

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779-89.

Supplementary Appendix

R1

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Supplement to: De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL Comparison of Dopamine and Norepinephrine as first Vasopressor Agent in the Treatment of Shock.

SUPPLEMENTARY TABLE 1: Example of trial drug administration chart

Single concentration: Add 800 mg of dopamine or 16 mg of norepinephrine (= 8 mg norepinephrine base) into 250 ml of G5%ED or NaCl 9%.

Trial drug dose		Rate of administration, ml/h:						
Dopamine mcg/kg/min	Norepinephrine mcg/kg/min	WEIGHT (kg)						
		40	50	60	70	80	90	100
1	0.01	1	1	1	1	2	2	2
2	0.02	2	2	2	3	3	3	4
3	0.03	2	3	3	4	5	5	6
4	0.04	3	4	5	5	6	7	8
5	0.05	4	5	6	7	8	9	10
6	0.06	5	6	7	8	9	10	11
7	0.065	5	7	8	9	11	12	13
8	0.07	6	8	9	10	12	14	15
9	0.08	7	9	10	12	14	15	17
10	0.09	8	10	12	13	15	17	19
11	0.10	8	10	13	14	17	19	21
12	0.11	9	11	14	16	18	20	23
13	0.12	10	12	15	17	20	22	25
14	0.13	11	13	16	18	21	24	27
15	0.14	11	14	17	20	23	26	29
16	0.15	12	15	18	21	24	27	30
17	0.16	13	16	20	22	26	29	32
18	0.17	14	17	21	23	27	31	34
19	0.18	14	18	22	25	29	32	36
20	0.19	15	19	23	26	30	34	38

SUPPLEMENTARY TABLE 2: Sources of sepsis

Source of sepsis	DOPAMINE	NOREPINEPHRINE
	542	502
Lungs	278	246
Pneumonia	270	241
Empyema	8	5
Abdomen	138	135
Primary peritonitis	13	19
Enteritis	14	12
Cholecystitis/angiocholitis	15	24
Diverticulitis/colitis	10	11
Abscess	17	16
Mesenteric ischemia	15	10
Mesenteric infarction	7	7
Occlusion	17	7
Perforation	21	13
Necrotizing pancreatitis	7	13
Fournier gangrene	2	3
Urine	51	42
Catheter	14	10
Endocarditis	9	11
Mediastinitis	10	15
Soft tissues	11	13
Other	15	20
Purpura fulminans	1	1
Necrotizing fasciitis	6	4
Meningitis	2	5
Miscellaneous	6	10

SUPPLEMENTARY FIGURE LEGENDS:

Supplementary Figure 1: Dose escalation in patients not treated with open label vasopressors at time of randomization

The rate of administration of the blind solution was determined according to a scale and using the estimated body weight. The recommended steps for increasing or decreasing the doses of the blinded solution were calculated to be equivalent to 2 mcg/kg/min for dopamine and 0.02 mcg/kg/min for norepinephrine, the investigator being free to use multiples of this increment in case of emergency. The maximal doses were 20 mcg/kg/min for dopamine and 0.19 mcg/kg/min for norepinephrine (these doses have been shown to have similar effects on mean arterial blood pressure^{1;2}).

When the maximal dose of the blinded solution was achieved, an open label perfusion of norepinephrine was added to achieve the desired blood pressure. Epinephrine and vasopressin were used only as rescue therapy. Weaning of vasopressor agents started with weaning of the open label norepinephrine (and other open label vasopressors, when applicable), followed by weaning of the blinded solution. If hypotension recurred, the blinded solution was resumed first (up to a maximal dose of 20 mcg/kg/min for dopamine and 0.19 mcg/kg/min for norepinephrine) and if needed an open label solution of norepinephrine was again added. When feasible, weaning of the vasopressors was again performed as previously described.

Supplementary Figure 2: Dose escalation in patients treated for less than 4 hours with open label vasopressors at time of randomization

When patients were already being treated with open label vasopressors at baseline, the blinded solution was rapidly incremented, and, if possible, doses of open label vasopressor agent decreased. When this open label vasopressor consisted of dopamine and it could not be fully weaned after introduction of the blinded solution, the open label dopamine was replaced by an open label norepinephrine infusion.

When the maximal dose of the blinded solution was achieved, an open label perfusion of norepinephrine was added to achieve the desired blood pressure. Epinephrine and vasopressin were used only as rescue therapy. Weaning of vasopressor agents started with weaning of the open label norepinephrine (and other open label vasopressors, when applicable), followed by weaning of the blinded solution. If hypotension recurred, the blinded solution was resumed first (up to a maximal dose of 20 mcg/kg/min for dopamine

and 0.19 mcg/kg/min for norepinephrine) and, if needed, an open label solution of norepinephrine was again added. When feasible, weaning of the vasopressors was again performed as previously described.

Supplementary Figure 3. Evolution of main hemodynamic variables (censored at 7 days).

Panel A: Heart rate

ANOVA: agent x time effect $P < 0.001$, effect of time $P < 0.001$, difference between agents $P < 0.001$. * $P < 0.05$ norepinephrine vs dopamine.

Panel B: Mean arterial pressure

ANOVA: agent x time effect $P = 0.67$, effect of time $P < 0.001$, difference between agents $P = 0.02$. * $p < 0.05$ norepinephrine vs dopamine.

Panel C: Central venous pressure

ANOVA: agent x time effect $P = 0.15$, effect of time $P < 0.001$, difference between agents $P = 0.04$.

Panel D: Central or mixed-venous oxygen saturation

ANOVA: agent x time effect $P = 0.08$, effect of time $P < 0.001$, difference between agents $P = 0.85$.

Supplementary Figure 4. Doses and use of vasopressor agents, use of fluids and fluid balance

Panel A: Doses of trial drug (censored at 7 days).

ANOVA: agent x time effect $P=0.26$, effect of time $P<0.001$, difference between agents $P=0.35$.

Panel B: Proportion of patients receiving trial drug at each time point

Panel C: Doses of open label norepinephrine

ANOVA: agent x time effect $P=0.64$, effect of time $P<0.001$, difference between agents $P=0.42$.

Panel D: Proportion of patients receiving open label norepinephrine

Pearson Chi-square $P=0.003$

Panel E: Doses of dobutamine

ANOVA: agent x time effect $P=0.032$, effect of time $P<0.001$, difference between agents $P=0.09$. * $P<0.05$ norepinephrine vs dopamine.

Panel F: Proportion of patients receiving dobutamine

Pearson Chi-square $P=0.02$

Panel G: Fluid administration

ANOVA: agent x time effect $P=0.29$, effect of time $P<0.001$, difference between agents $P=0.08$. * $P<0.05$ norepinephrine vs dopamine.

Panel H: Urine output

ANOVA: agent x time effect $P=0.15$, effect of time $P<0.001$, difference between agents $P=0.51$. * $P<0.05$ norepinephrine vs dopamine.

Panel I: Fluid balance

ANOVA: agent x time effect $P=0.07$, effect of time $P<0.001$, difference between agents $P=0.46$. * $P<0.05$ norepinephrine vs dopamine.

Supplementary Figure 5: Design of the Sequential Trial Analysis (triangular test) and results of the analysis

The log-rank statistic (Z) summarizes the difference in survival between the group of patients that received norepinephrine and the group that received dopamine. The variance of the log-rank statistic (V) represents the quantity of information accumulated since the beginning of the trial. Analyses were performed after availability of 28-day outcomes for the first 50 patients, the next 50, and then for every 100 patients. For each analysis, the two statistics, Z and V , were calculated and defined by one point on the graph. Three boundaries are shown: One indicating superiority of norepinephrine over dopamine, one indicating the superiority of dopamine over norepinephrine and one indicating no difference between the two agents. The trial was stopped on Oct 6, 2007, when the analysis with 1600 patients crossed the boundary indicating no difference between trial drugs.

Supplementary Figure 6: Cox proportional hazards regression model for 28-day survival

Variables were selected if univariate analysis was associated with a P value less than 0.2. APACHE II score was the only variable that significantly affected the model. There was no significant difference in 28-day outcome between dopamine and norepinephrine after correction for APACHE II score (OR 1.124 (0.982-1.287), $P=0.09$). APACHE II was significantly associated with outcome (OR 1.052 (1.045-1.059), $P<0.001$).

