Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

Gordon, A. C., Perkins, G. D., Singer, M., McAuley, D. F., Orme, R. M. L., Santhakumaran, S., ... Ashby, D. (2016). Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. New England Journal of Medicine. DOI: 10.1056/NEJMoa1609409

Published in:
New England Journal of Medicine

Document Version:
Publisher's PDF, also known as Version of record

ORIGINAL ARTICLE

Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

A.C. Gordon, G.D. Perkins, M. Singer, D.F. McAuley, R.M.L. Orme, S. Santhakumaran, A.J. Mason, M. Cross, F. Al-Beidh, J. Best-Lane, D. Brealey, C.L. Nutt, J.J. McNamee, H. Reschreiter, A. Breen, K.D. Liu, and D. Ashby

ABSTRACT

BACKGROUND

Levosimendan is a calcium-sensitizing drug with inotropic and other properties that may improve outcomes in patients with sepsis.

METHODS

We conducted a double-blind, randomized clinical trial to investigate whether levosimendan reduces the severity of organ dysfunction in adults with sepsis. Patients were randomly assigned to receive a blinded infusion of levosimendan (at a dose of 0.05 to 0.2 μg per kilogram of body weight per minute) for 24 hours or placebo in addition to standard care. The primary outcome was the mean daily Sequential Organ Failure Assessment (SOFA) score in the intensive care unit up to day 28 (scores for each of five systems range from 0 to 4, with higher scores indicating more severe dysfunction; maximum score, 20). Secondary outcomes included 28-day mortality, time to weaning from mechanical ventilation, and adverse events.

RESULTS

The trial recruited 516 patients; 259 were assigned to receive levosimendan and 257 to receive placebo. There was no significant difference in the mean (±SD) SOFA score between the levosimendan group and the placebo group (6.68±3.96 vs. 6.06±3.89; mean difference, 0.61; 95% confidence interval [CI], −0.07 to 1.29; P=0.053). Mortality at 28 days was 34.5% in the levosimendan group and 30.9% in the placebo group (absolute difference, 3.6 percentage points; 95% CI, −4.5 to 11.7; P=0.43). Among patients requiring ventilation at baseline, those in the levosimendan group were less likely than those in the placebo group to be successfully weaned from mechanical ventilation over the period of 28 days (hazard ratio, 0.77; 95% CI, 0.60 to 0.97; P=0.03). More patients in the levosimendan group than in the placebo group had supraventricular tachyarrhythmia (3.1% vs. 0.4%; absolute difference, 2.7 percentage points; 95% CI, 0.1 to 5.3; P=0.04).

CONCLUSIONS

The addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality. Levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrhythmia. (Funded by the NIHR Efficacy and Mechanism Evaluation Programme and others; LeoPARDS Current Controlled Trials number, ISRCTN12776039.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Gordon at ICU 11N, Charing Cross Hospital, Imperial College London, Fulham Palace Rd., London W6 8RF, United Kingdom, or at anthony.gordon@imperial.ac.uk.

A complete list of investigators in the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 5, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1609409

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1] and is a leading cause of death worldwide. Septic shock is the most severe form of the condition and results in circulatory and metabolic abnormalities.[2] Persisting hypotension despite adequate fluid resuscitation is due to a combination of profound vasodilatation, vascular hyporeactivity to catecholamines, and myocardial depression.[3] Although catecholamines are the recommended first-line therapy for septic shock,[4] high doses of administered catecholamines and high levels of circulating catecholamines are associated with poor outcomes and severe side effects, including myocardial injury and peripheral ischemia.[5-7]

Levosimendan is a calcium-sensitizing drug with inotropic and vasodilator properties that is licensed in numerous countries (not including the United States) to treat decompensated heart failure.[8] In contrast to catecholamines, levosimendan causes increased myocardial contraction with a minimal increase in oxygen demand,[9] and diastolic relaxation is not impaired. Small studies that have investigated the use of levosimendan in patients with septic shock have shown improvements in hemodynamic variables,[10] microcirculatory flow,[11] and renal[10] and hepatic[12] function, as compared with dobutamine. Other important noninotropic effects have also been shown, including antiinflammatory,[13] antioxidative,[14] and antiapoptotic[15] effects and possibly protection from ischemia and reperfusion injury.[16] A recent meta-analysis supported the use of levosimendan in patients with sepsis, but only 125 patients in total had been treated.[17] The Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial was designed to test whether the addition of levosimendan to standard care would reduce the severity of organ dysfunction among patients with septic shock and to assess its safety profile in patients with this condition.

Methods

Trial Design and Participants

We conducted this multicenter, randomized, double-blind, placebo-controlled clinical trial in 34 general adult intensive care units (ICUs) in the United Kingdom. The trial protocol, available with the full text of this article at NEJM.org, was designed by the trial management committee and has been published previously.[18] The London–Harrow Research and Ethics Committee approved the protocol.

The trial was funded by the National Institute for Health Research and Tenax Therapeutics and sponsored by Imperial College London. Data management and analysis were performed by the Imperial Clinical Trials Unit. Orion Pharma provided levosimendan and placebo free of charge. The funders, the sponsor, and Orion Pharma had no role in designing the trial, gathering or analyzing the data, writing the manuscript, or making the decision to submit the manuscript for publication. The first author vouches for the data and analyses, as well as for the fidelity of this report to the trial protocol.

