parents who go to enormous efforts to get cannabis for their children report a higher response rate than those who can easily obtain it.[7] Cannabidiol is not without side effects. The dropout rate in the active-treatment group was appreciable, and common side effects included vomiting, loss of appetite, and diarrhea. With additional experience, perhaps these effects can be modified with dose adjustment and other strategies.

A major aim in the field of the Dravet syndrome and other genetic encephalopathies is to develop precision therapies — treatments directed at the specific genetic defect.[8] Because the Dravet syndrome has a single-gene basis, it is an attractive target for precision medicine.[8] However, cannabidiol is not a precision treatment for the syndrome, because there is no established link of the cannabinoid receptors with the inhibitory interneuron pathology of the Dravet syndrome, and the response across the cohort of the current study was not uniform.

This trial represents the beginning of solid evidence for the use of cannabinoids in epilepsy. It requires replication. Future trials may answer further questions about the applicability of cannabinoids to the many other syndromes of childhood epilepsy and to treatment in adults. After an era dominated by anecdote and obfuscated by medicolegal issues and emotionally infused debate, more scientific studies are under way. Much more research is needed to understand the basic science, benefits, and risks of cannabinoids in epilepsy.

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

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Levosimendan for the Low Cardiac Output Syndrome after Cardiac Surgery

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The low cardiac output syndrome complicates 1 in 10 coronary bypass operations and is associated with a heightened risk of perioperative death.[1] The pathophysiology of this syndrome is complex, with likely contributions from reperfusion injury, systemic inflammation induced by cardiopulmonary bypass, and pulmonary and systemic vasoconstriction.[2]

Pharmacologic management of the low cardiac output syndrome typically includes positive inotropic drugs such as beta-adrenergic agonists and phosphodiesterase inhibitors. Although these agents may increase cardiac output, they also heighten the risk of atrial and ventricular arrhythmias, and they may exacerbate myocardial ischemia by increasing myocardial oxygen consumption. In two observational studies, patients receiving perioperative inotropes had higher rates of postoperative myocardial infarction, stroke, renal dysfunction, and in-hospital death than those not receiving inotropes.[3,4]

Levosimendan is a calcium-sensitizing agent with a mechanism of action that is distinct from those of other inotropes and with a prolonged duration of action.[5] By stabilizing the binding of calcium to troponin C, levosimendan enhances actin–myosin cross-bridging and increases contractile force. It also acts as a vasodilator by means of an effect on ATP-sensitive potassium channels in vascular smooth muscle. Since levosimendan acts without enhancing intracellular concentrations of free calcium, it does not increase myocardial oxygen demand. Although levosimendan is not approved by the Food and

Drug Administration, it is used extensively outside the United States.[6]

A series of small, randomized trials have compared the perioperative administration of levosimendan with dobutamine, milrinone, or placebo in patients undergoing cardiac surgery. Although none of the trials was individually powered to show a survival benefit, in two meta-analyses of these trials[7,8] postoperative mortality was significantly lower among patients assigned to levosimendan, particularly those with reduced ejection fraction, than among patients in the control groups. This issue of the *Journal* reports the primary results of the LEVO-CTS (Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass) trial[9] and CHEETAH (Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial),[10] two larger, randomized, placebo-controlled trials of levosimendan in cardiac surgery that were undertaken to confirm the findings of the meta-analyses.

The LEVO-CTS trial randomly assigned 882 patients with a left ventricular ejection fraction of 35% or less to preoperative use of levosimendan or placebo as a prophylactic approach for the prevention of the low cardiac output syndrome. By contrast, CHEETAH randomly assigned 506 patients with established postoperative low output syndrome, most of whom were already receiving either high-dose inotropes or intraaortic balloon-pump support, to receive either levosimendan or placebo. In the LEVO-CTS trial, levosimendan was administered as a fixed dose of 0.2 μg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1 μg per kilogram per minute for 23 hours. In CHEETAH, levosimendan was given at a starting dose of 0.05 μg per kilogram per minute and adjusted, at the discretion of the treating clinicians, from 0.025 μg per kilogram per minute to 0.2 μg per kilogram per minute for up to 48 hours or until discharge from the intensive care unit. Neither trial met its primary end point, and, in contrast to the meta-analyses, neither trial showed a significant benefit of levosimendan with respect to mortality at 30 days.

How should clinicians interpret the results of these two trials? The findings seem to undermine the suggestion from the previous meta-analyses of a mortality benefit with either prophylactic or postoperative use of levosimendan in cardiac surgery. Both trials, however, leave a number of questions unanswered. First, neither trial required systematic hemodynamic assessments, and it is therefore difficult to assess the effect of levosimendan on the incidence or duration of the low cardiac output syndrome. Among patients who had cardiac index measurements in CHEETAH, no important differences between groups were noted, but only approximately half the patients had such data. In the LEVO-CTS trial, the secondary end point of the low cardiac output syndrome was significantly more frequent in the placebo group than in the levosimendan group, but this end point was a composite that included the use of inotropes or mechanical cardiac support in addition to measurements of low cardiac output.

Second, for both trials, it is challenging to isolate the effects of levosimendan on clinical outcomes in the context of the use of other inotropic agents administered as part of routine clinical care. In CHEETAH, in which lower doses of levosimendan were administered, the use of additional inotropic support did not differ significantly between the trial groups. In the LEVO-CTS trial, in which a higher levosimendan dose was administered, secondary inotropes were used 24 hours after the initiation of the trial agent in 54.9% of the patients in the levosimendan group and in 62.7% of those in the placebo group, an indication of a greater inotrope requirement in the patients who were not receiving the active drug. The lack of difference in mortality at 30 days despite this differential use of conventional inotropic drugs argues against a unique benefit of levosimendan with respect to survival.

Overall, these data suggest that despite its unique mechanism of action, levosimendan has no clear advantage over conventional inotropic drugs for the management of perioperative low cardiac output syndrome in patients undergoing cardiac surgery. By highlighting the lack of a clear incremental advantage to levosimendan over routine care with the use of existing agents, these trials collectively challenge the previous endorsement of levosimendan use in the European literature[6] and argue against the approval of levosimendan for this indication in the United States.

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

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ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

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ABSTRACT

BACKGROUND

Acute left ventricular dysfunction is a major complication of cardiac surgery and is associated with increased mortality. Meta-analyses of small trials suggest that levosimendan may result in a higher rate of survival among patients undergoing cardiac surgery.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving patients in whom perioperative hemodynamic support was indicated after cardiac surgery, according to prespecified criteria. Patients were randomly assigned to receive levosimendan (in a continuous infusion at a dose of 0.025 to 0.2 μg per kilogram of body weight per minute) or placebo, for up to 48 hours or until discharge from the intensive care unit (ICU), in addition to standard care. The primary outcome was 30-day mortality.

RESULTS

The trial was stopped for futility after 506 patients were enrolled. A total of 248 patients were assigned to receive levosimendan and 258 to receive placebo. There was no significant difference in 30-day mortality between the levosimendan group and the placebo group (32 patients [12.9%] and 33 patients [12.8%], respectively; absolute risk difference, 0.1 percentage points; 95% confidence interval [CI], −5.7 to 5.9; P=0.97). There were no significant differences between the levosimendan group and the placebo group in the durations of mechanical ventilation (median, 19 hours and 21 hours, respectively; median difference, −2 hours; 95% CI, −5 to 1; P=0.48), ICU stay (median, 72 hours and 84 hours, respectively; median difference, −12 hours; 95% CI, −21 to 2; P=0.09), and hospital stay (median, 14 days and 14 days, respectively; median difference, 0 days; 95% CI, −1 to 2; P=0.39). There was no significant difference between the levosimendan group and the placebo group in rates of hypotension or cardiac arrhythmias.

CONCLUSIONS

In patients who required perioperative hemodynamic support after cardiac surgery, low-dose levosimendan in addition to standard care did not result in lower 30-day mortality than placebo. (Funded by the Italian Ministry of Health; CHEETAH ClinicalTrials.gov number, NCT00994825.)

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*A complete list of investigators in the Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial (CHEETAH) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Every year, more than 1 million patients undergo cardiac surgery in the United States and Europe.[1] Acute perioperative left ventricular dysfunction is a major complication affecting up to 20% of such patients[2,3] and is associated with increased mortality.[4] Inotropic drugs (catecholamines and phosphodiesterase type 3 [PDE-3] inhibitors) are the cornerstone of postoperative hemodynamic support.[3,5] However, no randomized, controlled trials have shown the superiority of any inotropic agent in terms of major clinical outcomes. Furthermore, meta-analyses and observational studies suggest that catecholamines and PDE-3 inhibitors may increase mortality.[6,7]

Levosimendan (Simdax, Orion) is an inotropic agent that has been shown to be associated with a higher rate of survival than other inotropic agents in meta-analyses,[8] especially those involving patients undergoing cardiac surgery.[9-11] A network meta-analysis ranked levosimendan as the most likely inotrope to reduce mortality among patients undergoing cardiac surgery.[12] Treatment with levosimendan results in greater cardiac output than does treatment with catecholamines or PDE-3 inhibitors, with minimal effect on myocardial oxygen consumption.[13,14] Moreover, it has antioxidant, antiinflammatory, and direct cardioprotective effects.[13] Accordingly, it is widely used in several countries.