Supplementary Figure 7: Kaplan-Meier curves for 28-day survival in predefined subgroups of septic, cardiogenic and hypovolemic shock

Panel A: Patients with septic shock (n=1044)

P value by log-rank test = 0.19

Panel B: Patients with cardiogenic shock (n=280)

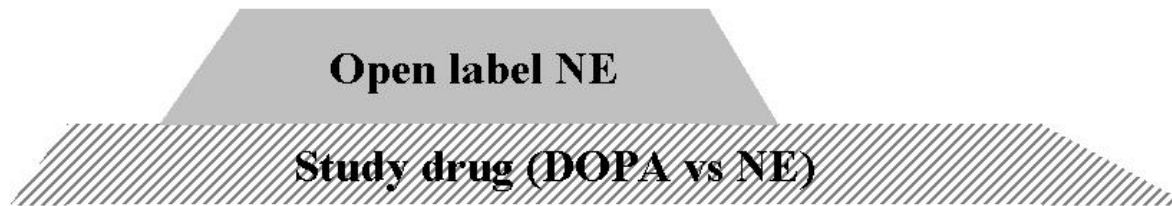
P value by log-rank test = 0.03

Panel C: Patients with hypovolemic shock (n=263)

P value by log-rank test = 0.84

Supplementary Figure 1: Dose escalation in patients not treated with open label vasopressors at time of randomization

Administration of vasoactive drugs:



- **Dose increments (study drug)*:**
 - 2 mcg/kg.min for DOPA
 - 0.02 mcg/kg.min for NE
- **Maximal dose (study drug)*:**
 - 20 mcg/kg.min for DOPA
 - 0.19 mcg/kg.min for NE

* Calculated after
Marik et al JAMA 272:1354;1994
De Backer et al CCM 31:1659;2003

Supplementary Figure 2: Dose escalation in patients already treated with open label vasopressors at randomization

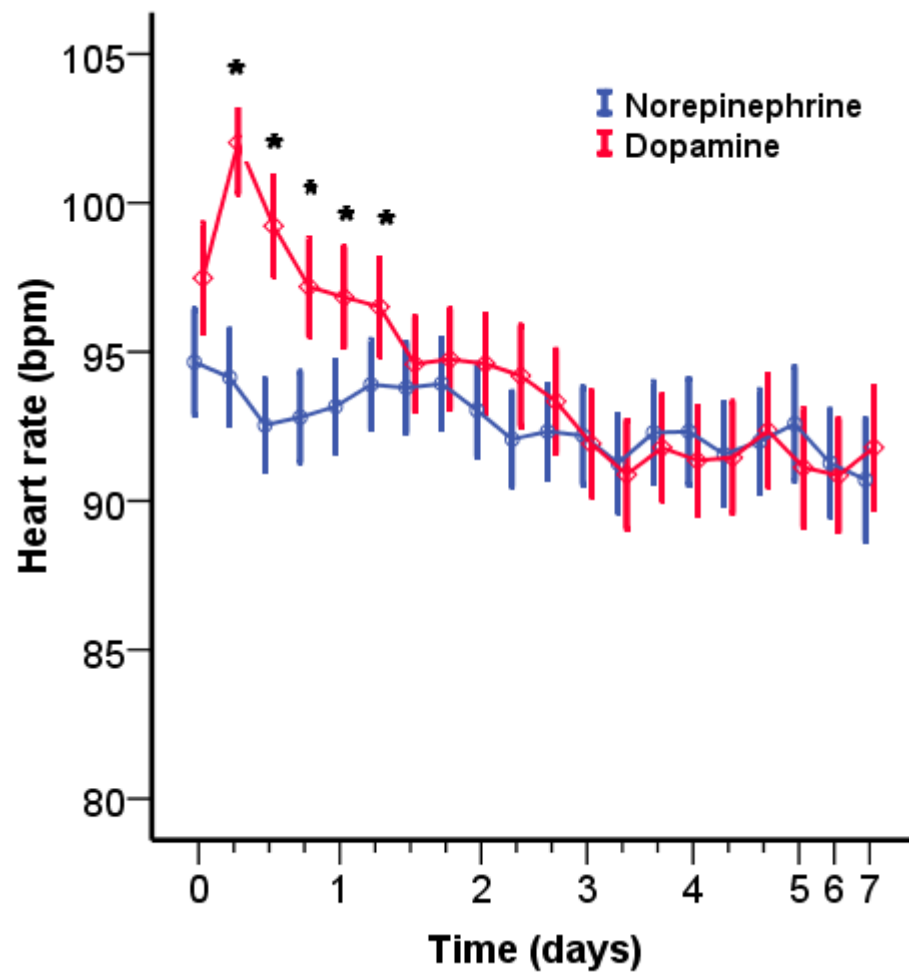
Administration of vasoactive drugs: (patient already on vasopressors)



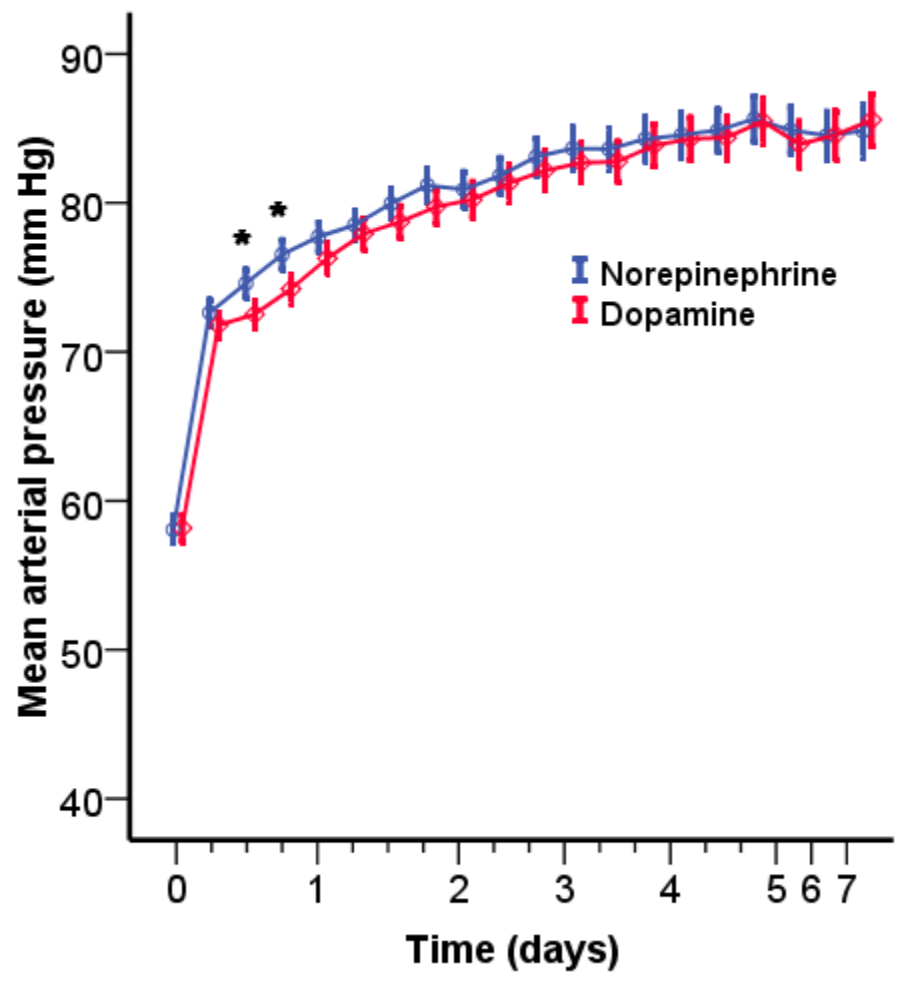
- **Dose increments (study drug)*:**
 - 2 mcg/kg.min for DOPA
 - 0.02 mcg/kg.min for NE
- **Maximal dose (study drug)*:**
 - 20 mcg/kg.min for DOPA
 - 0.19 mcg/kg.min for NE

* Calculated after
Marik et al JAMA 272:1354;1994
De Backer et al CCM 31:1659;2003

