EDITORIAL

Is There a Good MAP for Septic Shock?

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As fundamental as the issue is, there is no clear, high-level evidence to determine the most effective mean arterial pressure (MAP) for resuscitation of patients with septic shock. During hypotension, three salient aspects of cardiovascular physiology are important. First, the autoregulation of cerebral blood flow maintains an adequate level over a wide range of pressures until a critical pressure (about 50 mm Hg) is reached; below this level, as the pressure falls, so does cerebral blood flow. Second, chronic hypertension shifts the autoregulatory curve of the relationship between pressure and perfusion so that perfusion is decreased at a higher critical pressure; long-term antihypertensive treatment restores the autoregulatory curves toward normal. Third, there are differences among organs in the critical point for oxygen delivery: gut oxygen delivery decreases earlier in shock than oxygen delivery to other organs. The consequence of inadequate perfusion is ischemic injury to the kidney, gut, brain, and myocardium, followed by multiple organ dysfunction and death.

The goal of cardiovascular resuscitation of septic shock is to improve organ perfusion, often by increasing the MAP. Adequate fluid resuscitation is limited when the administration of fluids causes edema (e.g., acute lung injury). Vasopressors are added if fluid resuscitation does not restore adequate perfusion, but such therapy is limited by excessive vasoconstriction and organ ischemia. A common clinical problem is distinguishing between ischemia that is caused by inadequate resuscitation (e.g., as manifested by oliguria) and ischemia that is caused by excessive vasoconstriction.

Reviews[1,2] and sepsis guidelines[3] recommend a target MAP of more than 65 mm Hg in patients with septic shock. However, these recommenda-

tions are based on low-quality evidence. Accordingly, Asfar et al.[4] now report in the *Journal* the results of a large, randomized, controlled trial of targeting a low MAP (65 to 70 mm Hg) versus a high MAP (80 to 85 mm Hg) among patients with septic shock at 29 centers in France. By 28 days, there was no significant difference in mortality (the primary end point) between the low-target group and the high-target group. In the prospectively defined stratum of patients with chronic hypertension (more than 40% of the patients), those in the high-target group had less renal dysfunction and need for renal-replacement therapy than did those in the low-target group. However, there was a safety concern, since patients in the high-target group had an increased risk of new atrial fibrillation, which is independently associated with an increased risk of stroke.[5] Unfortunately, stroke was not evaluated by Asfar and colleagues.

The strengths of this trial are that the intervention was assigned by blinded randomization in a multicenter context in intensive care units; the two study groups were well balanced; the intervention was a pragmatic, real-world study; and the difference in ranges of MAP values between the two groups was significant. One limitation was that the interventions targeting a low or high MAP were not blinded.

How do these results align with those of other randomized, controlled trials of vasoactive interventions in shock? I compared intervention application and outcomes of this study with both published and unpublished data regarding the norepinephrine control groups of large, randomized, controlled trials of shock[6-10] (Table 1). As compared with the findings in the study by Asfar et al., the target and actual MAP on day 1 in trials in which vasoactive agents were used were simi-

Table 1. Comparison of Norepinephrine Control Groups and Intervention Groups in Randomized, Controlled Trials of Vasoactive Agents in Shock.*

Trial	Mean Arterial Pressure (MAP)			Norepinephrine Infusion Rate			Fluid Balance			Renal-Replacement Therapy	Death at 28 Days
	Target	Actual, Day 0	Actual, Day 1	Day 0	Day 1	Day 2	Day 0	Day 1	Days 0 to 4		
	mm Hg			*µg/kg/min*			*ml*			*%*	
Asfar et al.[4]†											
Low-target group											
All patients	65 to 70	74	74	0.35	0.45	0.16	1603	1016	2,800	35.8	34
Patients with chronic hypertension	65 to 70									42.2	
High-target group											
All patients	80 to 85	74	84	0.40	0.58	0.38	1595	1106	2,400	33.5	36
Patients with chronic hypertension	80 to 85									31.7	
Annane et al.[6]‡	70	70	80	0.94	1.09	0.65	1586	172	−2,767	24.8	34
De Backer et al.[7]	MD	58	76	0.54	0.82	0.68	2100	1700	8,300	17.0§	48
Myburgh et al.[8]¶	MD	70	73	0.26	0.17	0.07	2232	1782	5,712	22.1	26
Rivers et al.[9]‖	65	76	81	NA	NA	NA	3500	NA	10,602**	NA	49
Russell et al.[10]	65 to 75	72	73	0.28	0.20	0.08	1500	2500	11,000	43.6	39

