The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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ABSTRACT

BACKGROUND

Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other.

METHODS

In this multicenter, randomized trial, we assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 μg per kilogram of body weight per minute for dopamine or a dose of 0.19 μg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events.

RESULTS

The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan–Meier analyses).

CONCLUSIONS

Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (ClinicalTrials.gov number, NCT00314704.)

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N Engl J Med 2010;362:779-89.

Circulatory shock is a life-threatening condition that is associated with high mortality.[1,2] The administration of fluids, which is the first-line therapeutic strategy, is often insufficient to stabilize the patient's condition, and adrenergic agents are frequently required to correct hypotension. Among these agents, dopamine and norepinephrine are used most frequently.[3] Both of these agents influence alpha-adrenergic and beta-adrenergic receptors, but to different degrees. Alpha-adrenergic effects increase vascular tone but may decrease cardiac output and regional blood flow, especially in cutaneous, splanchnic, and renal beds. Beta-adrenergic effects help to maintain blood flow through inotropic and chronotropic effects and to increase splanchnic perfusion. This beta-adrenergic stimulation can have unwanted consequences as well, including increased cellular metabolism and immunosuppressive effects. Dopamine also stimulates dopaminergic receptors, resulting in a proportionately greater increase in splanchnic and renal perfusion, and it may facilitate resolution of lung edema.[4] However, dopaminergic stimulation can have harmful immunologic effects by altering hypothalamo–pituitary function, resulting in a marked decrease in prolactin and growth hormone levels.[5]

Thus, dopamine and norepinephrine may have different effects on the kidney, the splanchnic region, and the pituitary axis, but the clinical implications of these differences are still uncertain. Consensus guidelines and expert recommendations suggest that either agent may be used as a first-choice vasopressor in patients with shock.[6-8] However, observational studies have shown that the administration of dopamine may be associated with rates of death that are higher than those associated with the administration of norepinephrine.[3,9,10] The Sepsis Occurrence in Acutely Ill Patients (SOAP) study,[3] which involved 1058 patients who were in shock, showed that administration of dopamine was an independent risk factor for death in the intensive care unit (ICU). In a meta-analysis,[11] only three randomized studies, with a total of just 62 patients, were identified that compared the effects of dopamine and norepinephrine in patients with septic shock. The lack of data from clinical trials in the face of growing observational evidence that norepinephrine may be associated with better outcomes called for a randomized, controlled trial. Our study was designed to evaluate whether the choice of norepinephrine over dopamine as the first-line vasopressor agent could reduce the rate of death among patients in shock.

METHODS

STUDY PATIENTS

We conducted this multicenter trial between December 19, 2003, and October 6, 2007, in eight centers in Belgium, Austria, and Spain. All patients 18 years of age or older in whom a vasopressor agent was required for the treatment of shock were included in the study. The patient was considered to be in shock if the mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite the fact that an adequate amount of fluids (at least 1000 ml of crystalloids or 500 ml of colloids) had been administered (unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter). Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead.

PROTOCOL

Randomization was performed in computer-generated, permuted blocks of 6 to 10, stratified according to the participating ICU. Treatment assignments and a five-digit reference number were placed in sealed, opaque envelopes, which were opened by the person responsible for the preparation of the trial-drug solutions. The solutions of norepinephrine or dopamine were prepared in vials or syringes according to the preference of the local ICU. Each vial or syringe was then labeled with its randomly allocated number. The doctors and nurses administering the drugs, as well as the local investigators and research personnel who collected data, were unaware of the treatment assignments. The trial was approved by the ethics committee at each participating center. Written informed consent was obtained from all patients or next of kin.

The dose was determined according to the patient's body weight. Doses of dopamine could be increased or decreased by 2 μg per kilogram per minute and doses of norepinephrine by 0.02 μg per kilogram per minute (or more in emergency cases) (see Fig. 1 and 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An example of the dose-escalation table is provided in Table 1 in the Supplementary Appendix. The target blood pressure was determined by the doctor in charge for each individual patient. If the patient was still hypotensive after the maximum dose of either agent had been administered (20 μg per kilogram per minute for dopamine or 0.19 μg per kilogram per minute for norepinephrine — doses that have been shown to have similar effects on mean arterial blood pressure[12,13]), open-label norepinephrine was added. The dose of 20 μg per kilogram per minute for dopamine was selected as the maximal dose because this upper limit was the standard of care in the participating ICUs, in line with expert recommendations[14] and international guidelines.[15]

If the patient was already being treated with a vasopressor at baseline, that agent was replaced as soon as possible with the trial-drug solution. If the patient was already receiving dopamine and this agent could not be discontinued after introduction of the trial-drug solution, the dopamine was replaced with an open-label norepinephrine infusion. Open-label dopamine was not allowed at any time. Epinephrine and vasopressin were used only as rescue therapy. Inotropic agents could be used, if needed, to increase cardiac output.

When the patients were weaned from vasopressor agents, any open-label norepinephrine that was being administered was withdrawn first, after which the trial-drug solution was withdrawn. If hypotension recurred, the trial-drug solution was resumed first (at the same maximal dose) and an open-label solution of norepinephrine was added if needed.

The study period lasted a maximum of 28 days. The study drug was reinstituted, if necessary, in patients who were discharged from the ICU but were readmitted within 28 days after randomization, allowing maximal exposure to the study drug. After day 28, the choice of vasopressor agent was left to the discretion of the physician in charge.

If adverse events occurred during treatment with the study drug, the physician in charge could withdraw the patient from the study and switch him or her to open-label vasopressor therapy. All other treatment decisions were left to the discretion of the attending physicians.

