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**

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Raymond Poincaré Hospital (AP-HP), University of Versailles Saint Quentin, PRES UniverSud, Paris, France (Prof D Annanne MD); **Service de Réanimation Polyvalente, Hôpital Dupuytren, Limoges, France** (Prof P Vignon MD); **Centre d'Investigation Clinique INSERM 0203, Unité de Biométrie, Université de Rennes 1, Rennes, France** (A Renault PhD); **Service de Réanimation Médicale** (Prof P-E Bollaert MD) **and Service de Réanimation Chirurgicale** (C Charpentier MD), **Hôpital Central, Nancy, France; Département d'Anesthésie-Réanimation, CHU Nord (AP-HM), Marseille, France** (Prof C Martin MD); **Service de Réanimation, CH, Versailles, France** (G Troché MD); **Service de Réanimation Médicale, Hôpital Louis Mourier, Colombes, France** (Prof J-D Ricard MD); **Service de Réanimation, Institut Gustave Roussy, Villejuif, France** (G Nitenberg MD); **Service de Réanimation Médicale, CHU Sainte-Marguerite (AP-HM), Marseille, France** (Prof L Papazian MD); **Service de Réanimation Médicale, Hôpital Saint-Louis (AP-HP), Paris, France** (Prof E Azoulay MD); **and Centre d'Investigation Clinique INSERM 0203, Unité de Pharmacologie Clinique, Hôpital de Pontchaillou, Université de Rennes 1, Rennes, France** (Prof E Bellissant MD)

Correspondence to:
Prof Djillali Annane, Raymond Poincaré Hospital (AP-HP), University of Versailles Saint Quentin, PRES UniverSud, Paris, France
djillali.annane@rpc.aphp.fr

Summary

Background International guidelines for management of septic shock recommend that dopamine or norepinephrine are preferable to epinephrine. However, no large comparative trial has yet been done. We aimed to compare the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock.

Methods This prospective, multicentre, randomised, double-blind study was done in 330 patients with septic shock admitted to one of 19 participating intensive care units in France. Participants were assigned to receive epinephrine (n=161) or norepinephrine plus dobutamine (n=169), which were titrated to maintain mean blood pressure at 70 mm Hg or more. The primary outcome was 28-day all-cause mortality. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00148278.

Findings There were no patients lost to follow-up; one patient withdrew consent after 3 days. At day 28, there were 64 (40%) deaths in the epinephrine group and 58 (34%) deaths in the norepinephrine plus dobutamine group (p=0·31; relative risk 0·86, 95% CI 0·65–1·14). There was no significant difference between the two groups in mortality rates at discharge from intensive care (75 [47%] deaths *vs* 75 [44%] deaths, p=0·69), at hospital discharge (84 [52%] *vs* 82 [49%], p=0·51), and by day 90 (84 [52%] *vs* 85 [50%], p=0·73), time to haemodynamic success (log-rank p=0·67), time to vasopressor withdrawal (log-rank p=0·09), and time course of SOFA score. Rates of serious adverse events were also similar.

Interpretation There is no evidence for a difference in efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock.

Introduction

Sepsis places a huge burden on health-care systems. In the USA, the annualised increase in the incidence of sepsis is estimated to be about 9% and its associated mortality is about 18%.[1] Septic shock, the most severe form of sepsis, accounts for about 9% of admissions to intensive care units, and its short-term mortality ranges between 40% and 60%.[2] Septic shock is commonly defined by the need for vasopressors to reverse sepsis-induced hypotension.[3] At the time this study was designed, guidelines from the French Society of Intensive Care Medicine recommended the use of dopamine as first-line treatment for septic shock and norepinephrine plus dobutamine (in patients with low cardiac output despite adequate fluid resuscitation) or epinephrine alone in dopamine-resistant shock.[4] Both strategies enable induction of vascular and cardiac effects but the combination of norepinephrine and dobutamine has the theoretical advantage over epinephrine in allowing a precise modulation of these two types of effect. More recent international guidelines recommend dopamine or norepinephrine as first-line drugs for the management of septic shock and epinephrine in patients who respond poorly to dopamine or norepinephrine.[5,6] Indeed, when compared with norepinephrine in small randomised trials, epinephrine has shown deleterious effects on splanchnic blood flow[7–10] and on acid–base balance.[7,11–13] However, these adverse effects were transient,[7] and a recent systematic review on vasopressor therapy for management of septic shock concluded that there was no evidence for any difference on short-term mortality between epinephrine and norepinephrine.[14] However, there were few patients included in that review.

The question of an advantage of norepinephrine plus dobutamine (whenever needed) over epinephrine alone thus remains unanswered. To address this question, we did a large multicentre randomised controlled trial to assess and compare the efficacy and safety of norepinephrine plus dobutamine with those of epinephrine alone in the treatment of septic shock.

Methods

Patients

Patients over the age of 18 years admitted to participating intensive care units between Oct 12, 1999, and Dec 31, 2004, were eligible for assessment. The inclusion criteria were the presence, for less than 7 days, of: evidence of infection; at least two of the four criteria for systemic inflammatory response syndrome (temperature above 38°C or below 36°C, heart rate above 90 bpm, respiratory rate above 20 cycles per min and arterial CO_2 tension below 32 mm Hg or need for mechanical ventilation, polymorphonuclear neutrophil count above 12×10^9 cells per L or below 4×10^9 cells per L); and at least two signs of tissue hypoperfusion or organ dysfunction. These signs were

