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Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 2483–2495

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Review Article

The Effectiveness of Levosimendan on Veno-Arterial Extracorporeal Membrane Oxygenation Management and Outcome: A Systematic Review and Meta-Analysis

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Objectives: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides a temporary support system for patients with cardiogenic shock refractory to conventional medical therapies. It has been reported that levosimendan may facilitate VA-ECMO weaning and improve survival. The primary objective of this review was to examine the effect of levosimendan use on VA-ECMO weaning and mortality in critically ill patients on VA-ECMO.

Design: MEDLINE, EMBASE, and CENTRAL were searched. A pair of reviewers identified eligible clinical trials. Two reviewers extracted data and independently assessed the risk of bias. A random-effect model was used to combine data. The primary outcome was the success of weaning from VA-ECMO.

Measurements and Main Results: Seven studies of observational design, including a total of 630 patients, were selected in the final analysis. The sample size ranged from ten-to-240 patients, with a mean age between 53 and 65 years, and more than half of them underwent cardiac surgeries. The VA-ECMO durations varied between four and 11.6 days. Overall, levosimendan use was significantly associated with successful weaning compared with control (odds ratio [OR] 2.89, 95% CI, 1.53-5.46; $p_{\text{overall effect}} = 0.001$); $I^2 = 49\%$). For survival, six studies (n = 617) were

The study was approved by Hamad Medical Corporation through the Medical Research Center. Kindly, to the following to the acknowledgement section: *Open Access funding provided by the Qatar National Library*

R. Kaddoura: study design and methodology, literature search, pharmacologic background, risk of bias assessment, PROSPERO registration protocol, manuscript writing, and final revision. A.S. Omar: PROSPERO registration process, risk of bias analysis, manuscript writing, and final revision. M. Ibrahim: literature search, statistical analysis, and critical revision. A. Alkhulaifi: manuscript writing and final revision. R. Lorusso: manuscript writing and critical revision. H. Elsherbini: manuscript writing and final revision. O. Soliman: manuscript writing and final revision. K. Caliskan: manuscript writing and critical revision. All authors read and approved the final manuscript.

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https://doi.org/10.1053/j.jvca.2021.01.019

included in the meta-analysis involving 326 patients in the levosimendan group and 291 in the comparator group. Pooled results showed a significantly higher survival rate in the levosimendan group (OR 0.46, 95% CI, 0.30-0.71; $p_{overall\ effect} = 0.0004$; $I^2 = 20\%$).
Conclusions: Levosimendan therapy was significantly associated with successful weaning and survival benefit in patients with cardiogenic or postcardiotomy shock needing VA-ECMO support for severe cardiocirculatory compromise. To date, there is limited literature and absence of evidence from randomized trials addressing the use of levosimendan in VA-ECMO weaning. This study may be considered a hypothesis-generating research for randomized controlled trials to confirm its findings.

Key Words: cardiogenic shock; ECLS; extracorporeal life support; extracorporeal membrane oxygenation; levosimendan; weaning

DESPITE CONTEMPORARY advancements in the management of cardiogenic shock, the rates of morbidity and mortality still are very high.[1] Inadequate tissue perfusion characterizes cardiogenic shock of any etiology, resulting in global ischemia and imminent multiorgan failure.[2] During the last two decades, mechanical circulatory support devices, especially veno-arterial extracorporeal membrane oxygenation (VA-ECMO), emerged as a temporary support system for patients with cardiogenic shock refractory to conventional pharmacologic therapy, which allows time for potential cardiac recovery.[3] VA-ECMO increases mean arterial blood pressure and oxygen delivery, thereby improving tissue perfusion and gas exchange.[4] On the other hand, prolonged use of VA-ECMO can lead to serious complications such as bleeding, thromboembolic complications, acute brain or lung injury, and limb ischemia. However, weaning from VA-ECMO is challenging, and can be a prolonged process that may last for days or sometimes weeks.[5] VA-ECMO weaning usually is facilitated by the use of beta-adrenergic agonists, such as dobutamine, dopamine, and epinephrine, or phosphodiesterase inhibitors, such as milrinone and enoximone.[6] Prolonged use of beta-adrenergic agonists may cause tachyarrhythmias and myocardial ischemia,[7,8] increase myocardial oxygen demand, and impair myocardial relaxation that leads to increasing left ventricular (LV) myocardial strain.[6] Moreover, the undesirable effect on the overall outcome as a result of metabolic acidosis and vasoconstriction impairs the microcirculation and triggers a systemic inflammatory response.[9] Phosphodiesterase inhibitors may have some advantages over the catecholamines in facilitating VA-ECMO weaning, as they augment myocardial contractility through increasing intracellular calcium levels, reducing afterload, and decreasing LV strain. However, this is at the expense of increased myocardial oxygen consumption. Consequently, the risk of arrhythmias and cardiotoxicity remains an issue.[6] Although the pharmacologic support in VA-ECMO weaning is limited to beta-adrenergic agonists and phosphodiesterase inhibitors, the calcium-sensitizing inotropic agent levosimendan is gaining popularity.

