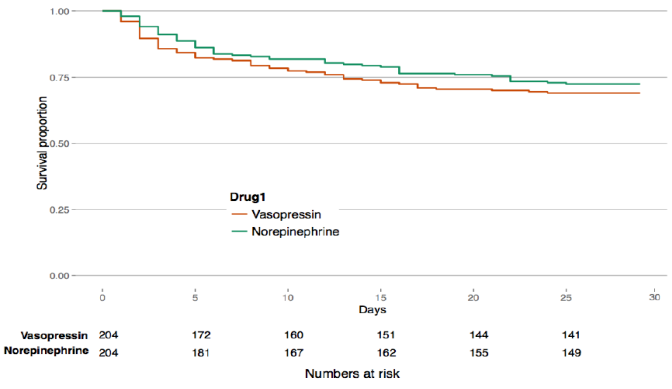
Russel NEJM 2008

JAMA Network

From: **Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial**

eFigure 4. Kaplan-Meier Survival Curves

a) Vasopressin vs Norepinephrine



Gordon JAMA 2016

JAMA Network

QUESTION For septic shock treated with norepinephrine, does selepressin, a selective vasopressin V1a receptor agonist, compared with placebo improve patient outcome, defined as an increase in the number of days alive and free of both vasopressors and ventilation?

CONCLUSION Compared with placebo, treatment with selepressin was not effective in improving ventilator- and vasopressor-free days.

POPULATION

487 Men 341 Women

Adults with proven or suspected infection and septic shock requiring more than 5 μg/min of norepinephrine

Mean age: 66.3 years

LOCATIONS

63 Hospitals in Europe and the United States

INTERVENTION

868 Patients randomized
828 Patients analyzed

562 266

Selepressin
Regimens of 1.7, 2.5, and 3.5 ng/kg/min via continuous infusions titrated according to hemodynamic parameters

Placebo
Placebo administered as continuous infusions titrated according to hemodynamic parameters

PRIMARY OUTCOME

Ventilator- and vasopressor-free days within 30 days of starting study drug

FINDINGS

Ventilator- and vasopressor-free days

Selepressin
15.0 Ventilator- and vasopressor-free days

Day 0 — Day 30: Ventilator- and vasopressor-free

Placebo
14.4 Ventilator-and vasopressor-free days

Day 0 — Day 30: Ventilator- and vasopressor-free

Between-group difference,
0.6 days
(95% CI, −1.3 to 2.4); $P = .30$

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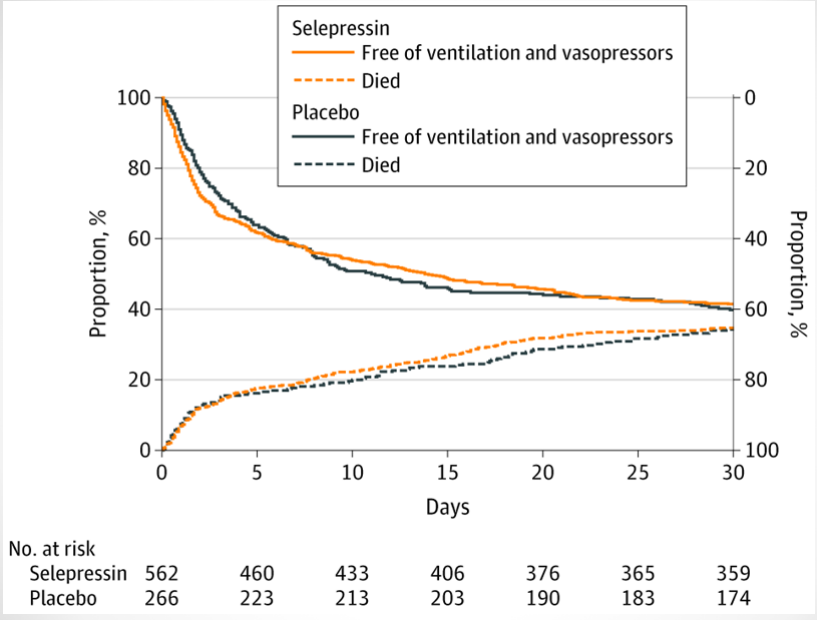
Laterre P-F, Berry SM, Blemings A, et al; SEPSIS-ACT Investigators. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT randomized clinical trial [published October 2, 2019]. *JAMA*. doi:10.1001/jama.2019.14607