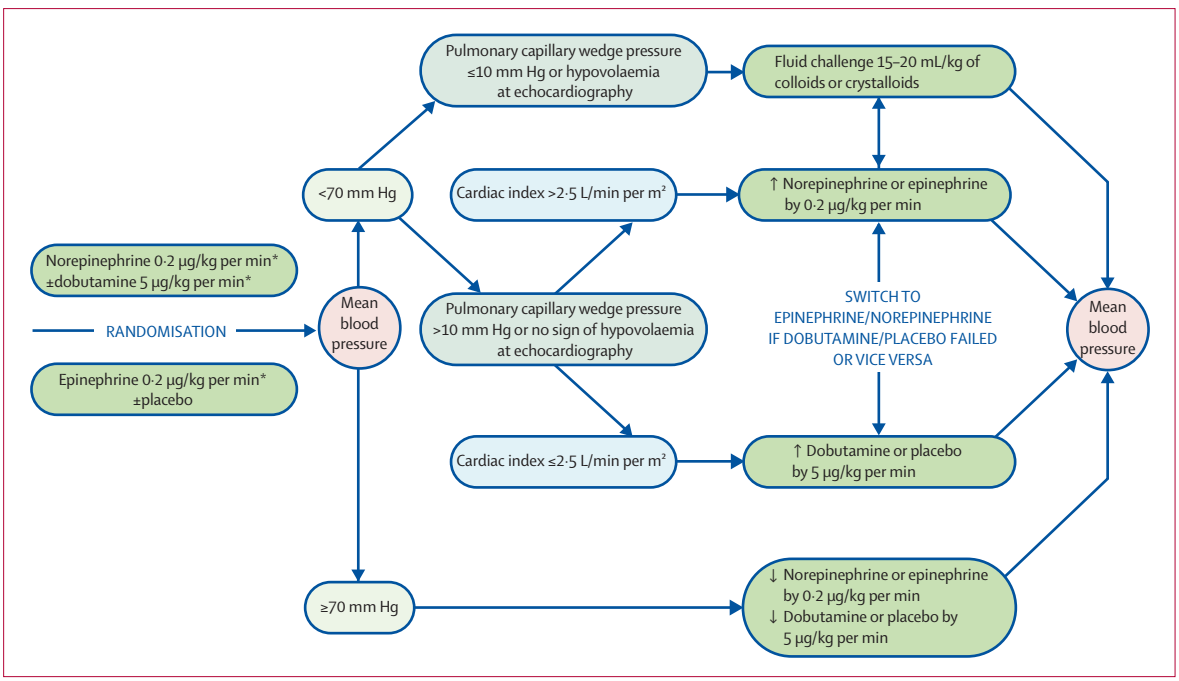

Figure 1: **Treatment algorithm**
*Starting dose.

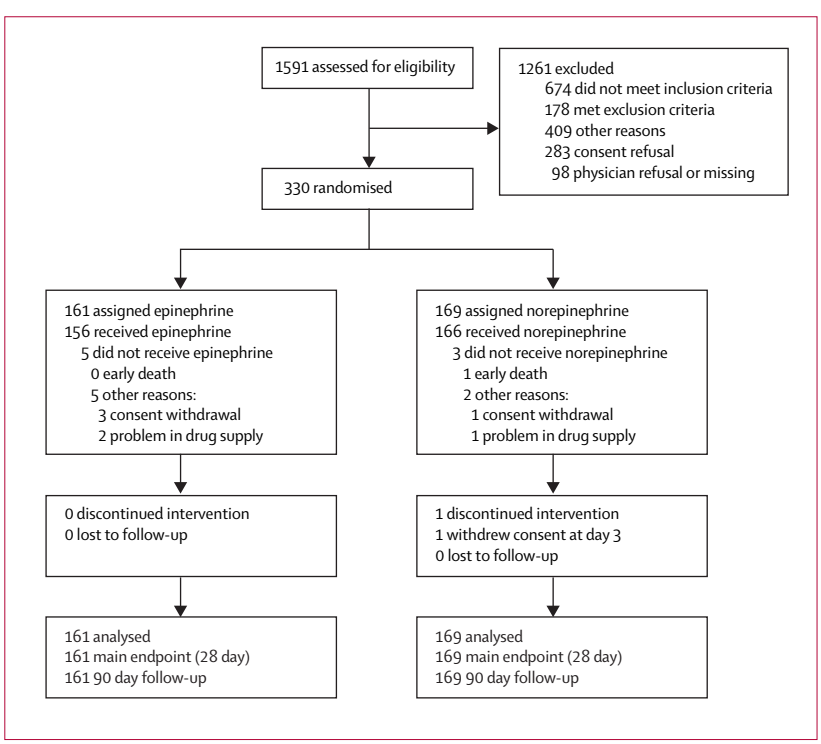

Figure 2: **Trial profile**

defined as a ratio of arterial oxygen tension over inspired fraction of oxygen of less than 280 mm Hg (if patient was mechanically ventilated), urinary output below 0·5 mL per kg of bodyweight per h or below 30 mL/h (for at least 1 h), or arterial lactate concentration above 2 mmol/L, platelet count below 100×10^9 cells per L. Additionally, patients had to meet the three following criteria for less than 24 h: systolic blood pressure below 90 mm Hg or mean blood pressure below 70 mm Hg; administration of fluid bolus of at least 1000 mL or capillary wedge pressure between 12 and 18 mm Hg; and need for more than 15 µg per kg of bodyweight per min of dopamine or any dose of epinephrine or norepinephrine. Reasons for exclusion were pregnancy; evidence of obstructive cardiomyopathy, acute myocardial ischaemia, or pulmonary embolism; advanced stage cancer, malignant haemopathy, or AIDS with a decision to withhold or withdraw aggressive therapies; persistent (longer than a week) polymorphonuclear neutrophil count of less than $0\cdot5\times10^9$ cells per L; and inclusion in another clinical trial.

The protocol was approved by the ethics committee of the French Society of Intensive Care and by the Consultative Committee for the Protection of People in Biomedical Research of Saint-Germain en Laye, France. Written informed consent was obtained from the patients themselves or their closest relatives.

