

Short- and Long-term Efficacy and Safety of Levosimendan in Venous-arterial Extracorporeal Membrane Oxygenation Weaning: The WEANILEVO Randomized Double-blind Multicenter Trial

Pierre-Grégoire Guinot, M.D., Ph.D., Vivien Berthoud, M.D., Agnes Soudry-Faure, Pharm.D., Ph.D., Osama Abou-Arab, M.D., Ph.D., Paul Michel Mertes, M.D., Ph.D., Marc-Olivier Fischer, M.D., Ph.D., Mouhamed Moussa, M.D., Ph.D., Omar Ellouze, M.D., Ph.D., Maxime Nguyen, M.D., Ph.D., Belaid Bouhemad, M.D., Ph.D., for WEANILEVO trial group*

ANESTHESIOLOGY 2026; 145:676–88



EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Weaning failure from venous-arterial extracorporeal membrane oxygenation (VA-ECMO) for refractory cardiogenic shock remains common and is associated with high mortality
- Levosimendan is a calcium sensitizer with inotropic and vasodilatory effects that has been proposed to facilitate VA-ECMO weaning
- A recent randomized trial (LEVOECMO) showed that early levosimendan, started within 48 h of VA-ECMO cannulation, did not improve weaning or survival at day 60

What This Article Tells Us That Is New

- In contrast to LEVOECMO, patients in WEANILEVO received levosimendan after first meeting weaning criteria because it was assumed that levosimendan would be most effective when partial recovery of myocardial function was achieved

ABSTRACT

Background: Liberation from venous-arterial extracorporeal membrane oxygenation (VA-ECMO) remains challenging. To date, there is limited evidence from observational studies supporting pharmacologic interventions to facilitate successful VA-ECMO weaning. The current study aimed to evaluate the efficacy and safety of a single dose of levosimendan in patients supported by VA-ECMO who met predefined criteria for weaning.

Methods: The WEANILEVO study was a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial. Eighty patients from five French centers who met VA-ECMO weaning criteria were randomly assigned 1:1 to receive either levosimendan ($0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or placebo for 24 h. The primary endpoint was VA-ECMO weaning failure, defined as absence of weaning within 48 h, recourse to another circulatory assistance device, or death within 7 days of weaning.

Results: Due to halted funding, the planned number of patients could not be recruited. The final modified intention-to-treat analysis included 80 patients (40 in the levosimendan group and 40 in the control group). VA-ECMO weaning failure occurred in 25% of patients in both the levosimendan and placebo groups (odds ratio, 1.00 [95% CI, 0.36 to 2.75]; $P = 1.00$). Acute kidney injury at day 30 was significantly more frequent in the levosimendan group (62.5% vs. 38.5%; odds ratio, 2.67 [95% CI, 1.08 to 6.62]; $P = 0.03$). Patients receiving levosimendan required more vasopressor support (47.5% vs. 28.2%; $P = 0.07$) and had longer intensive care unit stays (12 [7 to 24] vs. 6 [4 to 13] days; $P = 0.02$). Mortality rates at 30 days (18.0% vs. 33.3%; $P = 0.07$) and 1 yr (31.6% vs. 51.4%; $P = 0.08$) did not significantly differ between groups.

Conclusions: Levosimendan administration did not reduce VA-ECMO weaning failure in patients who already met weaning criteria; however, a clinically important benefit or harm cannot be ruled out. The observed higher incidence of acute kidney injury and longer intensive care unit stays in the levosimendan group are hypothesis generating and require confirmation in larger, adequately powered trials.

(ANESTHESIOLOGY 2026; 145:676–88)

- Both the levosimendan and control groups had identical rates of weaning failure, 25%
- A secondary analysis did not reveal a significantly reduced mortality in patients receiving levosimendan (18.0% vs. 33.3%); however, an exploratory *post hoc* Bayesian analysis reported a 95% probability of levosimendan superiority over placebo for 30-day mortality (odds ratio, 0.40) and 96% for 1-yr mortality (odds ratio, 0.42)
- These findings suggest the need for a larger multicenter randomized controlled trial to determine whether levosimendan improves 30-day and 1-yr mortality

Copyright © 2026 The Author(s). Published by Wolters Kluwer Health, LLC, on behalf of the American Society of Anesthesiologists. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. ANESTHESIOLOGY 2026; 145:676–88. DOI: 10.1097/ALN.0000000000006143

Abbreviations: AKI, acute kidney injury; CrI, credible interval; DSMB, data and safety monitoring board; LVEF, left ventricular ejection fraction; OR, odds ratio; VA-ECMO, venous-arterial extracorporeal membrane oxygenation; ICU, intensive care unit; VIS, vasoactive-inotropic score

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used in cardiogenic circulatory failure.¹ VA-ECMO provides early, adequate organ perfusion to prevent multiorgan failure and death.² Despite its growing use, morbidity and mortality remain high, with complications such as bleeding, ischemic, and infectious events.³ The multifactorial nature of patient conditions and the lack of robust clinical and echocardiographic criteria for predicting successful weaning contribute to failure rates as high as 50% in some cohorts.^{4–6} Improving the success rate of VA-ECMO weaning could significantly reduce associated morbidity, potentially leading to better long-term outcomes and decreased mortality.⁷

Levosimendan, an inodilator introduced in the 2000s, enhances actin-myosin sensitivity to calcium and contractility without increasing myocardial oxygen consumption, potentially providing anti-inflammatory and cardioprotective effects, and exhibits vasodilatory effects *via* potassium channel activation.^{8,9} Several observational studies suggest that levosimendan may reduce weaning failure and mortality when administered after VA-ECMO initiation.^{10–14} However, the available evidence remains limited to retrospective analyses and case series, with heterogeneous definitions of successful VA-ECMO weaning and no standardized approach to the timing of levosimendan administration—considerably limiting comparability across studies.^{10,11,15} Early administration of levosimendan may not be effective for patients with massive myocardial infarction and extensive myocardial necrosis, as a minimal degree of myocardial recovery is essential before inotrope administration to reduce the risk of weaning failure.¹³ It may also be ineffective for patients receiving extracorporeal cardiopulmonary resuscitation, with which neurologic recovery significantly affects both weaning and mortality. Levosimendan is generally considered only after hemodynamic stability has been achieved with VA-ECMO and/or during weaning rather than at the initiation of ECMO support. Thus, levosimendan may have better indication in patients meeting specific

criteria for VA-ECMO weaning, enhancing cardiac output and reducing organ failure risk and thus improving weaning.^{6,16} Given the pharmacologic beneficial effects of levosimendan, we hypothesized that levosimendan administration in patients supported by VA-ECMO and who met criteria for weaning may decrease the rate of VA-ECMO failure. We defined weaning failure, in accordance with the available literature, as a composite endpoint comprising the absence of VA-ECMO removal within 48 h, the need for a secondary mechanical circulatory support device, or death within 7 days of VA-ECMO liberation. The purpose of this prospective, randomized, placebo-controlled trial was therefore to evaluate the efficacy and safety of levosimendan compared with placebo in preventing VA-ECMO weaning failure. The trial was terminated early following interim analysis owing to withdrawal of sponsor funding. This decision was not based on a data and safety monitoring board (DSMB) recommendation for efficacy or futility.

Study Design and Methods

Trial Design and Oversight

We conducted a prospective multicentre randomized, double-blind study in five cardiovascular intensive care units (ICUs) in France located in Dijon, Lille, Amiens, Caen, and Strasbourg between 2020 and 2023. The study protocol was approved by the institutional review boards (French ethics committee CPP IDF II [Comités de Protection des Personnes Ile de France II], France; reference No. 2019-60) before the start of the study. The trial was registered on ClinicalTrials.gov (NCT04158674) before commencement. Written informed consent was obtained from all patients or their next of kin before inclusion. The current study was funded by a grant obtained from Orion and our institution. Orion was not involved in the conception, design, realization, statistical plan, or analysis of the study. The detailed protocol had been published previously.¹⁷

The article processing charge was funded by Centre Hospitalier Universitaire de Dijon. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Laurent Glance, M.D., served as Handling Editor for this article. Submitted for publication June 21, 2025. Accepted for publication April 22, 2026. Published online first on May 8, 2026.