Levosimendan is a novel, first-in-class calcium sensitizer, currently available in several countries in Europe and beyond, but has not yet been approved in the United States. Levosimendan enhances myocardial contractility by amplifying calcium sensitivity of cardiac myocytes, without increasing the intracellular calcium.[6,10] It increases cardiac output and stroke volume and reduces peripheral vascular resistance[11] without increasing myocardial oxygen consumption; thus, there is no increased risk of serious arrhythmogenic effects.[6,10,11] Furthermore, it has a long therapeutic effect that may last for weeks, due to the long half-life of one of its active metabolites (eg, OR-1896, OR-1855).[5,10] OR-1896 probably is the clinically relevant metabolite.[10] Additionally, levosimendan possesses anti-inflammatory and cardioprotective effects[11] and has been used successfully in patients with postcardiotomy myocardial dysfunction.[6,11] Potassium adenosine triphosphate channels, which are present in systemic, pulmonary, and coronary vascular smooth muscles, also are activated by levosimendan. The resultant smooth muscle relaxation improves coronary perfusion and decreases systemic and pulmonary vascular resistances; thus, unloading both ventricles. Theoretically, these pharmacodynamic properties may enhance myocardial recovery and facilitate VA-ECMO weaning.[6] Although the current evidence has suggested favorable effects of levosimendan on VA-ECMO weaning and survival in patients with cardiogenic shock after acute myocardial infarct, acute myocarditis, and after cardiac surgery, these findings have not been confirmed in large trials.[12] The objective of this study was to evaluate the effectiveness of levosimendan on VA-EMCO weaning and mortality in critically ill adult patients on VA-ECMO.

Methods

This systematic review and meta-analysis were conducted in compliance with the recommendations of the "Cochrane Handbook for Systematic Reviews,"[13] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[14-16] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[17] checklist. The review protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO 2019 CRD42019137208).[18]

Eligibility Criteria

All studies that used levosimendan for VA-ECMO weaning in critically ill adult subjects were included. Parenterally administered levosimendan as the intervention group was considered without any restrictions in terms of dose or duration of

administration. The comparator group included any type of control such as placebo, other inotropes, or no intervention.

Search Strategy

An electronic literature search was conducted on June 1, 2019, by two authors (R.K., M.I.) using MEDLINE, EMBASE, CENTRAL, Scopus, ScienceDirect, ProQuest Public Health, and Web of Science. Boolean terms "OR" and "AND," Medical Subject Headings (MeSH), Emtree, and broad key words were used. The search terms included "simendan," "levosimendan," "extracorporeal membrane oxygenation," "ECMO," "extracorporeal life support," "ECLS," "mechanical circulatory support," and "MCS." Search limitations were not applied. The literature search was updated on June 30, 2020, using MEDLINE, EMBASE, and CENTRAL, with the aforementioned terms. Additionally, unpublished studies were sought through US National Institutes of Health Registry (clinicaltrials.gov), ISRCTNregistry, and OpenGrey. The reference lists of the retrieved articles and other systematic reviews were manually screened. The detailed search strategy is described in Table S1.

Study Selection and Data Extraction

All titles and abstracts were reviewed. Irrelevant studies, duplicate publications, and nonadult studies were excluded. All potentially relevant abstracts were retrieved in full text and reviewed in duplicate to determine the final reports. The included studies were tabulated, and their data were extracted for the study objective(s), design, duration, sample size, criteria of inclusion and exclusion, interventions, comparators, relevant definitions, indication and duration of VA-ECMO, outcomes, results, limitations, and conclusions. A template of the data extraction tables is included in Table S2. The corresponding authors of the included studies were contacted for missing or additional details. The primary outcome was weaning from VA-ECMO. Weaning was defined according to each study. The secondary outcomes included mortality and any other relevant outcomes such as length of stay (intensive care unit [ICU], hospital), use of vasopressors, improvement in hemodynamic or echocardiographic parameters, and safety outcomes. According to data availability, a time-specific analysis of mortality (short- and/or long-term mortality) was conducted. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of evidence of the main outcomes.[19-26] The certainty in the body of evidence for each outcome was rated as high, moderate, low, or very low. The assessment included judgments about imprecision, risk of bias, indirectness, inconsistency, and publication bias.