Procedures

In this prospective, multicentre, randomised, double-blind study, eligible patients were randomly assigned, in a 1:1 ratio, to receive either epinephrine alone or norepinephrine plus dobutamine (whenever needed) according to a computer-generated random list. Randomisation was done centrally by an independent statistician to ensure appropriate concealment, was stratified by centre, and equilibrated by blocks of six. To ensure masking of treatment allocation, patients

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
Age (years)	63 (50–73)	65 (53–75)	60 (47–72)
Sex (M/F)	202 (61%)/128 (39%)	103 (64%)/58 (36%)	99 (59%)/70 (41%)
McCabe classification			
0: no fatal underlying disease	196 (59%)	98 (61%)	98 (58%)
1: life expectancy ≤5 years	101 (31%)	45 (28%)	56 (33%)
2: life expectancy <1 year	33 (10%)	18 (11%)	15 (9%)
Patient's location before ICU admission			
Home	93 (28%)	43 (27%)	50 (30%)
Ward	190 (58%)	95 (59%)	95 (56%)
Other ICU	38 (12%)	17 (11%)	21 (12%)
Long-term care facility	9 (3%)	6 (4%)	3 (2%)
ICU admission to randomisation delay (days)	2 (2–4)	2 (2–3)	2 (2–4)
SAPS II at admission	53 (40–65)	54 (42–67)	52 (38–64)
SIRS criteria			
Temperature (°C)	38·4 (36·8–39·1) (n=329)	38·4 (37·0– 39·1) (n=160)	38·4 (36·8–39·2) (n=169)
Heart rate (bpm)	114 (99–130)	112 (98–124)	118 (100–133)
Mechanically ventilated (yes)	312 (95%)	153 (95%)	159 (94%)
Leucocyte count (×10^9/L)	12·9 (7·6–20·7)	12·7 (7·3–21·7)	12·9 (7·7–20·2)
Tissue hypoperfusion/organ dysfunction			
PaO_2/FiO_2 (mm Hg)	151 (102–220) (n=316)	156 (96–225) (n=153)	150 (103–210) (n=163)
Urinary output (mL/24 h)	600 (200–1195) (n=328)	520 (200–1150) (n=159)	670 (210–1250) (n=169)
Lactate (mmol/L)	3·2 (1·9–5·1) (n=319)	2·9 (1·7–5·0) (n=155)	3·3 (2·1–5·1) (n=164)
Platelet counts (×10^9/L)	176 (93–267)	193 (92–275)	167 (99–236)
Haematocrit (%)	31·5 (6·2) (n=326)	32·4 (6·1) (n=158)	30·8 (6·1) (n=168)
Glasgow Coma Score	14 (7–15)	13 (7–15)	14 (8–15)
SOFA score	11 (9–14)	11 (9–13)	11 (9–14)
Shock criteria			
Systolic blood pressure (mm Hg)	100 (82–124)	100 (82–124)	100 (84–120)
Mean arterial blood pressure (mm Hg)	69 (19)	70 (19)	68 (19)
Fluid loading (mL)	1750 (1000–3500) (n=328)	1500 (1000–3500) (n=160)	2000 (1000–3625) (n=168)
Catecholamine requirements			
Dopamine >15 µg/kg per min	63 (19%)	38 (24%)	25 (15%)
Epinephrine	137 (42%)	61 (38%)	76 (45%)
Norepinephrine	102 (31%)	48 (30%)	54 (32%)
Dopamine and epinephrine	11 (3%)	6 (4%)	5 (3%)
Dopamine and norepinephrine	11 (3%)	6 (4%)	5 (3%)
Epinephrine and norepinephrine	6 (2%)	2 (1%)	4 (2%)
Specific concomitant therapies			
Adequate initial antibiotics	250 (76%)	119 (74%)	131 (78%)
Renal replacement therapy	31 (9%)	15 (9%)	16 (10%)
Corticosteroids			
None	67 (20%)	28 (17%)	39 (23%)
Hydrocortisone alone	148 (45%)	73 (45%)	75 (44%)
Hydrocortisone and fludrocortisone	115 (35%)	60 (37%)	55 (33%)
Eligible for activated protein C	119	57	62
Treated with activated protein C	25 (21%)	11 (19%)	14 (23%)

Data are mean (SD) or median (IQR) for continuous variables (samples sizes are also reported in case of missing data) and n (%) for categorical variables. ICU=intensive care unit. PaO_2/FiO_2=ratio of arterial oxygen tension to inspired fraction of oxygen.

Table 1: **General characteristics at randomisation**

randomly assigned to the epinephrine group were given epinephrine plus a placebo in place of dobutamine. Study treatments were provided by the pharmacist at each site as identical syringes for norepinephrine and epinephrine

(labelled in blue) and for dobutamine and its placebo (labelled in white). Treatments were titrated according to an algorithm designed to maintain mean blood pressure of 70 mm Hg or more (figure 1). Adherence to this algorithm was checked at each meeting of investigators.

Haemodynamic assessment required systematic continuous invasive monitoring of mean arterial blood pressure and central venous pressure, together with systematic assessment of hypovolaemia and cardiac index. Assessment of cardiac index was done in accordance with the standard of care of each participating intensive care unit—ie, by right heart catheterisation, echocardiography doppler, pulse contour cardiac output, or oesophageal doppler. Allocation of study treatments was concealed from patients, primary investigators, and all co-investigators until the release of the final statistical analysis (June 29, 2005). Concomitant treatments were left to the discretion of patients' primary physicians.