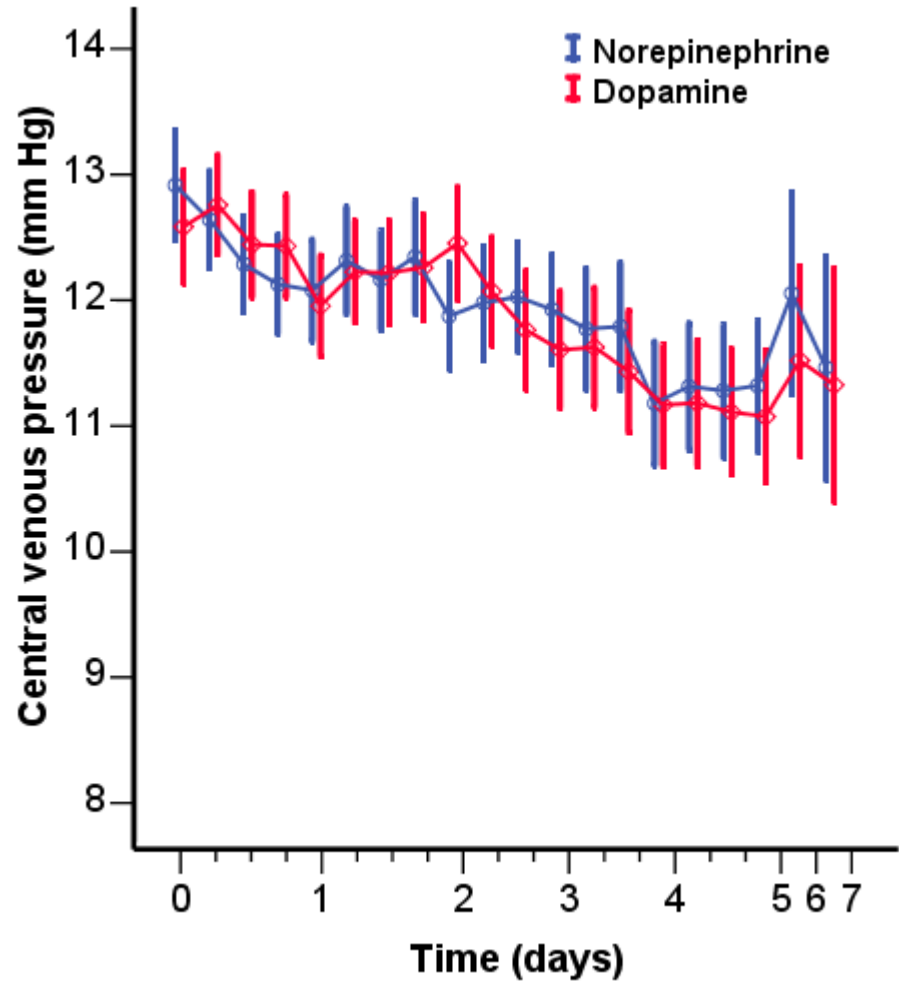
Supplementary Figure 3 Panel A: Heart rate



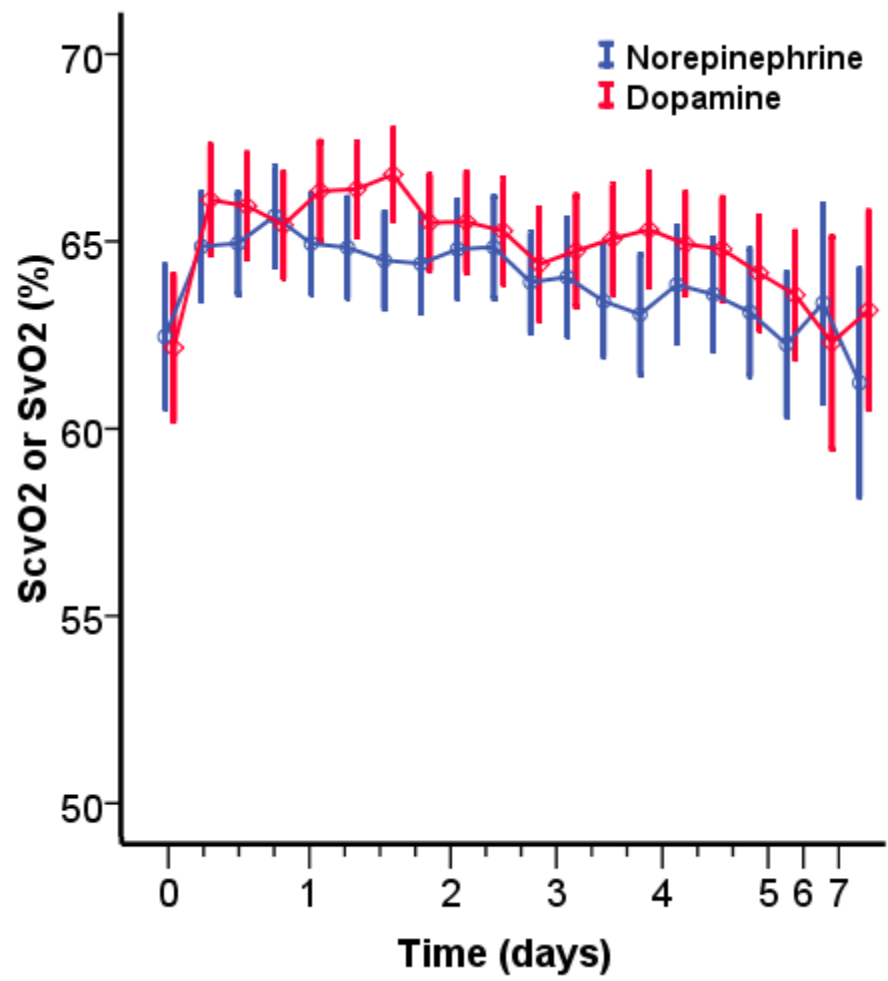
Supplementary Figure 3 Panel B: Mean arterial pressure



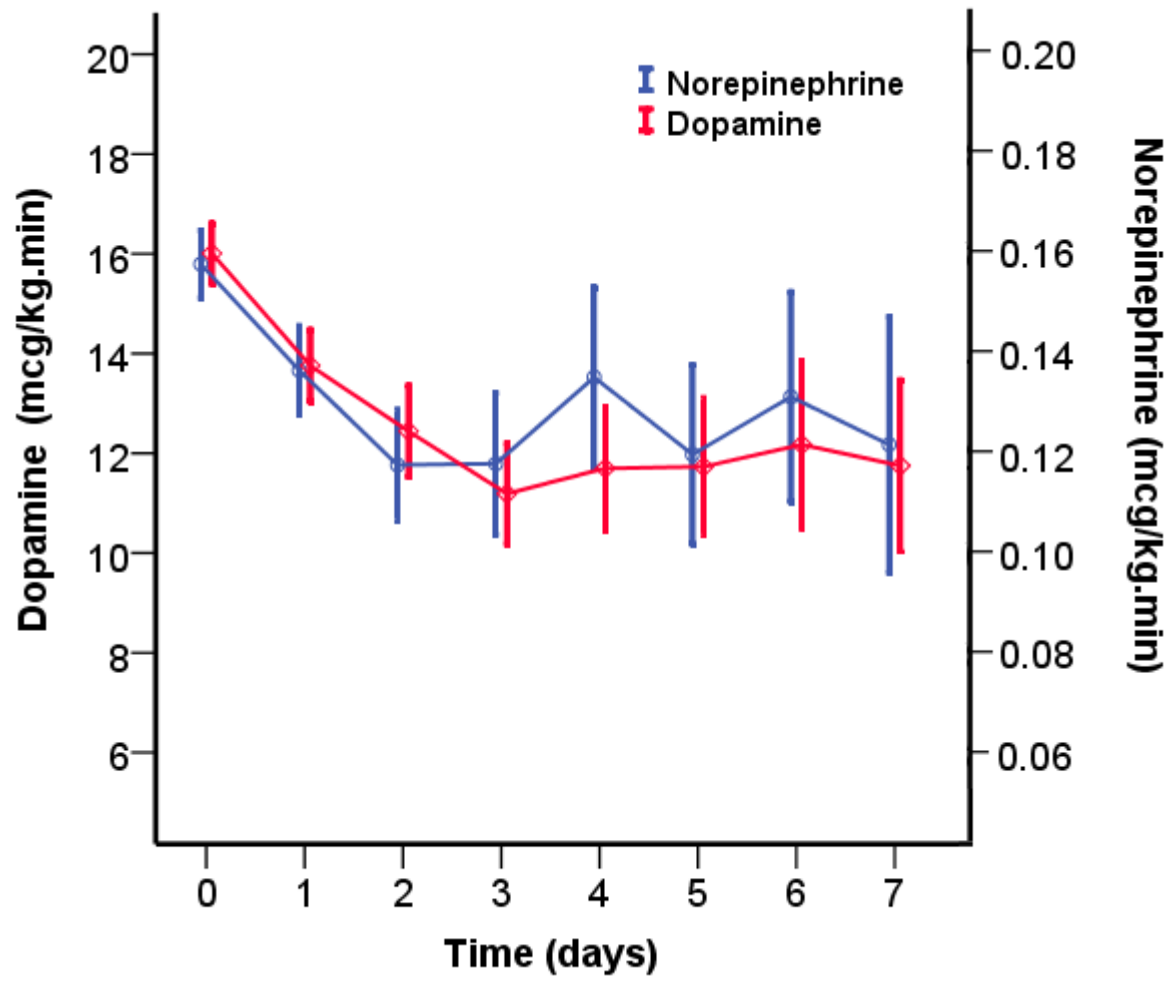
Supplementary Figure 3 Panel C: Central venous pressure