Risk of Bias Assessment

The validity of the observational studies was evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) risk of bias tool.[27,28] ROBINS-I tool assesses seven domains, and, accordingly, the level of bias was classified as low, moderate, serious, critical risk, or no information. The Cohen kappa coefficient[29] was used to measure the agreement on risk of bias (RoB) assessment of the included studies between two authors. Any disagreement was discussed until a consensus was reached.

Statistical Analysis

The odds ratios (OR) with 95% confidence intervals (CI) were calculated. The number-needed-to-treat (NNT) was calculated for the statistically significant pooled outcome results. Data were combined in systematic review, forest plots, and meta-analysis. Two studies were set as the minimum number for quantitative synthesis of data in a meta-analysis for each study outcome.[30] The meta-analysis was carried out using an aggregate data approach. In the initial stage, both of the individual study statistics and combinations of them were carried out. Then, the random-effects model was used. The analysis included the study of potential covariates, overall effect size, and the existence of heterogeneity. Inconsistency among studies was assessed by visual inspection of forest plots, CI and its minimal or no overlap, the Q statistic, and the inconsistency factor (I^2) value. I^2 values $\geq$50% were considered highly heterogeneous. The following thresholds have been suggested as a rough guide: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity.[31] The sensitivity analysis was explored for the dichotomous outcome measures. Studies were removed and included based on sample size or methodologic issue to check if the overall result, that is, OR and conclusions, were not affected. Sensitivity analysis involves undertaking the meta-analysis twice: first by including all studies and then by excluding studies and looking at the overall effect; that is, to check if the overall result and conclusions were not affected. The sensitivity analysis explored the impact of excluding or including studies in a meta-analysis based on sample size, methodologic quality, or variance.[32,33] The potential for publication or reporting bias was examined by visual inspection of the funnel plots. Review Manager Software 5 (Review Manager [RevMan] Version 5.3.) and SPSS version 26 (IBM Corp, Armonk, NY) were used for each analysis.

Results

The literature search (Fig 1) resulted in a total of 1,094 records that were screened. After eliminating duplicates and studies that did not meet the inclusion criteria, 26 full-text articles were assessed for eligibility. Twenty studies were excluded (Table S3) and seven[34-40] (Table 1) involving 630 patients were included in the analyses. One case report[41] was found to be relevant (Table S4). Four corresponding authors were contacted for missing data; two of them responded and only one[35] provided additional data. The search of the US National Institutes of Health Registry using "levosimendan" as a broad term resulted in 72 studies. Two registered

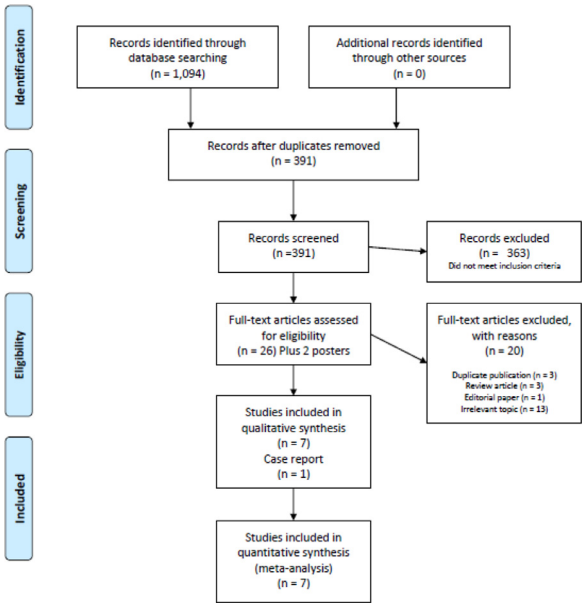

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram—study selection and exclusion.

unpublished studies have been identified (Table 2). The updated literature search resulted in 122 studies. Three databases were used: PubMed (17 studies), EMBASE (101 studies), and CENTRAL (four studies). There were 79 duplicates and 30 studies that did not meet the inclusion criteria. The remaining 13 studies also were excluded (Table S3).

The seven single-center studies used observational design. Five of them were published as full articles[34,35,37-39] and the remaining two as posters[36,40] with sufficient information. The studies were conducted in Europe between 2013 and 2019, with study periods ranging from one-to-11 years. The sample size ranged from ten-to-240 patients with a mean age range of 53-to-65 years. The largest study[35] (n = 240) accounted for approximately 40% of the patients in this review. Half of the patients (n = 304) from two studies[35,37] were patients after cardiac surgery. The remaining studies[34,36,38-40] enrolled surgical and nonsurgical patients (Table 3).