Considering the pharmacologic properties of levosimendan and the results of previous studies, we hypothesized that the administration of levosimendan, in addition to standard treatment, might result in lower mortality in this context. Accordingly, we designed the Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial (CHEETAH) to test the hypothesis that levosimendan treatment in addition to standard inotropic treatment would result in lower mortality than placebo among patients with perioperative cardiovascular dysfunction after cardiac surgery.

METHODS

TRIAL DESIGN

We performed this randomized, double-blind, placebo-controlled trial at 14 centers in Italy, Russia, and Brazil. The trial protocol (available with the full text of this article at NEJM.org) was approved by the ethics committee at all the participating centers. Details of the trial methods and statistical analysis plan have been published previously.[15]

The trial was funded by the Italian Ministry of Health and received a start-up grant from the European Association of Cardiothoracic Anesthesiologists. Levosimendan was provided free of charge by the manufacturer (Orion) to centers that recruited patients in Italy; all the centers in Russia and Brazil purchased the drug at full cost. The funders and Orion had no role in the trial design, the data collection and analysis, the writing of the manuscript, or the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and all analyses and for the fidelity of the trial to the protocol.

ENROLLMENT PROCEDURE, CRITERIA, AND RANDOMIZATION

All the patients who were scheduled for cardiac surgery at the trial centers provided preoperative written informed consent. Patients then underwent randomization if they met the enrollment criteria either in the operating room or in the intensive care unit (ICU). Patients were included if they had perioperative cardiovascular dysfunction, which was defined as the presence of at least one of the following criteria: a preoperative left ventricular ejection fraction of less than 25%, preoperative support with an intraaortic balloon pump, or the need for support with an intraaortic balloon pump or high-dose inotropic support (defined as a vasoactive–inotropic score of ≥10 as described in the Supplementary Appendix, available at NEJM.org) in order to be weaned from cardiopulmonary bypass or at any time within the first 24 hours after surgery.

Exclusion criteria were a previous adverse response to levosimendan, inclusion in another randomized trial, receipt of levosimendan in the previous 30 days, receipt of a kidney or liver transplant, liver cirrhosis, a decision to use extracorporeal membrane oxygenation, or the presence of a do-not-resuscitate order. Patients undergoing an emergency operation were also excluded because it would have been difficult to obtain informed consent.

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either levosimendan or placebo. Randomization was performed with the use of a computer-generated, permuted block sequence

stratified according to trial center. Trial-group assignments were concealed in sealed, opaque, sequentially numbered envelopes. Physicians, investigators, data collectors, and outcome assessors were unaware of the trial-group assignments.

CLINICAL REGIMEN

Patients were assigned to receive a blinded infusion of either levosimendan or placebo as prepared by dedicated trial personnel. Levosimendan was diluted as 12.5 mg in 100 ml of 5% glucose. A mixed-vitamins solution with a yellow color, devoid of relevant cardiovascular effects and indistinguishable in appearance from levosimendan, was used as placebo (see the Supplementary Appendix).

Levosimendan or placebo was initiated as a continuous infusion at a dose of 0.05 μg per kilogram of body weight per minute. The dose could then be increased or decreased at the discretion of the attending physician; the minimum dose was 0.025 μg per kilogram per minute, and the maximum dose 0.2 μg per kilogram per minute. The infusion could be continued for up to 48 hours (to allow for prolonged support in the most compromised patients) or until ICU discharge. In this pragmatic trial,[16] all clinical decisions, with the exception of the administration of the trial regimen, were left to the discretion of the attending physicians, including hemodynamic monitoring and management. However, an advisory flowchart for open-label inotrope management was provided to investigators (Fig. S1 in the Supplementary Appendix).

DATA COLLECTION AND FOLLOW-UP

We collected preoperative data on baseline characteristics and coexisting conditions, intraoperative and postoperative treatment data, postoperative laboratory values, duration of mechanical ventilation, durations of ICU and hospital stays, and major outcomes. Baseline hemodynamic data were collected at randomization (most patients were already receiving hemodynamic support with high-dose inotropic agents, an intraaortic balloon pump, or both). We also collected data on the incidence of hypotension, arrhythmias, and other adverse events during the administration of the infusion, as well as information on protocol deviations. Telephone follow-up was performed at 30 days and 180 days after randomization by an investigator who was unaware of the trial-group assignments.

OUTCOME MEASURES

The primary outcome of the trial was 30-day mortality. Prespecified secondary outcomes were the following: acute kidney injury,[17] a need for renal-replacement therapy, a composite outcome of death and need for renal-replacement therapy, duration of mechanical ventilation, and durations of stay in the ICU and hospital.[15] We also collected data on the following outcomes: need for advanced mechanical circulatory support, myocardial infarction, type 1 or type 2 neurologic damage,[18] need for tracheostomy, sepsis, pneumonia, and mediastinitis. Definitions of the outcome measures are provided in the Supplementary Appendix. Cause of death in the ICU and hospital was recorded with the use of previously validated criteria (see the Supplementary Appendix).[19]

STATISTICAL ANALYSIS

The sample-size calculation was based on a two-sided alpha error of 0.05 and 80% power. On the basis of meta-analyses that estimated that mortality would be reduced from 12.7% to 4.7% with levosimendan use,[9,10] we expected 10% mortality in the placebo group and 5% mortality in the levosimendan group. Accordingly, we calculated that a sample of 435 patients per group was needed. In order to account for protocol deviations and withdrawal of consent, we planned for 500 patients per group to undergo randomization.

Interim analyses were planned after enrollments of 25% and 50% of the sample size.[20,21] The first review by the data and safety monitoring board (at 25% enrollment) led to a decision to decrease the sample from 1000 to 500 patients, because a higher-than-expected overall mortality rate of 13.5% and a lower-than-expected withdrawal rate of 0% were observed. The second review by the data and safety monitoring board (at 50% of the originally planned enrollment) led to the decision to stop the trial on the grounds of futility (see the Supplementary Appendix).

Details of the statistical analysis plan have been published previously.[15] Primary analyses comparing levosimendan with placebo were performed according to the intention-to-treat principle. No imputation for missing data was applied. Per-protocol and as-treated analyses were also performed.

Data are presented as medians and interquartile ranges for nonnormally distributed variables and as means and standard deviations for normally distributed variables. Dichotomous data (including the primary outcome) were compared by two-tailed chi-square tests with the Yates correction or by Fisher's exact test as appropriate. The primary analysis was not adjusted for covariates. Continuous measurements were compared with the use of the Mann–Whitney U test. A logistic-regression model with stepwise selection was used to identify predictors of death (see the Supplementary Appendix). Prespecified subgroup analyses were performed as described in the Supplementary Appendix. In all the subgroup analyses, heterogeneity was estimated by the chi-square test for heterogeneity and the I^2 statistic.

All reported P values are two-sided. Data were stored electronically and analyzed with the use of Stata software, version 13 (StataCorp).

RESULTS

TRIAL POPULATION AND BASELINE CHARACTERISTICS

From November 2009 through April 2016, we obtained written informed consent from 4725 patients. Of these, 506 patients underwent randomization, with 248 patients being randomly assigned to receive levosimendan and 258 to receive placebo (Fig. 1). Most patients underwent randomization in the operating room because high doses of inotropes were indicated for weaning from cardiopulmonary bypass (61 patients [12.1%]) or in the ICU because of postoperative acute cardiovascular dysfunction (329 [65.0%]). Only a minority of patients underwent randomization preoperatively because of low ejection fraction (22 patients [4.3%]). The remaining 94 patients (18.6%) underwent randomization because they received support with an intraaortic balloon pump. The timing of the randomization of patients who underwent randomization in the ICU is shown in Figure S2 in the Supplementary Appendix. The baseline and intraoperative characteristics of the patients were similar in the levosimendan group and in the placebo group (Table 1, and Table S1 in the Supplementary Appendix).

INFUSION OF LEVOSIMENDAN OR PLACEBO

The mean (±SD) duration of the infusion was 33±14.6 hours in the levosimendan group and 32±13.5 hours in the placebo group (P=0.17). The mean dose was 0.066±0.031 μg per kilogram per minute in the levosimendan group, with a volume equivalent to a dose of 0.075±0.033 μg per kilogram per minute administered in the placebo group (P=0.002). An increase from the initial dose of 0.05 μg per kilogram per minute was performed in 127 patients (51.2%) in the levosimendan group, as compared with 159 (61.6%) in the placebo group (P=0.02). Reasons for the interruption of the infusion and for unblinding are reported in Tables S2 and S3, respectively, in the Supplementary Appendix.

HEMODYNAMIC VARIABLES AND PROCESS OF CARE

Hemodynamic data were not available for all patients, because hemodynamic monitoring was not required and was performed according to the clinical condition of the patient and the judgment of the physician. The available hemodynamic data, the rates of use of vasoactive drugs, and the inotropic score after randomization were similar in the two groups. There was no between-group difference in the available postoperative laboratory values. (Details are provided in Tables S4 through S8 in the Supplementary Appendix.)