END POINTS

The primary end point of the trial was the rate of death at 28 days. Secondary end points were the rates of death in the ICU, in the hospital, at 6 months, and at 12 months; the duration of stay in the ICU; the number of days without need for organ support (i.e., vasopressors, ventilators, or renal-replacement therapy); the time to attainment of hemodynamic stability (i.e., time to reach a mean arterial pressure of 65 mm Hg)[16]; the changes in hemodynamic variables; and the use of dobutamine or other inotropic agents. Adverse events were categorized as arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation, or atrial fibrillation), myocardial necrosis, skin necrosis, ischemia in limbs or distal extremities, or secondary infections.[17]

MEASURED VARIABLES

The following data were recorded every 6 hours for 48 hours, every 8 hours on days 3, 4, and 5, and once a day on days 6, 7, 14, 21, and 28: vital signs, hemodynamic variables (including systolic and diastolic arterial pressures, heart rate, central venous pressure, and, when possible, pulmonary-artery pressures), cardiac output, arterial and mixed-venous (or central venous) blood gas levels, doses of vasoactive agents, and respiratory conditions. Biologic variables, data on daily fluid balance, microbiologic data, and antibiotic therapy were recorded daily for the first 7 days and then on days 14, 21, and 28.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score[18] was calculated at the time of admission to the ICU and at the time of enrollment in the study, and the Sequential Organ Failure Assessment (SOFA) score[19] was calculated daily for the first 7 days and then on days 14, 21, and 28.

STATISTICAL ANALYSIS

On the basis of the results of the SOAP study,[3] which showed a rate of death of 43% among patients receiving dopamine and a rate of 36% among patients receiving norepinephrine, we estimated that with 765 patients in each group, the study would have 80% power to show a 15% relative dif-

ference in the rate of death at 28 days, at a two-sided alpha level of 0.05.

Since the magnitude of the effect derived from observational studies can be misleading, we opted for a sequential trial design with two-sided alternatives[20]; the trial design called for analyses to be performed after inclusion of the first 50 and 100 patients, and then after inclusion of each additional 100 patients, and allowed for the discontinuation of the trial according to the following predefined boundaries: superiority of norepinephrine over dopamine, superiority of dopamine over norepinephrine, or no difference between the two. An independent statistician who is also a physician monitored the efficacy analyses and the adverse events; on October 6, 2007, after analysis of the outcome in the first 1600 patients showed that one of the three predefined boundaries had been crossed, the statistician advised that the trial be stopped.

All data were analyzed according to the intention-to-treat principle. Differences in the primary outcome were analyzed with the use of an unadjusted chi-square test. Results are presented as absolute and relative risks and 95% confidence intervals. Kaplan–Meier curves for estimated survival were compared with the use of a log-rank test. A Cox proportional-hazards regression model was used to evaluate the influence of potential confounding factors on the outcome (factors were selected if the P value in the univariate analysis was <0.20).

A predefined subgroup analysis of the primary outcome was conducted according to the type of shock (septic, cardiogenic, or hypovolemic). A test for interaction was performed, and the results are presented in a forest plot.

Other binary end points were analyzed with the use of chi-square tests, and continuous variables were compared by means of an unpaired Student's t-test or a Wilcoxon rank-sum test, as appropriate, with the use of SPSS software, version 13.0 (SPSS). All reported P values are two-sided and have not been adjusted for multiple testing. The study statistician and investigators remained unaware of the patients' treatment assignments while they performed the final analyses.

RESULTS

PATIENTS

A total of 1679 patients were enrolled — 858 in the dopamine group and 821 in the norepinephrine group (Fig. 1). All patients were followed to day 28; data on the outcome during the stay in the hospital were available for 1656 patients (98.6%), data on the 6-month outcome for 1443 patients (85.9%), and data on the 12-month outcome for 1036 patients (61.7%). There were no significant differences between the two groups with regard to most of the baseline characteristics (Table 1); there were small differences, which were of questionable clinical relevance, in the heart rate, partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), and ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2). The type of shock that was seen most frequently was septic shock (in 1044 patients [62.2%]), followed by cardiogenic shock (in 280 patients [16.7%]) and hypovolemic shock (in 263 patients [15.7%]). The sources of sepsis are detailed in Table 2 in the Supplementary Appendix. Hydrocortisone was administered in 344 patients who received dopamine (40.1%) and in 326 patients who received norepinephrine (39.7%). Among patients with septic shock, recombinant activated human protein C was administered in 102 patients in the dopamine group (18.8%) and 96 patients in the norepinephrine group (19.1%).

Data on hemodynamic variables and doses of vasoactive agents are shown in Figure 3 and Figure 4 in the Supplementary Appendix. The mean arterial pressure was similar in the two treatment groups at baseline, and it changed similarly over time, although it was slightly higher from 12 to 24 hours in the norepinephrine group. The doses of the study drug were similar in the two groups at all times. More patients in the dopamine group than in the norepinephrine group required open-label norepinephrine therapy at some point (26% vs. 20%, P<0.001), but the doses of open-label norepinephrine that were administered were similar in the two groups. The use of open-label epinephrine at any time was similar in the two groups (administered in 3.5% of patients in the dopamine group and in 2.3% of those in the norepinephrine group, P=0.10), as was the use of vasopressin (0.2% in both groups, P=0.67). Dobutamine was used more frequently in patients treated with norepinephrine, but 12 hours after randomization, the doses of dobutamine were significantly higher in patients treated with dopamine. The mean (±SD) time to the achievement of a mean arterial pressure of 65 mm Hg was similar in the two groups (6.3±5.6 hours in the dopamine group and 6.0±4.9 hours in the norepinephrine group,

P=0.35). There were no major between-group differences in the total amounts of fluid given, although patients in the dopamine group received more fluids on day 1 than did patients in the norepinephrine group. Urine output was significantly higher during the first 24 hours after randomization among patients in the dopamine group than among those in the norepinephrine group, but this difference eventually disappeared, so that the fluid balance was quite similar between the two groups.

The increase in heart rate was greater in patients treated with dopamine than in patients treated with norepinephrine, up to 36 hours after randomization; the changes in the cardiac index, central venous pressure, venous oxygen saturation, and lactate levels were similar in the two groups.