* MD indicates clinician judgment, and NA not available.
† Listed are results for both the control (low-target) group and the intervention (high-target) group.
‡ In the study by Annane et al., fluid balance was reported for survivors only.
§ The percentage was 19.9% in the subgroup with septic shock.
¶ In the study by Myburgh et al., if no target MAP was ordered, the default target MAP was 70 mm Hg.
‖ In the study by Rivers et al., the control group received a combination treatment.
** Fluid balance was averaged over 3 days rather than 4.

lar to those in the low-target group and lower than those in the high-target group. Asfar and colleagues used less fluid and higher doses of norepinephrine than were used in some trials[8-10] but administered less norepinephrine and lower fluid levels than were used in another trial.[7] Thus, there is variability in how fluids and vasopressors are used to achieve target MAPs in randomized, controlled trials. Finally, rates of death in the trial by Asfar el al. were similar to those in two trials,[6,10] higher than those in one trial,[8] and lower than those in two other trials.[7,9] These mortality differences may arise from differences in the inclusion criteria used in these trials (septic shock,[4,6,10] severe sepsis,[9] and shock[7,8]) and trial location,[4,6-10] since mortality associated with septic shock varies according to country,[11] making comparisons between countries and continents difficult.

The findings of Asfar et al. have at least three major clinical implications. First, they show that there is no indication for routinely targeting a high MAP in patients with septic shock, since there was no significant between-group difference in mortality, although patients in the high-target group had an increased rate of atrial fibrillation. Second, a high MAP target may decrease the risk of renal injury and the need for renal-replacement therapy (number needed to treat of 9.5 to prevent one patient from needing renal-replacement therapy) in patients with hypertension. I make this point because of the well-known risks and costs of renal-replacement therapy. Thus, there are several target MAPs for septic shock, depending on the circumstances of the patient. In some randomized, controlled trials (and in clinical practice), practitioners use more fluid (increasing the risk of acute lung injury), whereas others use more vasopressors (increasing the risk of renal injury). Indeed, methods for

targeting a MAP among patients in septic shock are probably critical to the success of the strategy and deserving of greater investigation.

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ORIGINAL ARTICLE

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.)

EPTIC SHOCK IS CHARACTERIZED BY AR-
terial hypotension despite adequate fluid
resuscitation. The guidelines of the Surviv-
ing Sepsis Campaign[1] recommended initial re-
suscitation with vasopressors to reverse hypoten-
sion, 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 dif-
ferences 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. According-
ly, 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 physio-
logical mechanisms of chronic arterial hyperten-
sion showed that such hypertension causes a
rightward shift in cerebral pressure-flow auto-
regulation, which might justify targeting a high-
er mean arterial pressure.[11]

Since the selection of effective blood-pressure
targets is still controversial, we conducted a multi-
center, randomized, stratified, open-label trial
involving patients with septic shock to deter-
mine whether targeting a mean arterial pressure
of 80 to 85 mm Hg would decrease 28-day mor-
tality, as compared with targeting a mean arte-
rial pressure of 65 to 70 mm Hg. We also postu-
lated that the beneficial effects of a higher target
would be more pronounced among patients with
chronic hypertension. Therefore, at randomiza-
tion, patients were stratified according to wheth-
er 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 hyper-
tension (i.e., had been receiving antihypertensive
treatment or had a history of arterial hyperten-
sion). Given the pragmatic character of the trial,
it was impossible to obtain details on the pa-
tients' 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 un-
aware of the study-group assignments.