Enrollment Criteria and Randomization

Adult patients who had septic shock and had received vasopressors for at least 4 hours were eligible for inclusion. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. Patients had to be recruited within 24 hours after meeting the inclusion criteria. Written informed consent was obtained from either the patient or, in the event that the patient lacked capacity, a personal or professional legal representative before enrollment in the trial. Retrospective written informed consent was sought from the patient once capacity was regained.

Enrollment, randomization, and data collection were performed by means of an online system (InForm, Oracle). Patients were assigned in a 1:1 ratio to receive levosimendan or placebo, with the use of variable block sizes of four and six and computer-generated random numbers and with stratification according to recruitment center. The randomization sequence was prepared by an independent statistician. Trial-specific labeling and packaging, to ensure that trial packs were identical, was undertaken by Victoria Pharmaceuticals. Patients and clinical and research staff remained unaware of the trial-group assignment throughout the trial.

Clinical Treatment

Patients were assigned to receive a blinded infusion of either levosimendan or placebo for 24 hours in addition to standard care. Figure S1 in the Supplementary Appendix shows the infusion

algorithm. No bolus loading dose was given. The administration of levosimendan or placebo was started at a rate of 0.1 μg per kilogram of body weight per minute and, in the absence of rate-limiting side effects, was increased after 2 to 4 hours to 0.2 μg per kilogram per minute for a further 20 to 22 hours. Patients received intravenous fluid boluses for any clinically significant drop in blood pressure and, if necessary, vasopressors were adjusted to maintain an adequate blood pressure. If the patient had rate-limiting side effects — either hypotension or severe tachycardia (heart rate >130 beats per minute, or an increase of >20% if the heart rate was already >110 beats per minute) — at the dose of 0.2 μg per kilogram per minute, then the infusion rate was reduced to 0.1 μg per kilogram per minute. If necessary to avoid hypotension or severe tachycardia, the rate was reduced to 0.05 μg per kilogram per minute or even discontinued.

Other aspects of clinical care were at the discretion of the local physician and were based on the Surviving Sepsis Campaign guidelines (see the Supplementary Appendix).[4] The trial protocol recommended a mean arterial pressure of 65 to 70 mm Hg. This pressure could be varied for individual patients, but investigators were encouraged to use the lowest dose of vasopressor that maintained tissue perfusion in each patient. Additional inotropic agents could be used as clinically indicated (i.e., for ongoing low cardiac output after fluid resuscitation). Dobutamine was the recommended inotrope, with lowering of the dose and discontinuation once adequate oxygen delivery had been achieved.

OUTCOME MEASURES

The primary trial outcome was the mean daily Sequential Organ Failure Assessment (SOFA) score[19] while the patient was in the ICU, as measured from randomization to a maximum of 28 days. The daily SOFA score after baseline was calculated for each patient on the basis of five organ systems: cardiovascular, respiratory, renal, hepatic, and coagulation systems. (Scores for each system range from 0 to 4, with higher scores indicating more severe organ-system dysfunction; maximum score, 20.) The neurologic system was not included, as in some previous trials,[20,21] owing to the difficulties of accurately scoring the Glasgow Coma Score daily in the presence of sedation. Daily scores were totaled for each patient's ICU stay and divided by the number of days that they remained in the ICU in order to calculate the mean SOFA score for that patient.

To assess the effect of levosimendan on individual organ systems, the individual SOFA components were analyzed, and several other clinical outcomes were determined a priori for secondary analyses. These outcomes included the number of catecholamine-free and ventilator-free days, the time to weaning from mechanical ventilation, the proportion of patients with a major acute kidney event[22] over a period of 28 days (defined as death, new requirement for renal-replacement therapy, or sustained renal failure [stage 2 or 3 acute kidney injury[23]] at day 28), and the duration of renal-replacement therapy. Mortality rates at 28 days, at ICU discharge, and at hospital discharge, as well as the length of stay in the ICU and serious adverse events, were also recorded.

STATISTICAL ANALYSIS

We calculated that a sample of 500 patients would provide the trial with 90% power to detect a difference of 0.5 points in the mean SOFA score, assuming a standard deviation of 1.5 and a significance level of 0.05.[19] To allow for a 3% rate of withdrawal of consent, the recruitment target was 516 patients.

The primary analysis was unadjusted in the intention-to-treat population, and reported the difference in mean SOFA scores between the two trial groups. Because the mean SOFA score was not normally distributed, 95% confidence intervals of the mean difference were calculated with the use of bootstrapping, with the application of the percentile method with 100,000 samples. We used a priori defined regression models to investigate whether the main analysis was sensitive to adjustment for trial-center (i.e., ICU) effects, age, and severity of illness (according to the Acute Physiology and Chronic Health Evaluation [APACHE] II score) with bootstrapped confidence intervals.

Because levosimendan is an inotrope with prolonged hemodynamic effects but is not included as part of the cardiovascular scoring within the SOFA score, the primary analysis was repeated with the exclusion of the cardiovascular component as a sensitivity analysis. We prespecified the use of Bayesian models of multiple imputation for missing data, as described in the Supplementary Appendix; we also performed

post hoc analyses using imputation to account for any differential effect of treatment on the rates of ICU discharge or death before 28 days. Time-to-event data were described with the use of Kaplan–Meier plots and Cox regression, with adjustment for age and APACHE II score, allowing for clustering according to ICU.