PRIMARY AND SECONDARY OUTCOMES

No patient was lost to 30-day follow-up, and all the patients who underwent randomization were included in the intention-to-treat analysis (Fig. 1). At 30 days, there had been 32 deaths (12.9% of patients) in the levosimendan group and 33 deaths (12.8%) in the placebo group (absolute risk difference, 0.1 percentage points; 95% confidence interval [CI], −5.7 to 5.9; P=0.97) (Table 2). There were no significant differences in the cause of death (Table S9 in the Supplementary Appendix). No significant differences in secondary outcomes were observed (Tables 2 and 3). Kaplan–Meier survival plots showed no between-group difference in mortality rates over time (hazard ratio, 1.02; 95% CI, 0.65 to 1.59; P=0.94) (Fig. 2). Results of the as-treated and per-protocol analyses, which also showed no significant between-group differences, are reported in Tables S10 and S11, respectively, in the Supplementary Appendix.

Results of the prespecified and exploratory subgroup analyses are reported in Figures S3 and S4, respectively, in the Supplementary Appendix. There were no significant treatment-by-subgroup interactions. Analysis of 30-day mortality with stratification according to trial center did not identify

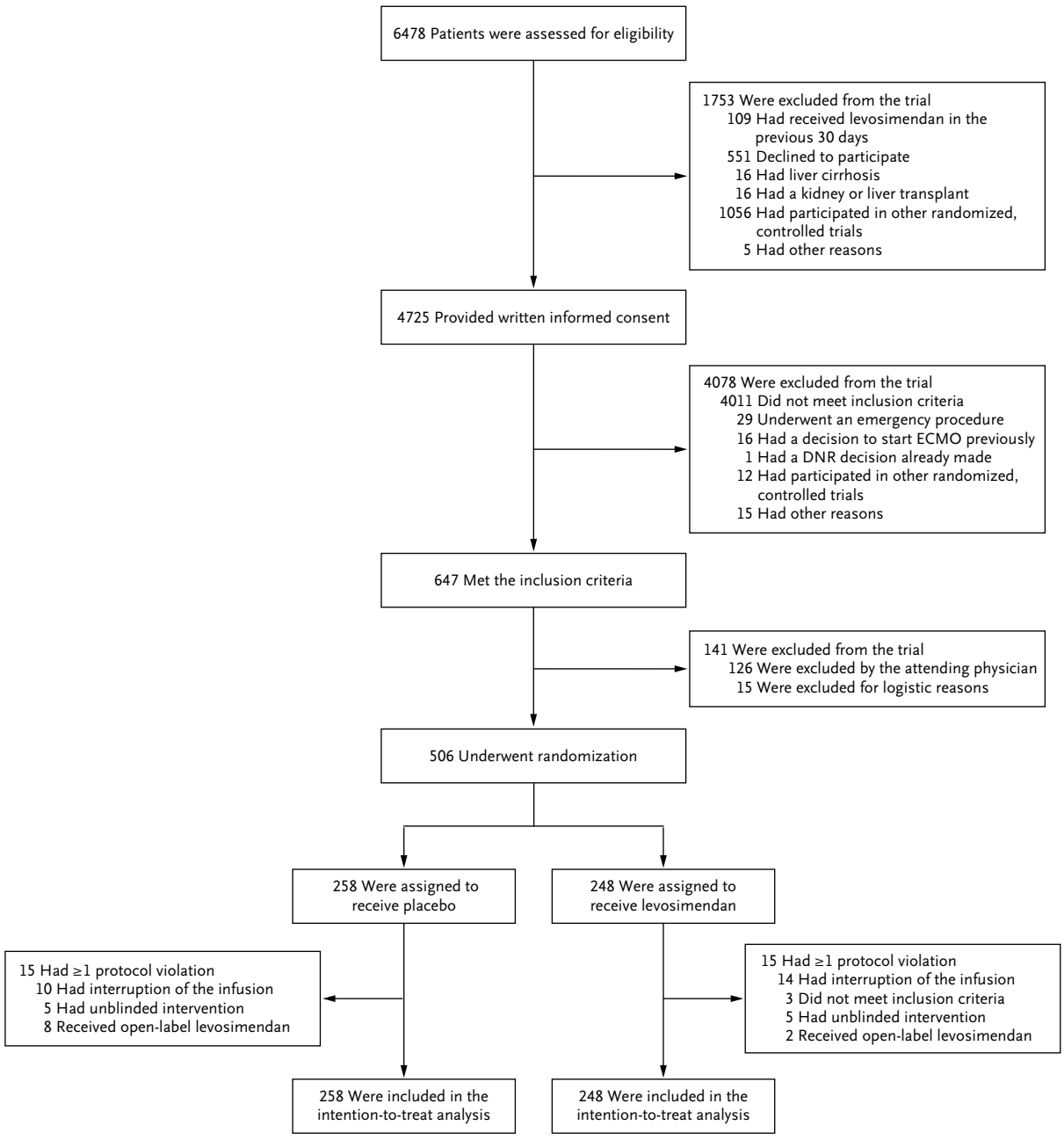


Figure 1. Recruitment, Randomization, and Analysis Populations.
DNR denotes do not resuscitate, and ECMO extracorporeal membrane oxygenation.

a significant interaction. Results of univariate and multivariate analyses of association of baseline variables with 30-day mortality confirmed the lack of effect of levosimendan. (Details are provided in Fig. S5 and Tables S12 and S13 in the Supplementary Appendix.)

Serious adverse events were reported in 107 of 245 patients (43.7%) in the levosimendan group and in 131 of 254 (51.6%) in the placebo group ($P=0.08$) (Table 3). Hypotension during the infusion was observed in 62 of 246 patients (25.2%) in the levosimendan group and in 54 of 253 (21.3%)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Levosimendan (N=248)	Placebo (N=258)
Age — yr		
Median	66	66
Interquartile range	58–74	58–72
Female sex — no. (%)	89 (35.9)	90 (34.9)
Weight — kg		
Median	74	75
Interquartile range	65–83	67–86
Height — cm	167±8.3	168±9.0
Body-mass index		
Median	26	27
Interquartile range	24–30	24–30
Previous cardiac surgery — no./total no. (%)	44/244 (18.0)	35/256 (13.7)
Myocardial infarction — no./total no. (%)	105/247 (42.5)	90/258 (34.9)
Atrial fibrillation — no./total no. (%)	73/247 (29.6)	81/258 (31.4)
Ongoing cardiogenic shock — no./total no. (%)†	6/247 (2.4)	7/258 (2.7)
NYHA classification — no./total no. (%)		
I	19/241 (7.9)	20/249 (8.0)
II	72/241 (29.9)	86/249 (34.5)
III	133/241 (55.2)	127/249 (51.0)
IV	17/241 (7.1)	16/249 (6.4)
COPD — no./total no. (%)	33/246 (13.4)	33/256 (12.9)
History of stroke or TIA — no./total no. (%)	18/247 (7.3)	19/257 (7.4)
Peripheral vascular disease — no./total no. (%)	26/247 (10.5)	42/257 (16.3)
Diabetes — no./total no. (%)	49/247 (19.8)	61/257 (23.7)
Left ventricular ejection fraction		
Median (interquartile range) — %	50 (37–59)	50 (40–60)
Distribution — no./total no. (%)		
<25%	11/238 (4.6)	11/251 (4.4)
25–40%	53/238 (22.3)	43/251 (17.1)
>40%	174/238 (73.1)	197/251 (78.5)
Preoperative medical therapy — no./total no. (%)		
Angiotensin-receptor blocker	33/244 (13.5)	35/257 (13.6)
ACE inhibitor	101/244 (41.4)	111/257 (43.2)
Diuretic	157/244 (64.3)	162/257 (63.0)
Digoxin	21/244 (8.6)	19/257 (7.4)
Beta-blocker	153/244 (62.7)	159/257 (61.9)
Nitrate	44/243 (18.1)	49/257 (19.1)
Amiodarone	15/244 (6.1)	24/257 (9.3)
Ivabradine	6/244 (2.5)	3/257 (1.2)
Ranolazine	4/244 (1.6)	1/257 (0.4)

Table 1. (Continued.)

Characteristic	Levosimendan (N=248)	Placebo (N=258)
Inclusion criteria — no. (%)‡		
Preoperative left ventricular ejection fraction <25%	11 (4.4)	11 (4.3)
Intraaortic balloon pump	50 (20.2)	44 (17.1)
High doses of inotropes received for weaning from cardiopulmonary bypass	33 (13.3)	28 (10.9)
High doses of inotropes administered in ICU	154 (62.1)	175 (67.8)

* Plus–minus values are means ±SD. There were no significant between-group differences in the characteristics listed here. Percentages may not sum to 100 because of rounding. Data were missing as follows: on age, for 1 patient in the placebo group; on weight, height, and body-mass index (the weight in kilograms divided by the square of the height in meters) for 1 in the levosimendan group; and on left ventricular ejection fraction for 10 in the levosimendan group and for 7 in the placebo group. ACE denotes angiotensin-converting enzyme, COPD chronic obstructive pulmonary disease, ICU intensive care unit, NYHA New York Heart Association, and TIA transient ischemic attack.