The following data were recorded at baseline: general characteristics; severity of underlying co-morbidities by the McCabe and Jackson[15] classification; severity of illness on the SAPS II[16] and SOFA[17] scores; systemic and pulmonary haemodynamics (when the patient had a pulmonary artery catheter); arterial lactate concentrations and blood gases; and results of standard laboratory tests, blood cultures, and cultures of specimen sampled in each presumed site of infection. Haemodynamics, arterial lactate concentrations, and blood gases were recorded twice daily and the SOFA score was calculated once a day from randomisation to day 28 (or to discharge from the intensive care unit, or death, depending on which occurred first).

For the safety assessment, careful neurological and cardiac examinations and a 12-lead electrocardiograph were done every day. Cardiac enzymes, echocardiography, coronary angiography, brain CT, or MRI were done whenever indicated by physical examination. Survival status was recorded during the 90 days after randomisation. For patients who left the hospital before 90 days, survival status was systematically confirmed by visit at an outpatient clinic or by telephone call.

The primary endpoint was day 28 all-cause mortality. Secondary endpoints were survival distribution from randomisation to day 90; mortality rates at day 7, day 14, at discharge from intensive care and from hospital, and at day 90; systemic haemodynamics; arterial pH and lactate; SOFA score; time to haemodynamic success (ie, a mean blood pressure above 70 mm Hg for at least 12 h consecutively); and time to vasopressor withdrawal (ie, the first interruption of study drugs for at least 24 h).

Safety was assessed daily from randomisation to day 28 (or to discharge from intensive care unit or death, depending on which occurred first) and mainly focused on the occurrence of serious adverse events such as supraventricular arrhythmias with ventricular rate above 150 bpm, ventricular arrhythmias, acute

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
Type of infection			
Community acquired	185 (56%)	88 (55%)	97 (57%)
Hospital acquired, postoperative	57 (17%)	31 (19%)	26 (15%)
Hospital acquired, others	88 (27%)	42 (26%)	46 (27%)
Primary source of infection			
Lung	155 (47%)	74 (46%)	81 (48%)
Abdomen	84 (25 %)	45 (28%)	39 (23%)
Primary septicaemia	67 (20%)	28 (17%)	39 (23%)
Urinary tract	40 (12%)	19 (12%)	21 (12%)
Bones/joints/soft tissues	34 (10%)	12 (8%)	22 (13%)
Mediastinum/endocarditis	10 (3%)	6 (4%)	4 (2%)
Central nervous system	8 (2%)	4 (3%)	4 (2%)
Catheter related	6 (2%)	4 (3%)	2 (1%)
Head and neck	2 (0·6%)	1 (0·6%)	1 (0·6%)
Others	5 (2%)	3 (2%)	2 (1%)
Positive blood cultures	118 (36%)	64 (40%)	54 (32%)
Causal microorganism			
None	63 (19%)	30 (19%)	33 (20%)
One	174 (53%)	88 (55%)	86 (51%)
More than one	93 (28%)	43 (27%)	50 (30%)
Gram-positive bacteria	154 (47%)	69 (43%)	85 (50%)
Gram-negative bacteria	158 (48%)	83 (52%)	75 (44%)
Anaerobes	28 (9%)	11 (7%)	17 (10%)
Mycobacterium	3 (1%)	2 (1%)	1 (0·6%)
Fungi	28 (9%)	12 (8%)	16 (10%)
Parasite	1 (0·3%)	1 (0·6%)	0 (0%)
Virus	3 (1%)	3 (2%)	0 (0%)

Data are number of patients (%).

Table 2: **Characteristics of infections**

	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**

	OR (logistic regression)	HR (Cox regression)
All covariates (n=308)	0·90 (0·54–1·49); p=0·67	0·87 (0·59–1·28); p=0·47
All covariates except appropriateness of antibiotic treatment (n=319)	0·82 (0·51–1·34); p=0·44	0·84 (0·58–1·22); p=0·36
All covariates except blood lactate concentration and appropriateness of antibiotic treatment (n=330)	0·82 (0·51–1·31); p=0·40	0·87 (0·61–1·24); p=0·43

Data are risk estimate (95% CI); p value.

Table 4: **Adjusted treatment effects on mortality rates at day 28**

coronary events, limb ischaemia or skin necrosis, and acute cerebrovascular events (whether haemorrhagic or ischaemic). These events were deemed to be related to catecholamine infusion when they occurred while patients were receiving study drugs.

Pharmacoeconomic analysis was done on the basis of a model that computes the medical cost of patients in intensive care.[18] This model takes into account the rate of invasive or surgical procedures and estimates the mean medical cost per patient in intensive care.

The data and safety monitoring board met three times during the study to analyse the conduct of the study, the results of interim analyses, and to review serious adverse events. Interim analyses were done on Nov 18, 2002, and Oct 1, 2003, after the assessment of 185 and 232 patients, respectively. After each analysis, the independent data and safety monitoring board advised the study chairmen to continue the study. A diagnosis validation committee also met three times during the study to grade, without knowledge of treatment allocation, the patients as having definite septic shock, probable septic shock, and probable non-septic shock,[19] and to assess the appropriateness of antibiotic treatments.

Statistical analysis

We expected an all-cause mortality rate at day 28 of 60% in the epinephrine group, on the basis of data from another trial we were doing in patients with septic shock when we planned this protocol.[20] We calculated that we would need a sample size of 340 patients to be able to detect, in a two-sided test done with a 0·05 type I error, an absolute reduction of 20% in the mortality rate at day 28 with 95% probability.

The two interim analyses were planned with an O'Brien and Fleming stopping boundary.[21] With this procedure, the differences between the two groups were considered significant if the critical Z values were higher than 3·471, 2·454, and 2·004 at the first, second, and final analyses, respectively (corresponding to nominal two-sided p values of <0·0005, <0·0141, and <0·0451).

The statistical analysis, prospectively defined, was done by intention to treat (ie, in all analyses, patients were grouped according to their original randomised treatment) with SAS statistical software (version 8.2; Cary, NC, USA). For continuous variables, the means and SD or the median (IQR), in case of significant non-normality of the distribution, are reported. The number of patients in each category and the corresponding percentages are given for categorical variables.