Laterre Jama 2020

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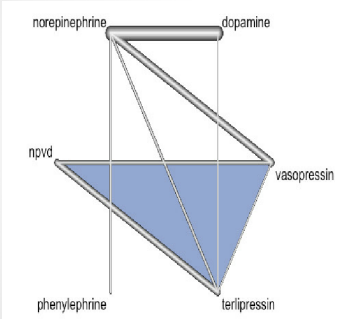
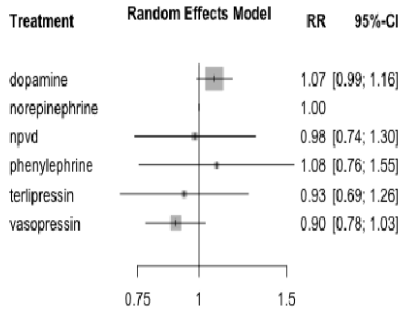
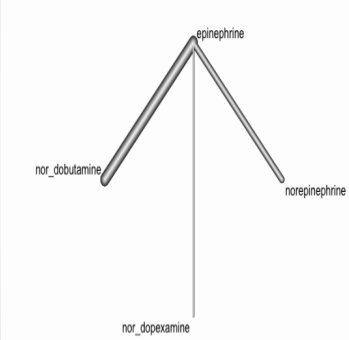
Norepinephrine vs other vasopressors

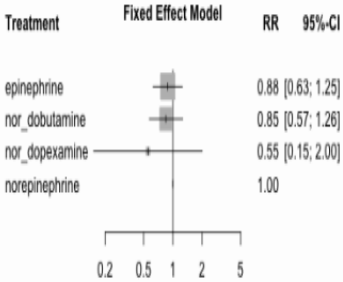




N=22 studies

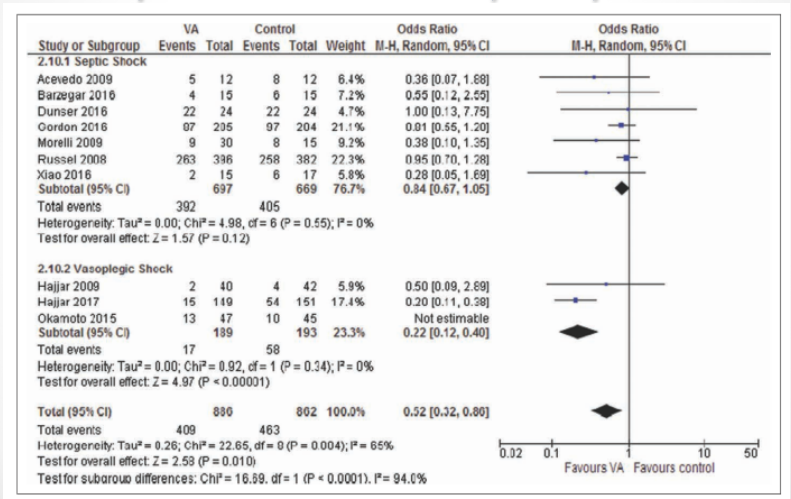
Norepinephrine vs *other vasopressors and beta2 agonists*





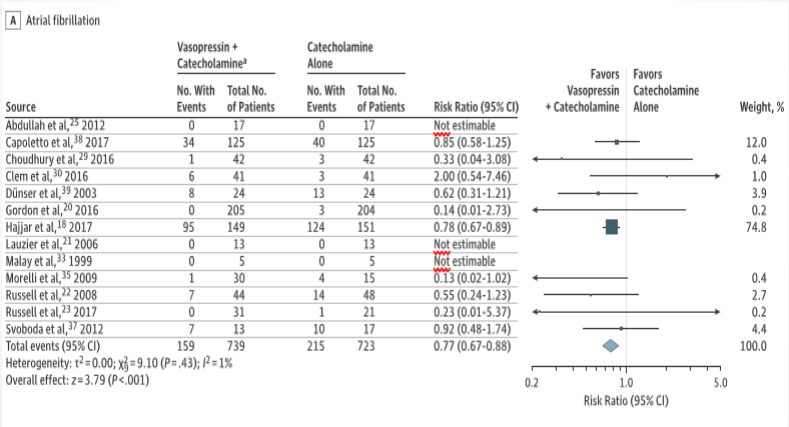
N=6 trials)

