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Levosimendan to Facilitate Weaning From ECMO in Patients With Severe Cardiogenic Shock
The LEVOECMO Randomized Clinical Trial

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IMPORTANCE Levosimendan may facilitate weaning from venoarterial extracorporeal membrane oxygenation (VA-ECMO) and improve survival, but supporting evidence remains limited.

OBJECTIVE To assess whether early administration of levosimendan reduces the time to successful VA-ECMO weaning in patients with severe but potentially reversible cardiogenic shock.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled trial conducted across 11 intensive care units (ICUs) in France. Between August 27, 2021, and September 10, 2024, 205 adult patients with acute cardiogenic shock who had started VA-ECMO in the preceding 48 hours were enrolled. Final follow-up was completed on November 10, 2024.

INTERVENTIONS Patients were randomized in a 1:1 ratio to receive levosimendan, 0.15 µg/kg per minute, to be increased to 0.20 µg/kg per minute after 2 hours (n = 101), or placebo (n = 104).

MAIN OUTCOMES AND MEASURES The primary outcome was time to successful ECMO weaning within 30 days following randomization. Secondary outcomes included ECMO-, mechanical ventilation–, and organ failure–free days, ICU and hospital lengths of stay, serious adverse events, and all-cause 30- and 60-day mortality.

RESULTS Among the 205 randomized patients (median age, 58 [IQR, 50-67] years; 149 [72.7%] male), main cardiogenic shock etiologies were postcardiotomy (79 [38.5%]), acute myocardial infarction (56 [27.3%]), and myocarditis (28 [13.7%]). Treatment dose was increased to 0.20 ± 0.01 µg/kg per minute in 93% of patients receiving levosimendan and in 96% of those receiving placebo. Within 30 days, 69 of 101 patients (68.3%) had a successful ECMO weaning in the levosimendan group compared with 71 of 104 (68.3%) in the placebo group (risk difference, 0.0% [95% CI, −12.8% to 12.7%]; subdistribution hazard ratio, 1.02 [95% CI, 0.74-1.39]; *P* = .92). In the levosimendan and placebo groups, respectively, median ECMO duration (5 [IQR, 4-7] days vs 6 [IQR, 4-11] days; *P* = .53), mean ICU length of stay (18 [SD, 15] days vs 19 [SD, 15] days; *P* = .42), and 60-day mortality (27.7% vs 25.0%; risk difference, 2.7% [95% CI, −9.0% to 15.3%]; *P* = .78) did not differ significantly. Ventricular arrhythmias occurred more frequently with levosimendan (18 [17.8%] vs 9 [8.7%]; absolute risk difference, 9.2% [95% CI, 0.4%-18.1%]).

CONCLUSIONS AND RELEVANCE Among patients with severe but potentially reversible cardiogenic shock supported by VA-ECMO, early levosimendan administration did not significantly reduce the time to successful weaning of ECMO compared with placebo.

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In patients with severe but potentially reversible cardiogenic shock (eg, myocarditis; myocardial stunning after myocardial infarction, cardiotomy, or cardiac arrest) requiring venoarterial extracorporeal membrane oxygenation (VA-ECMO), support can often be weaned after a few days, serving as a bridge to recovery. Although VA-ECMO is regarded as the ultimate lifesaving intervention for refractory cardiac failure, it remains associated with severe complications, including left ventricular stasis with thrombus formation, pulmonary edema, infections, hemorrhage, and peripheral vascular ischemia.[1] These complications become more frequent with prolonged support, contributing to significant morbidity and mortality, extended intensive care unit (ICU) and hospital stays, and increased health care costs.[1]

Levosimendan is an inodilator that enhances cardiac contractility by sensitizing myocardial contractile proteins to calcium without increasing intracellular calcium concentrations.[2] The drug also has anti-inflammatory, antioxidative, and cardioprotective effects.[3,4] Levosimendan has shown symptomatic benefits in acute decompensated heart failure but no survival advantage over dobutamine,[5] and evidence in cardiogenic shock remains limited, with the results from a randomized clinical trial (RCT) (NCT04020263) still pending. In other settings—including septic shock[6] and perioperative cardiac surgery[7-9]—large RCTs demonstrated no clinical benefit, although pooled data[10] suggested a possible mortality reduction in high-risk cardiac surgery patients with low ejection fraction. In patients receiving VA-ECMO for refractory cardiogenic shock, analyses and meta-analyses of retrospective, nonrandomized studies have suggested that levosimendan may facilitate and accelerate weaning and potentially improve survival[11-16]; however, the level of evidence supporting its use in this setting remains limited.

The Levosimendan to Facilitate Weaning From VA-ECMO trial (LEVOECMO) is the first multicenter, double-blind, placebo-controlled RCT designed to determine the effect of early administration of levosimendan on time to successful weaning from VA-ECMO in patients with severe but potentially reversible cardiogenic shock.