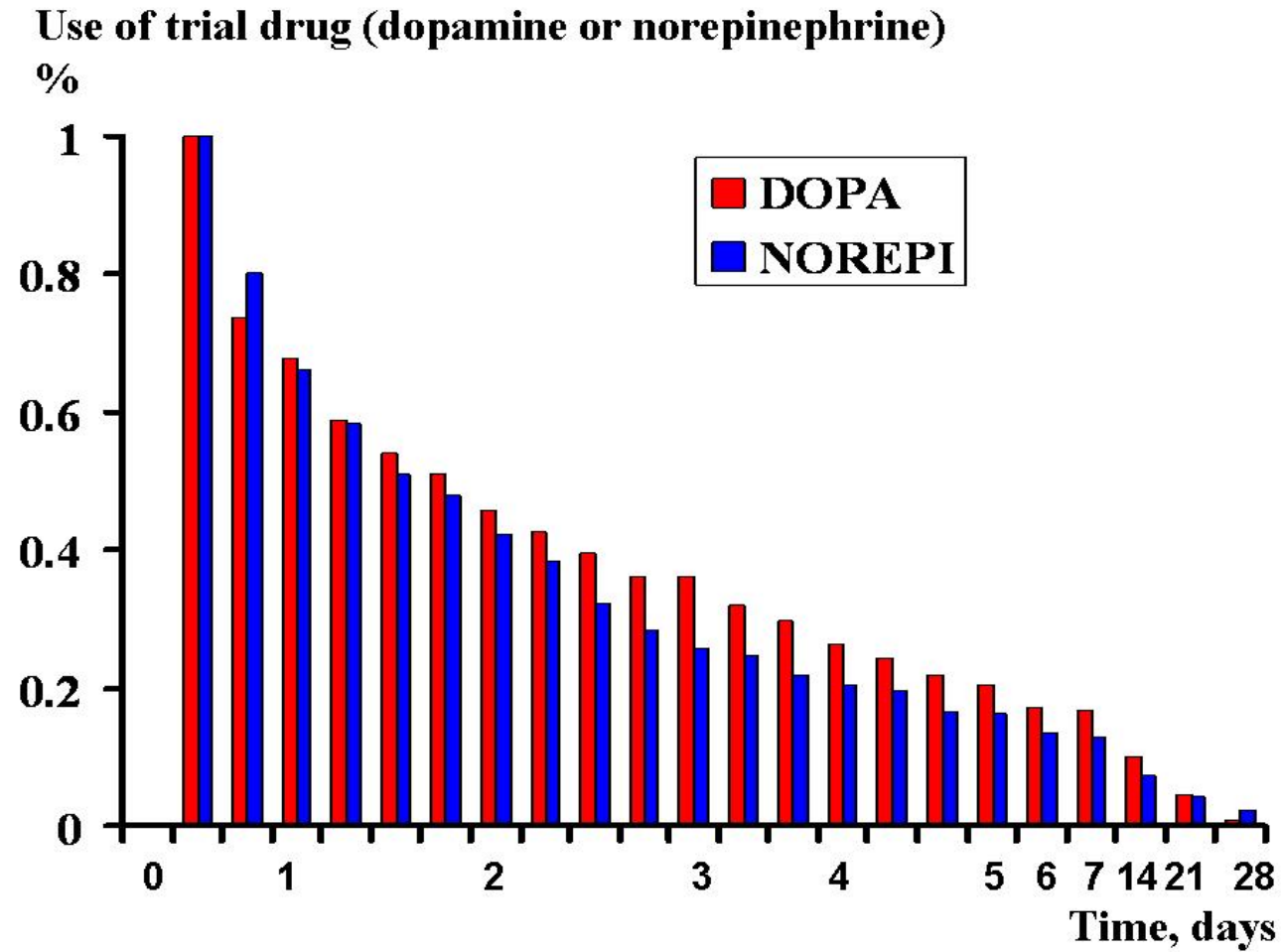
Supplementary Figure 3 Panel D: Central or mixed-venous oxygen saturation



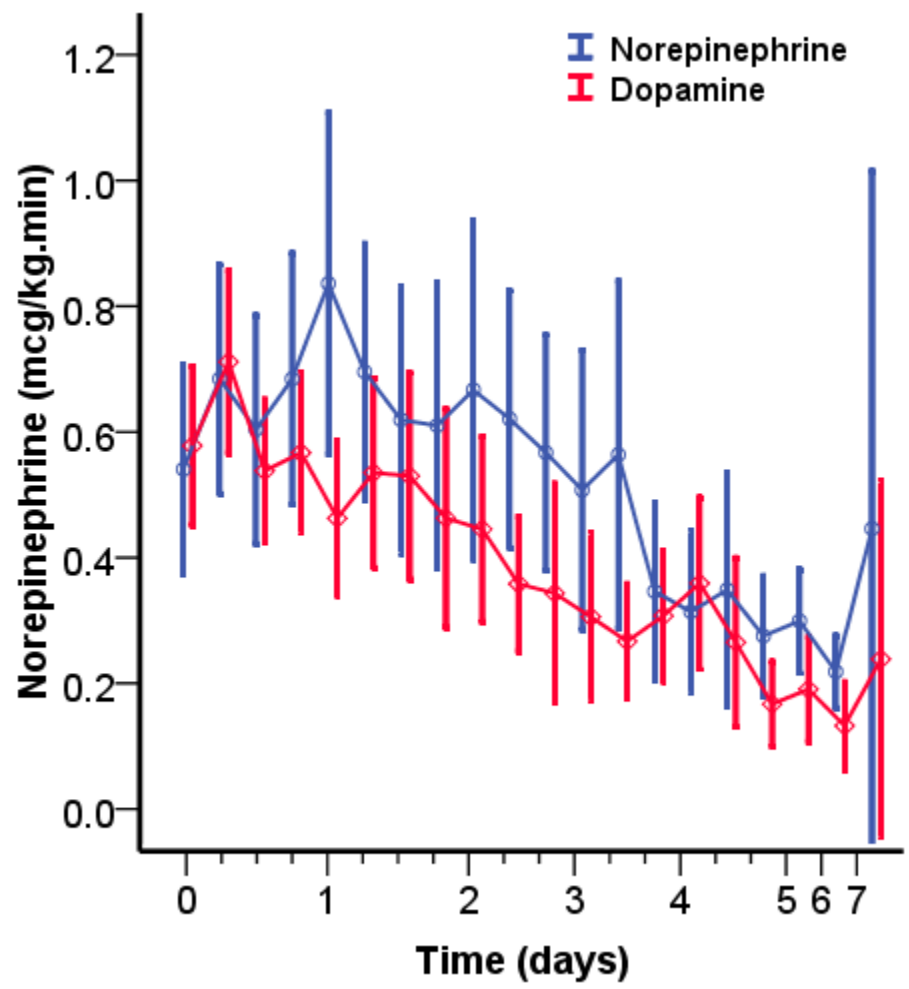
Supplementary Figure 4 Panel A: Doses of trial drug