† Ongoing cardiogenic shock was defined as a state of end-organ hypoperfusion due to cardiac failure. The definition included the following hemodynamic variables: persistent hypotension (systolic blood pressure of 80 to 90 mm Hg or a mean arterial pressure that was 30 mm Hg lower than the baseline value) with a severe reduction in cardiac index (<1.8 liters per minute per square meter of body-surface area without support or 2.0 to 2.2 liters per minute per square meter with support) and adequate or elevated filling pressure (e.g., a left ventricular end-diastolic pressure of >18 mm Hg or a right ventricular end-diastolic pressure of >10 to 15 mm Hg), as measured with a pulmonary-artery catheter or assessed by means of echocardiography.[22]

‡ The inclusion criteria were not mutually exclusive. We list the first single criterion that led to qualification for the trial.

in the placebo group (P=0.31). There were 89 cases of arrhythmias, with no significant difference between the two groups.

DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled trial involving patients who required hemodynamic support after cardiac surgery, the administration of levosimendan was not associated with lower 30-day mortality than placebo. There was also no significant between-group difference in mortality in any subgroup. No significant difference was seen between the levosimendan group and the placebo group in the incidence of hypotension or arrhythmias.

Previous meta-analyses of randomized, controlled trials[8-11] showed a higher rate of survival with levosimendan than with other treatment regimens among patients undergoing cardiac surgery. These findings were not confirmed in our trial. A benefit of levosimendan with regard to survival was also not shown in the LEVO-CTS (Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass) trial, the results of which have been published in the *Journal*.[23] A similar pattern of positive results from small randomized trials and meta-analyses of randomized trials of levosimendan,[8,10,24] contradicted by a subsequent pivotal trial, has been observed in patients with severe sepsis[25] or heart failure.[26,27]

Cardiac surgery was considered to be the most promising context for observing a beneficial effect of levosimendan, owing to the transient nature of postoperative myocardial dysfunction.[28,29] Myocardial stunning accounts for the majority of cases of perioperative heart failure,[2,28,29] and usually the heart recovers within 24 to 48 hours. Because of its pharmacologic characteristics (increase in cardiac output with little increase in myocardial oxygen consumption), levosimendan appeared to be the ideal inotropic agent to support heart function in such patients. However, in our trial, levosimendan did not result in lower mortality than placebo, nor did it improve other relevant outcomes in this context. Our findings do not support the administration of levosimendan in addition to standard care in the management of cardiac dysfunction after cardiac surgery.

Our trial differs from previous trials in cardiac surgery, which mostly investigated the use of levosimendan in patients undergoing coronary-artery bypass grafting (CABG). Less than half our patients underwent CABG, and a similar proportion underwent mitral-valve surgery. Thus, it is possible that perioperative cardiovascular dysfunction may have different pathophysiological features in

Table 2. Prespecified Clinical Outcomes.*

Outcome	Levosimendan (N=248)	Placebo (N=258)	Difference (95% CI)†	P Value
Primary outcome				
30-Day mortality — no. (%)	32 (12.9)	33 (12.8)	0.1 (–5.7 to 5.9)	0.97
Secondary outcomes				
Acute kidney injury, according to RIFLE criteria — no./total no. (%)‡				
Risk	41/247 (16.6)	55/258 (21.3)	–4.7 (–11.5 to 2.1)	0.18
Injury	26/247 (10.5)	27/258 (10.5)	0.1 (–5.3 to 5.4)	0.98
Failure	17/247 (6.9)	22/258 (8.5)	–1.6 (–6.3 to 3.0)	0.49
Renal-replacement therapy — no. (%)	24 (9.7)	33 (12.8)	–3.1 (–8.6 to 2.4)	0.27
Death or renal-replacement therapy — no. (%)	42 (16.9)	49 (19.0)	–2.1 (–8.7 to 4.6)	0.55
Duration of mechanical ventilation — hr				
Median	19	21	–2 (–5 to 1)	0.48
Interquartile range	14 to 40	14 to 41		
Duration of ICU stay — hr				
Median	72	84	–12 (–21 to 2)	0.08
Interquartile range	46 to 114	48 to 139		
Duration of hospital stay — days				
Median	14	14	0 (–1 to 2)	0.39
Interquartile range	8 to 21	9 to 21		
Need for open-label levosimendan — no. (%)	2 (0.8)	8 (3.1)	–2.3 (–4.7 to 0.1)	0.11
Interruption of infusion due to adverse events — no./total no. (%)	9/236 (3.8)	4/246 (1.6)	2.2 (–0.7 to 5.1)	0.17

* Data were missing as follows: on duration of mechanical ventilation for six patients in the levosimendan group and for four in the placebo group; on duration of ICU stay for four and three, respectively; and on duration of hospital stay for three in each group.

† Differences between percents are presented in percentage points and may not sum as expected because of rounding. Differences in other variables are presented in the units shown in the table.

‡ Acute kidney injury was assessed with the use of a five-category scoring system to evaluate risk, injury, failure, loss, and end-stage kidney injury (RIFLE).[17] Risk was defined as an increase in the serum creatinine level of at least 1.5 times the baseline value, a decrease in the glomerular filtration rate (GFR) of more than 25% from baseline, or a urine output of less than 0.5 ml per kilogram of body weight per hour for 6 hours. Injury was defined as an increase in the serum creatinine level of at least 2 times the baseline value, a decrease in the GFR of more than 50% from baseline, or a urine output of less than 0.5 ml per kilogram per hour for 12 hours. Failure was defined as an increase in the serum creatinine level of at least 3 times the baseline value, a serum creatinine level of at least 4 mg per deciliter, a decrease in the GFR of more than 75% from baseline, a urine output of less than 0.3 ml per kilogram per hour for 24 hours, or anuria for 12 hours.

these patients and hence result in a different response to levosimendan. However, in a prespecified subgroup analysis, we found no influence of the type of surgery on outcome.

Several previous studies of levosimendan in cardiac surgery, including the LEVO-CTS trial,[23] focused on patients with reduced preoperative ejection fraction.[11] In contrast, we enrolled patients with ongoing myocardial dysfunction requiring inotropic support. Although subgroup analyses involving patients with reduced ejection fraction at baseline did not show any beneficial effect of levosimendan in our trial, there were too few such patients for us to draw conclusions.

The dose of levosimendan that was used in our trial differs from that used in other studies. In most previous trials, a loading dose was administered, and in all previous trials, an infusion of at least 0.1 μg per kilogram per minute was used.[11,30] In our trial, we did not use a loading dose, and the infusion of levosimendan was started at 0.05 μg per kilogram per minute to avoid hypotension.

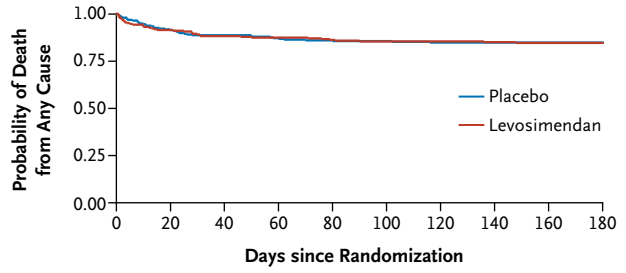
Table 3. Additional Clinical and Safety Outcomes.