STUDY OVERSIGHT

The data and safety monitoring committee over-
saw the trial conduct and the safety of the pa-
tients, 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 de-
cision 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 theo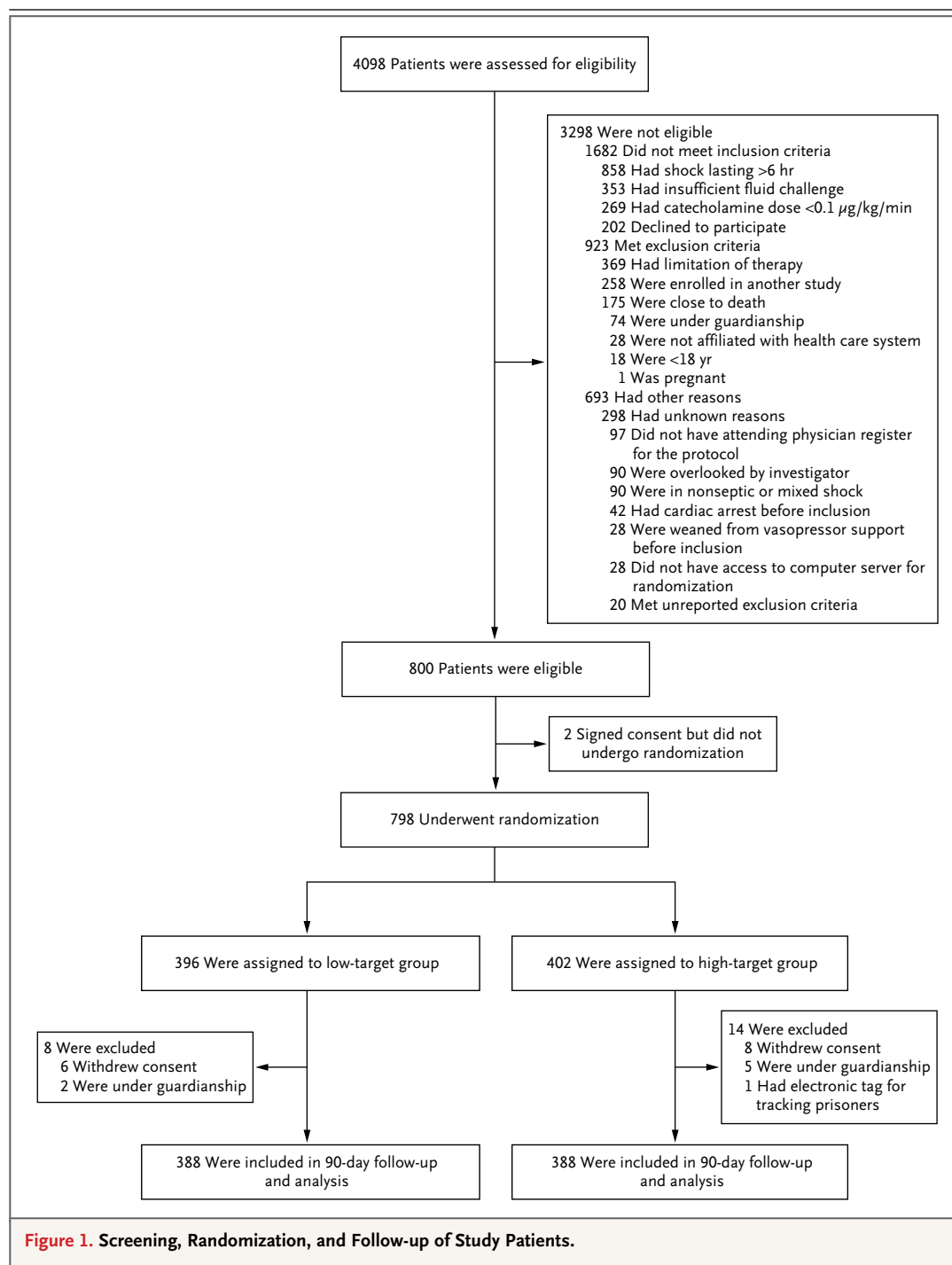rem) and the Wilcoxon rank-sum test when the sample size in one group was less than 30. We used chi-square tests or Fisher's exact test to compare qualitative variables, as appropriate. All comparisons were also performed with the use of the entire sample with stratification (as prespecified) according 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).