Key Points

Question In patients with severe but potentially reversible cardiogenic shock who are receiving venoarterial extracorporeal membrane oxygenation (VA-ECMO), does early administration of levosimendan improve time to successful ECMO weaning within 30 days following randomization?

Findings In this double-blind, placebo-controlled randomized clinical trial that included 205 patients receiving VA-ECMO, successful ECMO weaning at day 30 occurred in 69 (68.3%) in the levosimendan group compared with 71 (68.3%) in the placebo group, a nonsignificant difference.

Meaning In patients with potentially reversible cardiogenic shock supported by VA-ECMO, levosimendan did not reduce the time to successful weaning from ECMO compared with placebo.

Methods

Trial Design

LEVOECMO was an investigator-initiated, double-blind, multicenter RCT conducted at 11 sites in France from August 27, 2021, to September 10, 2024, with final follow-up on November 10, 2024. Participating ICUs were medical and surgical units experienced in adult VA-ECMO care. Trial design details are described in the trial protocol (Supplement 1) and statistical analysis plan (Supplement 2). The trial protocol was created by the scientific committee and approved by an institutional review board (Comité de Protection des Personnes Ouest III-Poitiers 20.10.06.44001). The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Patient safety was regularly monitored by an independent data and safety monitoring board, which analyzed adverse events in a blinded manner.

Patients

The trial enrolled adult patients with acute cardiogenic shock refractory to conventional therapy who started VA-ECMO support in the preceding 48 hours. The decision to start VA-ECMO was at the discretion of the treating team.

The main exclusion criteria were age younger than 18 years; initiation of VA-ECMO more than 48 hours prior; resuscitation for more than 30 minutes in the 48 hours before ECMO; irreversible neurological pathology; end-stage cardiomyopathy with no expectation of left ventricular function recovery; mechanical complication of myocardial infarction; aortic regurgitation greater than grade II; VA-ECMO in patients with heart transplant; patient moribund on the day of randomization; Simplified Acute Physiology Score II greater than 90; and history of torsades de pointes in the 30 days prior. (The eAppendix in Supplement 3 provides a complete list of the exclusion criteria.) Written informed consent was obtained at inclusion from close relatives or surrogates. If this was unavailable, emergency consent allowed randomization without it. In this situation, a patient, once clinically able, and/or the patient's representative were informed at the earliest opportunity and written informed consent for continuation of participation was obtained (eTable 1 in Supplement 3).

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive levosimendan or placebo. The computer-generated randomization process was implemented using the minimization method with a probability of assignment of 0.8 after the first 20 included patients (being assigned by balanced randomness) by a statistician of the Clinical Research Unit of Pitié Salpêtrière Hospital. Stochastic minimization was according to the primary etiology of cardiogenic shock (acute myocardial infarction, myocarditis, postcardiotomy, or other causes) and by center. Assignment of participants was concealed by use of a centralized 24-hour internet service (CleanWeb, Télémedecine Technologies).

Trial Intervention

A continuous infusion of levosimendan or placebo was administered over 24 hours, with no initial bolus. The starting

infusion rate was 0.15 µg/kg per minute and was increased to 0.20 µg/kg per minute after 2 hours in the absence of rate-limiting adverse effects. The placebo was made of polyvitamin (Cernevit, Baxter) containing riboflavin to reproduce the yellow color of levosimendan and was indistinguishable from the intervention drug. In the first phase of the trial (August 27, 2021, to March 29, 2023), levosimendan and placebo were provided by Orion Pharmaceuticals free of charge. During the second phase of the study (December 13, 2023, to September 10, 2024), Orion Pharmaceuticals partially funded the cost of levosimendan, while the placebo was purchased from Baxter. To maintain double-blind drug administration, a designated nurse prepared the treatments using boxes provided by the pharmacy, which contained either levosimendan or placebo. Both levosimendan and placebo were then administered as indistinguishable preparations. Trial participants, clinicians, and outcome assessors were masked to patient assignment. Study drug administration was discontinued in the event of an anaphylactic reaction, severe hypotension (see Outcomes section), or intractable arrhythmias.

Cointerventions

In both groups, patients received similar sedation, anticoagulation, hemodynamic, ECMO, and circuit management. Protocolized weaning of VA-ECMO was applied to both groups (Supplement 1).[17,18]

Data Collection

Patients' characteristics; severity of illness; etiology of cardiogenic shock; echocardiographic, laboratory, and hemodynamic parameters; and vasopressor and inotrope therapies were documented at enrollment. Intervention and cointervention data during ICU stay were recorded up to 60 days after randomization, including ECMO settings, Sequential Organ Failure Assessment (SOFA) score, left ventricular venting with an intra-aortic balloon pump or a microaxial flow pump (Impella, Johnson & Johnson MedTech), and vasopressor use. The number of patients for whom the treatment was prematurely stopped was documented.