Outcome	Levosimendan (N=248)	Placebo (N=258)	Difference (95% CI)*	P Value
Clinical outcomes				
ECMO — no./total no. (%)	3/245 (1.2)	2/257 (0.8)	0.4 (–1.3 to 2.2)	0.68
Ventricular assist device — no./total no. (%)	1/244 (0.4)	1/257 (0.4)	0.0 (–1.1 to 1.1)	0.99
Myocardial infarction — no./total no. (%)	14/243 (5.8)	15/257 (5.8)	–0.1 (–4.2 to 4.0)	0.99
Neurologic damage — no./total no. (%)†				
Type 1	11/247 (4.5)	9/258 (3.5)	1.0 (–2.4 to 4.4)	0.58
Type 2	30/247 (12.1)	37/258 (14.3)	–2.2 (–8.1 to 3.7)	0.47
Need for tracheostomy — no./total no. (%)	17/247 (6.9)	14/255 (5.5)	1.4 (–2.8 to 5.6)	0.52
Sepsis — no./total no. (%)	16/246 (6.5)	17/255 (6.7)	–0.2 (–4.5 to 4.2)	0.93
Severe sepsis — no./total no. (%)	9/245 (3.7)	13/255 (5.1)	–1.4 (–5.0 to 2.1)	0.43
Septic shock — no./total no. (%)	6/245 (2.4)	10/255 (3.9)	–1.5 (–4.6 to 1.6)	0.35
Mediastinitis — no./total no. (%)	1/242 (0.4)	4/253 (1.6)	–1.2 (–2.9 to 0.6)	0.37
Pneumonia — no./total no. (%)	15/243 (6.2)	15/253 (5.9)	0.2 (–4.0 to 4.4)	0.91
Transfusion in operating room or ICU				
Red-cell transfusion				
No. of patients (%)	125 (50.4)	141 (54.7)	–4.2 (–12.9 to 4.4)	0.34
Units per patient				
Median	2.0	3.0	–1.0 (–1.0 to 1.0)	0.21
Interquartile range	2.0 to 4.0	2.0 to 5.0		
Fresh-frozen plasma transfusion				
No. of patients (%)	72 (29.0)	90 (34.9)	–5.9 (–14.0 to 2.2)	0.16
Units per patient				
Median	3.0	3.0	0.0 (–1.0 to 1.0)	0.40
Interquartile range	2.0 to 4.0	2.0 to 7.0		
Platelet transfusion				
No. of patients (%)	17 (6.9)	26 (10.1)	–3.1 (–8.1 to 1.6)	0.19
Units per patient				
Median	1.0	1.0	0.0 (–1.0 to 1.0)	0.37
Interquartile range	1.0 to 2.0	1.0 to 3.0		
Death — no./total no. (%)				
In the ICU	24/248 (9.7)	19/258 (7.4)	2.3 (–2.6 to 7.2)	0.35
In the hospital	31/248 (12.5)	31/258 (12.0)	0.5 (–5.2 to 6.2)	0.87
At 180 days	38/248 (15.3)	39/254 (15.4)	0.0 (–6.3 to 6.3)	0.99
Safety outcomes				
Hypotension during infusion — no./total no. (%)	62/246 (25.2)	54/253 (21.3)	3.9 (–3.6 to 11.3)	0.31
Managed with vasoconstrictors	43/56 (76.8)	40/53 (75.5)	1.3 (–14.7 to 17.3)	0.87
Managed with dose reduction	26/50 (52.0)	19/45 (42.2)	10.7 (–9.2 to 30.6)	0.29
Arrhythmias during infusion — no./total no. (%)				
Supraventricular	35/246 (14.2)	43/254 (16.9)	–2.7 (–9.1 to 3.7)	0.41
Ventricular	4/246 (1.6)	7/254 (2.8)	–1.1 (–3.7 to 1.4)	0.55
Serious adverse event — no./total no. (%)				
Considered by investigator to be due to trial regimen	0/244	0/256	—	—
Any‡	107/245 (43.7)	131/254 (51.6)	–7.9 (–16.6 to 0.8)	0.08

* Differences between percent values are presented in percentage points and may not sum as expected because of rounding. Differences in other variables are presented in the units shown in the table.

† Neurologic damage type 1 was defined as death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack, or stupor or coma at the time of discharge.[18] Neurologic damage type 2 was defined as new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury.[18]

‡ This outcome included a composite of myocardial infarction, acute kidney injury (any stage), neurologic damage type 1 or type 2, septic shock, pneumonia, and mediastinitis.



No. at Risk										
Placebo	258	237	229	225	222	221	219	219	219	219
Levosimendan	248	227	219	217	214	212	212	211	210	210

Figure 2. Kaplan–Meier Survival Estimates of All-Cause Mortality.

Although attending physicians were permitted to increase the infusion dose, the mean infusion dose of levosimendan that was administered in our trial was 0.07 μg per kilogram per minute. We chose this conservative approach because loading doses and high-dose infusions have been associated with hypotension and a less marked beneficial effect on survival.[10] In a recent trial involving patients with sepsis, an infusion dose of 0.2 μg per kilogram per minute was associated with a higher incidence of hypotension and arrhythmias and a higher rate and longer duration of norepinephrine infusion than placebo[25] — effects that did not occur in our trial. At the lower dose we used, we found no difference in cardiac index over time between the two groups (although cardiac index was not systematically recorded in our patients). However, a hemodynamic effect of levosimendan is suggested by the greater number of attempts to increase the dose in the placebo group and the higher mean dose in the placebo group.

Our trial has some limitations. First, the trial was interrupted early on the grounds of futility for the primary outcome (30-day mortality). This situation may have increased the potential for type II error in the secondary outcomes. Second, despite the signals of a hemodynamic effect of levosimendan, we cannot rule out the possibility that higher doses might have been effective in reducing mortality, although higher doses might also have increased the risk of adverse effects such as hypotension and arrhythmias. Third, we investigated a mixed population of patients who were undergoing different cardiac surgical operations, including a few patients (2.2%) without cardiopulmonary bypass. However, none of the subgroup analyses suggested a benefit in association with levosimendan treatment. Fourth, we did not systematically collect cardiac-output data, which could have helped us understand and interpret the results of the trial. Owing to the fact that our enrollment criteria were based mainly on the need for hemodynamic support, we may have enrolled some patients who did not have underlying severe cardiac dysfunction.

In conclusion, in patients with perioperative left ventricular dysfunction requiring hemodynamic support after cardiac surgery, a low-dose infusion of levosimendan did not result in lower 30-day mortality than placebo nor did it positively affect any secondary-outcome measures as compared with placebo.

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

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APPENDIX

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ORIGINAL ARTICLE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

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ABSTRACT

BACKGROUND

Levosimendan is an inotropic agent that has been shown in small studies to prevent or treat the low cardiac output syndrome after cardiac surgery.

METHODS

In a multicenter, randomized, placebo-controlled, phase 3 trial, we evaluated the efficacy and safety of levosimendan in patients with a left ventricular ejection fraction of 35% or less who were undergoing cardiac surgery with the use of cardiopulmonary bypass. Patients were randomly assigned to receive either intravenous levosimendan (at a dose of 0.2 μg per kilogram of body weight per minute for 1 hour, followed by a dose of 0.1 μg per kilogram per minute for 23 hours) or placebo, with the infusion started before surgery. The two primary end points were a four-component composite of death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5; and a two-component composite of death through day 30 or use of a mechanical cardiac assist device through day 5.

RESULTS

A total of 882 patients underwent randomization, 849 of whom received levosimendan or placebo and were included in the modified intention-to-treat population. The four-component primary end point occurred in 105 of 428 patients (24.5%) assigned to receive levosimendan and in 103 of 421 (24.5%) assigned to receive placebo (adjusted odds ratio, 1.00; 99% confidence interval [CI], 0.66 to 1.54; P=0.98). The two-component primary end point occurred in 56 patients (13.1%) assigned to receive levosimendan and in 48 (11.4%) assigned to receive placebo (adjusted odds ratio, 1.18; 96% CI, 0.76 to 1.82; P=0.45). The rate of adverse events did not differ significantly between the two groups.

CONCLUSIONS

Prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass. (Funded by Tenax Therapeutics; LEVO-CTS ClinicalTrials.gov number, NCT02025621.)

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*A complete list of the investigators in the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Cardiac surgery with the use of cardiopulmonary bypass is a common procedure, with more than 1 million operations performed annually in the United States and Europe.[1] Increasingly, patients who are referred for cardiac surgery are older and have multiple coexisting conditions, as compared with those who were referred for these procedures in the past.[2] These patients benefit from cardiac surgery but are at increased risk for perioperative complications that result in high morbidity and mortality and a high use of health care services.[2-4] One such complication, the low cardiac output syndrome, occurs in 3 to 14% of patients who undergo cardiac surgery with the use of cardiopulmonary bypass.[3,5] Preexisting left ventricular dysfunction is associated with the low cardiac output syndrome.[6] This syndrome is managed with inotropic agents and with support by a mechanical cardiac assist device but remains associated with short-term mortality that is up to 15 times as high as that seen in cardiac surgical patients without this syndrome.[4,7] Unfortunately, most of the available inotropic agents have either known adverse effects or an inadequately evaluated safety profile.[8] The prevention of the low cardiac output syndrome is an important therapeutic objective for the improvement of outcomes in patients undergoing cardiac surgery with the use of cardiopulmonary bypass.

Levosimendan, a calcium-sensitizing inotrope and an ATP-sensitive potassium–channel opener, has been shown in small clinical trials and observational studies to be effective in the prevention and treatment of the low cardiac output syndrome after cardiac surgery. Levosimendan is currently used in more than 60 countries for the prevention and treatment of the low cardiac output syndrome.[9-15] We designed the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial to evaluate the efficacy and safety of prophylactic levosimendan started before and continued after surgery for the prevention of the low cardiac output syndrome and other adverse outcomes in high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass.[16]

Methods

Trial Design and Oversight

The design of this multicenter, randomized, double-blind, placebo-controlled, phase 3 trial has been described previously.[16] The trial protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review board or ethics committee at each participating site. The trial was designed by the first and last authors and the steering committee in collaboration with the sponsor, Tenax Therapeutics. Data were gathered by the participating site investigators and trial coordinators and analyzed by the trial statisticians (see the Supplementary Appendix, available at NEJM.org), who vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first and last authors, and all the authors made the decision to submit the manuscript for publication. The sponsor provided input into the trial design, conduct, and reporting, but the steering committee had final authority over these aspects of the trial.