Four subgroup analyses were planned a priori on the basis of the baseline measurement of the cardiac index, if measured (lowest third vs. middle and highest thirds), the central venous oxygen saturation (low [<70%], normal [70 to 85%], or high [>85%]), the serum lactate level (≤2 mmol per liter vs. >2 mmol per liter), and the dose of norepinephrine (below vs. above the median infusion rate). The heterogeneity of treatment effect according to subgroup was calculated with the use of a permutation test, which permuted both the subgroup and the trial-group assignment.[24] All the analyses were performed with the use of R software, version 3.2.2 (R Project for Statistical Computing).[25] A P value of less than 0.05 was considered to indicate statistical significance, with the use of two-sided tests; no corrections were made for multiple testing.

RESULTS

TRIAL PARTICIPANTS

The trial ran from January 2014 through December 2015, when the required sample of 516 patients were enrolled. Figure 1 shows the randomization and flow of patients in the trial; 259 patients were assigned to receive levosimendan and 257 to receive placebo. A total of 8 patients (4 patients in each group) did not receive the assigned trial regimen. The family of 1 patient in the levosimendan group withdrew consent after randomization but before the drug was administered. This patient was excluded from all the analyses. The other 7 patients were included in the intention-to-treat analysis.

The two groups were well balanced at baseline (Tables 1 and 2, and Tables S1 and S2 in the Supplementary Appendix). The median time to recruitment was 16 hours after the initiation of vasopressors, and the median dose of norepinephrine was 0.28 μg per kilogram per minute at the time of starting the infusion.

CARDIOVASCULAR EFFECTS

The infusion was discontinued before the 24-hour time point owing to hemodynamic instability (hypotension or tachycardia) in 33 of 244 patients (13.5%) in the levosimendan group, as compared with 19 of 248 patients (7.7%) in the placebo group. The mean arterial pressure was lower in the patients in the levosimendan group than in those in the placebo group in the first 24 hours (the duration of the infusion) but was similar thereafter in the two groups. The rate and duration of the norepinephrine infusion were higher in the levosimendan group than in the placebo group; there was also less frequent use of dobutamine in the levosimendan group. The heart rate over the first 4 days was significantly higher in patients in the levosimendan group than in those in the placebo group. Intravenous-fluid administration, fluid balance, and serum lactate levels were similar in the two groups. Details are provided in Table S3 and Figures S2 through S6 in the Supplementary Appendix.

OUTCOMES

The percentage of daily SOFA scores that were missing ranged from 2.3% for the cardiovascular component to 12.8% for the liver component. The primary outcome, the mean (±SD) SOFA score over the stay in the ICU, was 6.68±3.96 in the levosimendan group and 6.06±3.89 in the placebo group (mean difference, 0.61; 95% confidence interval [CI], −0.07 to 1.29; P=0.053) (Table 3). After adjustment for ICU, age, and APACHE II score in a regression model, the mean difference in the score was 0.59 (95% CI, −0.02 to 1.20; P=0.06). In an analysis that considered each component of the total SOFA score independently, the mean daily cardiovascular score was higher in the levosimendan group than in the placebo group (mean difference, 0.25; 95% CI, 0.04 to 0.46; P=0.01). The prespecified and post hoc sensitivity analyses did not materially change the result (Table 3, and Table S4 in the Supplementary Appendix). The total daily SOFA scores and individual component scores are shown in Figures S7 through S12 in the Supplementary Appendix.

Secondary outcomes are shown in Table 3. Mortality at 28 days was 34.5% in the levosimendan group and 30.9% in the placebo group (mean difference, 3.6 percentage points; 95% CI, −4.5 to 11.7; P=0.43). The Kaplan–Meier curves for survival to day 28 are shown in Figure 2. Among patients requiring mechanical ventilation at baseline, those in the levosimendan group were less likely than those in the placebo group to be successfully weaned from mechanical ventila-