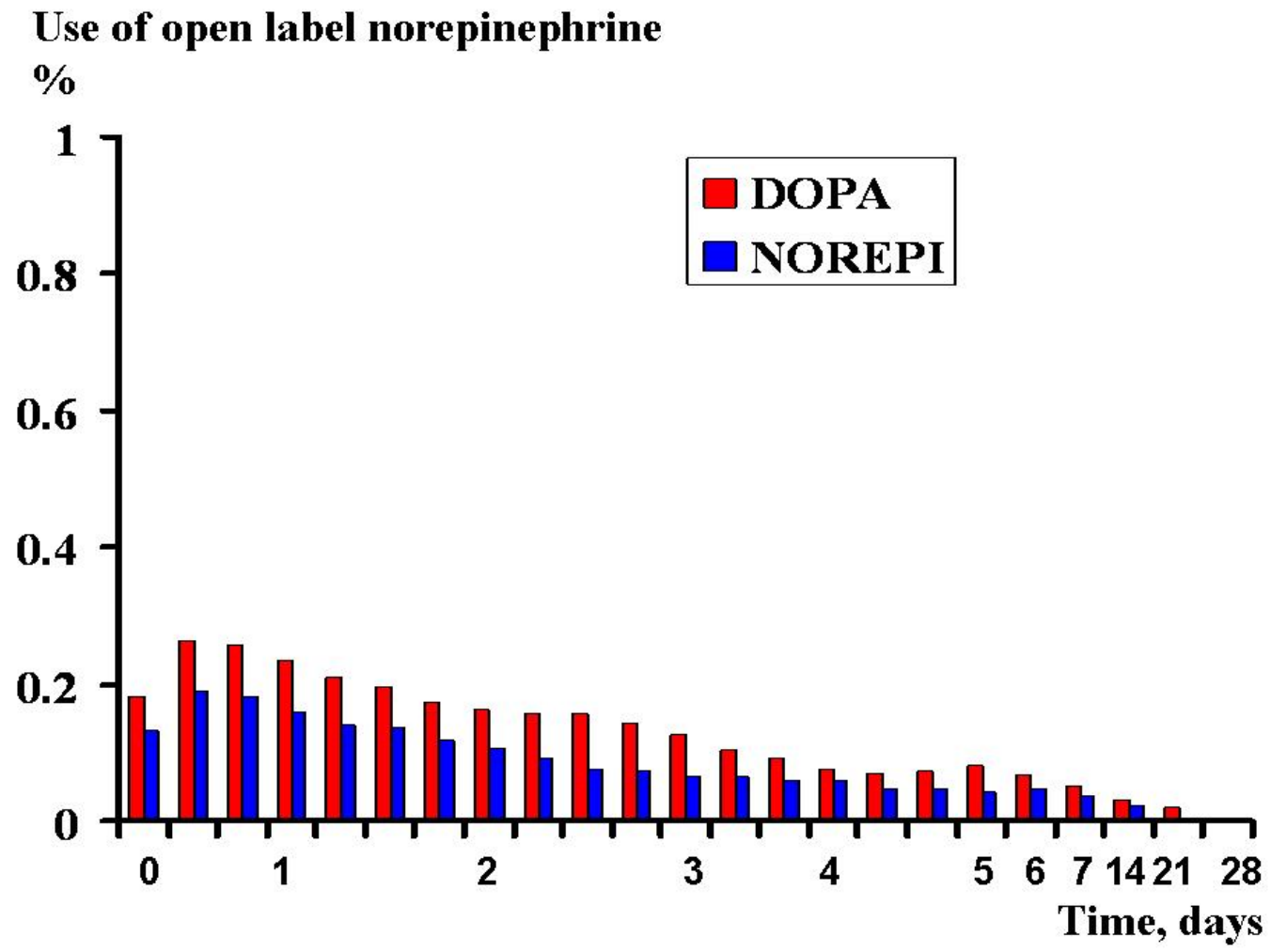
Supplementary Figure 4 Panel B: Proportion of patients receiving trial drug at each time



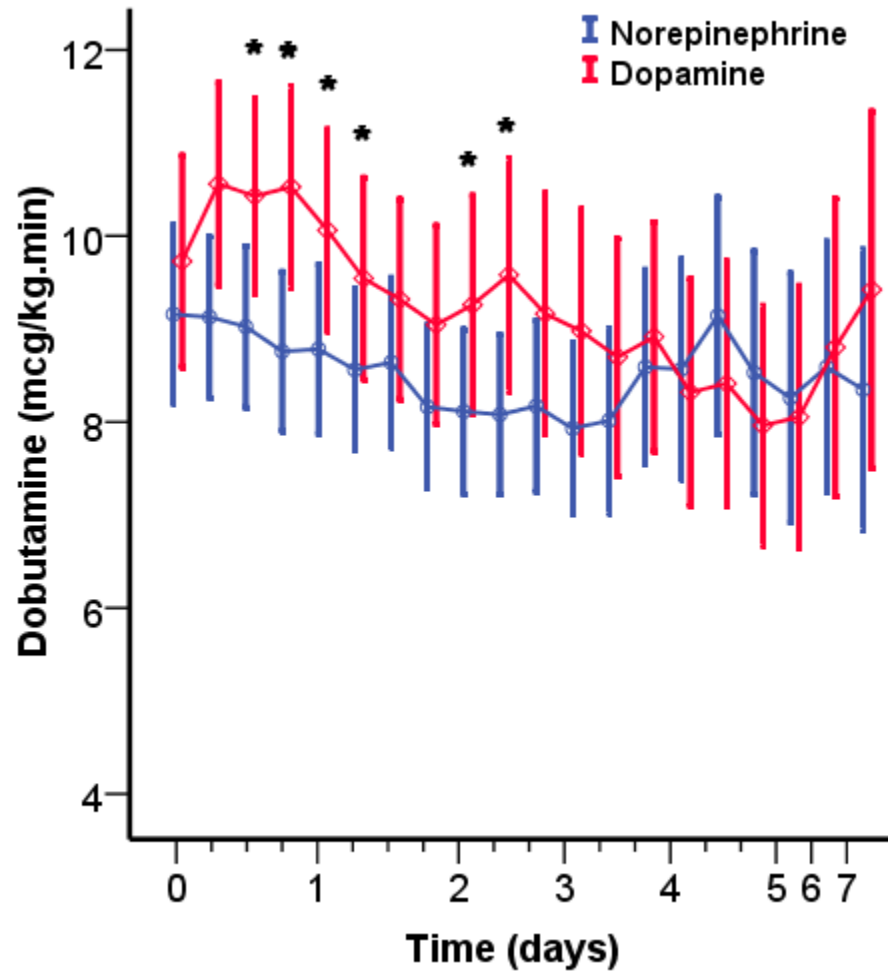
Supplementary Figure 4 Panel C: Doses of open label norepinephrine