The effects of treatments on the frequency of fatal events (mortality rates at day 7, day 14, day 28, at discharge from intensive care or from hospital, and day 90) were compared between groups by χ^2 tests. Corresponding relative risks (RR), together with their 95% CI, were estimated. Cumulative event curves (censored endpoints) were estimated with the Kaplan-Meier procedure. The effects of treatments on these endpoints were compared between groups with the log-rank test. For the primary endpoint, we did additional analyses with logistic and Cox regression models, adjusting for the main baseline factors that predict outcomes[22] (ie, McCabe and Jackson classification, SAPS II, SOFA, arterial lactate concentrations, and appropriateness of antibiotic treatments).[23] For these analyses, continuous variables were broken into two classes on the basis of their median values. Odds ratios (OR) and hazard ratios (HR), together with 95% CI, were estimated with these models. For day 90 survival, patients who were still alive at 90 days were treated as censored. For time to vasopressor therapy withdrawal, among patients who had more than one outcome event during the 28 days from randomisation, time to first event was used in the analyses. For this endpoint, the patients who died before vasopressor therapy could be withdrawn and those for whom vasopressor therapy could not be withdrawn during the 28 days from randomisation were treated as censored. The frequency of serious adverse events was compared between groups with the χ^2 test or Fisher's exact test as appropriate. In the pharmacoeconomic analysis, the rates of invasive or surgical procedures were compared between groups by the χ^2 test and the mean medical costs per patient in intensive care were compared between groups by the Wilcoxon test. All reported p values are two-sided.

This trial is registered with ClinicalTrials.gov, number NCT00148278.

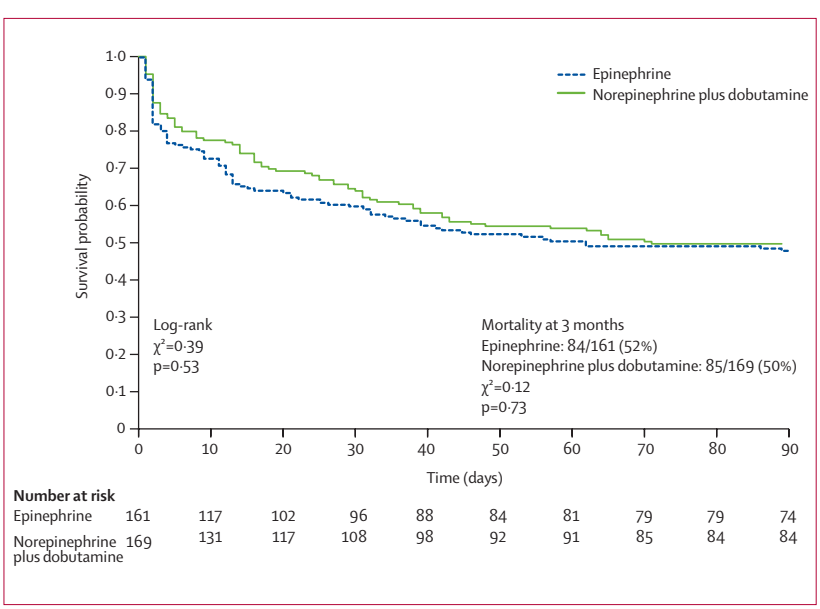

Figure 3: **Survival from randomisation to day 90**

Role of the funding source

The funding source had no role in the conduct of the study, the collection and interpretation of the data, or in the drafting of the report. All authors had full access to all the data of the study, and all agreed to submit the final manuscript for publication.

Results

1591 patients were assessed for eligibility, of whom 330 were randomly assigned to treatment (figure 2). The two treatment groups were well balanced at baseline except that the median age was slightly higher in the epinephrine group than in the norepinephrine plus dobutamine group (table 1). More than half of the patients had community-acquired infections; the lung was the commonest site of infection (table 2). The causal pathogen was identified in 267 (80%) cases (table 2). Antibiotic treatment was deemed to be appropriate in 250 (76%) cases. Use of corticosteroids and recombinant human activated protein C was much the same in the two groups (table 1).

At day 28, there was no significant difference in mortality rates between the two groups (table 3; RR 0·86, 95% CI 0·65–1·14; p=0·31). Adjusted analyses yielded similar results (table 4). There was no significant difference between the two groups for mortality rates at day 7 (0·81, 0·54–1·21; p=0·30), day 14 (0·75, 0·54–1·04; p=0·08), discharge from intensive care (0·95, 0·75–1·21; p=0·69) or hospital (0·93, 0·75–1·15; p=0·51), and at day 90 (0·96, 0·78–1·19; p=0·73). Survival until day 90 did not differ significantly between the two groups (p=0·53; figure 3).

Mean blood pressure increased to much the same extent in both groups after randomisation (figure 3). Compared with the norepinephrine plus dobutamine group, arterial pH was significantly lower on day 1 (p<0·0001), day 2 (p=0·0008), day 3 (p=0·0019), and day 4 (p=0·0007) in the epinephrine group (figure 3). Arterial lactate concentrations were also significantly increased at day 1 (p=0·0003) in patients given epinephrine only, compared with those given norepinephrine plus dobutamine (figure 4). SOFA score improved over time in both groups to much the same extent (data not shown). There were no significant differences between the two groups for the length of stay (p=0·71), the number of days not in intensive care until day 28 (p=0·14), the number of days not in intensive care until day 90 (p=0·31), the number of pressor-free days until day 28 (p=0·05), or the number of pressor-free days until day 90 (p=0·18; table 5). Likewise, there were no significant differences between the two groups in terms of the time to haemodynamic success (log-rank p=0·67; figure 5) and the time to vasopressor withdrawal (log-rank p=0·09, figure 4). The doses of vasopressors needed to achieve these effects were not different between the two treatment groups (figure 6).