Risk of acute kidney injury
Vasopressin vs norepinephrine



Nedel CCM 2018

Risk of atrial fibrillation
Vasopressin vs catecholamines



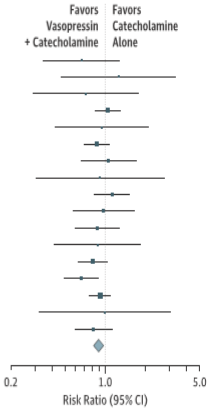
McIntyre Jama 2018

Risk of death
Vasopressin vs catecholamines

B 28-d or 30-d mortality

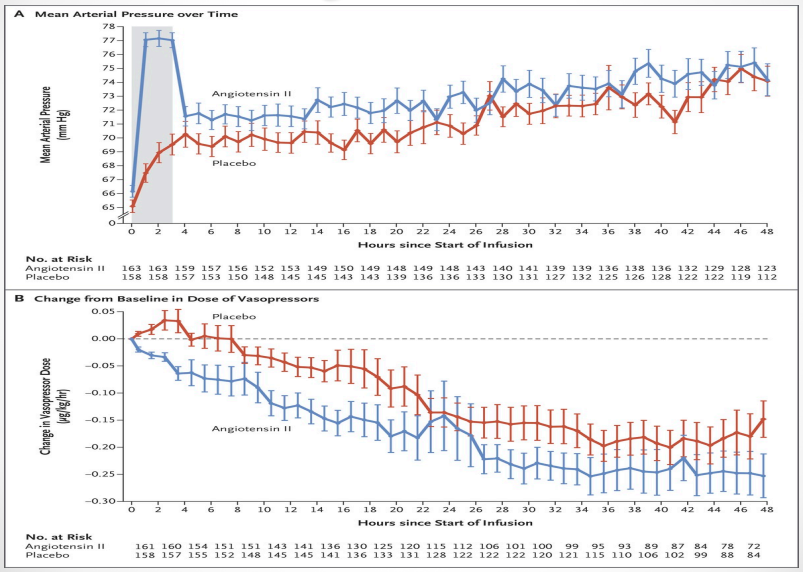
Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Acevedo et al,[26] 2009	6	12	9	12	0.67 (0.35-1.28)	1.6
Albanese et al,[27] 2005	5	10	4	10	1.25 (0.47-3.33)	0.7
Barzegar et al,[28] 2014	5	15	7	15	0.71 (0.29-1.75)	0.9
Capoletto et al,[38] 2017	71	125	68	125	1.04 (0.84-1.30)	14.1
Chen et al,[40] 2017	9	31	8	26	0.94 (0.43-2.09)	1.1
Choudhury et al,[29] 2016	31	42	36	42	0.86 (0.69-1.07)	14.6
Clem et al,[30] 2016	19	41	18	41	1.06 (0.65-1.70)	3.0
Fonseca Ruiz et al,[34] 2013	4	14	5	16	0.91 (0.30-2.75)	0.6
Gordon et al,[20] 2016	63	204	56	204	1.13 (0.83-1.52)	7.6
Hajjar et al,[18] 2017	23	149	24	151	0.97 (0.57-1.64)	2.5
Han et al,[31] 2012	27	66	34	73	0.88 (0.60-1.28)	4.8
Hua et al,[32] 2013	7	16	8	16	0.88 (0.42-1.84)	1.3
Oliveira et al,[36] 2014	65	191	83	196	0.80 (0.62-1.04)	10.6
Prakash et al,[41] 2017	37	91	57	93	0.66 (0.49-0.89)	7.9
Russell et al,[22] 2008	144	404	154	395	0.91 (0.76-1.09)	21.4
Russell et al,[23] 2017	6	29	4	19	0.98 (0.32-3.03)	0.5
Svoboda et al,[37] 2012	10	13	16	17	0.82 (0.59-1.13)	6.8
Total events (95% CI)	532	1453	591	1451	0.89 (0.82-0.97)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{16} = 11.29$ ($P = .79$); $I^2 = 0\%$
Overall effect: $z = 2.62$ ($P = .009$)