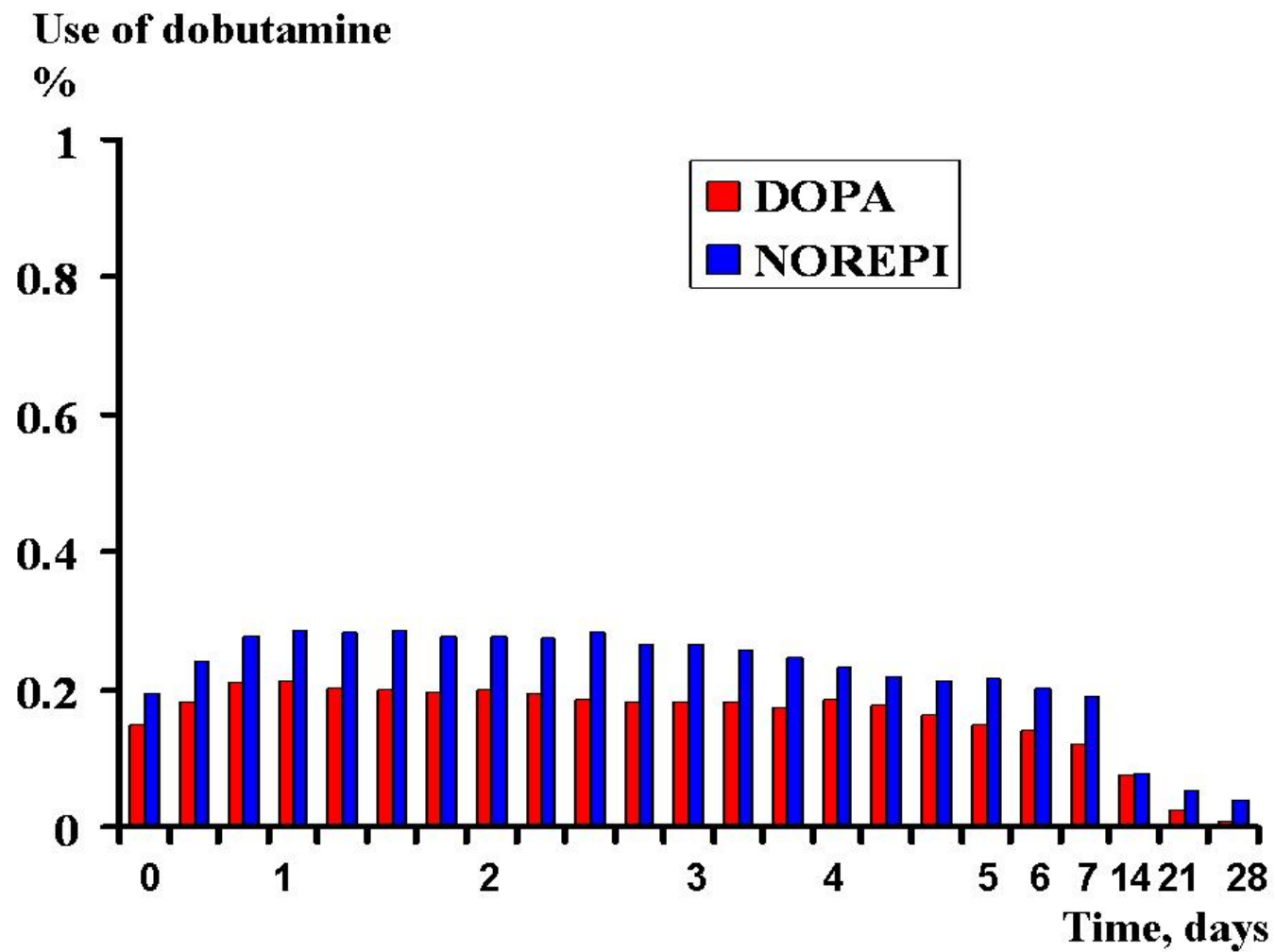
Supplementary Figure 4 Panel D: Proportion of patients receiving open label norepinephrine



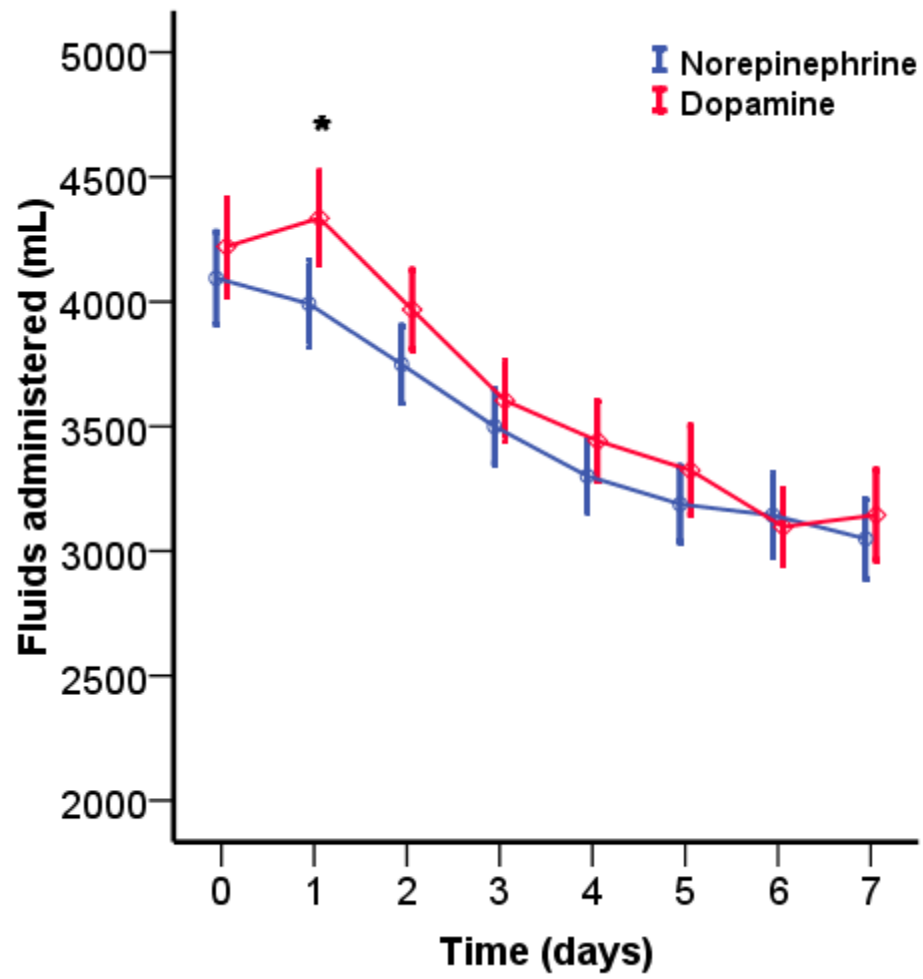
Supplementary Figure 4 Panel E: Doses of dobutamine



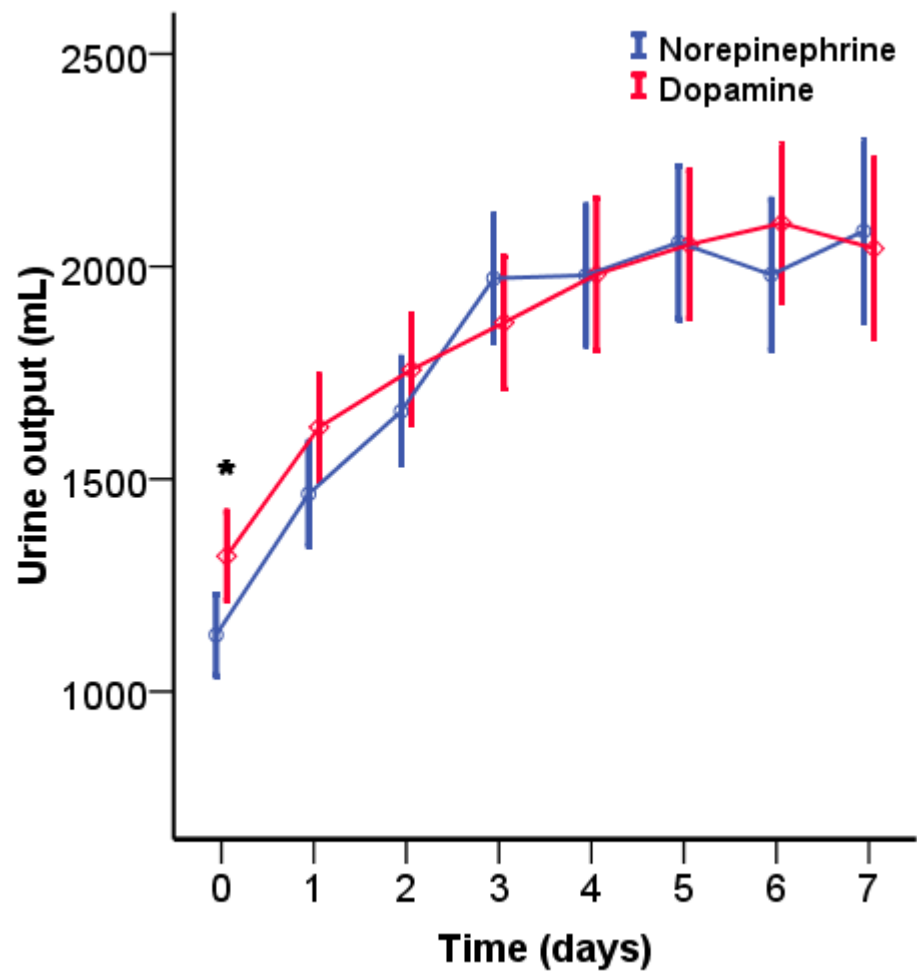
Supplementary Figure 4 Panel F: Proportion of patients receiving dobutamine at any time