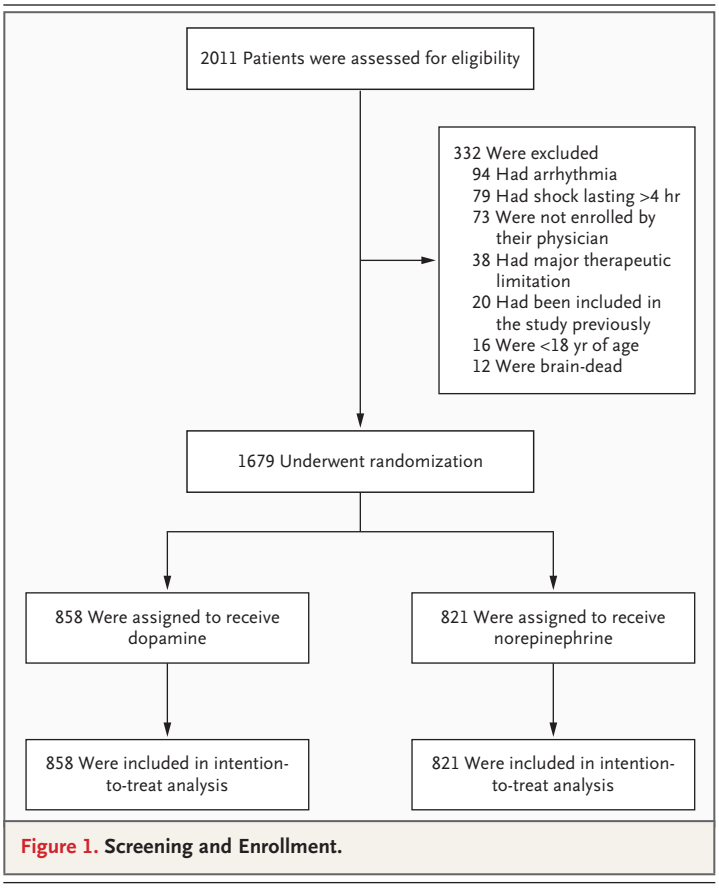

Figure 1. Screening and Enrollment.

OUTCOME

The boundary for stopping the trial owing to the lack of evidence of a difference between treatments at a P value of 0.05 was crossed (Fig. 5 in the Supplementary Appendix). There were no significant differences between the groups in the rate of death at 28 days or in the rates of death in the ICU, in the hospital, at 6 months, or at 12 months (Table 2). Kaplan–Meier curves for estimated survival showed no significant differences in the outcome (Fig. 2). Cox proportional-hazards analyses that included the APACHE II score, sex, and other relevant variables yielded similar results (Fig. 6 in the Supplementary Appendix). There were more days without need for the trial drug and more days without need for open-label vasopressors in the norepinephrine group than in the dopamine group, but there were no significant differences between the groups in the number of days without need for ICU care and in the number of days without need for organ support (Table 3). There were no significant differences in the causes of death between the two groups, although death from refractory shock occurred more frequently in the group of patients treated with dopamine than in the group treated with norepinephrine (P=0.05).

ADVERSE EVENTS

Overall, 309 patients (18.4%) had an arrhythmia; the most common type of arrhythmia was atrial fibrillation, which occurred in 266 patients (86.1%). More patients had an arrhythmia, especially atrial fibrillation, in the dopamine group than in the norepinephrine group (Table 3). The study drug was discontinued in 65 patients owing to severe arrhythmias — 52 patients (6.1%) in the dopamine group and 13 patients (1.6%) in the norepinephrine group (P<0.001). These patients were included in the intention-to-treat analysis. There were no significant differences between the groups in the incidences of other adverse events.

ADDITIONAL ANALYSES

A predefined subgroup analysis was conducted according to the type of shock — septic shock, which occurred in 1044 patients (542 in the dopamine group and 502 in the norepinephrine group); cardiogenic shock, which occurred in 280 patients (135 in the dopamine group and 145 in the norepinephrine group); or hypovolemic shock, which occurred in 263 patients (138 in the dopamine group and 125 in the norepinephrine group). The overall effect of treatment did not differ significantly among these subgroups (P=0.87 for interaction), although the rate of death at 28 days was significantly higher among patients with cardiogenic shock who were treated with dopamine than among those with cardiogenic shock who were treated with norepinephrine (P=0.03) (Fig. 3). The

Table 1. Baseline Characteristics of the Patients and Major Therapeutic Interventions at Baseline.*

Variable	Dopamine (N=858)	Norepinephrine (N=821)
Age — yr		
Median	68	67
Interquartile range	55–76	56–76
Male sex — no. (%)	507 (59.1)	449 (54.7)
APACHE II score†		
Median	20	20
Interquartile range	15–28	14–27
SOFA score‡		
Median	9	9
Interquartile range	7–12	6–12
Reason for admission — no. (%)		
Medical	565 (65.9)	532 (64.8)
Scheduled surgery	168 (19.6)	161 (19.6)
Emergency surgery	125 (14.6)	128 (15.6)
Cause of shock — no. (%)		
Sepsis	542 (63.2)	502 (61.1)
Lungs	278 (32.4)	246 (30.0)
Abdomen	138 (16.1)	135 (16.4)
Urine	51 (5.9)	42 (5.1)
Catheter	14 (1.6)	10 (1.2)
Endocardium	9 (1.0)	11 (1.3)
Mediastinum	10 (1.2)	15 (1.8)
Soft tissues	11 (1.3)	13 (1.6)
Other	15 (1.7)	20 (2.4)
Cardiogenic source	135 (15.7)	145 (17.6)
Myocardial infarction	75 (8.7)	86 (10.5)
Dilated cardiomyopathy	25 (2.9)	19 (2.3)
Tamponade	2 (0.2)	7 (0.9)
Pulmonary embolism	10 (1.2)	8 (1.0)
Valvular disease	4 (0.5)	5 (0.6)
After cardiopulmonary bypass	19 (2.2)	20 (2.4)
Other		
Hypovolemia	138 (16.1)	125 (15.2)
Hemorrhage	130 (15.2)	116 (14.1)
Trauma	17 (2.0)	23 (2.8)
Gastrointestinal bleeding	31 (3.6)	22 (2.7)
Bleeding at surgical site	64 (7.5)	57 (6.9)
Other	18 (2.1)	14 (1.7)
Dehydration	8 (0.9)	9 (1.1)
Other	48 (5.9)	44 (5.0)
Spinal	6 (0.7)	8 (1.0)
Peridural§	13 (1.5)	4 (0.5)
Intoxication-related¶	7 (0.8)	4 (0.5)
Anaphylactic	3 (0.3)	4 (0.5)
Miscellaneous	13 (1.5)	29 (3.5)
Hemodynamic, respiratory, and biologic variables		
Temperature — °C	36.6±1.5	36.6±1.5
Heart rate — beats/min	97±27	95±25‖
Mean arterial pressure — mm Hg	58±13	58±13
Mean pulmonary-artery pressure — mm Hg**	27±9	29±8‖