There was no significant difference between the two groups in the rates of invasive or surgical procedures: 69 (43%) patients in the epinephrine group and 71 (42%) in the norepinephrine plus dobutamine group underwent such procedures (p=0·88). There was no significant difference between the two groups in mean costs per patient: £5439 (SD 5715) in the epinephrine group and £5672 (5258) in the norepinephrine plus dobutamine group (p=0·73).

There were no significant differences between the two groups in the rate of severe arrhythmias, cerebrovascular or myocardial events, limb ischaemia, or any other side-effect possibly related to catecholamine administration (table 6).

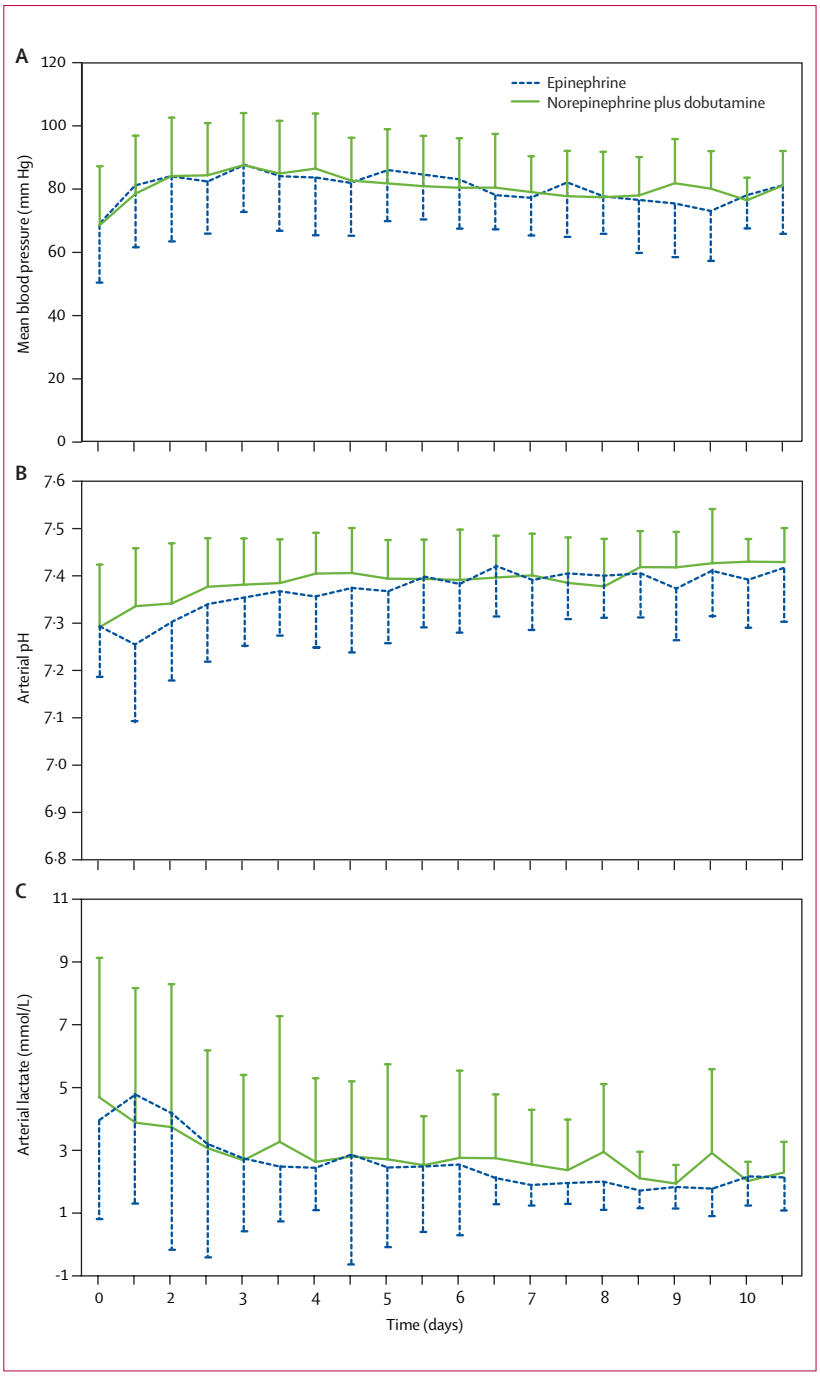

Figure 4: **Effects of treatment**
(A) Mean blood pressure. (B) Arterial pH. (C) Arterial lactate concentration. Error bars are SD.

	Epinephrine	Norepinephrine plus dobutamine	p*
Length of stay, days	15 (7–31)	16 (6–32)	0·71
Days not in intensive care until day 28	0 (0–13)	0 (0–14)	0·14
Days not in intensive care until day 90	9 (0–68)	31 (0–75)	0·31
Pressor-free days until day 28	20 (0–24)	22 (6–25)	0·05
Pressor-free days until day 90	53 (0–86)	66 (6–86)	0·18

Data are median (IQR). *Wilcoxon's test.