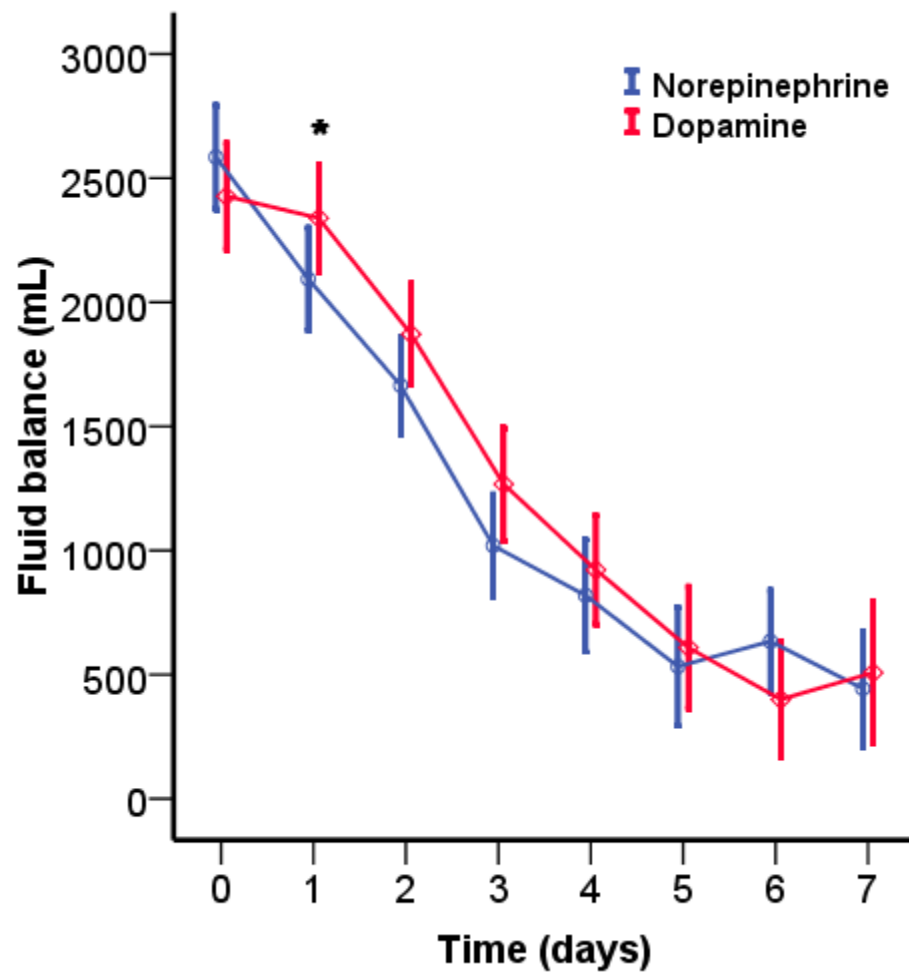
Supplementary Figure 4 Panel G: Fluid administration



Supplementary Figure 4 Panel H: Urine output

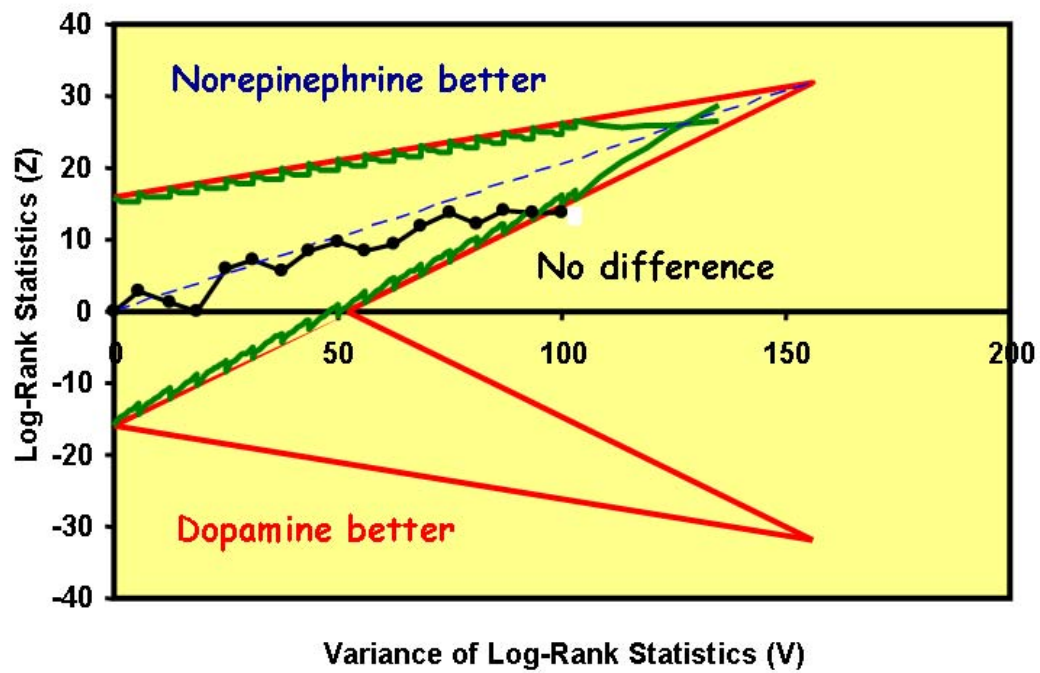


Supplementary Figure 4 Panel I: Fluid balance



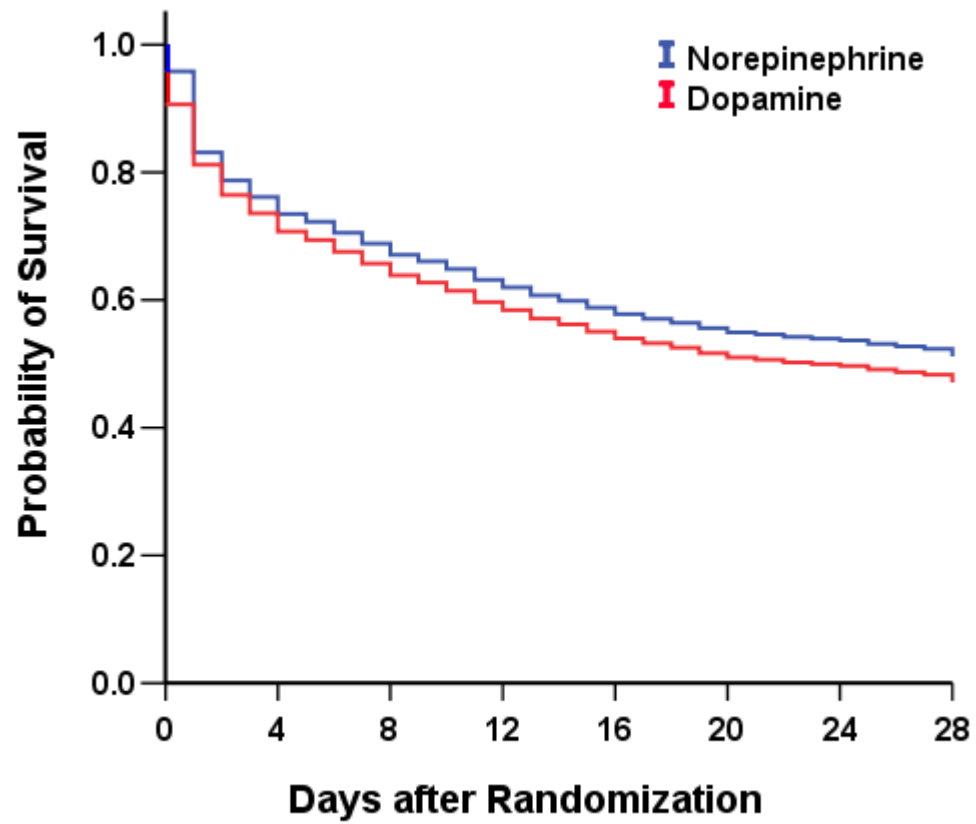
Supplementary Figure 5

Sequential Trial (1600 patients)

