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 levosimendan 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 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 85 pa-

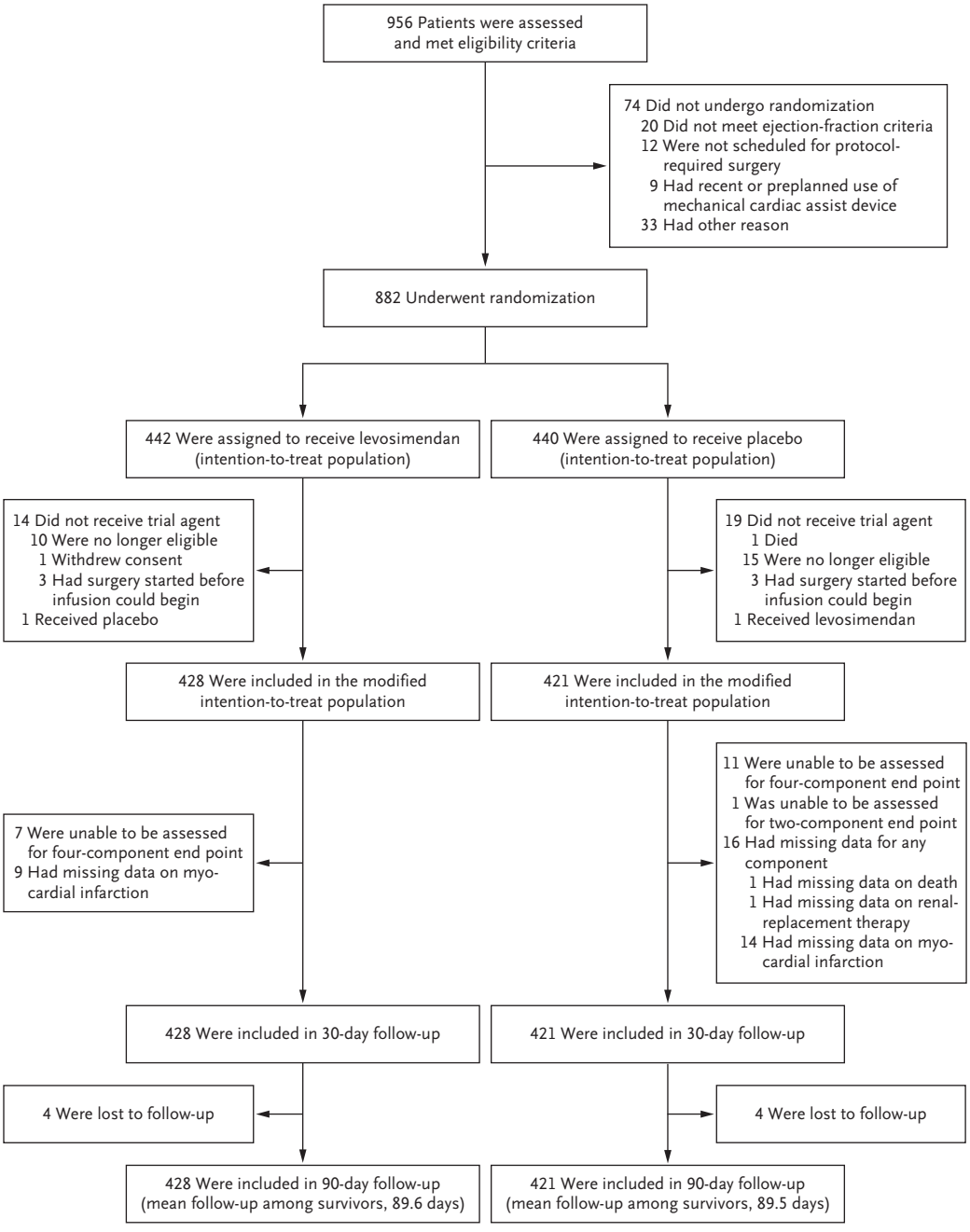

Figure 1. Randomization of the Patients, Analysis Populations, and Follow-up.

tients 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.

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.

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).

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)

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] 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

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.

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 output 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

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.

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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APPENDIX

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