Outcomes

The primary outcome was time to successful ECMO weaning within 30 days following randomization. ECMO weaning (ie, ECMO separation) was considered successful only if a patient was alive without ECMO, use of another mechanical circulatory support device, or heart transplant 30 days after ECMO removal. Two competing events were therefore considered: (1) weaning failure, defined as the need for a second ECMO run, other mechanical circulatory support device, or heart transplant or death within 30 days after ECMO separation and (2) death while receiving ECMO. Patients still alive and receiving ECMO 30 days after randomization without any competing events were censored. In patients for whom several competing events occurred, only the first competing event was considered in the analysis of the primary outcome. Thus, the qualification for successful ECMO weaning required 30 days of follow-up after ECMO removal (at the maximum of day 60 after randomization for an ECMO weaning performed on day 30 after randomization), and the date of ECMO removal was taken as the event time.

Predefined secondary outcomes included all-cause mortality at 30 days and 60 days; days alive without organ failure at day 30 (SOFA score 0-1 for each component); durations of ECMO and mechanical ventilation and ECMO- and ventilation-free days at 30 and 60 days (death counted as 0 days); duration of catecholamine support and days alive without it at day 30; duration of kidney replacement therapy and days alive without it at day 30; left ventricular ejection fraction by echocardiography at day 30; major adverse cardiovascular events (death, heart transplant, escalation to need for left ventricular assist device, stroke, dialysis, or heart failure rehospitalization) at days 30 and 60; and ICU and hospital lengths of stay. Time to hemodynamic improvement (mean blood pressure >60 mm Hg) was planned but not analyzed, as most patients remained stable; mean blood pressure evolution was instead evaluated graphically up to day 30.

Predefined adverse events were incidence of adverse drug events (such as atrial fibrillation and other supraventricular arrhythmias; ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes; hypokalemia; and severe hypotension, defined as a mean arterial blood pressure <45 mm Hg for >60 minutes despite vascular filling with two 500-mL successive crystalloid boluses and norepinephrine ≥4 µg/kg per minute or epinephrine ≥2 µg/kg per minute) and were assessed at 30-day follow-up.

Sample Size Calculation

We estimated the cumulative incidence of successful ECMO weaning in the placebo group at 50% in the presence of competing causes (death or weaning failure) from a 30-day cohort study of similar patients.[19] According to Latouche et al,[20] 206 participants in total (103 per group) were required for 80% power to detect a subdistribution hazard ratio of 1.75, corresponding to an estimated 70% successful weaning rate in the intervention group, with an $\alpha = .05$ (bilateral formulation).

Statistical Analysis

Baseline characteristics are reported as numbers and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables. Primary and secondary analyses were conducted according to intention-to-treat principles. The primary analysis was adjusted on minimization stratification factors.

The primary end point was time to successful ECMO weaning within the 30 days following randomization, in the presence of the competing risks of death and weaning failure. Cumulative incidence curves for these 3 competing events were calculated for each randomization group. The cumulative incidence of successful ECMO weaning was compared between groups using a Gray test. Subdistribution hazard ratios were estimated with their 95% confidence intervals for the 3 events using a Fine and Gray competing risk regression. The estimated subdistribution hazard ratio

associated with successful weaning represents an estimation of the total effect of the randomized interventions for the primary event of interest. Analyses of the primary end point were conducted in predefined subgroups of interest (ie, minimization stratification factor). A sensitivity analysis was also performed by estimating cause-specific hazard ratios and their 95% confidence intervals with a cause-specific Cox regression model. The cause-specific hazard ratio associated with successful weaning represents an estimation of the direct effect of the randomized interventions on the primary event of interest in a counterfactual world in which competing events are eliminated.

Categorical outcomes were compared with χ^2 or Fisher exact tests and continuous outcomes with the Wilcoxon rank sum test. Censored outcomes were analyzed over time using the Kaplan-Meier method and restricted mean survival time and were compared using log-rank tests. All analyses were conducted at a 2-sided $\alpha = .05$. All analyses were performed using R software, version 4.4.2 (R Foundation for Statistical Computing).

Results

Study Sites and Patients

From August 27, 2021, to September 10, 2024, 209 patients receiving ECMO for severe cardiogenic shock were assessed for eligibility, of whom 205 were randomized (101 to levosimendan and 104 to placebo) at a median of 25 (IQR, 18-41) hours after ECMO initiation (**Figure 1**). Two patients in the placebo group did not receive the assigned trial regimen. Two patients in the levosimendan group were lost to follow-up, 1 of whom was after collection of primary end point data. Patients' baseline characteristics were similar between the 2 groups (**Table 1**). The median age was 58 (IQR, 50-67) years and 56 patients (27.3%) were women. The leading causes of cardiogenic shock were postcardiotomy (79 [38.5%]), acute myocardial infarction (56 [27.3%]), and myocarditis (28 [13.7%]). At randomization, the median SOFA score was 12 (IQR, 9-15). Left ventricular venting with an intra-aortic balloon pump or a microaxial flow pump was performed in 37.6% and 5.0% of patients in the levosimendan group and in 36.5% and 5.8% of patients in the placebo group, respectively.