The VA-ECMO duration ranged from four days to 11.6 days. Weaning protocol was not stated in three studies.[35,36,40] Two studies[35,39] defined weaning failure as death during VA-ECMO support or death 24 hours after VA-ECMO removal. One study[37] defined successful weaning as 24-hour survival afterVA-ECMO removal without the need for repeat VA-ECMO. All the studies except two[36,40] stated levosimendan dosing regimen with an almost similar approach; that is, without loading dose, within the usual rate range, and for 24 hours. Timing of levosimendan initiation varied among studies; that is, pretreatment before weaning,[34,38] after VA-ECMO initiation[35] or cannulation,[39] or during weaning.[37] Traditional inotropes and vasopressors were

Table 1
Study General Characteristics

First Author	Year	Country	Number of Patients	Study Site	Study Design	Recruitment Period Study Duration
Affronti[34]	2013	Italy	17	Single center	Before-after design; case series	January to December 2011 (1 y)
Distelmaier[35]	2016	Austria	240	Single center	Observational retrospective registry	September 2003 to June 2014 (11 y)
Haffner[36] (poster)	2018	France	63	Single center	Observational retrospective	2014 to 2016 (2 y)
Jacky[37]	2018	Switzerland	64	Single center	Observational retrospective; before-after design	2007 to 2013 (6 y)
Sangalli[38]	2016	Italy	10	Single center	Observational prospective, before-after design	Not mentioned (before 2016)
Vally[39]	2019	France	150	Single center	Observational retrospective cohort	January 2010 to March 2017 (7 y)
Zipfel[40] (poster)	2018	Germany	86	Single center	Observational retrospective	January 2013 to December 2016 (4 y)

Table 2
Registered Clinical Trials

Trial Identifier*	Title (Acronym)	Agent (s)	Design (Phase)	Enrollment	Primary Outcome	Start Date	Status
NCT04323709	Levosimendan for Veno-arterial ECMO Weaning (WEANECMO)	Levosimendan vs control	Observational retrospective cohort	200	VA-ECMO weaning failure defined as death	January 2019	Completed (March 2020)
NCT04158674	Interest of Levosimendan in Reducing Weaning Failures of ExtraCorporeal Life Support-ECLS (Weanilevo)	Levosimendan vs Cernevit	Randomized (3)	206	ECLS withdrawal failure	December 2019	Not yet recruiting

* From http://clinicaltrials.gov. Accessed July 15, 2020.

Table 3
Patients' and Study Protocol Characteristics

First Author Year Sample Size (N)	Setting	Inclusion Criteria Exclusion Criteria	Mean Age Male Sex	Comorbidities Other Information	ECMO Indication ECMO Duration	Weaning Protocol
Affronti et al.[34] 2013 N = 17	■ ICU ■ OR	■ Inclusion: refractory CS on ECMO	■ 56 y ■ 53%	■ Pre-ECMO LVEF (16%) ■ CrCl: 113 mL/min (group A) vs 52 mL/min (group B) ■ Etiology of CS: AMI (48%), acute myocarditis (30%), and postcardiotomy (22%) ■ IABP use: 100% ■ Patients were on at least 2 high-dose inotropes	■ Cardiopulmonary failure not responding to pharmacologic and IABP support but potentially reversible (ELSO criteria) ■ Median 8-9 d (NS between groups)	Flow: ■ Reducing pump flow by 0.5 L/h (usually accomplished within 48 h) Routine monitoring: ■ ECHO ■ Swan-Ganz catheter: hemodynamic status ■ Mixed venous oxygen saturation, ABG, BNP, and lactate
Distelmaier et al.[35] 2016 N = 240	■ ICU	■ Inclusion: VA-ECMO support after CV surgery ■ Exclusion: age <18 y	■ 65 y ■ 71%	■ CAD (50%), HTN (70%), DM (25%) ■ IABP use: not stated ■ Median SAPS-3 = 43, median EuroSCORE = 10 (both are significantly different between groups; higher in levosimendan group) ■ Severely reduced LV function (35%) (significantly different between groups; sicker in levosimendan group)	■ Clinical signs of severe CS (eg, SBP <80 mmHg), and signs of end-organ failure, anaerobic metabolism, and metabolic acidosis despite optimized supportive measures (ie, inotropes, fluids, and IABP) ■ Weaning failure from cardiopulmonary bypass (60%), post-op CS (20%), immediate post-transplant cardiac graft failure (6%), post-op respiratory failure (4%), post-op bleeding or tamponade with CS (4%), and others (6%) ■ Median 4 d	■ Not stated ■ Weaning failure defined as death during ECMO support or death within 24 h after ECMO removal
Haffner et al.[36] 2018 (poster) N = 63	■ ICU	■ Inclusion: primary CS or postcardiotomy on AV-ECMO ■ Exclusion: death under VA-ECMO or bridge to long-term device or transplantation	■ Not stated ■ Not stated	■ Not stated ■ IABP use: not stated	■ CS or postcardiotomy ■ Duration not reported	■ Not stated
Jacky et al.[37] 2018 N = 64	■ ICU ■ OR	■ Inclusion: post−cardiac surgery on VA-ECLS ■ Exclusion: age <18 y, VV-right heart ECMO, bridging indication (eg, transplant), palliation (ie, no weaning trial)	■ 65 y ■ 78%	■ CAD (69%), HTN (64%), DM (23%), HF (25%), renal dysfunction (33%), lung disease (19%), valve disease (47%), CM (14%), CHD (31%), PAD (14%), mean SAPS II (51), smokers (59%) ■ IABP use: 26.5% ■ Sicker patients on levosimendan, ie, more sepsis and liver impairment	■ As per multidisciplinary decision ■ Duration not reported	■ Weaning starts when patient is stable during at least 48 h ■ ECLS flow was reduced in steps of 0.5 to 2.5 L/min under minimal inotropic support ■ After specified monitoring, ECLS flow was reduced in steps of 0.5 L/min. After 3 h of hemodynamic stability at 1 L/min, ECLS was removed ■ Successful weaning defined as 24-h survival after removal of ECLS without a need for re-ECLS