Table 1. (Continued.)

Variable	Dopamine (N=858)	Norepinephrine (N=821)
Pulmonary-artery occlusion pressure — mm Hg**	16±6	18±6‖
Central venous pressure — mm Hg††	13±6	13±5
Cardiac index — liters/min/m²‡‡	3.11±1.35	2.77±1.16‖
Arterial pH	7.32±0.13	7.32±0.14
$PaCO_2$ — mm Hg	42±16	41±14
PaO_2 — mm Hg	110±75	123±84§§
SaO_2 — %	95±5	96±4§§
SvO_2 — %¶¶	64±9	62±13
Lactate — mmol/liter		
Median	2.1	2.2
Interquartile range	1.2–4.3	1.2–3.8
Hemoglobin — g/dl	9.8±2.5	9.9±2.5
Creatinine — mg/dl		
Median	1.4	1.3
Interquartile range	0.8–2.4	0.8–2.3
Respiratory rate — per min	21±8	21±8
Ratio of PaO_2 to FIO_2	210±157	236±165§§
Major therapeutic interventions		
Mechanical ventilation — no. (%)	615 (71.7)	580 (70.6)
Tidal volume — ml/kg of ideal body weight	8.0±1.9	7.9±1.9
Positive end-expiratory pressure — cm of water	6±3	6±2
FIO_2	0.59±0.24	0.58±0.23
Renal-replacement therapy — no. (%)	63 (7.3)	61 (7.4)
Open-label norepinephrine		
Patients treated — no. (%)	157 (18.3)	107 (13.0)§§
Dose — μg/kg/min	0.58±0.80	0.54±0.87
Epinephrine		
Patients treated — no. (%)	13 (1.5)	9 (1.1)
Dose — μg/kg/min	1.1±2.8	1.3±1.9
Dobutamine		
Patients treated — no. (%)	127 (14.8)	159 (19.4)‖
Dose — μg/kg/min	10±6	9±6
Vasopressin		
Patients treated — no. (%)	2 (0.2)	2 (0.2)
Dose — U/min	0.03	0.03
Corticosteroids — no. (%)‖‖	101 (11.8)	76 (9.3)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. FIO_2 denotes fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, SaO_2 arterial oxygen saturation, and SvO_2 venous oxygen saturation.

† Scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale range from 0 to 71, with higher values indicating more severe disease.[18]

‡ Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction.[19]

§ Peridural shock refers to vasodilatory shock induced by peridural or epidural infusion in otherwise uncomplicated procedures.

¶ The 11 cases of intoxication were drug overdoses (5 cases) and voluntary intoxication with benzodiazepines (3), tricyclic antidepressants (2), and calcium-channel blockers (1).

‖ P<0.05 for the comparison of norepinephrine with dopamine.

** Data were available for 277 patients.

†† Data were available for 1249 patients.

‡‡ Data were available for 336 patients.

§§ P<0.01 for the comparison of norepinephrine with dopamine.

¶¶ Data were available for 357 patients.

‖‖ Corticosteroids administered at baseline included hydrocortisone and prednisolone.

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.

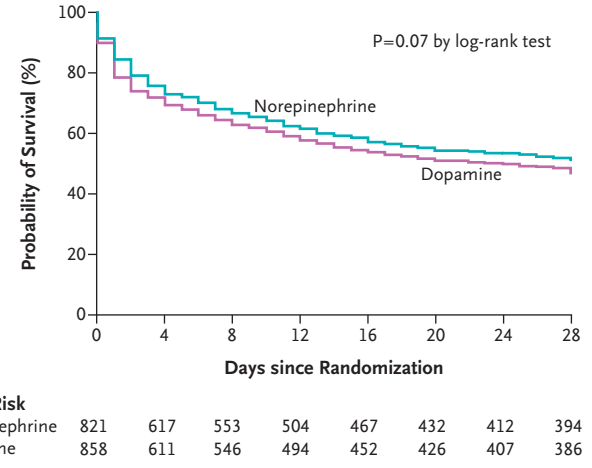

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

Kaplan–Meier curves for the subgroup analysis according to type of shock are shown in Figure 7 in the Supplementary Appendix.

DISCUSSION

In this multicenter, randomized, blinded trial comparing dopamine and norepinephrine as the initial vasopressor therapy in the treatment of shock, there was no significant difference in the rate of death at 28 days between patients who received dopamine and those who received norepinephrine. Dopamine was associated with more arrhythmic events than was norepinephrine, and arrhythmic events that were severe enough to require withdrawal from the study were more frequent in the dopamine group. In addition, dopamine was associated with a significant increase in the rate of death in the predefined subgroup of patients with cardiogenic shock.

The rate of death at 28 days in this study was close to 50%, which is to be expected in a study with very few exclusion criteria and is similar to the rate in previous observational studies.[3,9,21-24] Our trial was a pragmatic study that included all patients who were treated for shock states, and therefore, it has high external validity. The study design allowed for maximal exposure to the study drug, since we included patients who had received open-label vasopressors for a maximum of 4 hours before randomization and since during the 28-day study period, the study drug was withdrawn last when patients were weaned from vasopressor therapies and was resumed first if resumption of vasopressor therapy was necessary.