4098 Patients were assessed for eligibility

3298 Were not eligible
  1682 Did not meet inclusion criteria
    858 Had shock lasting >6 hr
    353 Had insufficient fluid challenge
    269 Had catecholamine dose <0.1 µg/kg/min
    202 Declined to participate
  923 Met exclusion criteria
    369 Had limitation of therapy
    258 Were enrolled in another study
    175 Were close to death
    74 Were under guardianship
    28 Were not affiliated with health care system
    18 Were <18 yr
    1 Was pregnant
  693 Had other reasons
    298 Had unknown reasons
    97 Did not have attending physician register
      for the protocol
    90 Were overlooked by investigator
    90 Were in nonseptic or mixed shock
    42 Had cardiac arrest before inclusion
    28 Were weaned from vasopressor support
      before inclusion
    28 Did not have access to computer server for
      randomization
    20 Met unreported exclusion criteria

800 Patients were eligible

2 Signed consent but did not undergo randomization

798 Underwent randomization

396 Were assigned to low-target group

402 Were assigned to high-target group

8 Were excluded
  6 Withdrew consent
  2 Were under guardianship

14 Were excluded
  8 Withdrew consent
  5 Were under guardianship
  1 Had electronic tag for tracking prisoners

388 Were included in 90-day follow-up and analysis

388 Were included in 90-day follow-up and analysis

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 (36.5%) 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
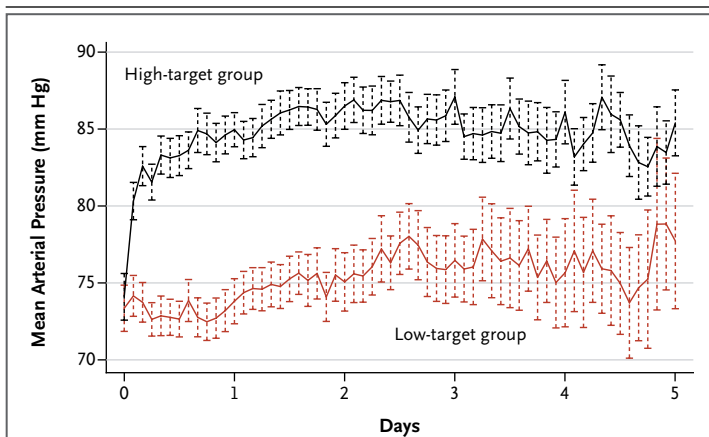
Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

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.

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

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

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
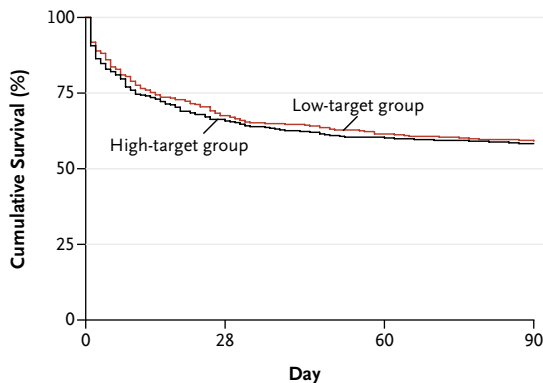
Figure 3. Kaplan–Meier Curves for Cumulative Survival.

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.

APPENDIX

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