(*continued on next page*)

Table 3 (*continued*)

First Author Year Sample Size (N)	Setting	Inclusion Criteria Exclusion Criteria	Mean Age Male Sex	Comorbidities Other Information	ECMO Indication ECMO Duration	Weaning Protocol
Sangalli et al.[38] 2016 N = 10	■ ICU (CT)	■ Inclusion: refractory CS due to AMI and LVEF <25% ■ Meeting institutional criteria for weaning*	■ 62 y ■ 50%	■ HTN (50%), DM (40%), smokers (40%), alcohol (20%), mean SAPS II (54.4) ■ IABP use: not stated	■ Refractory CS due to AMI with LVEF <25% ■ 11.5 d	■ Stepwise reduction of pump flow (0.5 L every 6-24 h), if inotropic score was ≤10 under serial ECHO assessment*
Vally et al.[39] 2019 N = 150	■ ICU (mixed)	■ Inclusion: ICU patients on VA-ECMO ■ Exclusion: age <18 y, VA-ECMO duration <2 d, and central VA-ECMO treatment	■ 53 y ■ Male (65%)	■ CAD (29%), HTN (43%), DM (36%), congestive HF (23%), CKD-HD (10%), COPD (5.3%), smokers (31%), alcohol (20%), mean SAPS II (59.2), mean GCS (12.7), mechanical ventilator (91%), RRT (40%) ■ IABP use: 28% ■ More patients on levosimendan had congestive HF (p = 0.04)	■ CS ■ Reasons: postcardiotomy (32.7%), post-AMI (29.3%) ■ Reasons varied between groups (p = 0.024) ■ 11.6 d	■ VA-ECMO flow gradually decreased to 1-1.5 L/min ■ VA-ECMO was removed when: MAP >65 mmHg; low doses of catecholamine; Pao_2/ Fio_2 ratio >100 mmHg; LVEF >20%; and aortic velocity−time integral >12 cm ■ Weaning failure defined as death during ECMO or as death within 24 h after ECMO removal
Zipfel et al.[40] 2018 (poster) N = 86	■ Not stated	■ All patients needed VA-ECLS	■ 59 y ■ Not reported	■ Not reported ■ IABP use: not stated	■ Any indication for VA-ECLS ■ 182 h vs 216 h (p = 0.21)	■ Not stated

Abbreviations: ABG, arterial blood gas; AMI, acute myocardial infarction; BNP, brain natriuretic peptide; CAD, coronary artery disease; ECHO, echocardiographic; CHD, congestive heart disease; CKD-HD, chronic kidney disease with hemodialysis; CM, cardiomyopathy; COPD, chronic obstructive pulmonary disease; CrCl, ceatinine clearance; CS, cardiogenic shock; CT, cardiothoracic; CV, cardiovascular; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; ELSO, Extracorporeal Life Support Organization; h, hour; ICU, intensive care unit; GCS, Glasgow Coma Scale score; HF, heart failure; HTN, hypertension; IABP, intra-aortic balloon pump; LV, left ventricular; LVEF, left ventricular ejection fraction; NS, not significant; OR, operating room; PAD, peripheral artery disease; RRT, renal replacement therapy; SAPS, simplified acute physiology score; SBP, systolic blood pressure; VA, veno-arterial; VV, veno-venous.

* Author referred to another study: Pappalardo F, Pieri M, Arnaez Corada B, et al.[42] Timing and strategy for weaning from venoarterial ECMO are complex issues. J Cardiothorac Vasc Anesth 2015;29:906-11.