Smaller observational studies have suggested that treatment with dopamine may be detrimental to patients with septic shock.[3,9,10] However, Póvoa et al. reported a lower rate of death among patients treated with dopamine than among those treated with norepinephrine.[25] In our study, which included more than 1000 patients with septic shock, there was no significant difference in the outcome between patients treated with dopamine and those treated with norepinephrine.

Among patients with cardiogenic shock, the rate of death was significantly higher in the group treated with dopamine than in the group treated with norepinephrine, although one might expect that cardiac output would be better maintained with dopamine[26-28] than with norepinephrine. The exact cause of the increased mortality cannot be

Table 3. Secondary Outcomes and Adverse Events.*

Variable	Dopamine (N=858)	Norepinephrine (N=821)	P Value
Support-free days through day 28			
Vasopressors not needed			
Trial drug	11.0±12.1	12.5±12.1	0.01
Open-label vasopressors	12.6±12.5	14.2±12.3	0.007
Mechanical ventilation not needed	8.5±11.2	9.5±11.4	0.13
Renal support not needed	12.8±12.4	14.0±12.3	0.07
Intensive care not needed	8.1±10.3	8.5±10.3	0.43
Length of stay — no. of days			
Intensive care unit			0.12
Median	5	5	
Interquartile range	1–11	2–12	
Hospital			0.22
Median	11	12	
Interquartile range	2–28	3–28	
Cause of death in hospital — no./total no. (%)			0.31
Refractory shock	196/426 (46)	155/381 (41)	
Withdrawal or withholding of therapy	193/426 (45)	190/381 (50)	
Brain death or severe postanoxic lesions	37/426 (9)	36/381 (9)	
Adverse events			
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			
No. of episodes			0.69
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)	

* Plus–minus values are means ±SD.
† Mild skin ischemia was defined as a cold and cyanotic skin area, with capillary refill time of more than 2 seconds.
‡ Severe skin ischemia was defined as cold and black skin, with no bleeding on puncture.
§ Arterial occlusion in an extremity was considered to be present if an extremity was cold, if the capillary refill time was prolonged (>2 seconds), and if there was no pulse in the nutritive artery. Vascular occlusion in the bowel was considered to be present if bowel ischemia was detected by laparotomy, computed tomography, or colonoscopy.

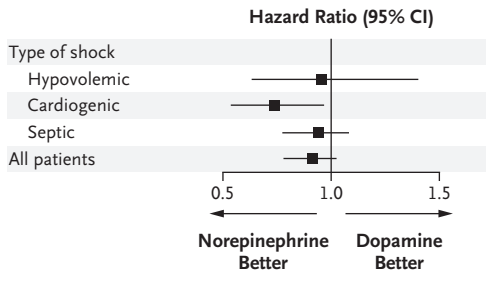

Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

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.

determined, but the early difference in the rate of death suggests that the higher heart rate with dopamine may have contributed to the occurrence of ischemic events. Whatever the mechanism may be, these data strongly challenge the current American College of Cardiology–American Heart Association guidelines, which recommend dopamine as the first-choice agent to increase arterial pressure among patients who have hypotension as a result of an acute myocardial infarction.[7]

This study has several limitations. First, dopamine is a less potent vasopressor than norepinephrine; however, we used infusion rates that were roughly equipotent with respect to systemic arterial pressure, and there were only minor differences in the use of open-label norepinephrine, most of which were related to early termination of the study drug and a shift to open-label norepinephrine because of the occurrence of arrhythmias that were difficult to control. Doses of open-label norepinephrine and the use of open-label epinephrine and vasopressin were similar between the two groups. Second, we used a sequential design, which potentially allowed us to stop the study early if an effect larger than that expected from observational trials occurred; however, the trial was eventually stopped after inclusion of more patients than we had expected to be included on the basis of our estimates of the sample size. Accordingly, all conclusions related to the primary outcome reached the predefined power.

In summary, although the rate of death did not differ significantly between the group of patients treated with dopamine and the group treated with norepinephrine, this study raises serious concerns about the safety of dopamine therapy, since dopamine, as compared with norepinephrine, was associated with more arrhythmias and with an increased rate of death in the subgroup of patients with cardiogenic shock.

Supported in part by the European Society of Intensive Care through support from the European Critical Care Research Network

Dr. Aldecoa reports receiving consulting fees from Covidien. No other potential conflict of interest relevant to this article was reported.

APPENDIX

Other investigators and participants in the trial are as follows: R. Kitzberger, U. Holzinger, Medical University of Vienna, Vienna; A. Roman, Centre Hospitalier Universitaire St. Pierre; D. De Bels, Brugmann University Hospital; S. Anane, Europe Hospitals St. Elisabeth, and S. Brimioulle, M. Van Nuffelen, Erasme University Hospital — all in Brussels; M. VanCutsem, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; J. Rico, J.I. Gomez Herreras, Rio Hortega University Hospital, Valladolid, Spain; H. Njimi (trial statistician), Université Libre de Bruxelles, Brussels; and C. Mélot (independent statistician and physician responsible for conducting sequential analysis and evaluation of serious adverse effects), Erasme University Hospital, Brussels.

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EDITORIALS

Treating Shock — Old Drugs, New Ideas

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Circulatory shock is a medical emergency that is characterized by hypotension and decreased tissue perfusion; if left untreated, it can lead to irreversible cellular injury and death. Hypotension associated with shock can be the result of any of a number of factors, depending on the type of shock; these include biventricular dysfunction, intravascular hypovolemia, and the vascular effects of inflammatory responses. Irrespective of the underlying cause of shock, the treatment includes initial resuscitation with vasopressors, volume expansion (performed cautiously in patients with heart failure), and additional therapy for multiorgan system dysfunction, concomitantly with correction of the underlying cause. A critical question is which vasopressor should be used initially. The answer is complicated by the difficulty in conducting prospective, randomized trials involving acutely ill patients.