Pierre-Grégoire Guinot, M.D., Ph.D.: Department of Anaesthesiology and Intensive Care, Dijon University Hospital, Dijon, France; University of Burgundy, Dijon, France; and Center for Translational and Molecular Medicine, INSERM UMR1231, Lipness Team, Dijon, France.

Vivien Berthoud, M.D.: Department of Anaesthesiology and Intensive Care, Dijon University Hospital, Dijon, France.

Agnes Soudry Faure, Pharm.D., Ph.D.: Université Bourgogne Europe, Centre Hospitalier Universitaire de Dijon Bourgogne, Pôle Recherche et Santé Publique, Unité de Soutien Méthodologique à la Recherche, Dijon, France.

Osama Abou-Arab, M.D., Ph.D.: Department of Anesthesiology and Intensive Care, Amiens University Hospital, Amiens, France.

Paul Michel Mertes, M.D., Ph.D.: Department of Cardiovascular Anesthesiology and Intensive Care, Strasbourg University Hospital, Strasbourg, France.

Marc-Olivier Fischer, M.D., Ph.D.: Anesthesiology and Critical Care Department, Normandie University Medical Center, UNICAEN, F-14000, Caen, France.

Mouhamed Moussa, M.D., Ph.D.: Department of Anaesthesia and Critical Care, Cardiovascular and Pulmonary Division, Centre Hospitalier Universitaire de Lille, Lille, France.

Omar Ellouze, M.D., Ph.D.: Department of Anaesthesiology and Intensive Care, Dijon University Hospital, Dijon, France.

Maxime Nguyen, M.D., Ph.D.: Department of Anaesthesiology and Intensive Care, Dijon University Hospital, Dijon, France.

Belaïd Bouhemad, M.D., Ph.D.: Department of Anaesthesiology and Intensive Care, Dijon University Hospital, Dijon, France; University of Burgundy, Dijon, France; and Center for Translational and Molecular Medicine, INSERM UMR1231, Lipness Team, Dijon, France.

*Members of the WEANILEVO trial group are listed in the appendix.

Study Population

The inclusion criteria were as follows: patients aged 18 yr or older with refractory cardiogenic shock treated by VA-ECMO who met the criteria for VA-ECMO weaning. These criteria included a vasoactive-inotropic score (VIS) less than 10, a left ventricular ejection fraction greater than 20%, a subaortic velocity time integral greater than 10 cm, arterial lactate levels lower than 2 mM, a right ventricular fractional area change greater than 30%, and a right ventricular end-diastolic diameter less than 35 mm.¹⁸ Additionally, the combined fraction of inspired oxygen for VA-ECMO and ventilator had to be less than 80%, with VA-ECMO weaning expected within 48 h. The exclusion criteria included patients with ongoing bacterial infection within 48 h before inclusion (no antibiotics introduced during the previous 48 h); patients with liver failure; patients with contraindications to levosimendan treatment or CERNEVIT (Baxter SAS, France) use; those not affiliated with a health insurance system; patients under legal protection; pregnant, parturient, or nursing women; patients with drug intoxication and previously normal left ventricular ejection fraction; and patients on the waiting list for cardiac transplantation or planned for left ventricular assist device.

Randomization

Randomization was performed directly through the secure CleanWeb (Telemedicine Technologies SAS, France) internet-based software after identification of the investigator by a personal password. An unblinded operator prepared the active drug or placebo to maintain blinding for investigators, nurse, and patients. The treatment algorithms were determined by the study statistician. This allocation was based on a minimization technique stratified by center, age (60 yr or older *vs.* less than 60 yr) and indication for VA-ECMO (medical or surgical). The patients were randomly assigned (1:1) to receive either levosimendan or a placebo infusion.

Intervention

The study treatments included either levosimendan or a placebo consisting of riboflavin in a multivitamin preparation (CERNEVIT, due to the yellow color of the diluted levosimendan). The study drugs were administered as continuous infusions over a period of 24 h at a fixed rate of $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. No loading dose was administered, and no dose modification was performed. The infusion was initiated 24 h before the scheduled date of VA-ECMO weaning (not exceeding 48 h) after randomization. All data were collected by clinical research assistants (blind to outcomes) and recorded on electronic case report forms available online on a dedicated website. All physician and nurse staff were blind to treatment group.

Outcomes

The primary endpoint was VA-ECMO weaning failure, defined as the absence of VA-ECMO weaning within

48 h of randomization, recourse to another VA-ECMO or other temporary circulatory assistance (Impella [Johnson & Johnson Medtech, USA] pump device or intra-aortic balloon pump), or death within 7 days of VA-ECMO weaning. Secondary endpoints included long-term circulatory assistance (*i.e.*, left ventricular assist device or total artificial heart) at day 30, heart transplant at day 30, renal insufficiency and/or renal replacement therapy at day 30, 30-day and 1-yr mortality regardless of cause, VIS, length of intensive care unit stay, and length of hospital stay. Endpoints associated with safety was rate of complications by day 30. There were no changes to the trial outcomes after the study start. The VIS was calculated as follows: $\text{dobutamine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) + \text{dopamine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) + \text{norepinephrine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \times 100 + \text{epinephrine dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \times 100 + \text{milrinone dose } (\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \times 10 + \text{vasopressin dose } (\text{units} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \times 10,000$.

Adverse Events

Adverse events were recorded from randomization to day 30 after VA-ECMO liberation. Serious adverse events were defined as any untoward medical occurrence that was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent disability, or was otherwise medically significant. Events were coded using the Medical Dictionary for Regulatory Activities (version 25.1). The trial vigilance unit defined the causality in case of a serious adverse event. Furthermore, an independent DSMB reviewed safety data throughout the trial. The DSMB comprised one methodologist-statistician, one cardiovascular intensivist, and one pharmacologist.

Statistical Analysis

Sample Size Estimation. WEANILEVO was designed as a superiority trial. Sample size was determined to detect a clinically significant 20% absolute reduction in the primary endpoint, VA-ECMO weaning failure. Assuming a weaning failure rate of 50% in the placebo group and 30% in the levosimendan group, 210 patients (105 per group) were required to achieve 80% power at a bilateral alpha level of 0.05, allowing for 10% nonevaluable cases. An interim analysis was planned after the enrollment of 80 patients to reassess sample size assumptions and evaluate safety. Based on the Peto-Haybittle method, a bilateral alpha level of 0.0001 was applied at the interim analysis to preserve the significance level of the final primary analysis. The trial was terminated early following interim analysis owing to withdrawal of sponsor funding. The final modified intention-to-treat analysis therefore includes 80 of the 210 planned patients (38%). This decision was not based on a DSMB recommendation for efficacy or futility.

General Analysis. Categorical variables are expressed as numbers and percentages. Continuous variables were presented

as means with standard deviations or medians with interquartile ranges according to their distribution. Balance between groups at baseline was assessed using the standardized mean difference. Safety was assessed by comparing the proportions of participants with complications and adverse events between the two groups.

Primary Analysis. The primary analysis was conducted according to the intention-to-treat principle on observed data and included all randomised patients. For the main comparison of VA-ECMO weaning failure between the two groups, a chi-square test was performed, followed by multivariable logistic regression adjusted for the randomization stratification factors: center, age (60 yr and older *vs.* less than 60 yr), indication for VA-ECMO (medical or surgical), and imbalanced baseline covariates (serum creatinine).