Table 4
Study Interventions and Findings

First Author Year Sample Size (N)	Levosimendan vs Comparator	Levosimendan vs Comparator			
		ECMO Weaning	Mortality	Length of Stay	Other Outcomes
Affronti et al.[34] 2013 N = 17	1. Levosimendan: infused for 24 h before planned weaning at 0.005 then increased up to 0.2 μg/kg/min within 1-2 h (no loading) 2. Traditional inotropes or vasopressors	1. Weaning rate: 83.3% vs 27.3% (p = 0.0498)	1. In-hospital: 33.3% vs 63.4% (NS)	1. ICU: median 18.5 vs 19 days (NS) 2. Hospital: median 28.5 vs 30 d (NS)	1. Inotropic or vasopressor support: 50% vs 100% (p = 0.00294) 2. ECMO-related complications: NS
Distelmaier et al.[35] 2016 N = 240	1. Levosimendan: 12.5 mg in 50 mL of 0.9% NaCl infusion (no bolus) within the first 24 h after initiation of ECMO 2. Traditional inotropes and vasopressors as per weaning strategy	1. Weaning failure: 19.5% vs 33.8%* 2. adj HR = 0.41 (95% CI, 0.22-0.80; p = 0.008) 3. Weaning failure: occurred in 23% of patients (overall)	1. 30-d: 62% vs 74%* 2. adj HR = 0.52 (95% CI, 0.30-0.89; p = 0.016) 3. long-term: adj. HR = 0.64 (95% CI, 0.42-0.987; p = 0.04)	-	■ Inotropic or vasopressor support 24 h post-ECMO: significantly more use and higher dose in levosimendan group
Haffner et al.[36] 2018 N = 63	■ Levosimendan: dose not stated ■ Comparator: control-no levosimendan	■ Weaning failure: 24% vs 20% (Pr = 0.34) Postcardiotomy sub-group: ■ Weaning failure: 12% vs 29% (Pr = 0.9); OR = 0.073 (Pr = 0.92)	■ Mortality: 34% vs 36% (Pr = 0.6)	-	■ Higher assistance duration, longer stay under mechanical ventilation, and longer duration of stay in ICU (levosimendan group)
Jacky et al.[37] 2018 N = 64	■ Levosimendan: started at rate 0.1 μg/kg/h (no bolus) ■ Comparator: milrinone at rate 10 μg/min (range 5-20 μg/min) ■ Both started during ECLS weaning	■ Successful weaning: 92% vs 79% (p = 0.18)	■ 28-d mortality: 35% vs 40% (p = 0.28) ■ 180-d mortality: 50% vs 44% (p = 0.80)	■ ICU: 27 vs 17 d (p = 0.017) ■ Hospital: 33 vs 22 d (p = 0.038)	■ IABP use during weaning: 7.7% vs 40% (p = 0.008) ■ Catecholamine use: no difference in NE use but in epinephrine's, ie, higher dose in levosimendan group
Sangalli et al.[38] 2016 N = 10	■ Levosimendan: started at rate 0.1 mcg/Kg/min (no loading). Infusion was interrupted after 24 h, then weaning test was attempted ■ Comparator: none	■ Successful weaning: in 90% of patients ■ ECMO blood flow reduced from 1.92 to 1.12 L/min/m^2 (p < 0.001)	■ One patient died immediately after decannulation ■ ICU survival rate: 80% (another patient died from septic shock while still in ICU 38 d after decannulation)	-	■ Cardiac index increased from 1.93 to 2.64 L/min/m^2 (p = 0.008) ■ Mixed venous oxygen saturation increased from 66.0% to 71.5% (p = 0.006) ■ Arterial lactate decreased from 1.25 to 1.05 mmol/L (p = 0.004) ■ FMD (absolute value): increased from 0.10 to 0.61 mm (p < 0.001) ■ FMD (%): increased from 3.2% to 17.8% (p < 0.001) ■ Peak blood flow increased from 49.7 to 149.3 mL/S (p = 0.002)
Vally et al.[39] 2019 N = 150	■ Levosimendan: 12.5 mg in 100 mL of 0.9% NaCl at rate 0.2 μg/kg/min (no bolus) for 24 h ■ Administered after 3.2 d after ECMO cannulation ■ Comparator: not specific; catecholamines ± IABP at physician's discretion	■ Weaning: 82.4% vs 61.6% (p = 0.01) ■ HR = 0.16 (0.04-0.7); p = 0.01 (after propensity matching)	■ Survival rate: 78.4% vs 49.5% (p = 0.02) ■ 30-d mortality, HR = 0.55 (0.27-1.1); p = 0.09 (after propensity matching)	-	In levosimendan groups: ■ LVEF increased from 21.5 to 30.7% (p < 0.0001) ■ Aortic velocity−time integral increased from 8.9 cm to 12.5 (p = 0.002)
Zipfel et al.[40] 2018 N = 86	■ Levosimendan: no details ■ Comparator: not stated	■ 64.8% vs 32.6% (p = 0.003)	■ In-hospital survival: 51.3% vs 23.4% (p = 0.005)	-	-

Abbreviations: Adj, adjusted; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; FMD, flow-mediated dilatation; HR, hazard ratio; ICU, intensive care unit; h, hour; NaCl, sodium chloride; NE, norepinephrine; NS, not significant; OR, odds ratio; Pr, probability.