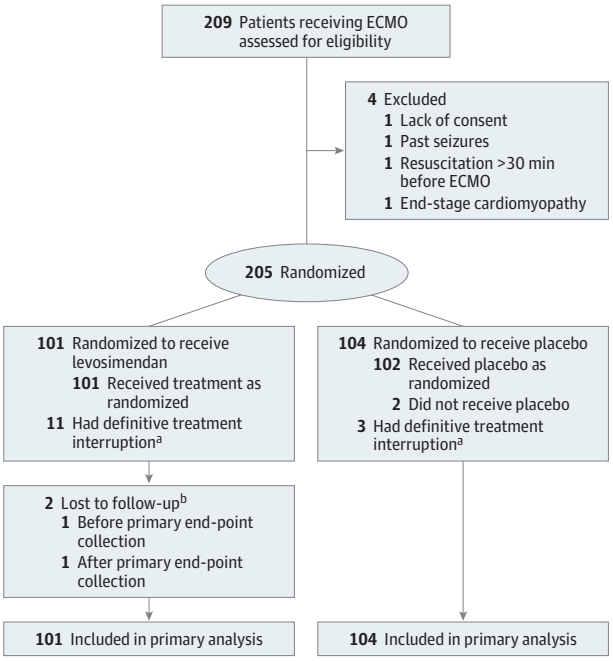
Intervention

The initial dose of the assigned treatment was 0.15 ± 0.01 µg/kg per minute in 97% of participants (99% of the levosimendan group and 94% of the placebo group). Treatment dose was increased to 0.20 ± 0.01 µg/kg per minute in 93% of the levosimendan group and 96% of the placebo group. The infusion was interrupted before 24 hours in 14 patients (11 in the levosimendan group and 3 in the placebo group).

Primary Outcome

Successful ECMO weaning within 30 days of randomization occurred in 69 of 101 patients (68.3%) in the levosimendan group and in 71 of 104 patients (68.3%) in the placebo group (risk difference, 0.0% [95% CI, −12.8% to 12.7%]; subdistribution hazard ratio, 1.02 [95% CI, 0.74-1.39]; $P = .92$) (**Table 2** and **Figure 2**). Similarly, ECMO weaning failure and death, the 2 other competing components of the primary outcome, were not significantly different between groups (Table 2; eFigures 1 and 2 in Supplement 3). Among patients with ECMO weaning failure, 23 were weaned from ECMO but died (11 patients in the levosimendan group and 12 patients in the placebo group), 5 in the placebo group had heart transplants, and 4 in each group received a left ventricular assist device (eTable 2 in Supplement 3). Of note, 1 patient in the levosimendan group was still receiving ECMO at day 30 and was therefore censored. A cause-specific analysis led to similar conclusions (eTable 2 in Supplement 3).

Figure 1. Flow Diagram of Patient Participation in the LEVOECMO Trial



ECMO indicates extracorporeal membrane oxygenation.

[a]Study drug administration was discontinued in the event of an anaphylactic reaction, intractable arrhythmias, or severe hypotension, defined as a mean arterial blood pressure <45 mm Hg for >60 minutes despite vascular filling with two 500-mL successive crystalloid boluses and norepinephrine ≥4 µg/kg per minute or epinephrine ≥2 µg/kg per minute.

[b]Patients were followed up until day 60 after randomization.

Secondary Outcomes

At day 60, 28 patients (27.7%) in the levosimendan group and 26 (25.0%) in the placebo group had died (absolute risk difference, 2.7% [95% CI, −9.0% to 15.3%]; relative risk, 1.11 [95% CI, 0.70-1.75]; $P = .78$) (eFigure 2 in Supplement 3). Median duration of ECMO (5 [IQR, 4-7] days vs 6 [IQR, 4-11] days in the levosimendan and placebo groups, respectively; $P = .53$) and mean ICU length of stay (18 [SD, 15] days vs 19 [SD, 15] days in the levosimendan and placebo groups, respectively; $P = .42$), catecholamine treatment and mechanical ventilation durations, number of days with organ failure, mean blood pressure, and incidence of major cardiac

Table 1. Baseline Participant Characteristics in the LEVOECMO Trial of Levosimendan