Secondary Outcomes. The frequencies of recourse to long-term mechanical circulatory support, heart transplantation, acute kidney injury (AKI), renal replacement therapy, and all-cause mortality at 30 days and 1 yr after VA-ECMO liberation were compared using chi-square tests. ICU length of stay and hospital length of stay were compared using the Mann-Whitney U test. Given the competing risk of death precluding AKI diagnosis, a sensitivity analysis for AKI was performed excluding patients who died before day 30. The fragility index and reverse fragility index were calculated for primary and secondary endpoints.

Sensitivity Analysis. A per-protocol analysis was additionally performed, excluding patients who did not complete the full 24-h study drug infusion, using the same statistical methods as the primary intention-to-treat analysis. Analysis was repeated, after reviewing, from case report forms, the documented reason for any delay beyond 48 h in ECMO removal. When the delay was attributable to logistical factors (*e.g.*, unavailability of the operating theatre) rather than clinical deterioration, the event was not counted as weaning failure in this prespecified sensitivity analysis. Analysis were adjusted for the randomization stratification factors: center, age (60 yr and older *vs.* less than 60 yr), indication for VA-ECMO (medical or surgical), and imbalanced baseline covariates (serum creatinine).

Bayesian Sensitivity Analysis. A *post hoc* Bayesian analysis was conducted to assess the probability of a mortality treatment effect at 30 days and 1 yr. Bayesian logistic regression models were fitted using Markov chain Monte Carlo sampling (four independent chains, 20,000 iterations per chain; Bernoulli likelihood). Three prior distributions were specified on the log-odds ratio (log-OR) scale to reflect a range of prior beliefs: (1) a noninformative (uniform) prior, representing prior equipoise; (2) a skeptical prior centered on the null hypothesis of no treatment effect ($OR = 1.0$; $N[\log(1.0), 0.35^2]$); and (3) an enthusiastic prior centered on a clinically meaningful 30% relative reduction in mortality ($OR = 0.70$; $N[\log(0.70), 0.35^2]$). For each model and prior,

we derived posterior distributions, 95% credible intervals (CrIs), and the corresponding Bayes factor as a measure of the strength of evidence for or against a treatment effect. The posterior probability of treatment superiority was defined as P (OR less than 1), and the probabilities of clinically meaningful absolute risk reductions exceeding 5, 10, and 15% were additionally computed. Prior specification followed the framework described by Zampieri *et al.*,¹⁹ and the results are reported in accordance with the structured Bayesian reporting approach proposed by Lammers *et al.*²⁰ All analyses were performed using SAS software, version 9.4 (SAS Institute, USA), and R software, version 4.4.2, with a two-sided significance level of 0.05.

Results

Trial Population

The WEANILEVO trial was terminated early after interim analysis owing to withdrawal of sponsor funding. The final modified intention-to-treat analysis therefore includes 80 of the 210 planned patients (38%). This decision was not based on a DSMB recommendation for efficacy or futility. The intention-to-treat analysis population included 40 patients in the levosimendan group and 40 patients in the control group on day 7 (fig. 1). The overall population primarily consisted of male patients, with a mean age of 61 ± 13 yr, who were admitted to the cardiovascular ICU for medical cardiogenic shock (44%) or postcardiotomy shock (40%). The baseline characteristics of the two treatment groups were well balanced in terms of age, comorbidities, IGS-II (Indice de Gravité Simplifié II) score, and indications for VA-ECMO support (table 1). Hemodynamic parameters at inclusion were comparable between groups (table 1), with a mean LVEF of $35 \pm 11\%$, a median arterial lactate of 1.3 (1.1–1.6) mmol/L, and a median VIS score of 0 (interquartile range, 0 to 5). The median time from VA-ECMO implantation to randomization was 4 (3 to 6) days.

VA-ECMO Weaning Failure. The primary outcome of VA-ECMO weaning failure were identical between the two groups, with a failure weaning rate of 25% in the levosimendan group and 25% in the placebo group (OR, 1.00 [95% CI, 0.36 to 2.75]; $P = 1.00$). For the analysis with adjustment for randomization stratification factors (center, age, and indication for VA-ECMO) and baseline serum creatinine, the results were consistent with the unadjusted analysis (adjusted OR; 1.03 [95% CI, 0.34 to 3.08]; $P = 0.96$). One patient in each group had new VA-ECMO implementation within the 7 days (table 2; fig. 2). The reverse fragility index was 10.

Secondary Endpoints. The incidence of AKI was higher in the levosimendan group, with 62.5% of patients developing AKI at day 30 compared to 38.5% in the placebo group (OR, 2.67 [95% CI, 1.08 to 6.62]; $P = 0.03$). Sensitivity

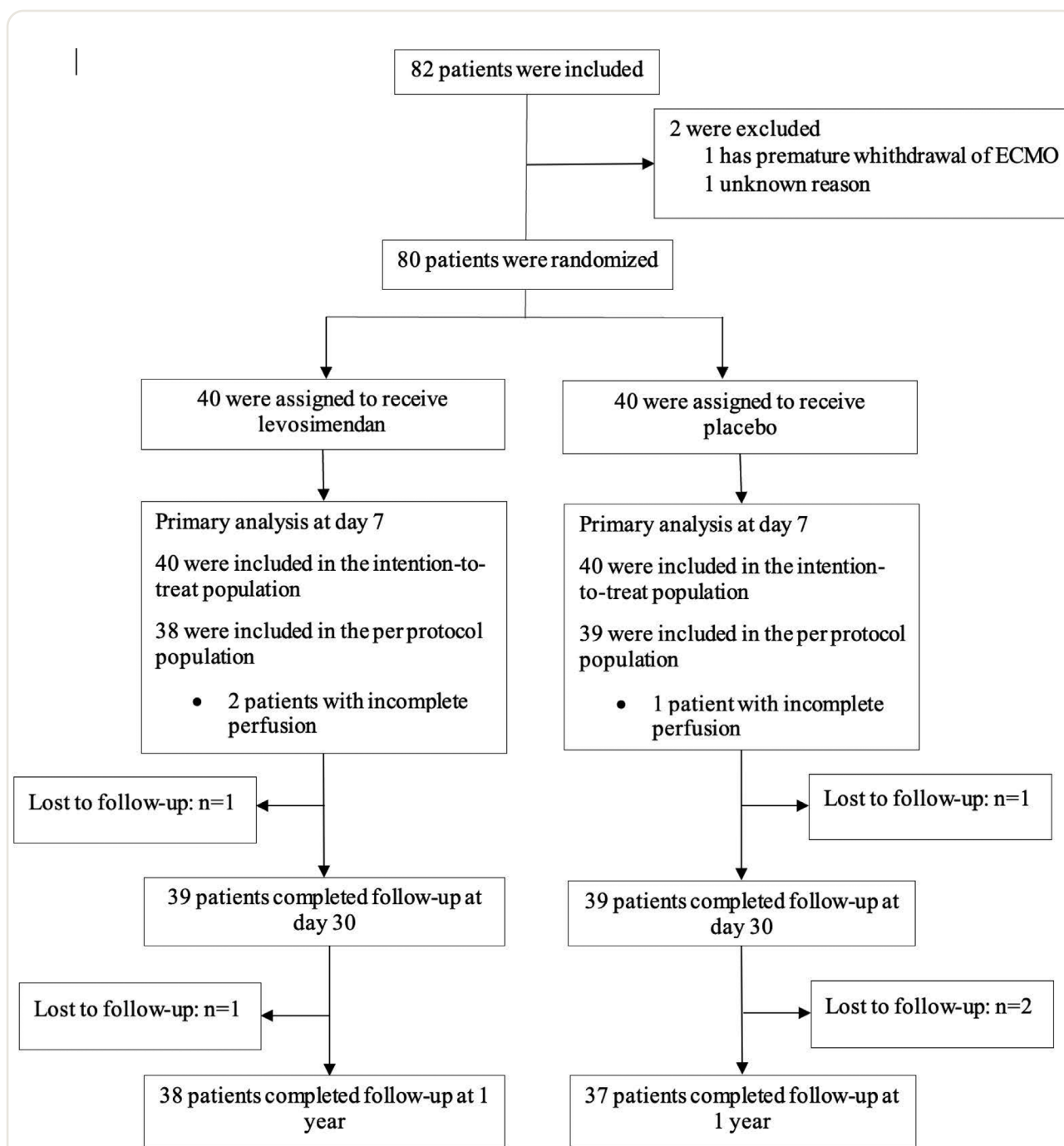


Fig. 1. Flow chart diagram of the study. ECMO, extracorporeal membrane oxygenation.

analysis excluding deceased patients at day 30 demonstrated an OR equal to 4.30 (95% CI, 1.42 to 12.99; $P = 0.01$; table 2; fig. 2). The fragility index was 1.