Clinicians make an initial choice of vasopressor on the basis of published guidelines, individual experience, and institutional bias. Dopamine, the precursor for norepinephrine in the sympathetic nervous system, is recommended as a first-line agent.[1,2] However, patients in shock may have a diminished response to indirect-acting agents such as dopamine.[3] In the case of patients with heart failure, a large component of the response to dopamine is neuronal release of norepinephrine.[3] When endogenous norepinephrine is depleted in shock states, indirect-acting agonists such as dopamine are less able to produce this response.[3] In this setting, direct-acting agents such as epinephrine or norepinephrine may have improved efficacy. Epinephrine is used for resuscitation and to treat anaphylaxis, but its β_2-adrenergic effects can cause hyperglycemia, acidosis, and other adverse effects. Norepinephrine is an endogenous α_1-adrenergic vasoconstrictor and a β_1-adrenergic agonist that is stored in the sympathetic nerve terminal. In recent years, vasopressin has been increasingly used to treat the hypotension associated with shock.[4] Vasopressin may be particularly effective in reversing mediator-induced vasodilatory shock in patients with sepsis or anaphylaxis.[4,5]

In this issue of the *Journal*, De Backer et al. report the results of a multicenter trial in which they randomly assigned 1679 patients to receive either dopamine or norepinephrine as first-line vasopressor therapy to treat circulatory shock.[6] The type of shock that occurred most frequently was septic shock (1044 patients, 62.2%), followed by cardiogenic shock (280 patients, 16.7%) and hypovolemic shock (263 patients, 15.7%). The primary outcome was the rate of death at 28 days after randomization; secondary end points included adverse events and the number of days without need for organ support. The use of corticosteroids was similar in the two groups (40.1% of patients in the dopamine group and 39.7% of those in the norepinephrine group), as was the use of activated human protein C in patients with septic shock (18.8% in the dopamine group and 19.1% in the norepinephrine group). There was no significant difference in the rate of death at 28 days between patients who were treated with dopamine (52.5; 95% confidence interval [CI], 49.2 to 55.9) and those who were treated with norepinephrine (48.5; 95% CI, 45.1 to 51.9). However, arrhythmias were more frequent in the dopamine group than in the norepinephrine group (24.1% vs. 12.4%, $P<0.001$), and among the patients with cardiogenic shock, the rate of death at 28 days was higher among those treated with dopamine than among those treated with norepinephrine ($P=0.03$ by Kaplan–

Meier analysis). The authors conclude that their study raises serious concerns about the safety of dopamine as a first-line therapy for shock.[6]

Two important limitations of this study are worth noting. First, the authors defined the adequate administration of fluids as at least 1 liter of crystalloids or 500 ml of colloids, unless hemodynamic monitoring suggested otherwise. This seems to be a relatively low amount of fluid, especially since 78% of the patients were in septic or hypovolemic shock, and correction of hypovolemia is an important initial therapy. Various degrees of volume depletion must have existed in this diverse patient population, and therapeutic goals for volume repletion are difficult to set and achieve with standard hemodynamic monitoring. The type and amount of volume resuscitation may have affected the outcomes. Second, the authors suggest that they used "equipotent" doses of vasopressors, equating 20 μg per kilogram of body weight per minute of dopamine with 0.19 μg per kilogram per minute of norepinephrine. Evidence that these doses of the two vasopressors are equipotent does not exist.

An additional question is how the authors defined the resolution of shock. The criteria for entry into the study included the presence of clinical signs of tissue hypoperfusion, such as altered mental state, mottled skin, oliguria, or blood lactate levels higher than 2 mmol per liter. However, the authors do not clearly state how they defined the resolution of shock — a process that may take varying amounts of time depending on the type of shock.

What are the clinical implications of this study? The data challenge consensus guidelines that recommend dopamine as the initial vasopressor for increasing arterial pressure in the case of septic shock[1] or cardiogenic shock.[2] A previous observational study involving 1058 patients in shock reached a similar conclusion, showing that dopamine administration was an independent risk factor for death in the intensive care unit.[7] Studies also consistently show that tachycardia is a frequent side effect of dopamine therapy.[7,8]

In addition, norepinephrine needs to be considered as an initial therapeutic agent for patients in circulatory shock. Norepinephrine has long been used as a first-line agent for the treatment of hypotension and shock among patients in intensive care units and among those who have just undergone cardiac surgery. Despite concerns regarding vasoconstriction in end organs, when norepinephrine was infused to achieve a mean arterial blood pressure of higher than 70 mm Hg in patients with sepsis, urine flow and creatinine clearance rate increased after 24 hours.[9]

A remaining question is the role of arginine vasopressin as a therapeutic agent for shock. De Backer et al. used vasopressin or epinephrine as rescue therapy, and only two patients in each group received vasopressin. Vasopressin is another direct-acting agent (acting on V1 and V2 receptors) that may be as effective as norepinephrine in restoring blood pressure in patients with circulatory shock, without the tachycardia associated with dopamine. Previous studies have compared norepinephrine and vasopressin among patients with septic shock.[8,10] A recent study in the *Journal* showed that low-dose vasopressin was effective, and among patients with septic shock who were treated with catecholamines, there was no difference in the rate of death between those who received vasopressin and those who received norepinephrine.[10] There are also reports of a benefit of vasopressin therapy among patients in anaphylactic shock, since this drug is able to reverse mediator-induced vasoplegia.[5] However, when a patient presents with circulatory shock, other reversible causes should always be considered, including pneumothoraxes, pericardial tamponade, and adrenal insufficiency.

Historically, there is a widespread clinical perception that the use of norepinephrine in patients with shock may increase the risk of death. As shown in the study by De Backer et al., shock from any cause carries a high risk of death, and vasopressors are temporizing agents that are administered until the underlying cause has been treated or the shock has resolved. The results of the study by De Backer et al. should also put an end to the outdated view that the use of norepinephrine increases the risk of death.

Financial and other disclosures provided by the author are available with the full text of this article at NEJM.org.

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Ethosuximide in Childhood Absence Epilepsy — Older and Better

Eileen P.G. Vining, M.D.