Patients

Eligible patients were 18 years of age or older, were scheduled to undergo cardiac surgery with the use of cardiopulmonary bypass, and had a left ventricular ejection fraction of 35% or less as assessed within 60 days before surgery. The cardiac surgical procedure could be coronary-artery bypass grafting (CABG), CABG plus aortic-valve surgery, isolated mitral-valve surgery, or any combination of these procedures. A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix. All the patients provided written informed consent.

Randomization and Trial Regimen

Patients underwent screening within 30 days before surgery. Eligible patients were randomly assigned, in a 1:1 ratio with the use of a Web-based randomization system without stratification, to receive either levosimendan or matching placebo in a blinded fashion. After the insertion of an arterial catheter and before skin incision, an intravenous infusion of levosimendan (or matching placebo) was started at a dose of 0.2 μg per

kilogram of body weight per minute for 1 hour, and the dose was then reduced to 0.1 μg per kilogram per minute for another 23 hours. The use of concomitant medications, including other inotropes and vasopressors, was left to the discretion of treating physicians. The concomitant use of nesiritide was prohibited because of synergism for hypotension. The use of a pulmonary-artery catheter for hemodynamic monitoring was encouraged but not required.

DATA COLLECTION AND FOLLOW-UP

Data on demographic characteristics, medical history, laboratory results, electrocardiographic results, surgical procedural details, concomitant medications, and serious and nonserious adverse events were collected through 30 days with the use of the Merge eClinicalOS System (IBM). Blood samples for the analysis of creatine kinase and creatine kinase MB levels were obtained and analyzed locally within 8 hours before surgery and at 3 and 5 days after surgery. Additional samples were obtained if clinically indicated for ischemic symptoms. Electrocardiograms were recorded at baseline and after surgery on days 0, 1, 2, 3, and 5 as well as on the day of and the day after any suspected ischemic event through 30 days. On day 30 (or within a 5-day window after day 30), patients were contacted by telephone to collect information regarding survival status, postoperative myocardial infarction, dialysis, or rehospitalization. On or after day 90 (or within a 5-day window after day 90), patients were contacted by telephone to assess survival.

END-POINT MEASURES

This trial had two composite primary efficacy end points. The first was the four-component composite of death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5. The second was the two-component composite of death through day 30 or use of a mechanical cardiac assist device through day 5.

Renal-replacement therapy included hemodialysis, peritoneal dialysis, or continuous venovenous hemodialysis. Perioperative myocardial infarction was defined as a creatine kinase MB level of more than 100 ng per milliliter or a level that was more than 10 times the upper limit of the normal range specified at the local laboratory, regardless of changes on the electrocardiogram, or a creatine kinase MB level that was more than 50 ng per milliliter or a level that was more than 5 times the upper limit of the normal range with new Q waves that were more than 30 msec in duration in two contiguous leads or new left bundle-branch block. Preoperative and postoperative electrocardiograms and levels of creatine kinase MB in all patients were reviewed by an independent clinical-events committee whose members were unaware of the trial-group assignments. Use of a mechanical cardiac assist device included the use of an intraaortic balloon pump, extracorporeal membrane oxygenator, or ventricular assist device.

Secondary end points included the incidence of the low cardiac output syndrome, postoperative use of secondary inotropes at or beyond 24 hours after the start of the infusion of levosimendan or placebo, and postoperative duration of stay in an intensive care unit. The low cardiac output syndrome was defined as the use of a mechanical cardiac assist device within 5 days after surgery, two consecutive measurements of low cardiac output (defined as a cardiac output of ≤2.0 liters per minute per square meter of body-surface area), one measurement of low cardiac output plus the use of two or more inotropes at or beyond 24 hours after surgery, or the use of two or more inotropes at or beyond 24 hours after surgery with the indicated reason being low cardiac output. Safety end points included hypotension (mean blood pressure, <60 mm Hg), new atrial fibrillation, ventricular tachycardia or fibrillation, resuscitated cardiac arrest, stroke, and death through 90 days.

STATISTICAL ANALYSIS

The sample size was based on an assumed event rate of the four-component end point of 32% in the placebo group, a 35% lower risk with levosimendan than with placebo, and a significance level of 0.01. We calculated that a sample of 760 patients would result in 201 events being observed for the analysis of the four-component end point at 80% power. We calculated that this same sample size would result in 113 events in the two-component end point being observed in the trial with 61% power to detect a risk of this end-point event that was 35% lower with levosi-

mendan than with placebo, assuming an 18% event rate among patients in the placebo group and a significance level of 0.04. After the review of the aggregate composite event rate among the first 600 patients, the sample was increased to 880 patients in order for the trial to obtain the prespecified number of events for the analysis of the four-component end point.

Statistical significance for the two primary end points was based on the alpha level adjusted for the planned interim review. By design, the two-component end point was tested at the 0.04 level and the four-component end point at the 0.01 level. Statistical significance for the secondary end points was based on a hierarchical procedure, in which each successive end point is tested at the alpha level of the significant primary end point until an end point is tested with a P value greater than this value. If neither of the primary end points indicated a significant difference, all the secondary end-point analyses would be considered to be exploratory.

All the analyses were conducted in the modified intention-to-treat population, which included all the patients who underwent randomization and received levosimendan or placebo. For the efficacy analyses, patients were included according to the randomized group assignment. For the safety analyses, patients were included according to the infusion received (levosimendan or placebo). Patients with missing end-point data were included in the analyses as not having had an event. Odds ratios and confidence intervals were estimated from a logistic-regression model with trial group, surgery type, left ventricular ejection fraction, age, and sex included as covariates.

The incidences of the low cardiac output syndrome and inotrope use after 24 hours were evaluated with the use of the same logistic model as the primary end points. The duration of stay in an intensive care unit was analyzed with the use of linear regression with the same covariates. Mortality at 90 days was summarized with the use of Kaplan–Meier estimates and log-rank tests. The chi-square test was used to compare prespecified postoperative events of interest. All the statistical tests were two-sided. All the statistical analyses were performed at the Duke Clinical Research Institute (Durham, North Carolina) with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

ENROLLMENT AND FOLLOW-UP OF THE PATIENTS

The randomization and follow-up of the patients are shown in Figure 1. Of the 956 patients who underwent screening and met the eligibility criteria, 882 were randomly assigned to receive levosimendan (442 patients) or matching placebo (440) at 70 sites in the United States and Canada between September 18, 2014, and November 23, 2016. A total of 849 patients (96.3%) received levosimendan or placebo and were included in the modified intention-to-treat population (428 patients in the levosimendan group and 421 in the placebo group). Vital status was assessed in all the patients but 1 (in the placebo group; 0.1% of the patients in the combined groups) at 30 days and in all the patients but 8 (4 patients in each group; 0.9% of the patients in the combined groups) at 90 days.

CHARACTERISTICS AT BASELINE

The characteristics of the patients in the modified intention-to-treat population reflected the high-risk population of patients who undergo cardiac surgery (Table 1). The median age of the patients was 65 years, and many patients had multiple coexisting conditions. The median left ventricular ejection fraction was 27%.

INFUSION, SURGERY, AND CONCOMITANT THERAPIES

Almost all the patients (96.0%) who received levosimendan or placebo began the infusion before surgery. The median time of the initiation of the infusion was 0.33 hours before surgery (Table 2). Most patients received levosimendan or placebo for the specified 24 hours. The infusion was temporarily discontinued in 25 patients (5.8%) assigned to receive levosimendan and in 16 (3.8%) assigned to receive placebo (P=0.17). The dose was adjusted in 56 patients (13.1%) assigned to receive levosimendan and in 29 (6.9%) assigned to receive placebo (P=0.003). Hypotension was the most common reason for the permanent discontinuation of the trial regimen, with no significant difference in incidence between the two groups.

Isolated CABG accounted for 66.3% of the surgeries (Table 3). Cardiopulmonary bypass was used in all but one patient. The median duration