The 30-day and 1-yr mortality rates did not significantly differ between the two groups: 18.0% vs. 33.3% (OR, 0.39 [95% CI, 0.14 to 1.11]; $P = 0.07$) and 31.6% vs. 51.4% (OR, 0.44 [95% CI, 0.17 to 1.11]; $P = 0.08$), respectively. The reverse fragility index was 3. The causes of death are

displayed in the supplemental table (<https://links.lww.com/ALN/E541>). No patients required long-term circulatory assistance or heart transplant within 30 days of VA-ECMO weaning.

The evolution of heart rate, mean arterial pressure, and creatinine values differed between the two groups, whereas those of LVEF did not differ (fig. 3; supplemental table, <https://links.lww.com/ALN/E541>). After levosimendan

Table 1. Characteristics of the Population

Characteristic	Levosimendan Group (n = 40)	Control Group (n = 40)	SMD
Age (mean ± SD), yr	60 ± 16	63 ± 11	0.22
Body mass index (mean ± SD), kg/m ²	29.0 ± 6	29.1 ± 6	0.02
Sex (male), n (%)	26 (65.0)	29 (72.5)	0.16
Indication for VA-ECMO, n (%)			
eCPR	6 (15.0)	7 (17.5)	0.07
Postcardiotomy	16 (40.0)	16 (40.0)	0
Medical cardiogenic shock	18 (45.0)	17 (42.5)	0.05
Ischemic	11	12	
Chronic heart failure	4	1	
Other (myocarditis, stress cardiomyopathy, etc.)	3	4	
IGS-II score (mean ± SD)	65 ± 20	66 ± 19	0.05
Duration of ECLS before weaning decision (median [IQR]), days	4 [3–7]	4 [3–6]	0.03
Left ventricular venting, n (%)	5 (13.5)	8 (22.2)	0.23
Native cardiac output (mean ± SD), l/min	3.8 ± 0.9	4.0 ± 1.3	0.18
High blood pressure, n (%)	21 (52.5)	28 (70.0)	0.37
History of ischemic or chronic heart failure, n (%)	25 (62.5)	18 (45.0)	0.36
Chronic renal insufficiency, n (%)	7 (17.5)	8 (20.0)	0.06
Diabetes, n (%)	10 (25.0)	10 (25.0)	0
Parameters at randomization			
Creatinine (mean ± SD), μmol/l	125 ± 60	105 ± 48	0.34
Arterial lactate (median [IQR]), mmol/l	1.3 [1.2–1.6]	1.2 [1.0–1.4]	0.28
LVEF (mean ± SD), %	33 ± 11	37 ± 12	0.35
Native cardiac index (mean ± SD), l · min ⁻¹ · m ⁻²	1.9 ± 0.5	2 ± 0.7	0.16
VA-ECMO blood flow (mean ± SD), l/min	1.92 ± 0.4	1.90 ± 0.4	0.04
Heart rate (mean ± SD), beats/min	88 ± 17	87 ± 16	0.06
Mean arterial pressure (mean ± SD), mmHg	80.3 ± 11.6	83.5 ± 9.7	0.30
Central venous pressure (mean ± SD), mmHg	9 ± 4	9 ± 5	0
VIS (median [IQR])	0 [0–5]	1 [0–5]	0.23

ECLS, extracorporeal life support; eCPR, ECMO cardiopulmonary resuscitation; IGS-II, Indice de Gravité Simplifié II; IQR, interquartile range; LVEF, left ventricular ejection fraction; SMD, standardized mean difference; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VIS, vaso-inotropic score.

administration, the median VIS was 2.9 [0 to 13.0] in the levosimendan group compared with 2.4 [0 to 5.6] in the control group ($P = 0.33$). On the day of VA-ECMO weaning, the median VIS was 12.2 [4.0 to 18.5] *versus* 6.0 [0 to 22.0] ($P = 0.30$). On the first day after VA-ECMO liberation, the median VIS was significantly higher in the levosimendan group compared with placebo (19.1 [2.8 to 40] *vs.* 4.8 [0 to 11]; $P = 0.01$). This difference persisted 2 days after VA-ECMO liberation (20 [2 to 38] *vs.* 1 [0–10]; $P = 0.008$). The need for norepinephrine support during the administration of the treatment concerned 19 patients (47.5%) in the levosimendan group compared to 11 patients (28.2%) in the control group ($P = 0.07$), with a median of 0.06 [0.02; 0.13] $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ *vs.* 0.05 [0.03; 0.10] $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P = 0.93$). No vasopressin was used.

The ICU length of stay was significantly longer in the levosimendan group, with a median of 12 (7 to 24) days compared to 6 (4 to 13) days in the control group ($P = 0.02$). The total hospital length of stay was also longer for the levosimendan group, with a median of 22 (12 to 47) days compared to 14 (10 to 32) days in the control group ($P = 0.05$).

Per Protocol and Sensitivity Analysis. Among the 80 randomized patients, 77 (96.3%) were included in the per-protocol

analysis (38 in the levosimendan group and 39 in the placebo group). VA-ECMO weaning failure occurred in 10 of 38 patients (26.3%) in the levosimendan group and 10 of 39 patients (25.6%) in the placebo group. The unadjusted analysis showed no significant difference between groups (OR, 1.04 [95% CI, 0.37 to 2.87]; $P = 0.95$). After adjustment, the results remained consistent with the primary analysis (adjusted OR, 1.12 [95% CI, 0.38 to 3.33]; $P = 0.84$). In the sensitivity analysis, VA-ECMO weaning failure occurred in 18 of 80 patients overall (22.5%): 10 patients (25.0%) in the levosimendan group and 8 patients (20.0%) in the placebo group. The unadjusted analysis did not demonstrate a significant difference between groups (OR, 1.33 [95% CI, 0.46 to 3.83]; $P = 0.59$). After adjustment, the results were consistent (adjusted OR, 1.45 [95% CI, 0.48 to 4.42]; $P = 0.51$).

Bayesian Analysis. In the *post hoc* Bayesian analysis, the posterior probability of levosimendan superiority over placebo was 95% for 30-day mortality (OR, 0.40; 95% CrI, 0.14 to 1.20) and 96% for 1-yr mortality (OR, 0.42; 95% CrI, 0.16 to 1.07) under the noninformative prior. The corresponding Bayes factors were 0.22 and 0.25, respectively, reflecting anecdotal evidence in favor of a treatment effect per the Jeffreys classification. Under the enthusiastic (OR, 0.70) and skeptical (OR, 1.0) priors, posterior probabilities

Table 2. Study Endpoints

Endpoint	Levosimendan Group (n = 40)	Control Group (n = 40)	OR [CI 95%]	P Value
Primary endpoints (day 7)				
VA-ECMO weaning failure, n (%)	10 (25.0)	10 (25.0)	1.00 [0.36; 2.75]	1.00*
Absence of VA-ECMO weaning within 48 h of randomization, n (%)	7 (17.5)	4 (10.0)		
Secondary VA-ECMO implementation, n (%)	1 (2.5)	1 (2.5)		
Impella pump device (Abiomed, USA), n (%)	0	0		
Intra-aortic balloon pump, n (%)	0	0		
Death, n (%)	4 (10.0)	7 (17.5)		
Secondary endpoints (day 30)				
Left ventricular assistance or heart transplantation, n (%)†	0	0	—	—
Acute kidney injury, n (%)‡	25 (62.5)	15 (38.5)	2.67 [1.08; 6.62]	0.03*
Death at day 30, n (%)†	7 (18.0)	13 (33.3)	0.39 [0.14; 1.11]	0.07*
Time between VA-ECMO weaning and death (days), median (IQR)	7 (1–15)	3 (2–9)		
ICU length of stay (days), median (IQR)	12 (7–24)	6 (4–13)	—	0.02§
Hospital length of stay (days), median (IQR)	22 (12–47)	14 (10–32)	—	0.05§