Characteristics	Levosimendan (n = 101)	Placebo (n = 104)
Age, median (IQR), y	59 (50-68)	58 (48-67)
Sex, No. (%)		
Female	26 (25.7)	30 (28.8)
Male	75 (74.3)	74 (71.2)
Body mass index, median (IQR)[a]	26 (23-30)	26 (23-31)
Sequential Organ Failure Assessment score, median (IQR)[b]	12 (10-15) [n = 98]	12 (9-14) [n = 100]
Simplified Acute Physiology Score II, median (IQR)[c]	43 (32-56)	38 (26-58)
Time since ECMO initiation, median (IQR), h	24 (18-41) [n = 99]	27 (18-41)
Receiving mechanical ventilation, No. (%)	87 (86.1)	80 (76.9)
Kidney replacement therapy for acute kidney injury, No. (%)	9 (8.9)	15 (14.4)
Cardiogenic shock etiology, No. (%)		
Postcardiotomy	39 (38.6)	40 (38.5)
Acute myocardial infarction	29 (28.7)	27 (26.0)
Myocarditis	12 (11.9)	16 (15.4)
Other	21 (20.8)	21 (20.2)
Cardiovascular history, No. (%)		
Hypertension	39 (38.6)	40/103 (38.8)
Current smoking	29 (28.7)	33/103 (32.0)
Previous percutaneous coronary intervention	26 (25.7)	12 (11.5)
Hypercholesterolemia	22 (21.8)	21/103 (20.4)
Long-term dialysis	1 (1.0)	0
Echocardiogram and hemodynamic parameters, median (IQR)		
Left ventricular ejection fraction, %	15 (10-25) [n = 82]	15 (10-25) [n = 94]
Aortic velocity time integral, cm[d]	8 (6-10) [n = 76]	8 (6-11) [n = 91]
Mean blood pressure, mm Hg	74 (68-82) [n = 100]	75 (69-82) [n = 103]
Heart rate, /min	93 (80-106)	99 (84-111)
Laboratory results, median (IQR)		
pH	7.43 (7.37-7.49)	7.45 (7.40-7.49)
<7.30, No. (%)	8 (7.9)	11 (10.6)
Arterial lactate, mmol/L	2.0 (1.4-2.9)	1.9 (1.4-2.6)
≥2, No. (%)	53 (52.5)	47 (45.2)
Creatinine, mg/dL	1.3 (1.0-2.1)	1.3 (0.9-2.0)
≥1.5, No. (%)	47 (46.5)	43 (41.3)
Alanine aminotransferase, U/L	89 (42-203) [n = 99]	72 (33-205) [n = 103]
≥80, No. (%)	52/99 (52.5)	49/103 (47.6)
Aspartate aminotransferase, U/L	221 (90-502) [n = 99]	173 (88-536)
≥80, No. (%)	81/99 (81.8)	80 (76.9)
High-sensitivity cardiac troponin, ng/L	4328 (998-12 990) [n = 86]	2027 (390-9950) [n = 87]
Medications		
Any vasopressor or inotrope used, No. (%)	96 (95.0)	99 (95.2)
Inotropic score, median (IQR), μg/kg/min[e]	29 (10-58)	23 (10-65)
Norepinephrine, No. (%)	72 (71.3)	76 (73.1)
Dose, median (IQR), μg/kg/min	0.20 (0.00-0.50)	0.18 (0.00-0.56)
Dobutamine, No. (%)	81 (80.2)	88 (84.6)
Dose, median (IQR), μg/kg/min	7 (3-10)	8 (4-11)
Epinephrine, No. (%)	2 (2.0)	0
Other medications, No. (%)[f]	6 (5.9)	4 (3.8)

Abbreviation: ECMO, extracorporeal membrane oxygenation.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] The Sequential Organ Failure Assessment score ranges from 0 to 24, with higher scores indicating a greater degree of organ dysfunction.

[c] The Simplified Acute Physiology Score II measures severity of illness 24 hours after admission to the intensive care unit. It is based on 12 physiological variables and 3 disease-related variables. The score ranges from 0 to 163, with higher scores indicating more severe disease and higher risk of death.

[d] Echographic aortic velocity time integral is the ultrasound-derived measurement of the distance that blood travels through the left ventricular outflow tract during 1 cardiac cycle, obtained by Doppler echocardiography.

[e] Inotropic score = (dobutamine dose × 1) + (epinephrine dose × 100) + (norepinephrine dose × 100). Higher scores indicate a greater degree of inotropic support.

[f] Other medications included vasopressin, isoprenaline, and milrinone.