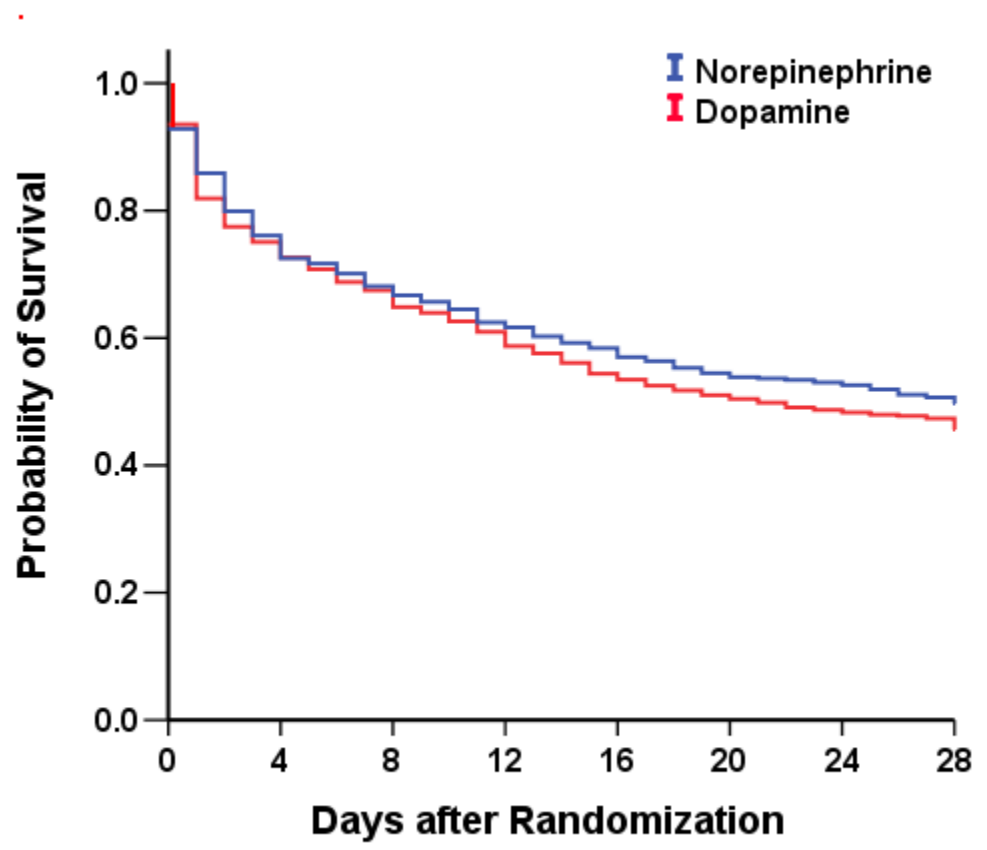


Death rate: Dopamine 52.0 % vs Norepinephrine 48.6 %

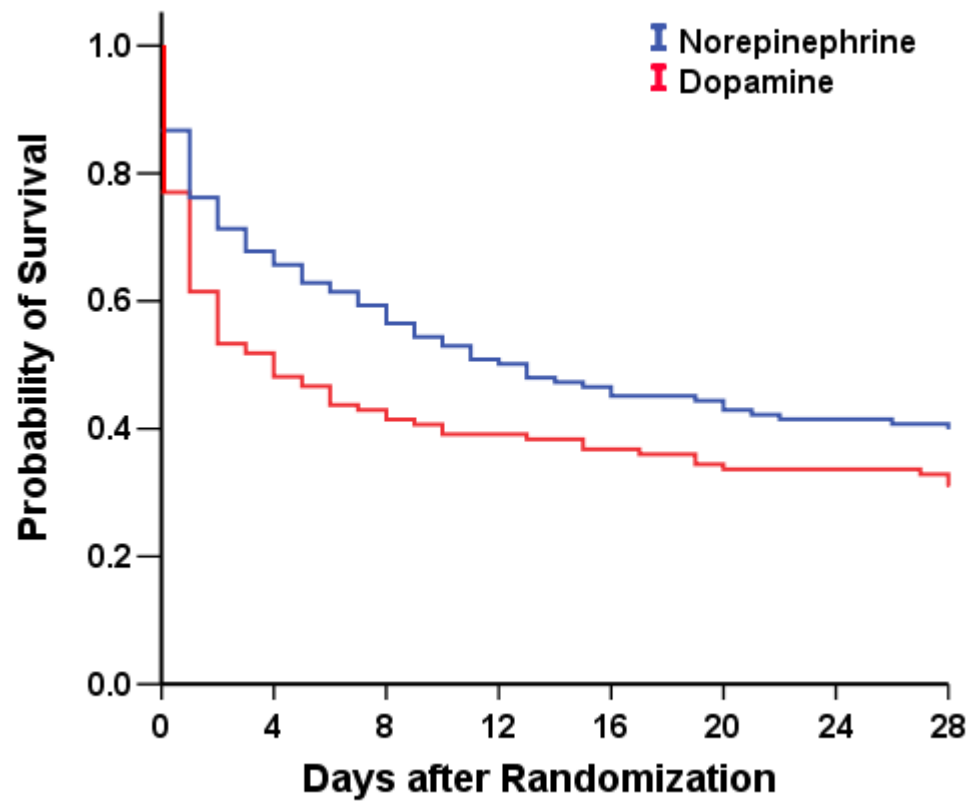
Supplementary Figure 6: Cox proportional hazards regression model for 28-day survival



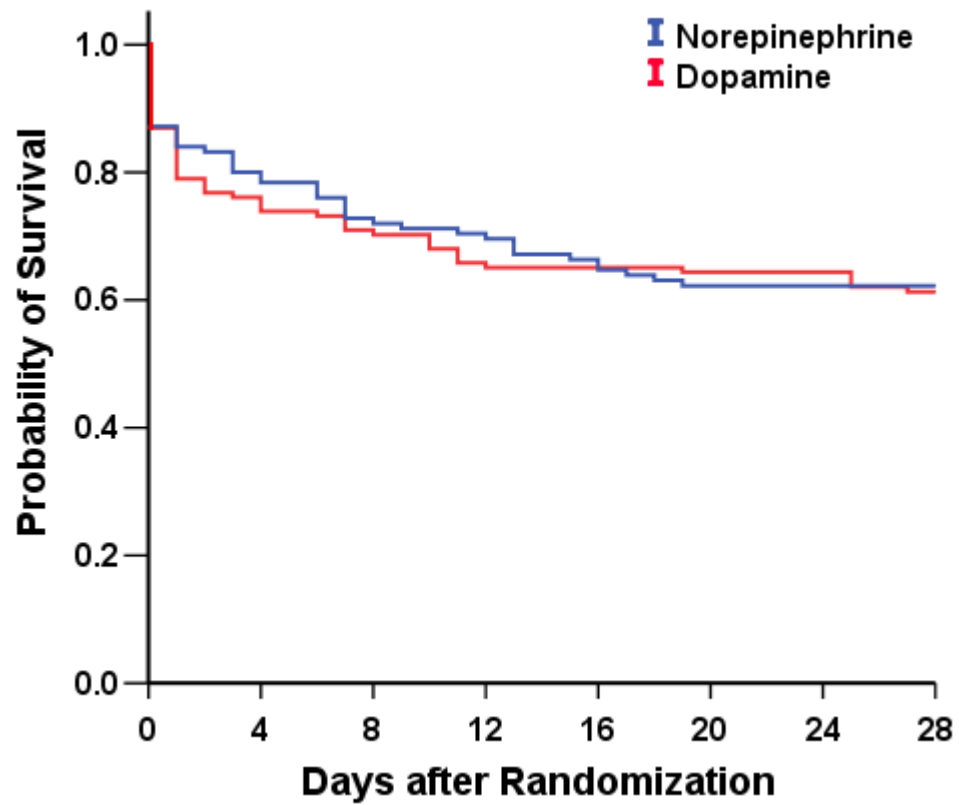
Supplementary Figure 7: Kaplan-Meier curves for 28-day survival in septic shock (Panel A)



Supplementary Figure 7: Kaplan-Meier curves for 28-day survival in cardiogenic shock (Panel B)



Supplementary Figure 7: Kaplan-Meier curves for 28-day survival in hypovolemic shock (Panel C)



Supplementary Reference List

- (1) Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994; 272:1354-1357.
- (2) De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659-1667.