*P value obtained using a logistic regression. †Missing data for n = 1 in each group. ‡Missing data for n = 1 in the control group. §P value obtained using a Mann–Whitney U test. —, not applicable; ICU, intensive care unit; IQR, interquartile range; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

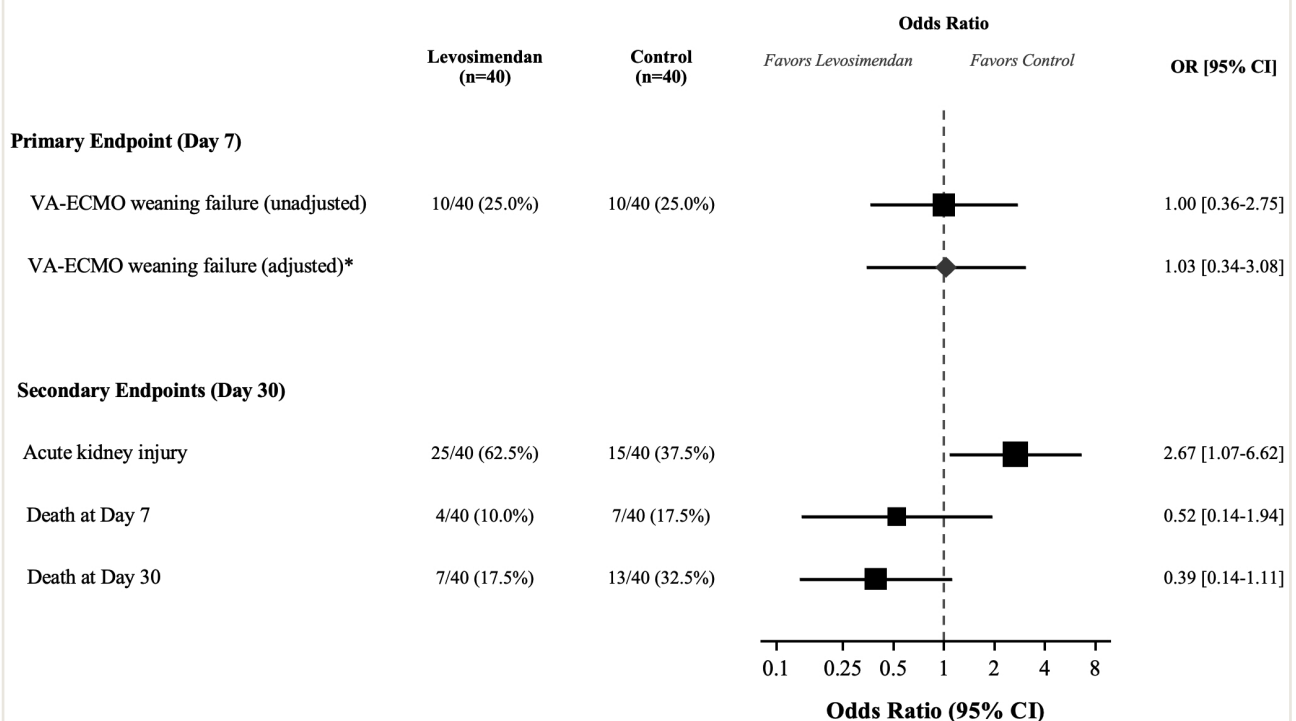


Fig. 2. Primary endpoints according to the group treatment. *Adjusted for predefined criteria of weaning failure including clinical, hemodynamic improvements, and creatinine. OR, odds ratio; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

of superiority ranged from 83 to 96% for 30-day mortality and from 91 to 97% for 1-yr mortality, demonstrating consistent directional findings across all prior specifications. Full posterior estimates are presented in table 3 and posterior distribution plots in supplemental figures (<https://links.lww.com/ALN/E541>).

Adverse Events. Overall, 87.5% versus 72.5% of patients experienced at least one adverse event. Renal events were the most clinically important differential finding: acute kidney injury occurred in 62.5% of levosimendan patients versus 38.5% of controls (OR, 2.67 [95% CI, 1.08 to 6.62]; $P = 0.03$), and this signal persisted after exclusion of patients who died before day

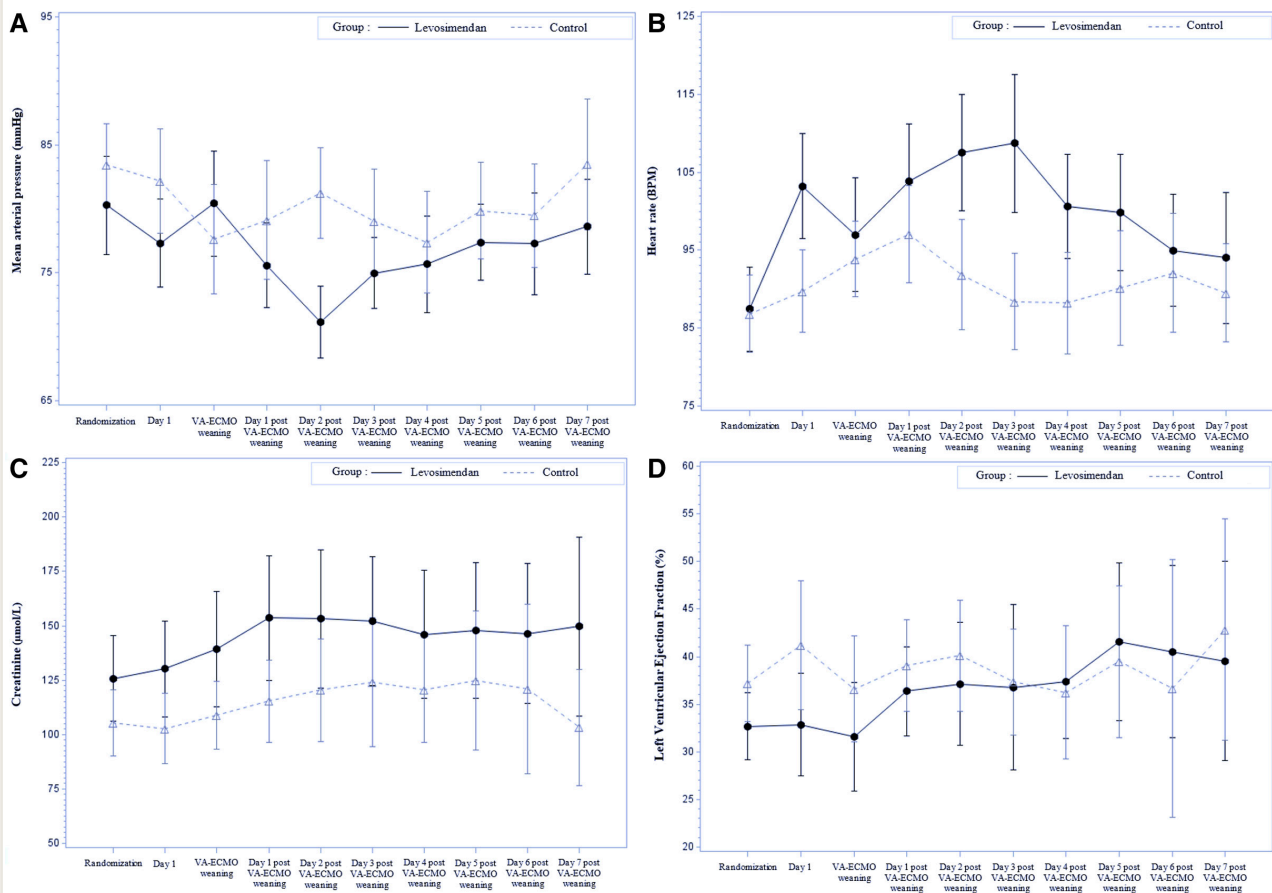


Fig. 3. Evolution of mean arterial blood pressure (A), heart rate (B), creatinine (C), and left ventricular ejection fraction (D) since the randomization. The data are presented as the median values with 95% CIs. BPM, beats/min; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 3. Bayesian Posterior Estimates of the Effect of Levosimendan on Mortality under Three Prior Specifications