Table 2. Primary and Secondary End Points in the LEVOECMO Trial of Levosimendan

Outcomes/events[a]	Levosimendan (n = 101)	Placebo (n = 104)	Risk difference, mean, median, or % (95% CI)[b]	Relative difference (95% CI)[c]	*P* value[d]
Primary outcome (day 30)[d]					
Successful ECMO weaning, No. (%)	69 (68.3)	71 (68.3)	0.0 (−12.8 to 12.7)	sHR, 1.02 (0.74-1.39)	.92
Competing events, No. (%)					
ECMO weaning failure[e]	15 (14.9)	21 (20.2)	−5.3 (−15.2 to 4.6)	sHR, 0.72 (0.37-1.38)	.32
Death before ECMO weaning	15 (14.9)	12 (11.5)	3.3 (−5.6 to 12.1)	sHR, 1.32 (0.62-2.79)	.47
Secondary outcomes					
All-cause 30-day mortality, No. (%)	26 (25.7)	23 (22.1)	3.6 (−8.0 to 15.4)	RR, 1.16 (0.71-1.90)	
All-cause 60-day mortality, No. (%)	28 (27.7)	26 (25.0)	2.7 (−9.0 to 15.3)	RR, 1.11 (0.70-1.75)	
No. of days free of ECMO by day 30, median (IQR)	24 (0-26)	23 (12-26)	1 (−1 to 4)		
Days of ECMO, median (IQR)	5 (4-7)	6 (4-11)	−1 (−2 to 1)		
Days in the intensive care unit by day 60, mean (SD)	18 (15) [n = 100]	19 (15)	−1 (−5 to 3)		
Days in the hospital by day 60, mean (SD)	28 (18) [n = 100]	35 (19)	−7 (−12 to −2)		
Ventricular arrhythmias, No. (%)[f]	18 (17.8)	9 (8.7)	9.2 (0.4 to 18.1)	RR, 2.06 (0.97-4.37)	

Abbreviations: sHR, subdistribution hazard ratio; RR, relative risk; ECMO, extracorporeal membrane oxygenation.

[a] Summary measures within each group: median and interquartile range for continuous variables, number and percentage for categorical variables, and restricted mean survival time and standard deviation for censored lengths of stay (patients still hospitalized at the end of the study follow-up). In the presence of missing data, the number of observations is reported in brackets.

[b] Absolute difference between groups (difference in medians for continuous variables, in percentages for categorical variables, or in restricted means for censored data), with 95% CIs estimated by nonparametric bootstrap resampling.

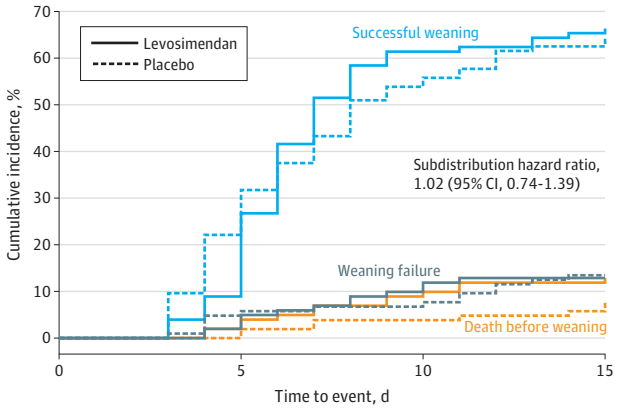
[c] Relative measure of effect expressed as sHR (95% CI) for the primary end point, estimated using the Fine and Gray model adjusted for cardiogenic shock etiology, and as RR (95% CI) for binary end points.

[d] Two patients in the levosimendan group were censored: 1 was still receiving ECMO at day 30 and 1 was lost to follow-up before any competing event. *P* values are not reported for secondary outcomes because of multiple testing concerns.

[e] ECMO weaning failure was defined as need for a second ECMO run, use of another mechanical circulatory support device, or heart transplant or death within 30 days after ECMO separation.

[f] Ventricular arrhythmias included ventricular fibrillation, ventricular tachycardia, and torsades de pointes.

Figure 2. Cumulative Incidence of Successful ECMO Weaning, Weaning Failure, and Death Before Weaning by Treatment Group and Competing Events Shown in Survival Curves



No. of patients at risk				
Levosimendan	101	88	20	10
Placebo	104	76	37	19
No. of patients with event				
Levosimendan	0	36	84	93
Placebo	0	41	70	89

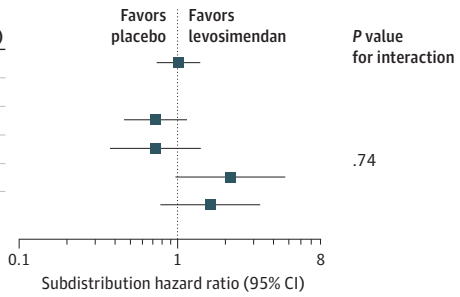
Extracorporeal membrane oxygenation (ECMO) weaning (ie, ECMO separation) was considered successful only if a patient was alive without ECMO, use of another mechanical circulatory support device, or heart transplant 30 days after ECMO removal. The date of ECMO removal was taken as the event time (eg, a patient weaned at day 10 and alive without further support until day 40 was considered successfully weaned at day 10). The y-axis shows the cumulative incidence of successful ECMO weaning, with death before weaning and unsuccessful weaning considered as competing risks. Curves are truncated at 15 days. Median observation time for successful weaning was 11 (IQR, 9-20) days in the levosimendan group and 16 (IQR, 12-19) days in the placebo group, estimated by a reverse Kaplan-Meier method.