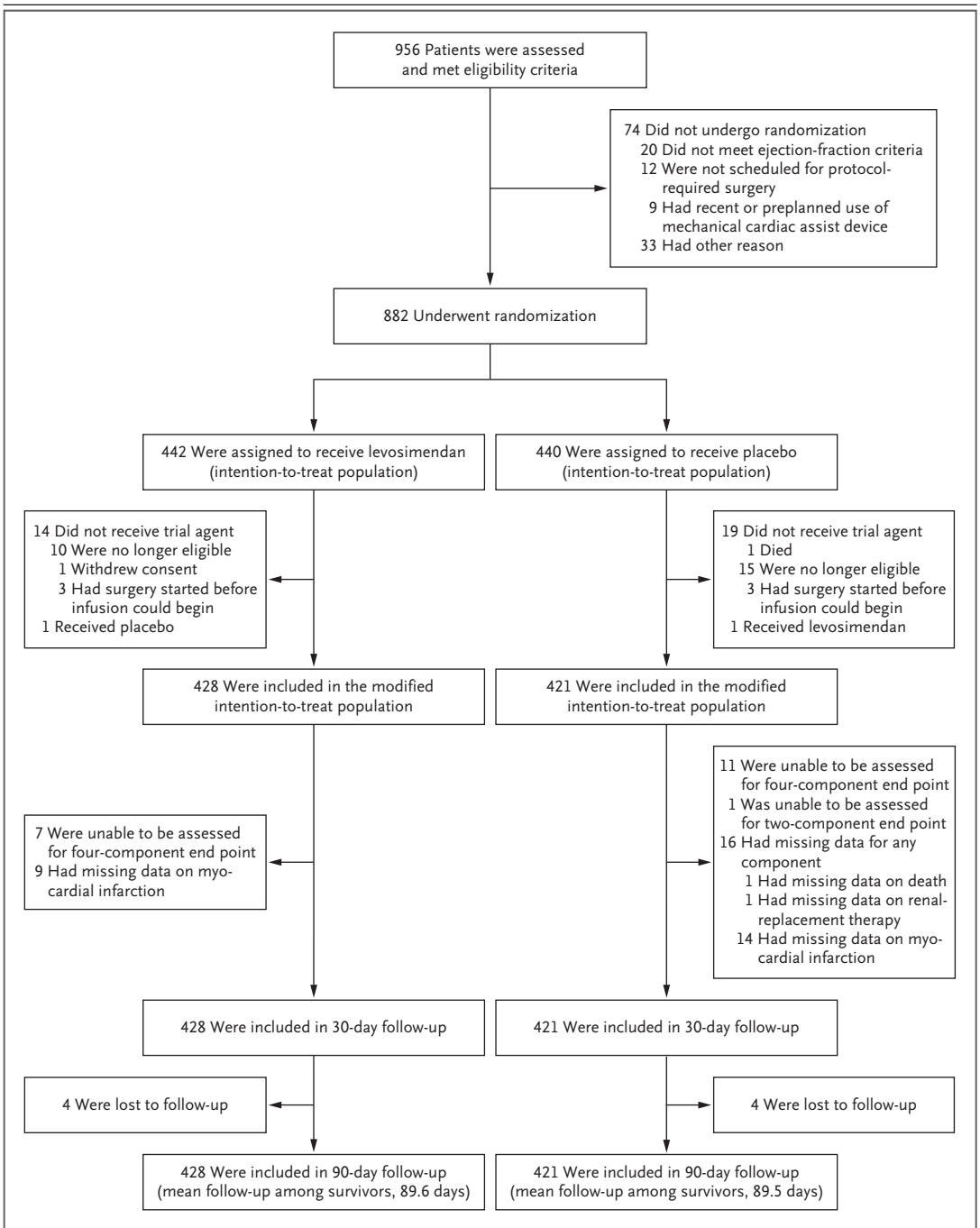

Figure 1. Randomization of the Patients, Analysis Populations, and Follow-up.

of aortic cross-clamp use was 78 minutes, and the median duration of cardiopulmonary bypass was 112 minutes.

END POINTS

The four-component primary end point occurred in 105 patients (24.5%) in the levosimendan group and in 103 (24.5%) in the placebo group (adjusted odds ratio, 1.00; 99% confidence interval [CI], 0.66 to 1.54; P=0.98) (Table 4). The two-component primary end point occurred in 56 patients (13.1%) in the levosimendan group and in 48 (11.4%) in the placebo group (adjusted odds ratio, 1.18; 96% CI, 0.76 to 1.82; P=0.45). Of the

Table 1. Characteristics of the Patients in the Modified Intention-to-Treat Population.*

Characteristic	Levosimendan (N=428)	Placebo (N=421)
Age — yr		
Median	65	65
Interquartile range	59–73	58–72
Female sex — no. (%)	81 (18.9)	89 (21.1)
Race — no./total no. (%)†		
White	385/423 (91.0)	375/419 (89.5)
Black	21/423 (5.0)	23/419 (5.5)
Other	17/423 (4.0)	21/419 (5.0)
Body-mass index‡		
Median	27.9	28.2
Interquartile range	24.9–31.4	25.4–32.6
Medical history — no./total no. (%)		
Hypertension	344/423 (81.3)	340/419 (81.1)
Diabetes mellitus	214/427 (50.1)	212/421 (50.4)
Hypercholesterolemia	333/422 (78.9)	331/418 (79.2)
Chronic lung disease	118/415 (28.4)	120/408 (29.4)
Chronic kidney disease§	131/420 (31.2)	134/413 (32.4)
Myocardial infarction	223/425 (52.5)	213/421 (50.6)
Myocardial infarction within previous 7 days	67/425 (15.8)	62/421 (14.7)
Stroke	30/423 (7.1)	33/419 (7.9)
Peripheral vascular disease	60/421 (14.3)	64/418 (15.3)
Cerebrovascular disease	58/423 (13.7)	49/419 (11.7)
Cardiac surgery	50/426 (11.7)	48/420 (11.4)
Heart failure	332/412 (80.6)	339/415 (81.7)
Preoperative cardiac status		
Heart rate — beats/min		
Median	74	75
Interquartile range	64–84	66–85
Systolic blood pressure — mm Hg		
Median	122	123
Interquartile range	111–136	111–139
Left ventricular ejection fraction — %		
Median	26	27
Interquartile range	24–32	22–31
Preoperative medication — no./total no. (%)		
Aspirin	287/409 (70.2)	284/410 (69.3)
Beta-blocker	325/409 (79.5)	333/410 (81.2)
ACE inhibitor or ARB	171/409 (41.8)	195/410 (47.6)

* The modified intention-to-treat population included all the patients who underwent randomization and received levosimendan or placebo. There were no significant differences between the two groups at baseline. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
† Race was determined by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Chronic kidney disease was defined as an estimated glomerular filtration rate of 60 ml or less per minute per 1.73 m^2 of body-surface area.

Table 2. Administration of Levosimendan or Placebo.

Variable	Levosimendan (N=428)	Placebo (N=421)
Infusion started before surgery — no. (%)	415 (97.0)	400 (95.0)
Time from infusion to surgery — hr		
Median	0.33	0.32
Interquartile range	0.18–0.53	0.17–0.48
Duration of infusion — no.(%)		
≤20 hr	42 (9.8)	31 (7.4)
>20–23.5 hr	25 (5.8)	17 (4.0)
>23.5–24.5 hr	345 (80.6)	358 (85.0)
>24.5 hr	16 (3.7)	15 (3.6)
Reason for premature permanent discontinuation of infusion — no. (%)		
Hypotension	26 (6.1)	21 (5.0)
Tachycardia or arrhythmia	2 (0.5)	3 (0.7)

85 patients who received a mechanical cardiac assist device, 37 (44%) had it placed within 4 hours after the start of surgery.

The effect of levosimendan versus placebo on the four-component and two-component primary end points in the prespecified subgroups is shown in Figures S1 and S2, respectively, in the Supplementary Appendix. In most subgroups, the effect of levosimendan versus placebo was similar to the effect observed in the overall population. However, there was an observed interaction between trial group and left ventricular ejection fraction for the two primary end points, with patients with a lower left ventricular ejection fraction having a trend toward better outcomes with levosimendan and patients with a higher left ventricular ejection fraction having a trend toward better outcomes with placebo.

SECONDARY END POINTS

Because no significant differences between the levosimendan group and the placebo group were found for either the four-component or two-component primary end point, all the analyses of the secondary end points were considered to be exploratory (Table 4). The median duration of stay in an intensive care unit did not differ significantly between groups. The incidences of the low cardiac output syndrome and secondary inotrope use at or beyond 24 hours were significantly lower among patients assigned to receive levosimendan than among those assigned to receive placebo. Among patients who had measurements made with the use of a pulmonary-artery catheter, the cardiac index after the infusion was significantly higher in the 359 patients who received levosimendan than in the 340 who received placebo (mean [±SD] cardiac index, 2.86±0.61 vs. 2.68±0.65 liters per minute per square meter; P<0.001).

The rates of prespecified safety end points, including hypotension, atrial fibrillation, ventricular tachycardia or fibrillation, resuscitated cardiac arrest, and stroke, did not differ significantly between the levosimendan group and the placebo group. There were also no significant between-group differences in the rates of other serious adverse events (Table S1 in the Supplementary Appendix). At 90 days, death had occurred in 4.7% of the patients in the levosimendan group and 7.1% of those in the placebo group (unadjusted hazard ratio, 0.64; 95% CI, 0.37 to 1.13; P=0.12) (Table 4, and Fig. S3 in the Supplementary Appendix).

DISCUSSION

In the LEVO-CTS trial, we randomly assigned patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass to receive either levosimendan or placebo, with the infusion started prophylactically before surgery and continued after surgery. Levosimendan was not associated with a rate of the composite of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass.