Length of Mortality	Noninformative Prior		Enthusiastic Prior (OR 0.70)		Skeptical Prior (OR 1.0)	
	OR (95% CrI)	Pp	OR (95% CrI)	Pp	OR (95% CrI)	Pp
30 days	0.40 (0.14 to 1.20)	95%	0.75 (0.34 to 1.05)	96%	0.76 (0.45 to 1.39)	83%
1 yr	0.42 (0.16 to 1.07)	96%	0.59 (0.34 to 1.02)	97%	0.60 (0.28 to 1.22)	91%

CrI, credible interval; OR, odds ratio; Pp, posterior probability of treatment superiority, defined as $P(\text{OR} < 1)$.

30 (OR, 4.30 [95% CI, 1.42 to 13.00]; $P = 0.01$). Infectious and cardiovascular adverse events were numerically more frequent in the levosimendan group and are detailed in the supplemental table (<https://links.lww.com/ALN/E541>).

Discussion

In this multicenter, double-blind, randomized controlled trial, levosimendan administration in patients having

VA-ECMO weaning criteria did not reduce the rate of weaning failure compared with placebo. However, levosimendan was associated with a significantly higher incidence of AKI at day 30, higher vasopressor requirements after ECMO liberation, and longer ICU stays. Mortality rates at 30 days and 1 yr did not significantly differ between groups, although a *post hoc* Bayesian analysis may suggest a long-term mortality benefit of levosimendan.

The current results are consistent with those of the recently published LEVOECMO trial,²¹ which similarly demonstrated no clinical benefit of levosimendan on VA-ECMO weaning success. When comparing these two studies, one important distinction must be acknowledged. LEVOECMO initiated levosimendan early, within 48 h of ECMO cannulation (*i.e.*, during the acute phase of cardiogenic shock), whereas the current study evaluated levosimendan at a later stage, only when patients had met criteria for weaning. The rationale for this timing was that a minimal degree of myocardial recovery may be a prerequisite for any inotropic effect to be clinically meaningful.¹³ These two trials therefore address complementary yet distinct clinical questions: whether levosimendan benefits patients during early ECMO support (LEVOECMO), and whether it specifically facilitates weaning (WEANILEVO).²¹ Both returned negative results for their respective primary endpoints. The wide 95% CI for the primary endpoint in our study, consistent with the LEVOECMO trial, does not establish futility. Rather, these findings support the conclusion that a definitive answer requires a larger, adequately powered trial.

Regarding VA-ECMO weaning failure, several factors may explain the discrepancy between our findings and previous results. First, previous studies exhibited considerable heterogeneity in timing and criteria for levosimendan administration.^{12,13,22} Most previous investigations did not standardize timing of levosimendan use, while our design focused on patients supported by VA-ECMO with specific criteria for VA-ECMO weaning. All included patients were evaluated after 4 days of VA-ECMO support. Second, our study implemented a standardized VA-ECMO weaning protocol, as inclusion criteria specifically required demonstration of factors associated with VA-ECMO success. In contrast, these factors had been strictly selected for VA-ECMO weaning based on previously published studies^{18,23} (*i.e.*, low VIS, low arterial lactate value, minimal cardiac output). Since patients were included only after meeting criteria for VA-ECMO weaning, we did not observe significant hemodynamic effects of levosimendan, such as increased LVEF, which might otherwise have contributed to improve weaning success. This rigorous selection likely contributed to the relatively low weaning failure rate observed in our study (25%) compared to rates reported in the literature and used for sample size calculation (up to 50%). The same rate was also observed in the LEVOECMO trial.²¹ Thus, our study validates these criteria for predicting successful VA-ECMO weaning.²⁴ It is noteworthy that most weaning failures were primarily attributable to death from shock or cardiac arrest, with difficulty weaning itself rarely being the primary cause. Nonetheless, our results align with those of a randomized study showing that levosimendan did not improve outcomes in acute heart failure.^{25,26}

More patients in the levosimendan group experienced adverse events, predominantly cardiovascular, infectious,

and renal. The higher rate of renal events may appear counterintuitive given that most published studies have suggested a beneficial effect of levosimendan on renal function through improved cardiac output and microvascular perfusion. However, those studies were conducted in observational settings with low native cardiac output and without VA-ECMO support. Two converging factors may provide a mechanistically plausible explanation for our results. First, despite apparent creatinine normalization at weaning, renal functional reserve remains persistently reduced after AKI,²⁷ leaving kidneys at near-maximal filtration capacity with little buffer against additional hemodynamic stress. Second, levosimendan's vasodilatory properties may generate a drug-specific hemodynamic second hit on this vulnerable kidney substrate: arterial vasodilation promotes hypotension requiring higher vasopressor doses, while venodilation promotes venous congestion; both being risk factors of AKI.²⁸ Once VA-ECMO was removed, we observed higher vasopressor requirements, lower mean arterial pressure, and higher central venous pressure in the levosimendan group. In addition, the prolonged half-life of levosimendan's active metabolite sustains these effects well beyond cessation of infusion. Consistent with this, Chan *et al.*²⁹ showed that renal benefit from levosimendan is restricted to patients with low cardiac output and reduced glomerular filtration rate at baseline—a profile that does not apply to patients meeting VA-ECMO weaning criteria. This hemodynamic susceptibility is further supported by a meta-analysis demonstrating a higher incidence of arterial hypotension, atrial fibrillation, and ventricular dysrhythmia with levosimendan,³⁰ adverse effects that are themselves nephrotoxic through impaired renal perfusion and neurohormonal activation.

This susceptibility-exposure framework may explain the differential AKI rate even in the absence of divergent early creatinine trajectories—a discrepancy that itself warrants explanation. The higher 30-day AKI rate despite apparent similar 7-day creatinine curves likely reflects two complementary phenomena: KDIGO criteria capture urine output-based events not detected by creatinine alone and delayed AKI episodes beyond day 7 fall outside the early monitoring window. A competing-risks interpretation further contributes to this apparent paradox—earlier deaths from cardiac arrest and multiorgan failure in the control group (four and two events *vs.* one and zero events, respectively) may have precluded subsequent AKI diagnosis, while the longer survival in the levosimendan group extended the observation window during which AKI could manifest. This observation is supported by the sensitivity analysis restricted to 30-day survivors, in which the AKI signal was substantially stronger (OR, 4.30; 95% CI, 1.42 to 13.00). Notably, AKI was not assessed as an outcome in the LEVOECMO trial, although severe hypotension was included as a stopping rule²¹—implicitly acknowledging the clinical relevance of levosimendan-induced vasodilation. Taken together, our findings suggest that the renal effects of levosimendan may be context-dependent: likely protective when renal perfusion

depends on restoration of cardiac output but potentially deleterious once cardiac function has recovered, particularly in patients with previous AKI whose reduced renal functional reserve renders them vulnerable to hemodynamic stress. This context dependency underscores the incremental value of systematic renal outcome assessment in future trials of levosimendan in the VA-ECMO setting.

