The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

# High versus Low Blood-Pressure Target in Patients with Septic Shock

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## ABSTRACT

### BACKGROUND

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

### METHODS

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

### RESULTS

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P=0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P=0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; P=0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

### CONCLUSIONS

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

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This article was published on March 18, 2014, at NEJM.org.

N Engl J Med 2014;370:1583-93.
DOI: 10.1056/NEJMoa1312173

Septic shock is characterized by arterial hypotension despite adequate fluid resuscitation. The guidelines of the Surviving Sepsis Campaign[1] recommended initial resuscitation with vasopressors to reverse hypotension, with a mean arterial pressure target of at least 65 mm Hg (grade 1C, indicating a strong recommendation with a low level of evidence). This recommendation is based on the findings of small studies, which showed no significant differences in lactate levels or regional blood flow when the mean arterial pressure was elevated to more than 65 mm Hg in patients with septic shock.[2,3]

However, as emphasized by the Surviving Sepsis Campaign guidelines, for patients with atherosclerosis or previous hypertension, a higher blood-pressure target may be better. Accordingly, values for mean arterial pressure exceeding 65 mm Hg are frequently observed, as confirmed by data from large, prospective, randomized, controlled trials that focused on resuscitation of patients with septic shock, which showed that patients had mean arterial pressures in the range of 75 to 95 mm Hg 24 hours after inclusion.[4-8] Moreover, a large, retrospective study showed that a mean arterial pressure of more than 75 mm Hg may be required to maintain kidney function.[9] The notion that a higher blood pressure can be useful was confirmed in a small, prospective, observational study.[10] Finally, a study of physiological mechanisms of chronic arterial hypertension showed that such hypertension causes a rightward shift in cerebral pressure-flow autoregulation, which might justify targeting a higher mean arterial pressure.[11]

Since the selection of effective blood-pressure targets is still controversial, we conducted a multicenter, randomized, stratified, open-label trial involving patients with septic shock to determine whether targeting a mean arterial pressure of 80 to 85 mm Hg would decrease 28-day mortality, as compared with targeting a mean arterial pressure of 65 to 70 mm Hg. We also postulated that the beneficial effects of a higher target would be more pronounced among patients with chronic hypertension. Therefore, at randomization, patients were stratified according to whether they had a history of chronic hypertension.

## Methods

### Study Design

From March 2010 through December 2011, we enrolled patients at 29 centers in France. The study was approved for all centers by the ethics committee at the Angers University Hospital. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision maker, as appropriate. If patients were unable to provide informed consent and neither their next of kin nor other designated person was available, a procedure for inclusion in the study in emergency situations was applied. A definitive post hoc consent form was ultimately obtained from patients who survived but had been initially treated on the basis of the emergency consent.

Randomization was performed with the use of a computer-generated assignment sequence in a centralized, blinded fashion and was stratified according to whether patients had chronic hypertension (i.e., had been receiving antihypertensive treatment or had a history of arterial hypertension). Given the pragmatic character of the trial, it was impossible to obtain details on the patients' adherence to the antihypertensive drug regimen or the adequacy of the antihypertensive treatment during the inclusion time window. Patients, research staff members, and members of the safety and writing committees were unaware of the study-group assignments.

### Study Oversight

The data and safety monitoring committee oversaw the trial conduct and the safety of the patients, with interim analyses performed after the inclusion of 200, 400, and 600 patients. Data were collected by the investigators and analyzed by the data-management committee. The steering committee vouches for the accuracy of the data, the completeness of the analysis, and the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org. Members of the steering committee made the decision to submit the manuscript for publication. The writing committee (the first author and the last three authors) had full access to all the data and collaborated with all the investigators in the writing of the manuscript. All the drugs used in

the study were purchased from the manufacturers, which had no role in the study.