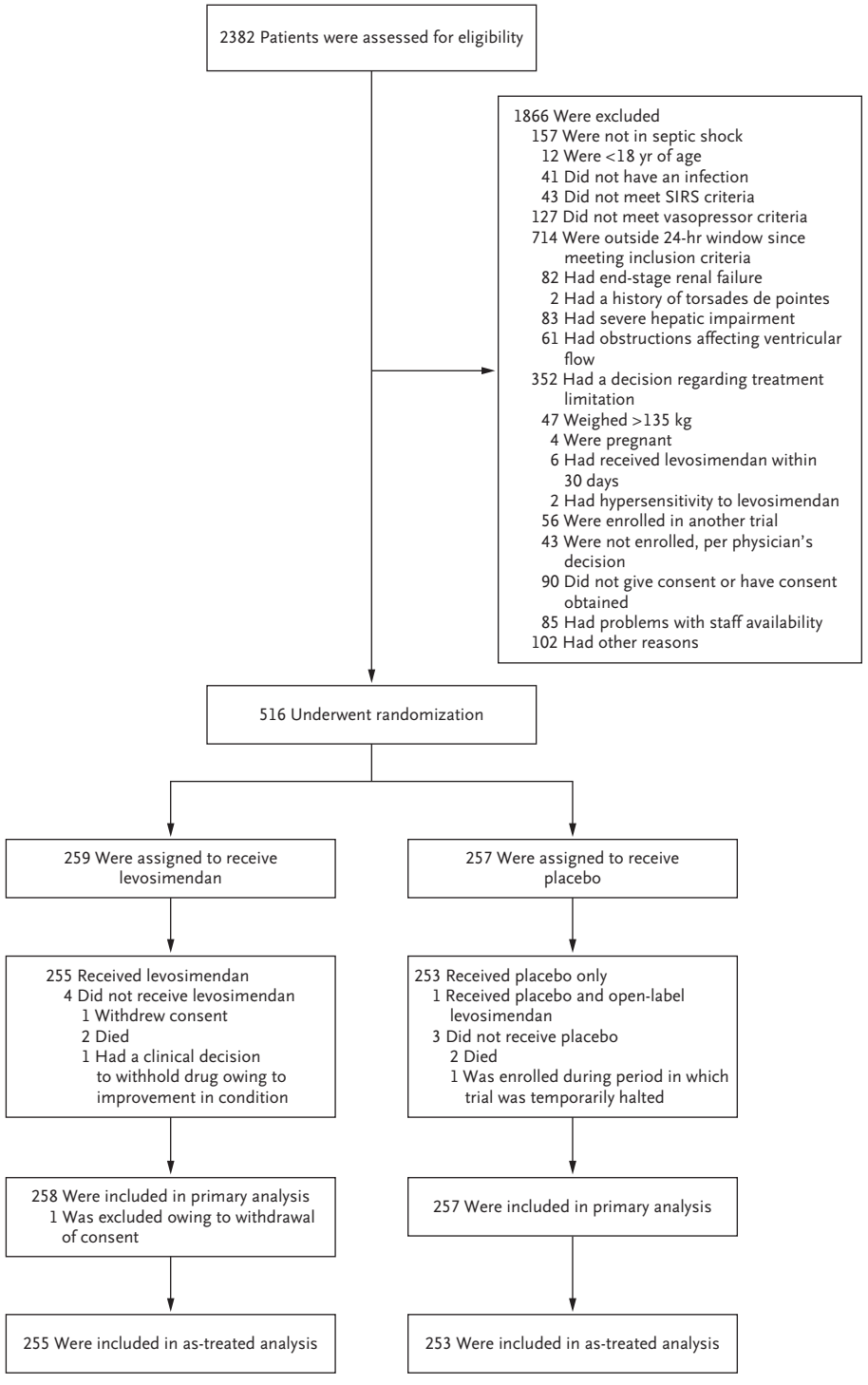


Figure 1. Recruitment and Randomization of the Patients.

Patients could meet more than one exclusion criterion. Other reasons for nonenrollment included unavailability of levosimendan or placebo, mental health problems, language barrier, and unspecified reasons (in 78 patients). SIRS denotes the systemic inflammatory response syndrome.

Table 1. Baseline Characteristics.*

Characteristic	Levosimendan (N=258)	Placebo (N=257)
Median age (IQR) — yr	67 (58–75)	69 (58–77)
Male sex — no. (%)	145 (56.2)	144 (56.0)
Median weight (IQR) — kg	76 (65–90)	80 (68–91)
Median body-mass index (IQR)†	27 (23–30)	28 (24–32)
Race — no. (%)‡		
Asian	11 (4.3)	10 (3.9)
Black	4 (1.6)	6 (2.3)
White	240 (93.0)	240 (93.4)
Other	3 (1.2)	1 (0.4)
History of recent surgery — no. (%)§	94 (36.4)	95 (37.0)
Preexisting condition — no. (%)		
Ischemic heart disease	46 (17.8)	31 (12.1)
Congestive heart failure	1 (0.4)	4 (1.6)
Cardiac failure	23 (8.9)	26 (10.1)
Severe COPD	16 (6.2)	11 (4.3)
Chronic renal failure	19 (7.4)	18 (7.0)
Cirrhosis	4 (1.6)	6 (2.3)
Immunocompromised condition	23 (8.9)	24 (9.3)
Diabetes	59 (22.9)	51 (19.8)
Beta-blockers normally taken — no. (%)	54 (20.9)	45 (17.5)
Median time from shock to randomization (IQR) — hr¶	16 (10–21)	15 (10–20)
Vasoactive-drug dose at randomization		
Norepinephrine		
No. of patients	255	253
Median dose (IQR) — μg/kg/min	0.29 (0.16–0.52)	0.27 (0.15–0.44)
Epinephrine		
No. of patients	21	21
Median dose (IQR) — μg/kg/min	0.14 (0.07–0.28)	0.13 (0.08–0.38)
Vasopressin		
No. of patients	33	37
Median dose (IQR) — units/min	0.03 (0.02–0.04)	0.03 (0.02–0.04)
Dobutamine		
No. of patients	18	22
Median dose (IQR) — μg/kg/min	5.7 (3.5–8.8)	5.0 (4.4–6.2)

* There were no significant between-group differences in the demographic characteristics at baseline. The rates of missing values are shown in Table S1 in the Supplementary Appendix. COPD denotes chronic obstructive pulmonary disease, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for six patients in the levosimendan group and for three in the placebo group.
‡ Race was determined from medical records.
§ Recent surgery was defined as admission to the intensive care unit from the operating room.
¶ The onset of shock was defined as the initiation of vasopressors.