Table 5: **Length of stay in intensive care, days not in intensive care, and pressor-free days until day 28 and day 90**

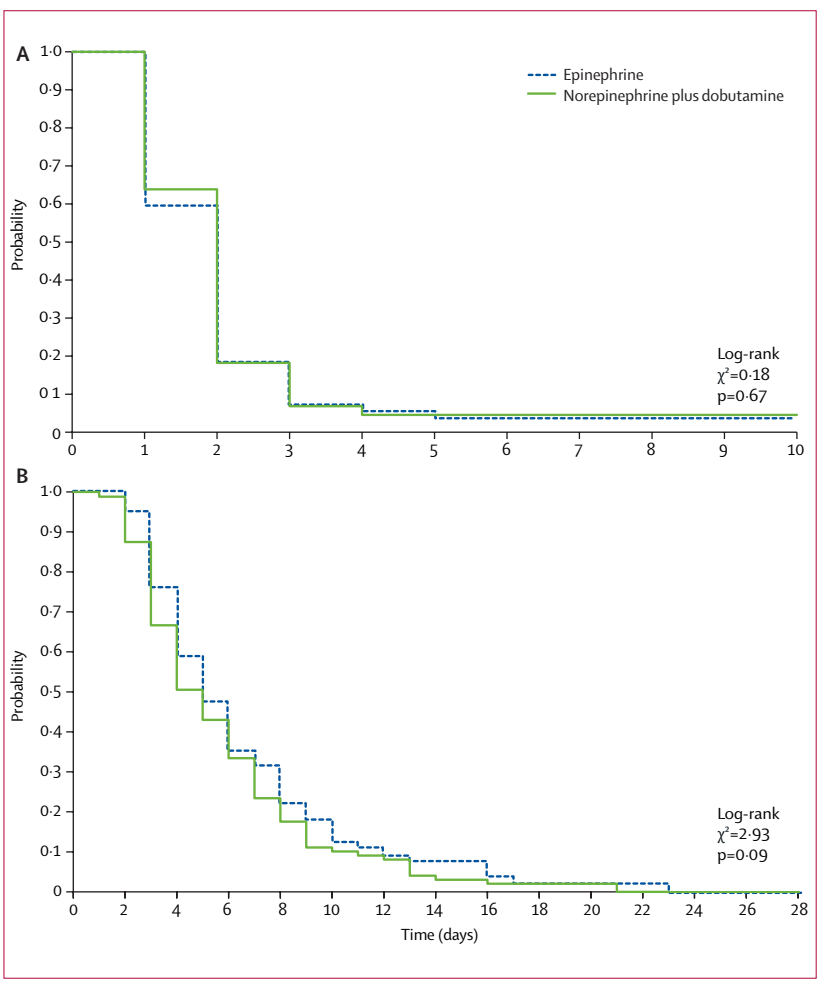

Figure 5: **Kaplan-Meier plots of time to (A) haemodynamic success and (B) vasopressor withdrawal**

Discussion

We found no evidence for a difference in all-cause mortality, in either the short term or the long term, between patients with septic shock treated with epinephrine and those treated with norepinephrine plus dobutamine (whenever needed). Furthermore, we found no evidence for a difference between the two therapeutic options in terms of delay in haemodynamic stabilisation, resolution of organ dysfunction, or adverse events.

Our findings accord with those of a systematic review on vasopressor therapy for management of septic shock.[14] That review identified two small (52 patients in total), single-centre randomised trials that compared mortality from septic shock between patients treated with norepinephrine and dobutamine and those treated with epinephrine. There were 13 (50%) deaths in the norepinephrine plus dobutamine group and 13 (50%) in the epinephrine group, with a relative risk of death of 0·98 (95% CI 0·57–1·67).

Our study population was similar to that reported in most recent clinical investigations in terms of demographic data, severity of illness, source of infection, type of pathogens, and crude mortality rate.[19] At baseline, treatment groups were well balanced, except that patients allocated epinephrine were slightly older on average, which could have favoured the norepinephrine plus dobutamine group.[2,24] Logistic and Cox's proportional hazard regression analyses did not show any evidence for a difference between groups in the main endpoint with adjustment for the main baseline factors that predict outcome; age was not incorporated into this model because it was included in SAPS II. The numbers of patients treated with corticosteroids or activated protein C, which could favourably affect septic shock mortality,[20,25] were comparable between the two groups.

This study was designed with the expectation of a mortality rate of 60% in patients treated with epinephrine on the basis of previous work and studies we were doing when this study was planned.[2,7,20] This assumption was supported by the results of a European cohort study that showed a 30-day mortality rate close to 60% in patients with shock who received epinephrine alone or in combination with other catecholamines.[26] We expected a 20% absolute reduction in 28-day mortality with norepinephrine combined with dobutamine. Indeed, we thought that potentially deleterious regional haemodynamic and metabolic effects of epinephrine could have been associated with a substantial increase in mortality. Additionally, given that norepinephrine and dobutamine are more expensive than epinephrine, and because administration and titration of two catecholamines is more cumbersome and requires monitoring of cardiac output, we hoped that such treatment would be associated with substantial improvement in clinical outcomes. In fact, the observed crude mortality rate in the epinephrine group was 40% at day 28. This difference from our expectation could be related to the generalised use of corticosteroids and, to a lesser extent, of activated protein C. However, the lower than expected mortality rate with epinephrine slightly increased the study power, allowing, for instance, the detection of a 15% difference between groups with 85% probability. In fact, to test the

hypothesis that the absolute difference observed between groups in the day 28 all-cause mortality rate was real, 5000 patients would be needed to show statistical significance with a 95% probability. Such a large clinical trial is very unlikely to be done in patients with septic shock, since they account for only 9% of admissions to intensive care;[2] even if half of all such patients were eligible for a study, recruitment of an adequate sample size would require 100 intensive care units to recruit for 2–3 years or 20 units to recruit for 10–15 years.

Epinephrine was associated with some delays in the normalisation of arterial pH and lactate concentrations compared with norepinephrine plus dobutamine. This finding is in keeping with those of previous studies that have compared the short-term effects of epinephrine with those of norepinephrine plus dobutamine,[7,12] dopamine,[11] or dopexamine.[13] These metabolic effects are probably the result of exaggerated aerobic glycolysis through Na^+K^+ ATPase stimulation within the muscles, rather than persistent tissue dysoxia.[27] The metabolic effects recovered within 4 days and had no effect on the time to haemodynamic stabilisation, recovery of organ dysfunction, or on survival.