### STUDY PATIENTS

Patients older than 18 years of age were enrolled if they had septic shock that was refractory to fluid resuscitation, if they required vasopressors (norepinephrine or epinephrine) at a minimum infusion rate of 0.1 μg per kilogram per minute, and if they were evaluated within 6 hours after the initiation of vasopressors. Refractoriness to fluid resuscitation was defined as a lack of response to the administration of 30 ml of normal saline per kilogram of body weight or of colloids or was determined according to a clinician's assessment of inadequate hemodynamic results on the basis of values obtained during right-heart catheterization, pulse-pressure measurement, stroke-volume measurement, or echocardiography (although study investigators did not record the values for these variables). Septic shock was defined by the presence of two or more diagnostic criteria of the systemic inflammatory response syndrome, proven or suspected infection, and sudden dysfunction of at least one organ.[12] Exclusion criteria were legal protection (i.e., incompetence to provide consent and no guardian or incarceration), no affiliation with the French health care system, pregnancy, recent participation in another biomedical study or another interventional study with mortality as the primary end point, or an investigator's decision not to resuscitate.

### STUDY TREATMENTS

Fluid resuscitation was performed as recommended by the French intensive care societies,[13] with norepinephrine administered as a first-line vasopressor, except at one center, in which epinephrine was used. The use of activated protein C and hydrocortisone was left to the discretion of the attending physician, and the following treatments were prohibited: the use of diuretics, except for compelling indications, such as hypoxemia attributed to symptomatic sodium and water overload or life-threatening hyperkalemia; the use of nonsteroidal antiinflammatory drugs; the use of iodinated contrast agents unless necessary for imaging; and the use of nephrotoxic antibiotics unless judged necessary by the attending physician. Any use of the above-mentioned drugs after study entrance was recorded.

Renal-replacement therapy was initiated if at least one of the following criteria was present: anuria, hyperkalemia with electrocardiographic changes, pure metabolic acidosis with a pH of less than 7.2, or a blood urea nitrogen level of more than 84 mg per deciliter (30 mmol per liter) or a creatinine level of more than 5.65 mg per deciliter (499 μmol per liter). Administration of sedative and analgesic drugs or muscle relaxants was left to the discretion of the clinician; doses were reassessed at least daily to achieve values ranging from −3 to 0 on the Richmond Agitation–Sedation Scale (which ranges from −5 to 4, with lower scores indicating deeper sedation, 0 indicating a calm and responsive patient, and higher scores indicating increasing agitation); all doses of sedative and analgesic drugs were recorded daily.

After enrollment, patients were assigned to vasopressor treatment that was adjusted to maintain a mean arterial pressure of 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The target mean arterial pressure was to be maintained for a maximum of 5 days or until the patient was weaned from vasopressor support; after that, the target pressure was determined by the attending physician. For patients in whom the assigned target pressure was not reached despite the administration of increasing doses of vasopressors, group assignments were not modified, and data analysis was conducted on an intention-to-treat basis. (The vasopressor-weaning strategy is described in the Supplementary Appendix, available at NEJM.org.)

In the high-target group, a reduction in vasopressor doses to maintain a mean arterial pressure of 65 to 70 mm Hg was recommended if any of the prespecified serious adverse events that were potentially related to an increased rate of vasopressor infusion occurred. These events were as follows: clinically relevant bleeding (i.e., transfusion requirements of at least 2 units of packed red cells), myocardial infarction (defined as typical electrocardiographic changes, with a concomitant increase in troponin, and segmental echocardiographic hypokinesia or akinesia,

with the infarction confirmed, when possible, by means of coronary angiography), major ventricular arrhythmia, poorly tolerated supraventricular arrhythmia, mesenteric ischemia, and distal-limb ischemia. Data analysis for serious adverse events was performed for all patients on an intention-to-treat basis.

### STUDY OUTCOMES

The primary outcome was death from any cause by 28 days after inclusion. Secondary outcomes were 90-day mortality, days alive and free from organ dysfunction by day 28, and the length of stay in the intensive care unit (ICU) and hospital. Survival by day 28 without organ support was defined as the number of days without catecholamine infusion, mechanical ventilation, or renal-replacement therapy.[14] Serious adverse events were recorded and classified as cardiac, ischemic, or other.

### STATISTICAL ANALYSIS

We determined that the enrollment of 800 patients would provide a power of 80% to show an absolute between-group difference of 10 percentage points in the primary outcome, at a two-sided alpha level of 0.05, assuming a rate of death of 45%. We decided not to compensate for dropouts caused by the withdrawal of consent. All analyses were performed by the study statistician before the randomization code was broken, in line with both the International Conference on Harmonization–Good Clinical Practice guidelines and our statistical analysis plan (which is available in the protocol).