Table 2. Acute Illness and Physiological Variables at Baseline.*

Variable	Levosimendan (N=258)	Placebo (N=257)
Median APACHE II score (IQR)†	25 (21–31)	25 (21–30)
Median SOFA score (IQR)‡	10 (8–12)	10 (7–12)
Organ failure — no./total no. (%)§		
Respiratory	99/257 (38.5)	101/256 (39.5)
Renal	77/258 (29.8)	74/256 (28.9)
Hepatic	6/252 (2.4)	8/252 (3.2)
Coagulation	16/256 (6.2)	13/255 (5.1)
Neurologic	117/224 (52.2)	111/212 (52.4)
Source or site of initial infection — no./total no. (%)		
Lung	98/257 (38.1)	103/257 (40.1)
Abdomen	95/257 (37.0)	96/257 (37.4)
Urinary tract	12/257 (4.7)	17/257 (6.6)
Primary bacteremia	7/257 (2.7)	3/257 (1.2)
Neurologic site	4/257 (1.6)	1/257 (0.4)
Soft tissue or catheter	16/257 (6.2)	10/257 (3.9)
Other	25/257 (9.7)	27/257 (10.5)
Positive microbiologic culture — no./total no. (%)¶	109/258 (42.2)	112/256 (43.8)
Mechanical ventilation — no. (%)	207 (80.2)	210 (81.7)
Renal-replacement therapy — no. (%)	44 (17.1)	45 (17.5)
Moderate or severe ARDS — no. (%)	72 (27.9)	59 (23.0)
Heart rhythm — no./total no. (%)		
Sinus rhythm	201/258 (77.9)	218/255 (85.5)
Atrial fibrillation	32/258 (12.4)	21/255 (8.2)
Paced	3/258 (1.2)	2/255 (0.8)
Other irregular rhythm	22/258 (8.5)	14/255 (5.5)
Median values for physiological variables (IQR)‖		
Mean arterial pressure — mm Hg	74 (68–80)	73 (67–79)
Heart rate — beats/min	97 (82–111)	94 (80–110)
Central venous pressure — mm Hg	11 (9–15)	12 (8–16)
Cardiac index — liters/min/m^2	2.7 (2.2–3.7)	3.3 (2.2–4.0)
Stroke volume — ml	55.7 (40.0–73.5)	67.0 (49.4–79.7)
Arterial oxygen saturation — %	97 (95–98)	97 (95–98)
Central venous oxygen saturation — %	75 (69–81)	76 (70–81)
Lactate — mmol/liter	2.2 (1.4–3.5)	2.3 (1.5–3.9)
Pa_{O_2}:F_{IO_2} — mm Hg	216 (151–294)	215 (152–296)
Creatinine — mg/dl	1.6 (1.0–2.4)	1.5 (1.1–2.4)
Bilirubin — mg/dl	0.8 (0.5–1.5)	0.9 (0.5–1.6)
Hemoglobin — g/liter	108 (94–123)	108 (93–125)
Platelet count per mm^3	212,000 (134,000–299,000)	216,000 (144,000–308,000)
Glasgow Coma Scale score	9 (3–15)	8 (3–15)

* There were no significant between-group differences in the characteristics at baseline, except for stroke volume (P=0.02). ARDS denotes the acute respiratory distress syndrome, F_{IO_2} fraction of inspired oxygen, and Pa_{O_2} partial pressure of arterial oxygen.

† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 72, with higher scores indicating more severe illness and a higher risk of death.

‡ Scores on the Sequential Organ Failure Assessment (SOFA) were calculated on the basis of six organ systems at baseline. Scores range from 0 to 24, with higher scores indicating more severe illness.

§ Renal failure was defined as having an acute kidney injury of stage 3 (urinary-output criteria omitted because data were unavailable)[23]; other organ failures were defined as a SOFA score of 3 or higher. Cardiovascular failure is not listed here because it was an inclusion criterion.

¶ The types of organisms that were identified are shown in Table S2 in the Supplementary Appendix.

‖ The cardiac index and stroke volume were measured in 84 patients in the levosimendan group and in 73 in the placebo group. The numbers of missing values for other physiological variables listed here are shown in Table S1 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a greater depression of consciousness.

tion over the period of 28 days (hazard ratio, 0.77; 95% CI, 0.60 to 0.97; P=0.03) (Fig. S13 in the Supplementary Appendix). The number of catecholamine-free days was 22 days in the levosimendan group and 23 in the placebo group (difference, –1.0 day; 95% CI, –4.5 to 1.0; P=0.09). A total of 32 patients in the levosimendan group had a serious adverse event, as compared with 23 in the placebo group. Supraventricular tachyarrhythmia was significantly more common in the levosimendan group than in the placebo group. There were no significant differences over time between the two groups in the cardiac index, stroke volume, central venous oxygen saturations or pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and the serum creatinine and bilirubin levels (Figs. S14 through S20 in the Supplementary Appendix).

There were no significant between-group differences in the mean SOFA score or in 28-day mortality in the prespecified subgroups. There was no significant heterogeneity of treatment effect in any of the subgroup analyses (Fig. S21 in the Supplementary Appendix).

DISCUSSION

In this trial, the addition of levosimendan to standard care was not associated with less severe organ dysfunction in adult patients with septic shock. Patients who were treated with levosimendan required more norepinephrine, had higher heart rates, had a higher rate of arrhythmia, and underwent mechanical ventilation for longer than those who received placebo.