The current study did not demonstrate a statistically significant difference in mortality with levosimendan, a finding that should be interpreted in light of the trial's limited statistical power, as further underscored by the fragility index. Absence of statistical significance, however, should not be equated with absence of benefit. The *post hoc* Bayesian analysis provides a complementary perspective: under a noninformative prior, the posterior probability that levosimendan was superior to placebo reached 95% for 30-day mortality and 96% for 1-yr mortality. Critically, this signal was robust across all prior specifications—ranging from 83 to 96% at 30 days and from 91 to 97% at 1 yr under skeptical and enthusiastic priors, respectively—consistently suggesting a clinically meaningful mortality benefit irrespective of previous assumptions and warranting confirmation in adequately powered trials. A plausible mechanistic substrate for this signal lies in levosimendan's pleiotropic properties—including anti-inflammatory and antiapoptotic effects^{16,31}—which may confer myocardial protection that partially offsets the renal risk. This hypothesis is further supported by the LEVOHR and LION studies, which reported an association between levosimendan use and improved mortality rates.^{25,32} Taken together, these findings, rather than indicating futility, may suggest that a clinically meaningful mortality benefit cannot be excluded. Nevertheless, all mortality findings must be interpreted as strictly exploratory and hypothesis generating, given the early termination of the trial, limited statistical power for mortality outcomes, and the *post hoc*, nonprespecified nature of this analysis.

The mortality rate observed in the current study may appear higher than the 25% reported in the LEVOECMO trial. However, the mortality reported in LEVOECMO is notably lower than that typically observed in contemporary VA-ECMO cohorts, including registries from the same participating centers,^{33,34} and substantially lower than mortality reported in the HYPO-ECMO trial, which was conducted in same French intensive care units. This discrepancy suggests that LEVOECMO may have enrolled a highly selected subset of patients with a better prognosis, potentially limiting the generalizability of its neutral finding. In contrast, the current study may be more representative of real-world VA-ECMO population typically encountered in clinical practice.³³

In summary, although our study showed no clinical benefit for VA-ECMO weaning success, the current findings do not preclude levosimendan's potential utility in cardiogenic shock settings. Despite not reaching statistical significance, the small sample size and the fragility index of our results may support further research on the noninotropic

effects of levosimendan, such as its pleiotropic and antiapoptotic properties, which may confer cardioprotection and potential mortality benefits. It should be noted that levosimendan is not currently approved by the U.S. Food and Drug Administration (Silver Spring, Maryland) and remains investigational in the United States, where milrinone and dobutamine are the standard inotropic drugs considered in patients supported by VA-ECMO.

We acknowledge several limitations in our study. One factor to consider is the indication for VA-ECMO support. Previous observational studies suggest that the benefits of levosimendan may vary depending on the specific indication for VA-ECMO; for instance, levosimendan may improve weaning success and mortality rates in cases of extracorporeal cardiopulmonary resuscitation compared to postcardiotomy shock. Additionally, our study did not reach the initially planned sample size, which may affect the robustness of our findings. Given the contradictory results from different studies, we had planned an interim analysis as part of the study design. This interim analysis revealed no difference in the primary endpoint with a high rate of adverse events in the levosimendan group. Given the low inclusion rate exacerbated by the COVID-19 crisis (the trial was temporally stopped because of the prioritization of COVID-19 research), the high rate of events in the interventional group, the study sponsor decided to stop funding the study, which has been halted. Given the sample size and low event rates, secondary endpoints such as AKI have demonstrated low fragility, supporting the fact that the study may be underpowered on these endpoints that may be considered as hypothesis generating. These limitations underscore the need for further research to explore the optimal timing, patient selection, and indications for levosimendan use in VA-ECMO patients. We also observed a lower rate of VA-ECMO weaning failure in our study compared to the literature, which may have affected the required sample size. As previously discussed, most published studies are observational with broad definitions; therefore, we based our sample size calculation on a review of existing literature.

Conclusions

Levosimendan did not provide a superior clinical benefit over placebo in improving VA-ECMO weaning success in patients who met criteria for weaning. Levosimendan use may be associated with a higher rate of AKI. Short- and long-term mortality were not statistically different between the two groups. These findings highlight the importance of further research to establish its optimal use in this setting.

Research Support

Supported by investigator-initiated research (2018). The WEANILEVO study was supported in part by a grant from Orion (Issy-les-Moulineaux, France).

Competing Interests

Dr. Guinot has received fees for lectures from AOP Health (Meudon, France), Baxter (Deerfield, Illinois), Medtronic (Paris, France), Edwards (Herblay-Sur-Seine, France), and Vygon (Ecouen, France), and is a consultant for Abbott. Dr. Nguyen has received fees for lectures from Baxter. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: guinotpierregregoire@gmail.com. Raw data available at: guinotpierregregoire@gmail.com.

Correspondence

Address correspondence to Dr. Pierre-Grégoire: Service d'Anesthésie Réanimation CHU Dijon, BP 77908, 21000 Dijon, France. guinotpierregregoire@gmail.com

Supplemental Digital Content

Supplemental materials: Flow chart diagram, sensitivity analysis, and adverse events, <https://links.lww.com/ALN/E541>

References

1. Le Gall A, Follin A, Cholley B, Mantz J, Aissaoui N, Pirracchio R: Venous-arterial-ECMO in the intensive care unit: From technical aspects to clinical practice. *Anaesth Crit Care Pain Med* 2018; 37:259–68. doi:10.1016/j.accpm.2017.08.007
2. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD: Venous-arterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. *Circ Heart Fail* 2018; 11:e004905. doi:10.1161/CIRCHEARTFAILURE.118.004905
3. Peña-López Y, Machado MC, Rello J: Infection in ECMO patients: Changes in epidemiology, diagnosis and prevention. *Anaesth Crit Care Pain Med* 2024; 43:101319. doi:10.1016/j.accpm.2023.101319
4. Geller BJ, Sinha SS, Kapur NK, et al.; American Heart Association Acute Cardiac Care and General Cardiology Committee of the Council on Clinical Cardiology; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Council on Cardiovascular Surgery and Anesthesia: Escalating and de-escalating temporary mechanical circulatory support in cardiogenic shock: A scientific statement from the American Heart Association. *Circulation* 2022; 146:e50–68. doi:10.1161/CIR.0000000000001076
5. Lüsebrink E, Stremmel C, Stark K, et al.: Update on weaning from veno-arterial extracorporeal membrane oxygenation. *J Clin Med* 2020; 9:992. doi:10.3390/jcm9040992
6. Pappalardo F, Pieri M, Arnaez Corada B, et al.: Timing and strategy for weaning from venoarterial ECMO are complex issues. *J Cardiothorac Vasc Anesth* 2015; 29:906–11. doi:10.1053/j.jvca.2014.12.011
7. Tohme J, Piat C, Aissat N, et al.: Weaning-related shock in patients with ECMO: Incidence, mortality, and pre-disposing factors. *J Cardiothorac Vasc Anesth* 2021; 35:41–7. doi:10.1053/j.jvca.2020.07.069
8. Papp Z, Agostoni P, Alvarez J, et al.: Levosimendan efficacy and safety: 20 years of SIMDAX in clinical use. *J Cardiovasc Pharmacol* 2020; 76:4–22. doi:10.1097/FJC.0000000000000859
9. Nieminen MS, Buerke M, Cohen-Solal A, et al.: The role of levosimendan in acute heart failure complicating acute coronary syndrome: A review and expert consensus opinion. *Int J Cardiol* 2016; 218:150–7. doi:10.1016/j.ijcard.2016.05.009
10. Affronti A, di Bella I, Carino D, Ragni T: Levosimendan may improve weaning outcomes in venoarterial ECMO patients. *ASAIO J* 2013; 59:554–7. doi:10.1097/MAT.0b013e3182a4b32e
11. Alonso-Fernandez-Gatta M, Merchan-Gomez S, Gonzalez-Cebrian M, et al.: Levosimendan in veno-arterial extracorporeal membrane oxygenator supported patients: Impact on the success of weaning and survival. *Artif Organs* 2021; 45:717–25. doi:10.1111/aor.13899
12. Massol J, Simon-Tillaux N, Tohme J, et al.: Levosimendan in patients undergoing extracorporeal membrane oxygenation after cardiac surgery: An emulated target trial using observational data. *Crit Care* 2023; 27:51. doi:10.1186/s13054-023-04328-6
13. Chen Y-W, Lee W-C, Wu P-J, et al.: Early levosimendan administration improved weaning success rate in extracorporeal membrane oxygenation in patients with cardiogenic shock. *Front Cardiovasc Med* 2022; 9:912321. doi:10.3389/fcvm.2022.912321
14. Hau M, Fong K-M, Au S-Y: Levosimendan's effect on venoarterial extracorporeal membrane oxygenation weaning. *Int J Artif Organs* 2022; 45:571–9. doi:10.1177/03913988221098773
15. Kaddoura R, Omar AS, Ibrahim MIM, et al.: The effectiveness of levosimendan on veno-arterial extracorporeal membrane oxygenation management and outcome: A systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2021; 35:2483–95. doi:10.1053/j.jvca.2021.01.019
16. Farmakis D, Alvarez J, Gal TB, et al.: Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. *Int J Cardiol* 2016; 222:303–12. doi:10.1016/j.ijcard.2016.07.202