The analyses were performed in the intention-to-treat population, which was defined as all patients who had undergone randomization except for those who did not provide consent for the use of their data. We used Cox regression models to calculate between-group differences in mortality at 28 days and 90 days. We analyzed Schoenfeld residuals to test the assumption of proportional hazards and used the Kaplan–Meier method to calculate survival curves. We expressed quantitative variables as means (±SD) and used t-tests to compare them when the sample size in each group was 30 or more (in accordance with the central limit theorem) and the Wilcoxon rank-sum test when the sample size in one group was less than 30. We used chi-square tests or Fisher's exact test to compare qualitative variables, as appropriate. All comparisons were also performed with the use of the entire sample with stratification (as prespecified) according to the presence or absence of chronic hypertension. Multiple logistic-regression analyses were conducted in the intention-to-treat population to adjust for known risk factors for acute kidney injury, such as chronic renal failure or the use of diuretics, vancomycin, aminoglycosides, iodine-containing contrast material, or long-term use of nonsteroidal antiinflammatory drugs.

Interim analyses were performed for the primary outcome of 28-day mortality, according to the Haybittle–Peto method. Statistical significance was indicated by a P value of 0.001 in the three interim analyses and a two-sided P value of 0.0492 in the final analysis. To detect a possible interaction between group and stratum covariates, logistic-regression analyses were performed for dichotomous dependent variables, whereas analysis-of-variance models were used for continuous dependent variables. All analyses were performed with the use of Stata software, version 12.1.

## RESULTS

### STUDY POPULATION

We enrolled 776 patients and followed them for 90 days; we conducted the analyses according to the group to which the patients were randomly assigned (Fig. 1). Baseline characteristics were similar in the two groups (Table 1, and Table S1 and Fig. S1 in the Supplementary Appendix). Overall, 167 of 388 patients (43.0%) in the high-target group and 173 of 388 (44.6%) in the low-target group had a history of chronic hypertension. All the enrolled patients were critically ill, as defined by the Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) score, serum lactate levels, and norepinephrine infusion rates at study entry. During the 5 protocol-specified days, the mean arterial pressures in the low-target group were significantly lower than those in the high-target group, yet they exceeded the target values of 65 to 70 mm Hg (Fig. 2).