Where did our wisdom about treating epilepsy originate? The ketogenic diet came from ancient teachings. The mistaken belief that seizures were caused by sexual excess led to bromides. Modern medications are developed through screening processes and, now, by drug design. However, establishing the actual clinical efficacy of a specific treatment is quite difficult. In most seizure disorders, a treatment is assumed to have resulted in optimal control if no seizures occur over a considerable period of observation. The patient and the physician cross their fingers and tick off the seizure-free days, weeks, and months before deeming a treatment successful. But the determination of therapeutic efficacy in epilepsy is different from that in many other medical conditions, such as hypertension, infection, or diabetes, in which clinicians can measure blood pressure, check a culture, or measure blood glucose levels.

Where do we obtain credible evidence that a certain medication is the right one for someone who has seizures? How are our prescribing habits formed? Finding answers to these questions is not a simple process.[1] We are influenced by the wisdom of mentors, textbooks, observational studies, standards established by professional organizations, and careful (but often clinically irrelevant) studies designed to demonstrate efficacy to the Food and Drug Administration.

Recognizing this challenge, Glauser and colleagues conducted a study of drug therapies for childhood absence epilepsy in which success could be measured more definitively and in a timely manner, and they report the results in this issue of the *Journal*.[2] Their double-blind, randomized trial compared the efficacy, adverse-event profile, and attentional effects of ethosuximide, valproic acid, and lamotrigine in children with previously untreated absence epilepsy. No studies have conclusively demonstrated efficacy of any drug treatment in this disorder. This common epilepsy syndrome is one in which there could be an objective end point: freedom from treatment failure. The authors defined failure as the persistence of absence seizures, as well as a number of other important outcomes, including a generalized tonic–clonic seizure, excessive drug-related systemic toxicity, dose-limiting toxicity, and the desire of the parents or physician to simply withdraw the study treatment. The three study medications were chosen because they are the agents most commonly prescribed and because their use has spanned decades — from the oldest (ethosuximide) to the newest (lamotrigine).

One particular advantage of studying absence epilepsy is that the clinician can induce hyperventilation at the bedside to determine whether the child is still subject to seizures and can also rely on the sensitivity of an electroencephalogram. In this study, the researchers were able to objectively measure another important aspect of therapy — that is, whether the medication interferes with the patient's attentiveness. They concluded that ethosuximide was the optimal initial therapy for children with childhood absence epilepsy in terms of both seizure control and attentional effects. Their work meets critical criteria for clinical as well as statistical relevance.

CORRESPONDENCE

Comparison of Dopamine and Norepinephrine in Shock

TO THE EDITOR: The Sepsis Occurrence in Acutely Ill Patients (SOAP) II study, reported by De Backer and colleagues (March 4 issue),[1] is a major multicenter effort to find the elusive answer to the question of whether one vasopressor is superior to another as first-line therapy for patients with circulatory shock. The use of dopamine was associated with a greater number of adverse events in the overall population and an unexpected increase in the rate of death in the subgroup of patients with cardiogenic shock. As is known, patients in various states of circulatory shock have in common the need for timely and appropriate fluid resuscitation and for vasopressor drugs as priority actions for recovery. However, among patients with septic shock — approximately two thirds of the study population — the early initiation of effective antibiotic therapy and complementary measures for control of the focus of the infection (e.g., percutaneous drainage, débridement of infected necrotic tissue, or surgery) are of great importance with respect to survival.[2-4] In this context, it would be interesting to know whether in the subgroup of patients with septic shock these measures were implemented similarly in both groups of the protocol. This information could be very relevant to the proper interpretation of the results in this subgroup of patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: De Backer et al. report in the subgroup analysis that the rate of death at 28 days among patients with cardiogenic shock was significantly higher among those who were treated with dopamine than among those who were treated with norepinephrine. This finding strongly challenges the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which recommend dopamine as the vasopressor of choice to increase arterial pressure in patients who have hypotension due to an acute myocardial infarction.[1]

An important limitation is that the authors do not address whether the underlying cause was appropriately treated. The most common cause of cardiogenic shock is an acute myocardial infarction, in which case the treatment of choice is immediate coronary reperfusion therapy.[2] Prompt

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revascularization by means of percutaneous coronary intervention or coronary-artery bypass surgery has been shown to decrease the risk of death.[3,4] Vasopressors are transitory agents that are instituted until the underlying cause can be treated. Therefore, without addressing whether the underlying cause of cardiogenic shock was properly treated, one cannot confidently conclude that dopamine is associated with a higher rate of death than is norepinephrine.

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TO THE EDITOR: De Backer et al. find no significant difference in the rate of death at 28 days between the two study groups. However a subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients in cardiogenic shock. This increase in the rate of death was ascribed to a higher incidence of arrhythmic events in the dopamine group.

The current guidelines for the treatment of cardiogenic shock[1] recommend the insertion of an intraaortic balloon pump if the inotropic agent fails to restore systolic blood pressure and signs of organ hypoperfusion persist (class of recommendation, I; level of evidence, C).

The authors should clarify whether a procedure to insert an intraaortic balloon pump was performed in the patients with cardiogenic shock. These data would be relevant to explaining the higher rate of death among patients in cardiogenic shock treated with dopamine, since an intraaortic balloon pump may be helpful in decreasing the inotropic dose and thus reducing the potential risk of arrhythmias.