* Provided by the corresponding author.

stated as comparators in two studies,[34,35] milrinone in one,[37] and none or unspecified in the remaining studies[36,38-40] (Tables 3 and 4).

Risk of Bias

All the studies were at risk of bias due to confounding (Tables S5 and S6), which affected the overall judgment of bias for the two main outcomes—VA-ECMO weaning and mortality (Table 5). For VA-ECMO weaning, kappa values for agreement between the two reviewers ranged between 0.731 and 1.00. Although, for mortality, kappa values ranged from 0.432 to 0.632.

Outcomes

VA-ECMO Weaning

VA-ECMO weaning was reported in all studies (n = 630); 336 patients in the levosimendan group and 294 in the comparators group. Successful weaning was found statistically significant in four studies.[34,35,39,40] Overall, levosimendan use was significantly associated with successful weaning compared with the control arm (OR 2.89, 95% CI, 1.53-5.46; $p_{\text{overall effect}} = 0.001$). The higher the weight the more influence it has on the overall measure of heterogeneity; $I^2 = 49\%$; $p = 0.07$) (Fig 2 and Fig S1). The GRADE confidence in this estimate was very low (Table 6). Sensitivity analysis (Table S7, Figs S2 and S3) by excluding the 2two studies[36,40] at critical risk of bias showed comparable results (OR 3.64, 95% CI, 1.59-8.33; $I^2 = 49\%$).

Table 5
Overall Risk of Bias (ROBIN-I)

Domain	ECMO Weaning	Mortality
Bias due to confounding	Critical	Critical
Bias in selection of participants into the study	Serious	Serious
Bias in classification of interventions	Serious	Serious
Bias due to deviations from intended interventions	Low	Low
Bias due to missing data	No information	No information
Bias in measurement of outcomes	Moderate	Low
Bias in selection of the reported result	Moderate	Low
Overall	Critical	Critical

Mortality

All the studies reported the occurrences of death. Six studies (n = 620) were included in the meta-analysis involving 326 patients in the levosimendan group. Pooled results showed a decreased risk of mortality in the levosimendan group (OR 0.46, 95% CI, 0.30-0.71; $p_{\text{overall effect}} = 0.0004$), without apparent heterogeneity among the studies ($I^2 = 20\%$, $p = 0.28$) (Fig 3 and Fig S4). The NNT was five (Table S8). The GRADE confidence in this estimate was very low (Table 6). When the two studies[36,40] at critical risk of bias were removed at the same time, the heterogeneity was reduced to 16% and the results were comparable as well (OR 0.46, 95% CI, 0.28-0.76; $I^2 = 16\%$) (Table S9 and Fig S5).

Other Outcomes

Lengths of stays were reported in three studies.[34,36,37] Only one[37] of them had significant differences in both ICU and hospital lengths of stay, which were longer in the levosimendan group ($p = 0.017$ and $p = 0.038$, respectively). However, levosimendan had favorable effects on other reported hemodynamic[38] and echocardiographic[39] parameters. Intra-aortic balloon pump (IABP) use or need during weaning was significantly less in the levosimendan arm[37] ($p = 0.008$) (Table 4). None of the trials reported adverse drug events.

Publication Bias

The funnel plot illustrates the issue of bias and precision. The funnel plots indicated a reasonable symmetry (Fig. 4 and 5) and a lack of heterogeneity and publication bias in the meta-analyses.

Discussion

This systematic review and meta-analysis of observational studies examined the effectiveness of levosimendan in VA-ECMO weaning in ICU patients. The review included seven studies that compared levosimendan with control, including traditional vasoactive drugs, milrinone, or none. The included studies were of small size and enrolled patients from various settings, with the majority being recruited after cardiac surgery. Pooled data showed that treatment with levosimendan in patients on VA-ECMO was associated with significant VA-ECMO weaning success and lower risk of mortality.