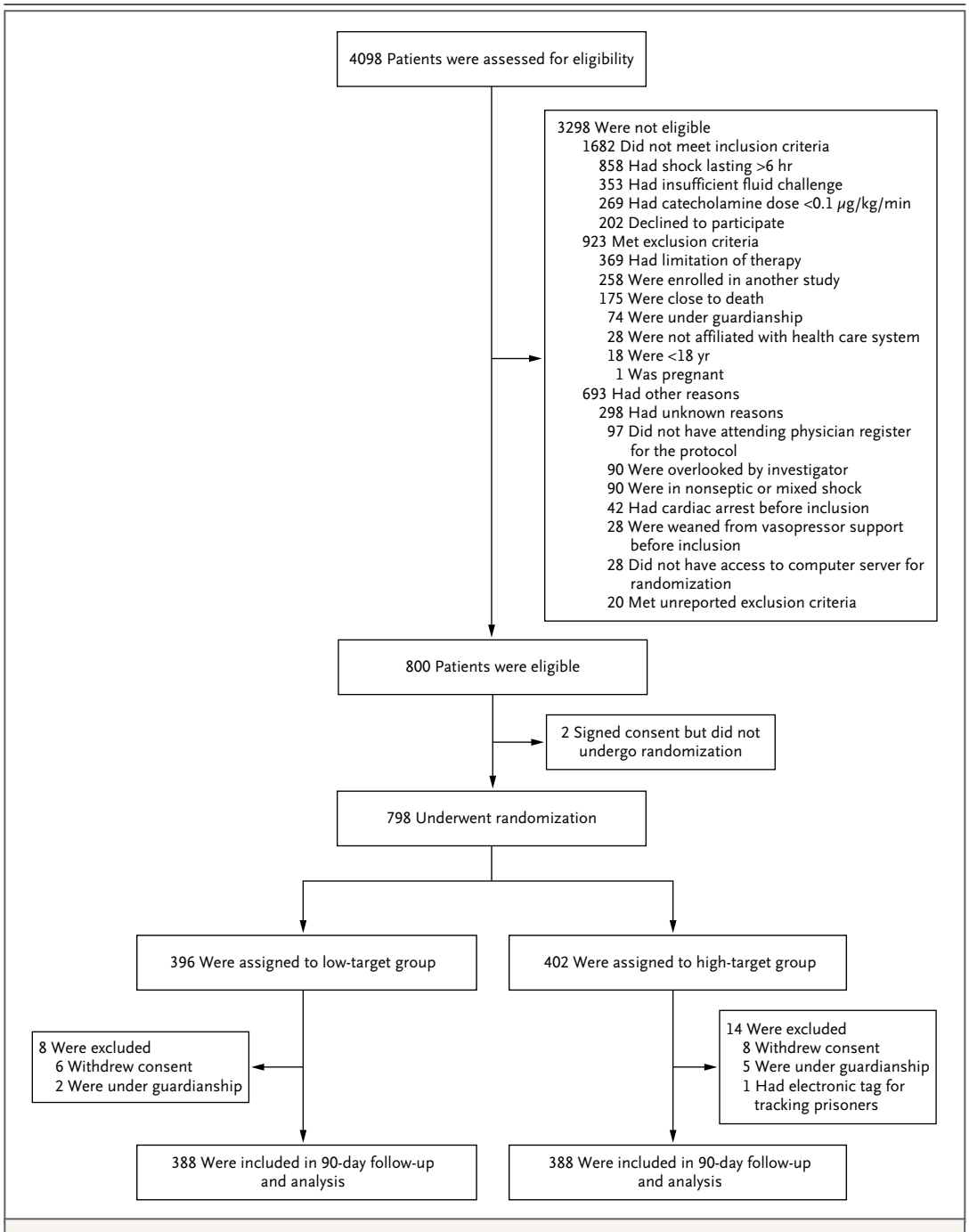


**Figure 1. Screening, Randomization, and Follow-up of Study Patients.**

### VASOPRESSOR USE AND FLUID BALANCE

The infusion rates of vasopressors were significantly higher, and the duration of vasopressor treatment significantly longer, in the high-target group than in the low-target group (Table 2, and Table S2A in the Supplementary Appendix). A total of 64 patients (16.5%) in the high-target group and 40 patients (10.3%) in the low-target

group (P=0.01) did not reach targets for mean arterial pressure because of the attending physician's decision to limit the vasopressor infusion rates. In 14 patients (3.6%) in the high-target group, vasopressor infusion rates were adjusted downward to maintain a mean arterial pressure of 65 to 70 mm Hg because of adverse effects. Values for total fluid administration and total urine output during the 5 days specified in the protocol were similar in the two study groups (Table S2B in the Supplementary Appendix).

### PRIMARY OUTCOME

At 28 days, there was no significant between-group difference in the rate of death, with deaths reported in 142 of 388 patients (36.6%) in the high-target group and 132 of 388 patients (34.0%) in the low-target group (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P=0.57). There was also no significant between-group difference in mortality at 90 days, with 170 deaths (43.7%) and 164 deaths (42.3%), in the two groups, respectively