Levosimendan is an inotropic agent with a mechanism of action that differs from that of catecholamines. By sensitizing cardiomyocytes to existing levels of intracellular calcium, an increase in the force of myocardial contraction is achieved with a minimal increase in myocardial oxygen demand, in contrast to catecholamines.[9] As calcium levels fall in diastole, relaxation of the myocardium is not impaired with levosimendan, which may be an additional benefit over catecholamines.[26] Although levosimendan has a half-life of approximately 1 hour, its active metabolite OR-1896 has a half-life of 80 hours. Therefore, a single 24-hour infusion should provide hemodynamic effects over the course of a week,[27] which is long enough to support the majority of patients with septic shock until hemodynamic recovery.[20]

Preclinical and small clinical trials have shown a potential benefit of levosimendan on renal,[10] hepatic,[12] and pulmonary[28] function in patients with sepsis. Therefore, the mean daily SOFA score was chosen as the primary outcome in this trial to fully assess the clinical efficacy and biologic effect of levosimendan. However, there was no evidence of any beneficial effect on the total SOFA score or on any individual component of the score or on any other clinical outcome. The cardiovascular SOFA score was higher in the levosimendan group than in the placebo group, which reflects the higher doses of norepinephrine that were required to maintain the mean arterial pressure.

Mortality in our trial population was lower than in previous studies of levosimendan in patients with septic shock. This difference is, at least in part, a consequence of the fact that we recruited a wide range of patients with sepsis, without requiring a low cardiac output as an enrollment criterion. Myocardial dysfunction, although present in more than 50% of patients with septic shock,[3] may not always be clinically evident, even when cardiac-output monitoring is used.[29] There were four planned subgroup analyses to examine the effect of levosimendan in high-risk patients, including those with a low cardiac output, those with impaired oxygen delivery to the tissues, and those receiving high-dose catecholamines. There was no evidence of a beneficial effect of levosimendan in any of these prespecified subgroups.

Although levosimendan does not stimulate β-adrenoreceptors, a significantly higher heart rate was seen in the levosimendan group than in the placebo group, most likely owing to vasodilatation but possibly related to the higher rate of infusion (i.e., higher dose) of norepinephrine in the levosimendan group.[30] Similarly, there was a higher rate of tachyarrhythmia among patients in the levosimendan group than among those in the placebo group. These observations may have contributed to the lack of overall clinical benefit and are consistent with recent data that suggest a potential benefit in treating persistent tachycardia in patients with sepsis with the use of beta-blockers.[31] It is also possible that the higher rate of norepinephrine use in the levosimendan group than in the placebo group may have con-

Table 3. Clinical Outcomes.*

Outcome	Levosimendan (N=258)	Placebo (N=257)	Absolute Difference (95% CI)†	P Value
Primary outcome				
Mean daily total SOFA score	6.68±3.96	6.06±3.89	0.61 (–0.07 to 1.29)	0.053
Respiratory	1.70±1.18	1.56±1.15	0.14 (–0.06 to 0.34)	0.23
Coagulation	0.75±1.05	0.75±1.02	0.00 (–0.18 to 0.17)	0.55
Hepatic	0.51±0.84	0.45±0.77	0.06 (–0.08 to 0.19)	0.65
Cardiovascular	2.27±1.20	2.02±1.20	0.25 (0.04 to 0.46)	0.01
Renal	1.46±1.49	1.28±1.38	0.18 (–0.07 to 0.42)	0.32
Mean daily SOFA score excluding cardiovascular score	4.41±3.13	4.05±3.07	0.36 (–0.17 to 0.90)	0.12
Mean daily total SOFA score in the sensitivity analysis‡	7.19±3.72	6.78±3.74	0.41 (–0.24 to 1.06)	—
Secondary outcomes				
Death — no./total no. (%)§				
At 28 days	89/258 (34.5)	79/256 (30.9)	3.6 (–4.5 to 11.7)	0.43
At ICU discharge	83/258 (32.2)	76/257 (29.6)	2.6 (–5.4 to 10.6)	0.59
At hospital discharge	97/258 (37.6)	84/256 (32.8)	4.8 (–3.5 to 13.0)	0.30
Median no. of catecholamine-free days (IQR)	22 (0 to 26)	23 (0 to 26)	–1.0 (–4.5 to 1.0)	0.09
Median no. of ventilation-free days (IQR)	16 (0 to 25)	19 (0 to 25)	–3.0 (–9.5 to 1.0)	0.14
Major acute kidney event over period of 28 days — no./total no. (%)	148/258 (57.4)	139/256 (54.3)	3.1 (–5.5 to 11.6)	0.54
Need for new renal-replacement therapy	62/257 (24.1)	62/257 (24.1)	0.0 (–7.4 to 7.4)	>0.99
Sustained renal failure at day 28 or ICU discharge if before 28 days	118/258 (45.7)	108/257 (42.0)	3.7 (–4.9 to 12.3)	0.45
Median duration of renal-replacement therapy (IQR) — days	3.0 (1.0 to 8.0)	5.0 (2.0 to 9.0)	–2.0 (–3.0 to 0.0)	0.24
Median length of ICU stay (IQR) — days				
All patients	7.3 (3.2 to 14.8)	8.3 (3.9 to 13.5)	–1.0 (–2.6 to 0.8)	0.66
Survivors	9.1 (5.0 to 16.1)	9.0 (4.9 to 14.1)	0.2 (–2.0 to 2.7)	0.31
Nonsurvivors	3.2 (1.4 to 8.9)	5.7 (2.2 to 11.7)	–2.6 (–5.7 to –0.8)	0.09
Median length of hospital stay (IQR) — days				
All patients	19.6 (10.1 to 40.4)	22.7 (11.7 to 42.3)	–3.1 (–7.0 to 2.2)	0.24
Survivors	30.1 (16.8 to 48)	27.7 (18 to 52.3)	2.5 (–5.9 to 8.2)	0.81
Nonsurvivors	8.2 (3.4 to 18.6)	11.3 (5.1 to 25.7)	–3.1 (–6.5 to 0.7)	0.25
Safety outcomes				
Any serious adverse event — no. (%)	32 (12.4)	23 (8.9)	3.5 (–2.3 to 9.2)	0.26
Any life-threatening arrhythmia — no. (%)	15 (5.8)	6 (2.3)	3.5 (–0.3 to 7.3)	0.08
Supraventricular tachyarrhythmia	8 (3.1)	1 (0.4)	2.7 (0.1 to 5.3)	0.04
Bradycardia	0	2 (0.8)	–0.8 (–2.2 to 0.7)	0.48
Ventricular fibrillation or tachycardia	7 (2.7)	3 (1.2)	1.5 (–1.2 to 4.3)	0.34
Myocardial infarction or acute coronary syndrome — no. (%)	3 (1.2)	1 (0.4)	0.8 (–1.1 to 2.7)	0.62
Other — no. (%)¶	18 (7.0)	17 (6.6)	0.4 (–4.3 to 5.1)	>0.99