Table 3. Protocol-Defined Adverse Drug Events in the Intention-to-Treat Population

Events	No. (%)		Absolute risk difference, %
	Levosimendan (n = 101)	Placebo (n = 104)	
Any serious adverse event	59 (58.4)	61 (58.7)	−0.2
Any arrhythmia	63 (62.4)	55 (52.9)	9.5
Atrial fibrillation	35 (34.7)	29 (27.9)	6.8
Supraventricular tachyarrhythmia	49 (48.5)	48 (46.2)	2.4
Bradycardia	4 (4.0)	1 (1.0)	3.0
Torsades de pointes	0	0	0.0
Ventricular fibrillation or tachycardia	18 (17.8)	9 (8.7)	9.2
Ventricular arrhythmia leading to electric shock	4 (4.0)	1 (1.0)	3.0
Hypokalemia	1 (1.0)	2 (1.9)	−0.9
Suspected adverse drug event leading to temporary or definitive cessation of treatment	12 (11.9)	4 (3.8)	8.0

Figure 3. Subdistribution Hazard Ratios for the Primary Outcome of Successful ECMO Weaning in Predefined Subgroups of Patients Depicted in Dot Plots

Subgroup	No./total No. (%)		Subdistribution hazard ratio (95% CI)
	Placebo	Levosimendan	
All patients	71/104 (68.3)	69/101 (68.3)	1.02 (0.74-1.39)
Cardiogenic shock etiology			
Postcardiotomy	32/40 (80.0)	28/39 (71.8)	0.73 (0.46-1.15)
Acute myocardial infarction	17/27 (63.0)	15/29 (51.7)	0.73 (0.37-1.40)
Myocarditis	10/16 (62.5)	11/12 (91.7)	2.16 (0.97-4.80)
Other[a]	12/21 (57.1)	15/21 (71.4)	1.61 (0.78-3.33)



ECMO indicates extracorporeal membrane oxygenation.

[a]Other causes of cardiogenic shock (eTable 6 in Supplement 3) included cardiac arrest prior to ECMO initiation, acute cardiac arrhythmia, Takotsubo cardiomyopathy, decompensated dilated cardiomyopathy, acute valvular disease, and miscellaneous conditions such as sepsis, late complications of congenital heart disease, and thyrotoxic cardiomyopathy.

adverse events were not significantly different between groups (Table 2; eTables 3-5 and eFigures 3-6 in Supplement 3). Hospital length of stay was longer in the placebo group (Table 2; eFigure 7 in Supplement 3).

Adverse Events

Rates of adverse drug events were similar between groups except for a higher incidence of ventricular arrhythmias in the levosimendan group (18 [17.8%] vs 9 [8.7%]; absolute risk difference, 9.2% [95% CI, 0.4%-18.1%]) (**Table 3**; eFigure 8 in Supplement 3). The incidence of ventricular arrhythmias requiring electrical cardioversion was 4 (4.0%) in the levosimendan group vs 1 (1.0%) in the placebo group (Table 3).

Subgroup Analyses

There was no statistically significant heterogeneity of treatment effect between the 2 study groups across any of the prespecified subgroups (**Figure 3**; eFigure 9 in Supplement 3).

Discussion

In this double-blind, placebo-controlled RCT involving patients receiving VA-ECMO for severe but potentially reversible cardiogenic shock, early treatment with levosimendan was not associated with a shorter time to successful ECMO weaning. Survival at days 30 and 60; ECMO-, organ failure-, and mechanical ventilation–free days; and ICU length of stay were not different between groups.

Levosimendan is an inodilator commonly used in Europe, Asia, Australia, and New Zealand, although it is not currently approved in North America. The drug improves cardiac contractility by increasing the sensitivity of myocardial contractile proteins to calcium without raising intracellular calcium levels.[4,7] Unlike traditional inotropic agents such as dobutamine, levosimendan does not elevate myocardial oxygen consumption or impair diastolic function.[4] Additionally, it modulates adenosine triphosphate-sensitive potassium channels,[21] including those in vascular smooth muscle cells, resulting in coronary, pulmonary, and peripheral vasodilation.[4,22] It has also been shown to exhibit anti-inflammatory, antioxidative, antiapoptotic, antistunning, and cardioprotective effects.[4] Due to its long-lasting action (up to 7-9 days) mediated by the formation of an active metabolite, levosimendan can be administered as a single 24-hour infusion.[2]