Previous studies have shown that levosimendan increases cardiac output and stroke volume and reduces peripheral vascular resistance without increasing myocardial oxygen demand. These effects occur several hours after the initiation of the infusion. Levosimendan has been associated with higher rates of weaning from cardiopulmonary bypass, lower rates of inotrope use, a lower incidence of periprocedural myocardial infarction, and lower lactate levels resulting from better tissue perfusion than placebo,[9-11,13-15] dobutamine,[17]

Table 3. Details of Surgery and Discharge Medical Therapy.*

Variable	Levosimendan (N=428)	Placebo (N=421)
Type of surgery — no. (%)†		
CABG	283 (66.1)	280 (66.5)
Mitral valve	36 (8.4)	31 (7.4)
CABG and mitral valve	50 (11.7)	48 (11.4)
CABG and aortic valve	36 (8.4)	34 (8.1)
Mitral and aortic valves	10 (2.3)	14 (3.3)
CABG and mitral and aortic valves	10 (2.3)	10 (2.4)
Aortic valve	3 (0.7)	3 (0.7)
Cardiopulmonary bypass		
Duration of cross-clamp use — min		
Median	78	79
Interquartile range	55–110	56–109
Duration of cardiopulmonary bypass — min		
Median	110	113
Interquartile range	83–149	85–151
Medication on day of discharge — no./total no. (%)		
Aspirin	403/421 (95.7)	396/410 (96.6)
Beta-blocker	392/421 (93.1)	386/410 (94.1)
ACE inhibitor or ARB	232/421 (55.1)	225/410 (54.9)
Calcium-channel blocker	54/421 (12.8)	54/410 (13.2)
HMG-CoA reductase inhibitor	363/421 (86.2)	362/410 (88.3)
Diuretic	369/421 (87.6)	372/409 (91.0)
Antiarrhythmic agent	245/421 (58.2)	195/410 (47.6)

* CABG denotes coronary-artery bypass grafting, and HMG-CoA 3-hydroxy-3-methylglutaryl coenzyme A.
† One patient in the placebo group did not undergo surgery.

or milrinone.[18] A meta-analysis of randomized trials involving patients undergoing cardiac surgery showed that levosimendan was associated with lower mortality than placebo, with a greater effect among patients who had lower preoperative left ventricular systolic function than among those with higher preoperative left ventricular systolic function.[14] In the largest single study in the meta-analysis, a regimen of prophylactic levosimendan that was similar to that used in our trial was associated with a lower incidence of postoperative low cardiac output syndrome and lower 30-day mortality than placebo among patients undergoing CABG surgery who had a left ventricular ejection fraction of less than 25%.[9] However, an initial report from the recent Levosimendan in Coronary Artery Revascularization (LICORN) trial involving 340 patients with a reduced left ventricular ejection fraction who were undergoing CABG surgery did not show a benefit of levosimendan on a more broadly defined end point of the low cardiac output syndrome than that used in our trial.[19,20]

We investigated the use of prophylactic levosimendan in this trial. In contrast, the effect of levosimendan for treatment rather than prophylaxis in patients in whom the low cardiac output syndrome develops after cardiac surgery is being investigated in the Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: a Multicenter Randomized Controlled Trial (CHEETAH).[21] Collectively, these trials may define the role of levosimendan, prophylactically or as treatment for postoperative low cardiac out-

Table 4. End Points.*

End Point	Levosimendan (N=428)	Placebo (N=421)	Odds Ratio (95% CI)†	P Value
Primary end points — no. (%)				
Four-component end point‡	105 (24.5)	103 (24.5)	1.00 (0.66–1.54)	0.98
Two-component end point§	56 (13.1)	48 (11.4)	1.18 (0.76–1.82)	0.45
Components of primary end points — no. (%)				
Death at 30 days	15 (3.5)	19 (4.5)	0.77 (0.38–1.53)	0.45
Renal-replacement therapy at 30 days	9 (2.1)	16 (3.8)	0.54 (0.24–1.24)	0.15
Myocardial infarction at 5 days	67 (15.7)	63 (15.0)	1.06 (0.73–1.53)	0.78
Use of mechanical cardiac assist device at 5 days	47 (11.0)	38 (9.0)	1.24 (0.79–1.95)	0.34
Secondary end points¶				
Duration of stay in ICU — days‖				
Median	2.8	2.9	—	0.25
Interquartile range	1.6–4.8	1.8–4.9		
Low cardiac output syndrome — no. (%)‖	78 (18.2)	108 (25.7)	0.62 (0.44–0.88)	0.007
Use of inotrope at or beyond 24 hr after infusion initiation — no. (%)‖	235 (54.9)	264 (62.7)	0.71 (0.53–0.94)	0.02
Other efficacy end points — no. (%)				
Rehospitalization at 30 days‖	54 (12.6)	48 (11.4)	1.14 (0.75–1.7)	0.55
Myocardial infarction at 6–30 days	1 (0.2)	0	—	—
Safety end points — no. (%)				
Death at 90 days	20 (4.7)	30 (7.1)	0.64 (0.37–1.13)	0.12
Any adverse event	238 (55.6)	232 (55.1)	—	0.86
Adverse event considered by site investigator to be related to trial regimen	9 (2.1)	13 (3.1)	—	0.34
Any serious adverse event	77 (18.0)	70 (16.6)	—	0.62
Serious adverse event necessitating permanent discontinuation of trial regimen	6 (1.4)	3 (0.7)	—	0.42
Common prespecified postoperative events — no. (%)**				
Hypotension	155 (36.2)	138 (32.8)	—	0.29
Atrial fibrillation	163 (38.1)	139 (33.0)	—	0.12
Ventricular tachycardia or fibrillation	46 (10.7)	41 (9.7)	—	0.63
Resuscitated cardiac arrest	8 (1.9)	7 (1.7)	—	0.82
Stroke	15 (3.5)	10 (2.4)	—	0.33
Deep venous thrombosis	3 (0.7)	3 (0.7)	—	0.98
Pulmonary embolism	0	3 (0.7)	—	0.08
Mechanical ventilation for >24 hr	35 (8.2)	37 (8.8)	—	0.75
Pneumonia	9 (2.1)	14 (3.3)	—	0.27
Congestive heart failure	46 (10.7)	57 (13.5)	—	0.21
Wound infection	13 (3.0)	12 (2.9)	—	0.87

* ICU indicates intensive care unit.
† The analyses used 95% confidence intervals for all the end points with the exception of the four-component composite primary end point, for which a 99% confidence interval was used, and the two-component composite primary end point, for which a 96% confidence interval was used. For the analysis of death at 90 days, an unadjusted hazard ratio is presented.
‡ The analysis for the four-component primary end point was adjusted; trial group, surgery type, left ventricular ejection fraction, age, and sex were included as covariates. Data were missing for 7 patients in the levosimendan group and for 11 in the placebo group. Patients with missing data were included in the primary end-point analyses as not having had an event.
§ The analysis for the two-component primary end point was adjusted; trial group, surgery type, left ventricular ejection fraction, age, and sex were included as covariates. Data were missing for 1 patient in the placebo group.
¶ Because there were no significant between-group differences for either of the two primary end points, all the analyses of the secondary end points were considered to be exploratory.
‖ The analysis of this end point was adjusted; trial group, surgery type, left ventricular ejection fraction, age, and sex were included as covariates.
** The values of these end points were compared with the use of the chi-square test.

put syndrome, in high-risk patients undergoing cardiac surgery.

There are many potential reasons for the heterogeneous results of clinical trials with levosimendan in the context of cardiac surgery.[9-14,17,18,22,23] As suggested in our trial and in a previous meta-analysis, levosimendan may benefit only patients who have severe left ventricular dysfunction at baseline.[14] Higher bolus doses of levosimendan than that used in our trial may have been more effective, although such regimens have been associated with a higher incidence and greater severity of hypotension and other adverse effects.[9,15,19] In addition, the timing of preoperative administration of levosimendan may be important, and levosimendan that is started just before surgery may not be effective at preventing perioperative myocardial injury. We included patients who were undergoing CABG, CABG plus valve surgery, or valve surgery alone and observed some suggestion of a differential effect of levosimendan in these populations (see the Supplementary Appendix). Because levosimendan has multiple potential mechanisms of action, its effects may differ between patients who have left ventricular dysfunction that is due to ischemic heart disease and patients who have left ventricular dysfunction that is due to pressure or volume overload.[24]

A critical challenge to the study of levosimendan in patients undergoing cardiac surgery is the choice of end point. A potential end point is mortality. However, even among high-risk patients, an adequately powered trial assessing the effect of levosimendan on mortality would require the enrollment of approximately 3000 patients. Renal failure and the use of renal-replacement therapy constitute an important outcome with relatively clear criteria, but this outcome occurs in only 1 to 2% of patients. One would expect that the use of a mechanical cardiac assist device would capture the effect of levosimendan on the low cardiac output syndrome. However, there are large differences among geographic regions, institutions, and individual surgeons in the threshold for the placement of a mechanical cardiac assist device.

We found lower incidences of the low cardiac output syndrome and secondary inotrope use with levosimendan than with placebo. Because LEVO-CTS was a placebo-controlled trial, one interpretation of these exploratory findings is that if inotropic therapy is initiated prophylactically, it is less likely that it will need to be initiated for the treatment of the low cardiac output syndrome after surgery. We also found a nonsignificant between-group difference in mortality through 90 days. These data suggest that prophylactic levosimendan may have the potential to prolong survival among patients at risk for undergoing cardiac surgery.

In conclusion, prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass.

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

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APPENDIX

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