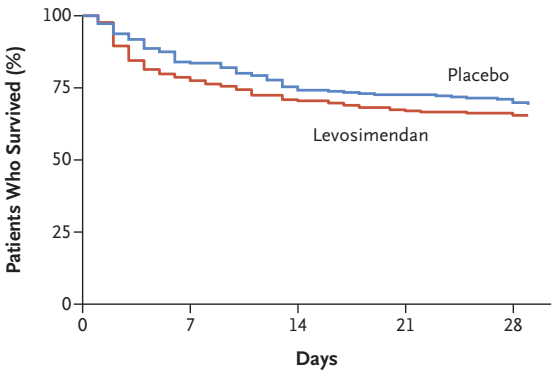
* Plus–minus values are means ±SD. Absolute differences between percent values are percentage points. Confidence intervals were calculated with the use of bootstrap methods for all continuous variables. P values for continuous outcomes were calculated with the use of a Mann–Whitney test and for binary outcomes with the use of a chi-square test. ICU denotes intensive care unit.

† Values may be different than expected owing to rounding.

‡ A prespecified sensitivity analysis that implemented Bayesian models was performed with the use of Markov chain Monte Carlo methods (see the Supplementary Appendix). The absolute difference in this analysis is presented with 95% credible intervals, and P values are not applicable to this type of analysis.

§ One patient in the placebo group declined follow-up after discharge from the ICU but before day 28 and hospital discharge.

¶ Other events were defined as any serious adverse event that was not a life-threatening arrhythmia and not a myocardial infarction or acute coronary syndrome.



No. at Risk					
Levosimendan	258	203	183	174	171
Placebo	257	216	194	186	182

Figure 2. Kaplan–Meier Estimates of the Probability of Survival to Day 28.
The adjusted hazard ratio for death in the levosimendan group, as compared with the placebo group, was 1.24 (95% CI, 0.91 to 1.67; P=0.17).

tributed to further catecholamine-induced myocardial dysfunction.

This trial has several limitations. We investigated levosimendan as added to standard care rather than a comparison of levosimendan with an alternative inotrope, such as dobutamine. Less than 10% of the patients in the placebo group received dobutamine, although the rate of use in the placebo group was higher than in the levosimendan group and may explain in part why the cardiac index and stroke volume were not higher in the levosimendan group than in the placebo group. There was no significant difference in outcome seen in the prespecified subgroup analysis involving patients with a low cardiac index; however, the number of patients with a measured low cardiac index was small (52 patients). Similarly, no echocardiographic analyses were performed to provide additional detailed information about changes in myocardial function with levosimendan treatment. Therefore, this trial cannot provide guidance as to which inotrope is best to use in the management of sepsis if a low cardiac index is present. The target mean arterial pressure of 65 to 70 mm Hg, which was recommended in the protocol and reiterated at investigator meetings, was frequently exceeded (as in other trials involving patients with shock[20,32,33]), which suggests that the norepinephrine doses that were administered could have been reduced in the two trial groups.

In conclusion, in adult patients with septic shock, the addition of levosimendan to standard care was not associated with less severe organ dysfunction or lower mortality. Patients who were assigned to receive levosimendan required more norepinephrine, were less likely to be successfully weaned from mechanical ventilation, and had more tachycardia and a higher rate of supraventricular arrhythmia than those assigned to receive placebo.

The views expressed in this article are those of the authors and not necessarily those of the Medical Research Council (MRC), the National Health Service (NHS), the National Institute for Health Research (NIHR), or the Department of Health.

Supported by the Efficacy and Mechanism Evaluation Programme, an MRC and NIHR partnership, an NIHR Clinician Scientist Award (NIHR/CS/009/007, to Dr. Gordon), and Tenax Therapeutics. The NIHR Comprehensive Biomedical Research Centre (based at Imperial College Healthcare NHS Trust and Imperial College London) and the U.K. Intensive Care Foundation provided general research support.

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

We thank the staff of the NIHR Critical Care Clinical Research Network and the Northern Ireland Clinical Research Network for help with recruitment of patients and data acquisition.