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Low-Target Group (N=388) | High-Target Group (N=388) |
|---|---|---|
| Age — yr | 65±15 | 65±13 |
| Male sex — no. (%) | 250 (64.4) | 267 (68.8) |
| Simplified Acute Physiology Score II† | 57.2±16.2 | 56.1±15.5 |
| Sequential Organ Failure Assessment score‡ | 10.8±3.1 | 10.7±3.1 |
| Recent surgical history — no. (%) | | |
| Elective | 5 (1.3) | 2 (0.5) |
| Emergency | 55 (14.2) | 47 (12.1) |
| Preexisting conditions — no. (%) | | |
| Ischemic heart disease | 39 (10.1) | 39 (10.1) |
| Chronic heart failure | 53 (13.7) | 59 (15.2) |
| Chronic obstructive pulmonary disease | 47 (12.1) | 58 (14.9) |
| Chronic kidney disease | 30 (7.7) | 20 (5.2) |
| Chronic kidney disease requiring long-term dialysis | 12 (3.1) | 5 (1.3) |
| Liver cirrhosis | 28 (7.2) | 29 (7.5) |
| Diabetes | 90 (23.2) | 75 (19.3) |
| Cancer or autoimmune disease | 135 (34.8) | 142 (36.6) |
| Chronic arterial hypertension | 173 (44.6) | 167 (43.0) |
| Source of infection — no. (%) | | |
| Lung | 200 (51.5) | 202 (52.1) |
| Abdomen | 67 (17.3) | 65 (16.8) |
| Urinary tract | 44 (11.3) | 44 (11.3) |
| Other§ | 73 (18.8) | 72 (18.6) |
| Community-acquired infection — no. (%) | 253 (65.2) | 262 (67.5) |
| Hemodynamic and biochemical variables | | |
| Mean arterial pressure — mm Hg | 73±14 | 74±15 |
| Heart rate — beats/min | 103±24 | 104±27 |
| Arterial pH | 7.30±0.13 | 7.30±0.12 |
| Serum lactate level — mmol/liter | 3.7±3.7 | 3.3±3.2 |
| Fluid therapy before inclusion — ml | 2946±1360 | 2973±1331 |

**Table 1. (Continued.)**

| Characteristic | Low-Target Group (N=388) | High-Target Group (N=388) |
|---|---|---|
| Vasoactive drug infusions at randomization — no. (%) | | |
| Norepinephrine | 368 (94.8) | 373 (96.1) |
| Epinephrine | 20 (5.2) | 15 (3.9) |
| Dobutamine | 21 (5.4) | 16 (4.1) |
| Median vasopressor dose at randomization — μg/kg/min (IQR) | | |
| Norepinephrine | 0.35 (0.20–0.61) | 0.40 (0.20–0.62) |
| Epinephrine | 0.23 (0.17–0.32) | 0.22 (0.13–0.64) |
| Mechanical ventilation — no. (%) | 286 (73.7) | 308 (79.4) |
| $Pao_2$:$FIo_2$ ratio — mm Hg | 198±120 | 199±126 |
| Acute kidney injury — no./total no. (%)¶ | 188/386 (48.7) | 173/384 (45.1) |
| Serum creatinine at inclusion — mg/dl | 1.96±1.39 | 1.93±1.47 |

* Plus–minus values are means ±SD. The target mean arterial pressure was 80 to 85 mm Hg in the high-target group and 65 to 70 mm Hg in the low-target group. None of the differences between the two groups were significant at baseline. To convert the values for creatinine to micromoles per liter, multiply by 88.4. $FIo_2$ denotes fraction of inspired oxygen, IQR interquartile range, and $Pao_2$ partial pressure of oxygen in arterial blood.
† The Simplified Acute Physiology Score II is based on 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.
‡ The score on the Sequential Organ Failure Assessment (SOFA) includes subscores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure.
§ Other sources of infection included blood, soft tissue, skin, central nervous system, bones and joints, cardiac system, reproductive organs, and unknown sources.
¶ Acute kidney injury was defined as a renal SOFA score of 2 or more (plasma creatinine level, >1.9 mg per deciliter [168 μmol per liter]; or urinary output, <500 ml per day).

(hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P=0.74) (Table 2 and Fig. 3).

In addition, there were no significant differences in the secondary outcomes: need for mechanical ventilation, length of stay in the ICU and hospital, and the SOFA score by day 7 (Table 2, and Tables S2C and S2D in the Supplementary Appendix). However, in patients with chronic arterial hypertension, there was a significant interaction between study group and hypertension stratum with respect to the doubling of the blood creatinine level (P=0.009) and with respect to the need for renal-replacement therapy (P=0.04). Multivariate logistic-regression analysis indicated that none of the potentially nephrotoxic therapies influenced this result.