There is some evidence that epinephrine might induce serious myocardial side-effects, thus favouring the use of norepinephrine.[6] However, we found no evidence for a difference in the occurrence of arrhythmias, ischaemic damage to the brain or the heart, or any other serious adverse event related to the two therapeutic strategies.

In practice, physicians could use either epinephrine alone, or norepinephrine alone or in combination with dobutamine in patients with low cardiac index. Future trials should compare the efficacy and safety of epinephrine, or norepinephrine, with those of dopamine, and more importantly should clarify the optimum haemodynamic goals of a vasopressor therapy in septic shock.

Contributors

DA, PEB, and EB designed the study protocol. DA and EB obtained funds from the French Ministry of Health to conduct the study, and wrote the report. AR and EB were responsible for data management and statistical analyses. All authors contributed to the report.

CATS Study Group

Study chairs—Djillali Annane, Eric Bellissant *Statisticians*—Véronique Sébille, Alain Renault. *Steering committee*—Djillali Annane, Eric Bellissant, Pierre Edouard Bollaert, Claude Martin, Gérard Nitenberg, Gilles Troché, Philippe Vignon. *Independent data and safety monitoring board*—Christian Brun-Buisson, Claude Perret, Christian Perronne. *Independent diagnosis validation committee*—Daniel Debacker, Jean-François Timsit, Jean-Paul Mira. *Monitoring*—Caroline Fisch, Chanfi Maoulida, Nathalie Zinsou. *Data management*—Delphine Serra. *Quality assurance*—Catherine Mouchel. *Pharmacists*—Annick Tibi, Blandine Lehmann. *Other investigators*—D Caen (CH-Sud Francilien, Corbeil Essonne, France); C Guérot (Hôpital Européen Georges Pompidou, AP-HP, Paris, France); J Carlet (Hôpital Saint Joseph, Paris, France); H Outin (Hôpital de Poissy Saint Germain, Poissy, France); A Parrot (Hôpital Tenon AP-HP, Paris, France); L Brinquin (Hôpital du Val de Grâce, Paris, France); J S Lemaire (CH de Roubaix, Roubaix, France).

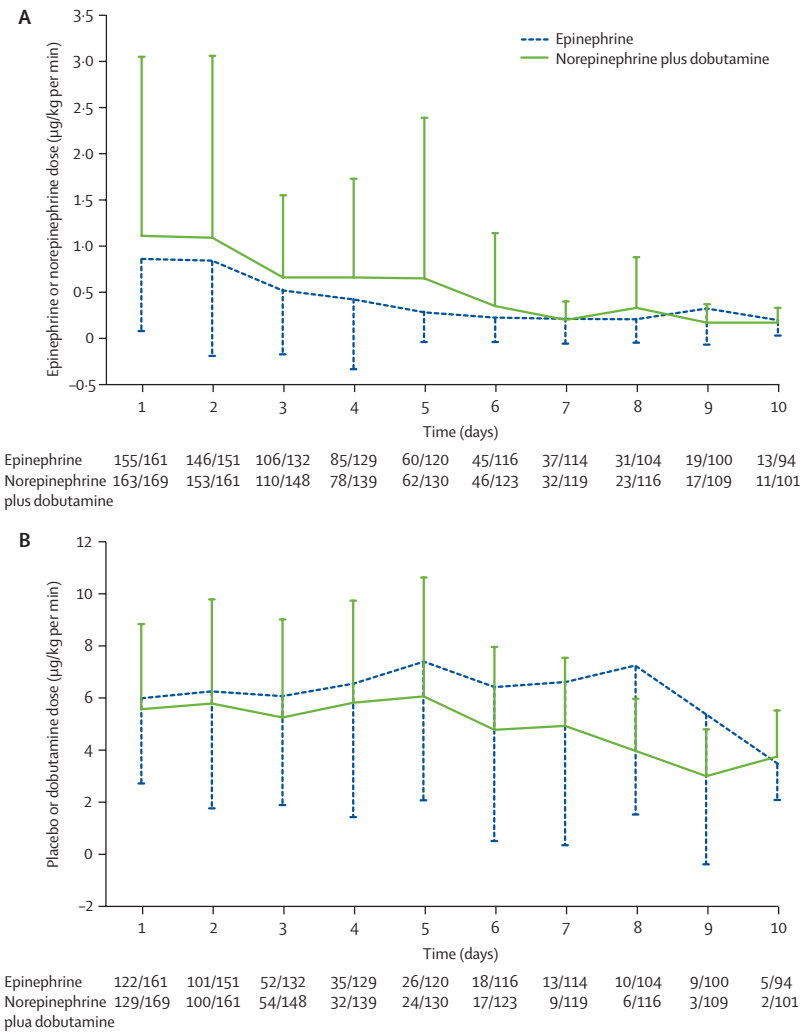

Figure 6: **Drug doses over time**
(A) Epinephrine or norepinephrine. (B) Placebo or dobutamine. Error bars are SD.

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
During catecholamine infusion			
Supraventricular tachycardia >150 bpm	41 (12%)	19 (12%)	22 (13%)
Ventricular arrhythmias	20 (6%)	12 (7%)	8 (5%)
Acute coronary event	8 (2%)	5 (3%)	3 (2%)
Limb ischaemia	8 (2%)	2 (1%)	6 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Central nervous system bleeding	3 (0·9%)	3 (2%)	0 (0%)
After catecholamine infusion			
Arrhythmias	13 (4%)	6 (4%)	7 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Other neurological sequelae	2 (0·6%)	1 (0·6%)	1 (0·6%)
Others	6 (2%)	3 (2%)	3 (2%)

Data are n (%).

Table 6: **Serious adverse events**

Conflict of interest statement

We declare that we have no conflict of interest.

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