APPENDIX

The authors' full names and academic degrees are as follows: Anthony C. Gordon, M.D., Gavin D. Perkins, M.D., Mervyn Singer, M.D., Daniel F. McAuley, M.D., Robert M.L. Orme, M.B., Ch.B., Shalini Santhakumaran, M.Sc., Alexina J. Mason, Ph.D., Mary Cross, B.A., Farah Al-Beidh, Ph.D., Janis Best-Lane, M.Sc., David Brealey, M.D., Christopher L. Nutt, M.B., B.Ch., James J. McNamee, M.B., Henrik Reschreiter, M.D., Andrew Breen, M.B., Ch.B., Kathleen D. Liu, M.D., Ph.D., and Deborah Ashby, Ph.D.

The authors' affiliations are as follows: the Section of Anaesthetics, Pain Medicine and Intensive Care Medicine, the Department of Surgery and Cancer, Imperial College London and Imperial College Healthcare NHS Trust (A.C.G., F.A.-B., J.B.-L.), Bloomsbury Institute of Intensive Care Medicine, the Division of Medicine, University College London (M.S.), Imperial Clinical Trials Unit Imperial College London (S.S., M.C., F.A.-B., J.B.-L., D.A.), the Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine (A.J.M.), and the Division of Critical Care, University College London Hospitals (D.B.), London, Warwick Clinical Trials Unit, University of Warwick and Heart of England NHS Foundation Trust, Coventry (G.D.P.), the Centre for Experimental Medicine, Queen's University of Belfast (D.F.M., J.J.M.), and the Regional Intensive Care Unit, the Royal Hospitals (D.F.M., J.J.M.), Belfast, the Department of Critical Care, Gloucestershire Hospitals NHS Foundation Trust, Cheltenham (R.M.L.O.), Intensive Care Unit, Antrim Area Hospital, Antrim (C.L.N.), Intensive Care Unit, Poole Hospital NHS Foundation Trust, Poole (H.R.), and Intensive Care Unit, Leeds Teaching Hospitals NHS Trust, Leeds (A.B.) — all in the United Kingdom; and the Department of Medicine, University of California at San Francisco, San Francisco (K.D.L.).

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
2. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.
3. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008;36:1701-6.
4. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
5. Dünser MW, Ruokonen E, Pettilä V, et al. Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. Crit Care 2009;13:R181.
6. Boldt J, Menges T, Kuhn D, Diridis C, Hempelmann G. Alterations in circulating vasoactive substances in the critically ill — a comparison between survivors and non-survivors. Intensive Care Med 1995;21:218-25.
7. Schmittinger CA, Torgersen C, Luckner G, Schröder DC, Lorenz I, Dünser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. Intensive Care Med 2012;38:950-8.
8. Nieminen MS, Fruhwald S, Heunks LM, et al. Levosimendan: current data, clinical use and future development. Heart Lung Vessel 2013;5:227-45.
9. Ukkonen H, Saraste M, Akkila J, et al. Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. Clin Pharmacol Ther 1997;61:596-607.
10. Morelli A, De Castro S, Teboul J-L, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005;31:638-44.
11. Morelli A, Donati A, Ertmer C, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care 2010;14:R232.
12. Memiş D, Inal MT, Sut N. The effects of levosimendan vs dobutamine added to dopamine on liver functions assessed with noninvasive liver function monitoring in patients with septic shock. J Crit Care 2012;27(3):318.e1-6.
13. Wang Q, Yokoo H, Takashina M, et al. Anti-inflammatory profile of levosimendan in cecal ligation-induced septic mice and in lipopolysaccharide-stimulated macrophages. Crit Care Med 2015;43(11):e508-e520.
14. Hasslacher J, Bijuklic K, Bertocchi C, et al. Levosimendan inhibits release of reactive oxygen species in polymorphonuclear leukocytes in vitro and in patients with acute heart failure and septic shock: a prospective observational study. Crit Care 2011;15:R166.
15. Parissis JT, Adamopoulos S, Antoniades C, et al. Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure. Am J Cardiol 2004;93:1309-12.
16. du Toit EF, Genis A, Opie LH, Pollesello P, Lochner A. A role for the RISK pathway and K(ATP) channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. Br J Pharmacol 2008;154:41-50.
17. Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials. J Crit Care 2015;30:908-13.
18. Orme RM, Perkins GD, McAuley DF, et al. An efficacy and mechanism evaluation study of Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS): protocol for a randomized controlled trial. Trials 2014;15:199.
19. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754-8.
20. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA 2016;316:509-18.
21. Gordon AC, Mason AJ, Perkins GD, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med 2014;42:1325-33.
22. Palevsky PM, Molitoris BA, Okusa MD, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin J Am Soc Nephrol 2012;7:844-50.
23. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
24. Anderson MJ, Ter Braak CJF. Permutation tests for multi-factorial analysis of variance. J Stat Comput Simul 2003;73:85-113.
25. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2015.
26. Jörgensen K, Bech-Hanssen O, Houltz E, Ricksten SE. Effects of levosimendan on left ventricular relaxation and early filling at maintained preload and afterload conditions after aortic valve replacement for aortic stenosis. Circulation 2008;117:1075-81.
27. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikäinen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther 2002;40:465-71.
28. Morelli A, Teboul J-L, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 2006;34:2287-93.
29. Shahul S, Gulati G, Hacker MR, et al. Detection of myocardial dysfunction in septic shock: a speckle-tracking echocardiography study. Anesth Analg 2015;121:1547-54.
30. Gordon AC, Wang N, Walley KR, Ashby D, Russell JA. The cardiopulmonary effects of vasopressin compared with norepinephrine in septic shock. Chest 2012;142:593-605.
31. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-91.
32. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
33. Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370:1583-93.