### ADVERSE EVENTS

There was no significant difference between the two study groups in the overall incidence of serious adverse events (P=0.64) (Table 2, and Table S2E in the Supplementary Appendix). Although the total number of cardiac adverse events did not differ between the groups, the incidence of newly diagnosed atrial fibrillation was significantly higher in the high-target group, with events reported in 26 patients (6.7%) in the high-target group and 11 patients (2.8%) in the low-target group (P=0.02). The frequencies of ischemic events and bleeding complications were similar in the two study groups.

## DISCUSSION

In this multicenter, randomized, open-label trial, we compared the strategy of targeting a high mean arterial pressure (80 to 85 mm Hg) with the strategy of targeting a low pressure (65 to 70 mm Hg) in patients with septic shock. The high-target group received significantly higher doses of vasopressor catecholamines over a significantly longer time period, but we found no significant difference in 28-day mortality. There was no significant between-group difference in early

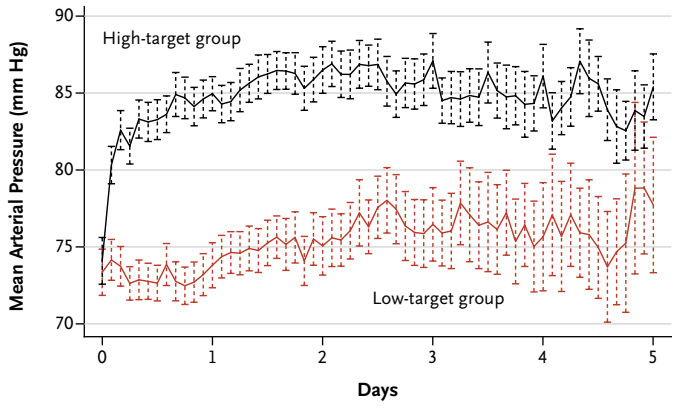


**Figure 2. Mean Arterial Pressure during the 5-Day Study Period.**

Mean arterial pressures were significantly lower in the low-target group than in the high-target group during the 5 protocol-specified days (P=0.02 by repeated-measures regression analysis), although the values exceeded the target values of 80 to 85 mm Hg in the high-target group and 65 to 70 mm Hg in the low-target group. The I bars represent 95% confidence intervals.

fluid balance, and the fluid balance was lower than those reported previously,[7,8] possibly because our population of patients differed from those in previous studies or because of more restrictive protocols for fluid administration in France. In addition, there were no significant between-group differences in the overall rates of organ dysfunction or death at 90 days. However, in patients with a history of chronic arterial hypertension, targeting a mean arterial pressure of 80 to 85 mm Hg reduced both the incidence of a doubling of the blood creatinine level and the rate of renal-replacement therapy. There was no significant between-group difference in the overall rate of serious adverse events, but patients in the high-target group had significantly more episodes of atrial fibrillation.

No differences in the primary and secondary outcomes were observed between the two groups. Our study was prospectively powered to detect an absolute difference of 10 percentage points in the rate of death on the basis of an expected rate of 45% in the low-target group, at an alpha level of 0.05 and a beta level of 0.20, with the use of a two-tailed test. The expected overall death rate in our study was consistent with the rates among patients with septic shock that were reported in previous multicenter trials (37%,[5] 39%,[8] 47%,[4] and 49%[6]) at the time the trial was designed. The absolute reduction of 10 percentage points in mortality was chosen in our study because the trials that were available in the literature when the protocol was designed in 2008 had tested the hypothesis of absolute reductions of 20 percentage points,[5] 15 percentage points,[4] and 10 percentage points[8] in rates of death. Two other trials that were published after we started recruiting patients tested the hypothesis of an absolute mortality reduction of 7 percentage points[7,15] and 10 percentage points.[16] Hence, the anticipated risk reduction in our study was close to the risk reductions tested in previous studies. However, our observed rate of death at 28 days was lower than the rate in some other studies, although it was in line with the rate in more recent trials, in which death rates ranging from 25 to 57% were reported.[7,15] Nevertheless, the lower-than-expected rate of death led to an underpowered study. Therefore, we may not have detected differences in the incidence of some adverse events, especially rare events such as myocardial infarction.