McIntyre Jama 2018

Angiotensin II



Khanna NEJM 2017

Table 2 Main serious adverse reactions associated with vasoactive drugs

Molecules	Arrhythmias		Vascular				Metabolic
	Supra-ventricular	Ventricular	Myocardial ischemia	Stroke	limbs	Other tissues/ organs	
Dopamine	Atrial fibrillation; multifocal atrial tachycardia; cardiac conduction abnormalities	Ventricular tachycardia/fibrillation	+	+	+	+	Not described
Dobutamine	Atrial fibrillation; multifocal atrial tachycardia,	Ventricular tachycardia/fibrillation	+	Not described	Not described	Not described	Hypokalemia
Epinephrine[a]	Atrial fibrillation; multifocal atrial tachycardia,	Ventricular tachycardia/fibrillation	+++	+	+	+	Lactic acidosis; hyperglycaemia; hypoglycaemia; insulin resistance; hypokalemia;
Norepinephrine	Atrial fibrillation; multifocal atrial atchycardia, bradycardia	Ventricular tachycardia/fibrillation	++	+	+	+	Not described
Vasopressin	Atrial fibrilation; bradycardia	Ventricular tachycardia/fibrillation	++	+	+	+	hyponatremia
AngiotensinII[b]	±	Ventricular tachycardia	Not described	Not described	+	Not described	Not described
Levosimendan	Atrial fibrillation; multifocal atrial tachycardia; junctional tachycardia	Ventricular tachycardia/fibrilation	Not described	Not described	Not described	Not described	Metabolic alkalosis; hypokalemia
Esmolol/ Landiolol	Bradycardia; conduction abnormalities; sinus arrest; asystole		+	Not described	+	Not described	Hyperkalemia; metabolic acidosis

[a] Epinephrine my also be associated with brain haemorrhage

[b] Synthetic human angiotensin II

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ARTICLES

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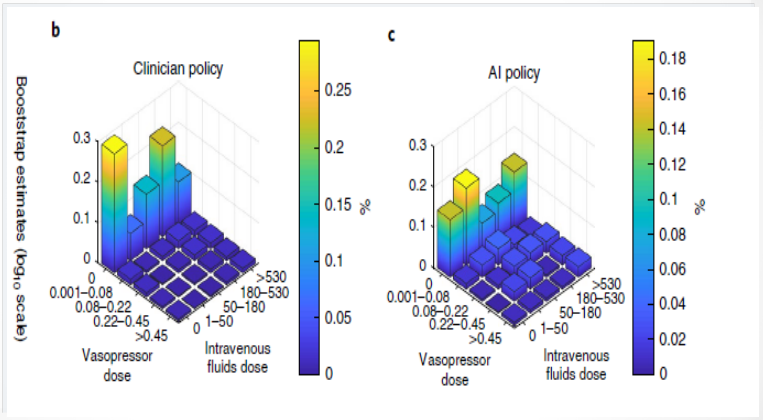
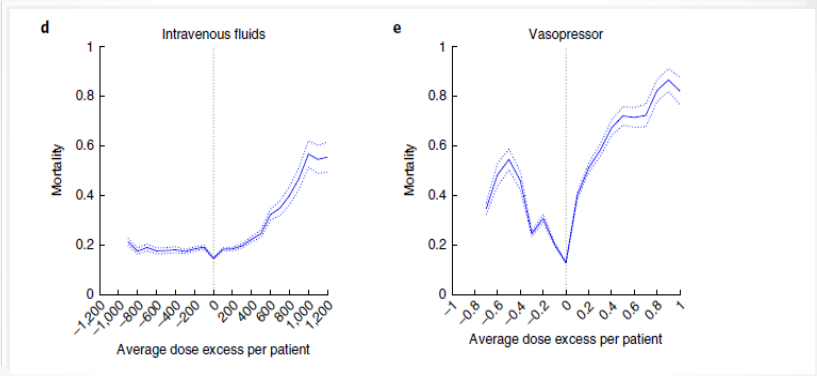
The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care

Matthieu Komorowski[1,2,3], Leo A. Celi[3,4], Omar Badawi[3,5,6], Anthony C. Gordon[1*] and A. Aldo Faisal[2,7,8,9*]



Plus de remplissage et moins de vasopresseurs



Equal proportion given too much / too little fluid - On average too much fluid (~80ml/h)

75% given too low vasopressor dose – median dose deficit 0.13 µg/kg/min

In summary

- Norepinephrine should be considered as the first line agent in patients who require catecholergic agents
- Epinephrine and Norepinephrine are equivalent in restoring global hemodynamic
- There are differences in regional hemodynamic and metabolic effects
- However, these differences in hemodynamics did not translate into survival differences
- Vasopressin is not inferior to norepinephrine in septic shock
- It should be used in combination to NE to help sparring NE
- Waiting for publication of Phase III study on Selepressin
- What matters is pre- defined hemodynamic goals!