17. Ellouze O, Soudry Faure A, Radhouani M, et al.: Levosimendan in venoarterial ECMO weaning. Rational and design of a randomized double blind multicentre trial. *ESC Heart Fail* 2021; 8:3339–47. doi:10.1002/ehf2.13427
18. Burgos LM, Seoane L, Diez M, et al.: Multiparameters associated to successful weaning from VA ECMO in adult patients with cardiogenic shock or cardiac arrest: Systematic review and meta-analysis. *Ann Card Anaesth* 2023; 26:4–11. doi:10.4103/aca.aca_79_22
19. Zampieri FG, Casey JD, Shankar-Hari M, Harrell FE, Harhay MO: Using Bayesian methods to augment the interpretation of critical care trials. An overview of theory and example reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. *Am J Respir Crit Care Med* 2021; 203:543–52. doi:10.1164/rccm.202006-2381CP
20. Lammers D, Richman J, Holcomb JB, Jansen JO: Use of Bayesian statistics to reanalyze data from the pragmatic randomized optimal platelet and plasma ratios trial. *JAMA Netw Open* 2023; 6:e230421. doi:10.1001/jamanetworkopen.2023.0421
21. Combes A, Saura O, Nessler N, et al.; LEVOECMO Trial Group and the International ECMO Network (ECMONet): Levosimendan to facilitate weaning from ECMO in patients with severe cardiogenic shock: The LEVOECMO randomized clinical trial. *JAMA* 2026; 335:60–9. doi:10.1001/jama.2025.19843
22. Gaisendrees C, Schlachtenberger G, Gerfer S, et al.: The impact of levosimendan on survival and weaning from ECMO after extracorporeal cardiopulmonary resuscitation. *Artif Organs* 2023; 47:1351–60. doi:10.1111/aor.14540
23. Braun J, Sahli SD, Spahn DR, et al.: Predicting survival for veno-arterial ECMO using conditional inference trees—A multicenter study. *J Clin Med* 2023; 12:6243. doi:10.3390/jcm12196243
24. Singh G, Hudson D, Shaw A: Medical optimization and liberation of adult patients from VA-ECMO. *Can J Cardiol* 2020; 36:280–90. doi:10.1016/j.cjca.2019.10.038
25. Pözl G, Altenberger J, Comín-Colet J, et al.; LeoDOR Investigators: Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period: The multinational randomized LeoDOR trial. *Eur J Heart Fail* 2023; 25:2007–17. doi:10.1002/ehfj.3006
26. Follath F, Cleland JGF, Just H, et al.; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study: Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind trial. *Lancet* 2002; 360:196–202. doi:10.1016/s0140-6736(02)09455-2
27. Husain-Syed F, Ferrari F, Sharma A, et al.: Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery. *Nephrol Dial Transplant* 2019; 34:308–17. doi:10.1093/ndt/gfy227
28. Ohara H, Yoshihisa A, Horikoshi Y, et al.: Renal venous stasis index reflects renal congestion and predicts adverse outcomes in patients with heart failure. *Front Cardiovasc Med* 2022; 9:772466. doi:10.3389/fcvm.2022.772466
29. Chan C-C, Lee K-T, Ho W-J, Chan Y-H, Chu P-H: Levosimendan use in patients with acute heart failure and reduced ejection fraction with or without severe renal dysfunction in critical cardiac care units: A multi-institution database study. *Ann Intensive Care* 2021; 11:27. doi:10.1186/s13613-021-00810-y
30. Zhou S, Li D, Zhang L, Li J: The anti-inflammatory and haemodynamic effects of levosimendan on advanced heart failure patients: A meta-analysis of published studies. *J Int Med Res* 2023; 51:3000605221148402. doi:10.1177/03000605221148402
31. Parissis JT, Andreadou I, Bistola V, Paraskevaidis I, Filippatos G, Kremastinos DT: Novel biologic mechanisms of levosimendan and its effect on the failing heart. *Expert Opin Investig Drugs* 2008; 17:1143–50. doi:10.1517/13543784.17.8.1143
32. Comín-Colet J, Manito N, Segovia-Cubero J, et al.; LION-HEART Study Investigators: Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: The LION-HEART multicentre randomised trial. *Eur J Heart Fail* 2018; 20:1128–36. doi:10.1002/ehfj.1145
33. Lang CN, Kaier K, Zotzmann V, et al.: Cardiogenic shock: Incidence, survival and mechanical circulatory support usage 2007–2017—Insights from a national registry. *Clin Res Cardiol* 2021; 110:1421–30. doi:10.1007/s00392-020-01781-z
34. Levy B, Girerd N, Amour J, et al.; HYPO-ECMO Trial Group and the International ECMO Network (ECMONet): Effect of moderate hypothermia vs. normothermia on 30-day mortality in patients with cardiogenic shock receiving venoarterial extracorporeal membrane oxygenation: A randomized clinical trial. *JAMA* 2022; 327:442–53. doi:10.1001/jama.2021.24776

Appendix. WEANILEVO Collaborative Study Group

The following investigators participated in the WEANILEVO Collaborative Study Group: Vivien Berthoud, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier

Universitaire de Dijon, Dijon, France. Valentin Kabbout, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France.

Mohamed Radhouani, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Audrey Martin, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Tiberiu Constandache, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Bastien Durand, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Sandrine Grosjean, M.D., Ph.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Pierre Alain Bahr, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Jean-Baptiste Anciaux, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Corentin Evezard, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Eugénie Bernard, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Vincenzo Caruso, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Siham Ghalifa, PharmD, PhD: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Dijon, Dijon, France. Olivier Bouchot, Ph.D, M.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de Dijon, Dijon, France. Marie-Catherine Morgant, Ph.D, M.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de

Dijon, Dijon, France. Saed Jazzayeri, M.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de Dijon, Dijon, France. Chloé Bernard, M.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de Dijon, Dijon, France. Amélie Cransac, Pharm.D., Ph.D.: Département de Pharmacie, Centre Hospitalier Universitaire de Dijon, Dijon, France. Mouhamed Samb, Ph.D.: Département de Recherche Clinique, Centre Hospitalier Universitaire de Dijon, Dijon, France. Decros Jean-Baptiste, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Caen, Caen, France. Stéphane Debroczi, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Caen, Caen, France. Richard Descamps, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Caen, Caen, France. Christophe Beyls, M.D., Ph.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire d'Amiens, Amiens, France. Walid Oulehri, M.D., Ph.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France. Mircea Cristinar, M.D.: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France. Michel Kindo, M.D., Ph.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France. André Vincentelli, M.D., Ph.D.: Département de Chirurgie Cardiaque, Centre Hospitalier Universitaire de Lille, Lille, France.