Septic shock is a major risk factor for atrial fibrillation,[17] and in our study, atrial fibrillation was significantly more common in the high-target group than in the low-target group. This adverse effect might be related to the significantly higher doses of catecholamine and the longer duration of catecholamine infusions in the high-target group. However, given the small number of episodes of atrial fibrillation, other confounding factors cannot be ruled out. The association between atrial fibrillation and septic shock should be considered only as a hypothesis-generating concept for future trials.

At randomization, patients were stratified according of the presence or absence of chronic hypertension. More than 40% of the patients reported having a history of chronic hypertension, which is in line with rates in previous studies.[18] Among patients with chronic hypertension, a rightward shift of the curve for organ pressure-flow autoregulation is expected, which means that an increased mean arterial pressure could hypothetically result in improved organ perfusion[11] and, eventually, in improved survival rates. No significant differences in adverse effects between patients with chronic hypertension and those without chronic hypertension were evident. The results in the subgroup with chronic

**Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.**

| Variable | Low-Target Group (N=388) | High-Target Group (N=388) | P Value |
|---|---|---|---|
| Cumulative fluid intake from day 1 to day 5 — liters | 10.0 (5.8–14.0) | 10.5 (5.5–14.0) | 0.89 |
| Cumulative urine output from day 1 to day 5 — liters | 6.7 (2.9–10.7) | 6.9 (2.4–10.7) | 0.87 |
| Cumulative fluid balance from day 1 to day 5 — liters | 2.8 (0.0–6.2) | 2.4 (0.0–6.0) | 0.74 |
| Median dose of norepinephrine (IQR) — μg/kg/min | | | |
| Day 1 | 0.45 (0.17–1.21) | 0.58 (0.26–1.80) | <0.001 |
| Day 2 | 0.16 (0.03–0.48) | 0.38 (0.14–0.90) | <0.001 |
| Day 3 | 0.02 (0.00–0.16) | 0.14 (0.01–0.50) | <0.001 |
| Day 4 | 0.00 (0.00–0.05) | 0.03 (0.00–0.22) | <0.001 |
| Day 5 | 0.00 (0.00–0.03) | 0.01 (0.00–0.15) | <0.001 |
| Duration of catecholamine infusion — days | 3.7±3.2 | 4.7±3.7 | <0.001 |
| Primary outcome: death at day 28 — no. (%)* | 132 (34.0) | 142 (36.6) | 0.57 |
| Secondary outcomes — no./total no. (%) | | | |
| Death at day 90† | 164 (42.3) | 170 (43.8) | 0.74 |
| Survival at day 28 without organ support‡ | 241 (62.1) | 235 (60.6) | 0.66 |
| Doubling of plasma creatinine | 161 (41.5) | 150 (38.7) | 0.42 |
| No chronic hypertension | 71/215 (33.0) | 85/221 (38.5) | 0.32 |
| Chronic hypertension | 90/173 (52.0) | 65/167 (38.9) | 0.02 |
| Renal-replacement therapy from day 1 to day 7 | 139 (35.8) | 130 (33.5) | 0.50 |
| No chronic hypertension | 66/215 (30.7) | 77/221 (34.8) | 0.36 |
| Chronic hypertension | 73/173 (42.2) | 53/167 (31.7) | 0.046 |
| Serious adverse events — no. (%) | | | |
| Any | 69 (17.8) | 74 (19.1) | 0.64 |
| Acute myocardial infarction§ | 2 (0.5) | 7 (1.8) | 0.18 |
| Atrial fibrillation | 11 (2.8) | 26 (6.7) | 0.02 |
| Ventricular fibrillation or tachycardia | 15 (3.9) | 22 (5.7) | 0.24 |
| Digital ischemia | 9 (2.3) | 10 (2.6) | 0.82 |
| Mesenteric ischemia | 9 (2.3) | 9 (2.3) | 1.00 |
| Bleeding | 42 (10.8) | 31 (8.0) | 0.22 |

* The hazard ratio for death at 28 days was 1.07 (95% confidence interval [CI], 0.84 to 1.38) in the high-target group, as compared with the low-target group.
† The hazard ratio for death at 90 days was 1.04 (95% CI, 0.83 to 1.30) in the high-target group, as compared with the low-target group.
‡ Organ support refers to the use of vasopressors, mechanical ventilation, or renal-replacement therapy.
§ Acute myocardial infarction was defined as typical electrocardiographic changes, with a concomitant increase in troponin, and segmental echocardiographic hypokinesia or akinesia, with the infarction confirmed, when possible, by means of coronary angiography.

hypertension may indicate that targeting a higher mean arterial pressure is acceptable because it was not associated with greater harms.