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TO THE EDITOR: De Backer et al. report that dopamine, as compared with norepinephrine, was associated with more arrhythmias and an increased rate of death among patients in cardiogenic shock. Dopamine and norepinephrine, at the doses used in this study, have been shown to have similar effects on arterial blood pressure.[1,2] Actually, the increase in arterial pressure was similar in the dopamine and norepinephrine groups, but the increase in heart rate was significantly greater in the dopamine group than in the norepinephrine group (Fig. 3A and 3B in the Supplementary Appendix of the article, available at NEJM.org). The findings indicate that the doses were equipotent in terms of alpha-adrenergic effects, but beta-adrenergic effects were more potent with dopamine than with norepinephrine. This difference explains the fact that there were worse outcomes in the dopamine group than in the norepinephrine group. Because norepinephrine therapy is associated with a relatively stable heart rate, one might expect to find even more favorable outcomes than those seen in this article if the maximum dose of norepinephrine is increased. In the study by De Backer et al., open-label norepinephrine was add-

ed in some patients without inducing complications. In several other studies, higher doses of norepinephrine than those used in this study showed excellent outcomes.[3,4] The dose-range of norepinephrine in the treatment of patients with shock warrants further study.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the article by De Backer et al., I was surprised to find that 15.7% of the cohort represented patients who were in hypovolemic shock (primarily hemorrhagic). Previous studies[1] and animal models[2] have shown a possible trend toward harm (or no benefit) in treating hemorrhagic shock with vasopressors. The primary treatment remains the cessation of hemorrhage and volume replacement with either crystalloids or blood products. De Backer et al. state that adequate fluids for resuscitation were defined as 1000 cc of crystalloid or 500 cc of colloid, but there is no mention of controlling for blood products or of interventions to manage hemorrhage. Since the study was powered to detect a 15% difference in the rate of death, the fact that 15.7% of the cohort comprised patients in hypovolemic shock raises the probability of a type II error. The wide confidence interval in the Forest plot for the subgroup in hypovolemic shock may represent treatment equivalence; however the possibility of equivalent harm in a subgroup for which vasopressors are not indicated is a potential confounder that may bias the overall results of the study erroneously toward the null hypothesis.

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No potential conflict of interest relevant to this letter was reported.

1. Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. J Trauma 2008;64: 9-14.
2. Chernow B, Lake CR, Barton M, et al. Sympathetic nervous system sensitivity to hemorrhagic hypotension in the subhuman primate. J Trauma 1984;24:229-32.

TO THE EDITOR: We believe that the results of SOAP II study, reported by De Backer et al., might be confounded by the use of open-label norepinephrine. According to the study design, open-label norepinephrine was administered if the patient remained hypotensive after the maximum dose of dopamine or norepinephrine had been used. The authors report that about 26% of patients in the dopamine group and 20% of patients in the norepinephrine group were treated with open-label norepinephrine, with the maximum dose of 0.7 and 0.8 μg per kilogram per minute, respectively. These doses were much higher than the maximum dose of norepinephrine (0.16 μg per kilogram per minute) in the norepinephrine group, which might confound the results of the comparison between dopamine and norepinephrine. Accordingly, an a priori analysis of the primary outcome (the rate of death at 28 days) comparing the subgroup of patients who took open-label norepinephrine with the subgroup of patients who did not may better explain the treatment effect of the trial agents and open-label vasopressors.

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THE AUTHORS REPLY: The therapy for shock includes not only the use of vasopressor agents but other supportive measures and the treatment of the underlying cause. In our study, we took great care to ensure that these measures were adequately provided.

Romero rightly emphasizes the importance of administering appropriate antibiotics in patients with septic shock. We did not collect data on the results of bacteriologic tests and on the type of antibiotic administered, but we did collect infor-

mation on any change in antibiotic therapy. The antibiotic therapy was changed within 48 hours after a patient's inclusion in the study in only 9 of 502 patients in the norepinephrine group (1.8%) and 12 of 542 patients in the dopamine group (2.2%) (nonsignificant difference), providing indirect evidence that the antibiotic therapy was adequate in the vast majority of patients. Lee emphasizes the importance of reperfusion therapy in patients with cardiogenic shock.[1] Percutaneous angioplasty was attempted in most of the 161 patients who were in shock as a result of acute myocardial infarction. However, in contrast to Lee's statement, the need for vasopressor agents in these patients was seldom transient, since in our trial, it lasted for a mean (±SD) duration of 3±5 days. As De Santis et al. mentioned, the use of intraaortic counterpulsation is often recommended, even though its effect on the outcome is still controversial,[2] but we did not collect information on the use of intraaortic balloon pumps. Altogether, the patients in the trial were treated according to international recommendations, and there is no evidence that there was an imbalance between the two groups with respect to other therapies.

As indicated in our discussion, we agree with Tomoda that the greater increase in heart rate in the dopamine group as compared with the norepinephrine group suggests that there was a stronger beta-adrenergic stimulation with dopamine than with norepinephrine, and this may have played a role in the increased rate of death among patients with cardiogenic shock receiving dopamine. In response to Paolo's comments about hypovolemic and especially traumatic shock: vasopressor agents were also administered according to international guidelines and were used only when fluids failed to maintain tissue perfusion while physicians were attempting to find and control the source of the hemorrhage. Of note, trauma was the cause of shock in only 15.2% of patients with hypovolemic shock and 2.4% of patients with shock from any cause. To increase the external validity of our results, we decided to include all types of shock, since it is not always feasible to discriminate the type of shock initially.

In response to Du et al.: the analysis of the data without the use of open-label norepinephrine did not show a significant difference in the outcome between the dopamine group and the norepinephrine group ($P=0.45$). We agree with Tomoda that norepinephrine may be safer than is sometimes considered.

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Since publication of their article, the authors report no further potential conflict of interest.

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Management of Varices in Cirrhosis

TO THE EDITOR: The comprehensive review of management of variceal bleeding by Garcia-Tsao and Bosch (March 4 issue)[1] highlights the special difficulties in managing bleeding gastric varices, particularly with the limited availability of vasoactive agents and the lack of licensed tissue-adhesive "glue" (cyanoacrylate) in the United States. An important alternative to "gluing" gastric varices is to "clot" with an endoscopic thrombin or thrombin–fibrinogen complex injection[2]; the latter method was reported with bovine thrombin in the early 1990s.[3] The availability of human thrombin has reduced fears related to the transmission of variant Creutzfeldt–Jakob disease. Data from uncontrolled case series suggest that thrombin is effective and has an acceptable safety profile for acute hemostasis, with the hemostasis rate comparable to that of gluing (see Table 1 in