In acute decompensated heart failure, levosimendan improves symptoms and natriuretic peptides compared with placebo, but the SURVIVE trial[5] showed no mortality advantage

over dobutamine. In cardiogenic shock, robust randomized data are still lacking; the ongoing LevoHeartShock trial (NCT04020263) is designed to evaluate whether early levosimendan administration improves 30-day outcomes, but results have not yet been reported. In septic shock, the LeoPARDS[6] trial demonstrated no organ support benefit and more arrhythmias, discouraging its use in sepsis. In the perioperative cardiac surgery setting, large RCTs (LICORN,[7] LEVO-CTS,[8] CHEETAH[9]) similarly found no reduction in low cardiac output syndrome or mortality. However, a pooled analysis of LICORN[7] and LEVO-CTS[8] suggested that prophylactic levosimendan may reduce 90-day mortality of patients with low ejection fraction undergoing isolated coronary artery bypass graft surgery.[10]

The neutral results of this RCT in VA-ECMO patients differ from analyses[14,16,23-25] and meta-analyses[11-13] of retrospective, nonrandomized studies that suggested that levosimendan might facilitate and accelerate VA-ECMO weaning, thereby reducing ECMO duration, limiting complications and costs, and potentially improving survival. The latest meta-analysis,[11] which included data from 15 retrospective studies encompassing 1772 VA-ECMO patients, found a significantly higher weaning success rate in the levosimendan group compared with the placebo group (odds ratio, 2.78 [95% CI, 1.80-4.30]; $P < .001$; $I^2 = 65\%$). Notably, the beneficial effect on weaning success was statistically significant only at a dosage of 0.2 µg/kg per minute (odds ratio, 2.45 [95% CI, 1.11-5.40]; $P = .03$; $I^2 = 38\%$). Additionally, levosimendan was associated with a reduction in 30-day mortality (odds ratio, 0.47 [95% CI, 0.28-0.79]; $P = .004$; $I^2 = 73\%$).

However, recent single-center, propensity-matched, case-controlled studies involving a limited number of patients with postcardiotomy,[26] medical,[19] or mixed[27] indications for ECMO have failed to demonstrate a significant improvement in VA-ECMO weaning success rates. These observational designs have important limitations, including heterogeneous definitions of successful weaning, residual confounding despite statistical adjustment, and small sample sizes, all of which may have led to an overestimation of levosimendan's efficacy.

In contrast, the present multicenter, double-blind, placebo-controlled RCT did not show any reduction in ECMO duration or mortality with levosimendan. Patients were enrolled across a spectrum of potentially reversible cardiogenic shock etiologies, and the primary outcome combined 30-day mortality with a stringent definition of ECMO weaning success assessed 30 days after device removal. Unlike prior observational studies, this trial minimized bias through randomization, blinded treatment allocation, and standardized outcome definitions. Despite more than 95% of patients reaching the full dose of 0.2 µg/kg per minute without major hemodynamic instability—a key limitation in earlier trials of patients with sepsis[6] or undergoing cardiac surgery[7,9]—levosimendan showed no signal of benefit in either the primary end point or secondary outcomes, and across subgroups.

It is worth noting that the rate of successful weaning was high (68%), and the 26% 60-day mortality was lower than in other populations of VA-ECMO patients with similar case mix, likely reflecting that the trial was conducted in highly experienced centers. Adverse effects were infrequent and drug discontinuation was rare. However, ventricular arrhythmias occurred more often in the levosimendan group. The longer mean hospital stay in the placebo group, despite similar ICU durations, may reflect the non-statistically significantly higher mortality in the levosimendan group, especially in the first 2 weeks of the trial; a greater number of patients with transplant in the placebo group; or other unmeasured organizational factors, rather than treatment allocation.

Limitations

This trial has several limitations. First, the study was underpowered because the sample size calculation assumed a 50% weaning failure rate, whereas the observed rate was 32%. As a result, a smaller yet clinically meaningful treatment effect cannot be ruled out. However, the consistency of the end points and the absence of any signal of benefit strongly argue against the clinical utility of the drug in this indication. Second, the possibility cannot be excluded that the drug might improve outcomes in specific subgroups of patients with cardiogenic shock receiving ECMO, such as those with myocarditis. Third, recent studies have shown that the pharmacokinetics of levosimendan and its metabolites are altered in neonates and children receiving ECMO support. Similar alterations may also occur in adult patients, potentially compromising the drug's efficacy.[28] Fourth, although treatment allocation remained blinded to both patients and investigators throughout the study, a designated nurse responsible for reconstituting the treatments was aware of the assigned therapy during the second phase of the trial.

Conclusions

Among patients with severe but potentially reversible cardiogenic shock, early administration of levosimendan did not significantly shorten time to successful VA-ECMO weaning. These findings do not support the routine use of levosimendan to improve outcomes in this patient population.

ARTICLE INFORMATION

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