The guidelines of the Surviving Sepsis Campaign recommend targeting a mean arterial pressure of at least 65 mm Hg. According to our study design, investigators were invited to follow these guidelines in the low-target group. However, the observed mean arterial pressures in the low-target group (target range, 65 to 70 mm Hg) were for the most part between 70 and 75 mm Hg. Similarly, the observed values in the high-target group

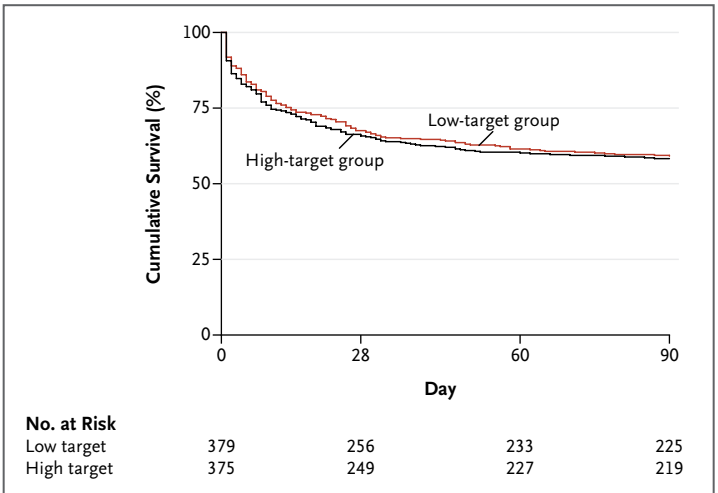


**Figure 3. Kaplan–Meier Curves for Cumulative Survival.**

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

were also higher (between 85 and 90 mm Hg) than the predefined target range of 80 to 85 mm Hg. Thus, the target between-group difference was well maintained. Whether higher achieved mean arterial pressures in the two groups influenced the results is impossible to ascertain. However, given the pragmatic nature of the trial, these data were not recorded as protocol violations. In addition, the higher mean arterial pressures in the two groups may reflect the reluctance of some attending physicians to decrease the vasopressor infusion rate when the mean arterial pressure is about 70 mm Hg, as recently reported by Poukkanen et al.[19] In that study, patients spent more than 75% of the time at a mean arterial pressure of more than 70 mm Hg. Finally, the generalizability of our trial results may be limited because of the frequent use of glucocorticoids and activated protein C and because of the large number of patients who were excluded because of the narrow inclusion window.

In conclusion, among patients with septic shock, 28-day and 90-day mortality did not differ significantly between those who were treated to reach a target mean arterial pressure of 80 to 85 mm Hg and those who were treated to reach a target of 65 to 70 mm Hg.

Presented in part at the annual meeting of Société de Réanimation de Langue Française, Paris, January 16–18, 2013; the International Symposium on Intensive Care and Emergency Medicine, Brussels, March 19–22, 2013; the annual meeting of the European Society of Intensive Care Medicine, Paris, October 5–9, 2013; and the annual meeting of the German Interdisciplinary Society for Intensive and Emergency Medicine, Leipzig, December 4–6, 2013.

Supported by the French Ministry of Health.

Dr. Asfar reports receiving lecture fees from LFB; Dr. Meziani, receiving grant support from LFB; Dr. Mira, receiving honoraria and travel support from LFB and Eisai and honoraria from AstraZeneca; Dr. Weiss, receiving lecture fees from Gore; Dr. Gonzalez, receiving travel support from Merck Sharp and Dohme and Novartis; and Dr. Mercat, receiving grant support from Covidien, Maquet, and General Electric, consulting fees from Air Liquide Medical Systems, and fees for serving on a steering committee from Faron Pharmaceuticals and being named as an inventor on a patent related to methods of evaluating a patient for positive end-expiratory pressure therapy (US 12/834,354), which is to be licensed to General Electric. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

## APPENDIX

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