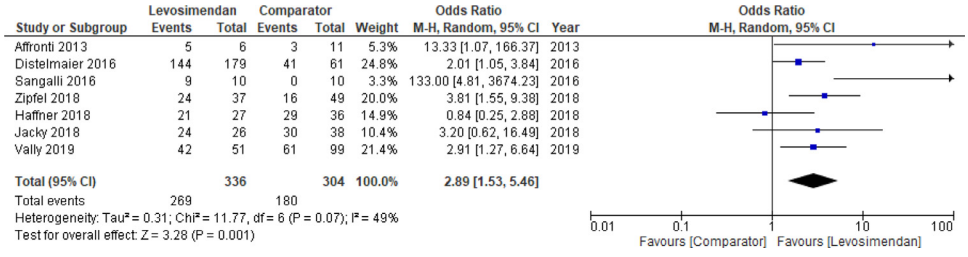

Fig 2. Forest plot—veno-arterial extracorporeal membrane oxygenation weaning success.

Table 6
GRADE Quality Assessment

Outcome	No. of Studies	Quality Assessment					Summary of Findings (Sof)				Quality
		Risk of Bias (Limitations)	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients		Relative effect (95% CI)	Absolute Risk (95%)	
							Levo	Usual Care		Levo / Usual Care	
VA-ECMO Weaning	7	Serious*	Very serious†	Not serious	Very serious	Strongly suspected	336	294	OR 2.89 (1.53-5.46)	801 per 1,000 / 592 per 1,000	Very low ⊕◯◯◯
Mortality	6	Serious*	No serious	Not serious	Serious	Undetected	326	291	OR 0.46 (0.30-0.71)	491 per 1,000 / 574 per 1,000	Very low ⊕◯◯◯

GRADE Working Group grades of evidence: High quality: The authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: The authors are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: The authors' confidence in the effect estimate was limited: The true effect may be substantially different from the estimate of the effect. Very low quality: The authors have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Imprecision was decided based on the 95% confidence interval, ie, the range of relative treatment effect around the no-effect line.
Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; Levo, levosimendan; No., number; OR, odds ratio; RR, relative risk.
* Serious limitations. Failure to adjust for confounders.
† Serious inconsistency. Point estimates vary widely across studies; CIs show minimal overlap; heterogeneity test shows a low p value; I^2 is large.

VA-ECMO is a contemporary life-saving intervention that allows hemodynamic stability, restores tissue perfusion, and allows the myocardium to resume its physiologic functions. However, the challenge after myocardial recovery is weaning from this device.[6] A study suggested that early weaning should be attempted because both VA-ECMO duration and bleeding complications were predictors of poor outcomes.[42] Moreover, the pioneer study on the timing of VA-ECMO discontinuation encouraged weaning from VA-ECMO after 48-to-72 hours due to the lack of additional benefits afterward.[43] In this systematic review, weaning from VA-ECMO was the primary outcome of interest as, in the authors' opinion, it would be more reflective of the patient's management course during the ICU stay. The underlying cause of mortality in ICU patients is highly alterable and usually is affected by diverse factors. Thus, surrogate endpoints may be alternative indicators of treatment effect that may improve its sensitivity.[44] In this systematic review, successful weaning from VA-ECMO and mortality rates were reported in the seven included studies and ranged from 65% to 92% in the levosimendan group, as compared with 27% to 88% in the comparators group. Likewise, mortality rates ranged from 20% to 62%, as compared with 36% to 77%, respectively. In a nationwide Japanese study[45] on VA-ECMO patients (n = 5,263), the rate of weaning was 64.4%, with an in-hospital mortality rate of about 65% for all underlying diseases. However, weaning from VA-ECMO was not always associated with in-hospital survival. The reported mortality was ≥38% for the successively weaned patients.

The use of levosimendan to facilitate weaning was first reported by Affronti et al., who found that the 24-hour pretreatment with levosimendan before beginning VA-ECMO weaning was associated with successful weaning and reduced need for inotropic or vasopressor support, but without reducing in-hospital mortality rate or length of hospital stay.[34] Distelmaier et al. administered levosimendan during the first 24 hours of VA-ECMO initiation after cardiovascular surgery. Weaning failure, 30-day mortality, and long-term mortality were significantly less. However, the use of inotropes or vasopressors 24 hours after VA-ECMO was significantly more with higher doses of levosimendan.[35] A study conducted by Sangalli et al. prospectively investigated the effect of levosimendan on endothelial function and hemodynamic parameters in cardiogenic shock patients. This was the only study in this systematic review that did not have a comparator group. Levosimendan was administered for 24 hours before attempting to wean from VA-ECMO. Successful weaning and survival rate were reported in 90% and 80% of the patients, respectively, in addition to the improvements in endothelial function and hemodynamics.[38] The protective effects of levosimendan on endothelium function and its anti-inflammatory potential probably are beneficial while using VA-ECMO, which may provoke a proinflammatory effect and endothelial damage.[39] Jacky et al. were the first to compare levosimendan use during VA-ECMO weaning with a specific inotrope, milrinone, in a historic group of patients after cardiac surgery. The study showed significant benefit of levosimendan in terms of less IABP use during weaning, but without significant effects on

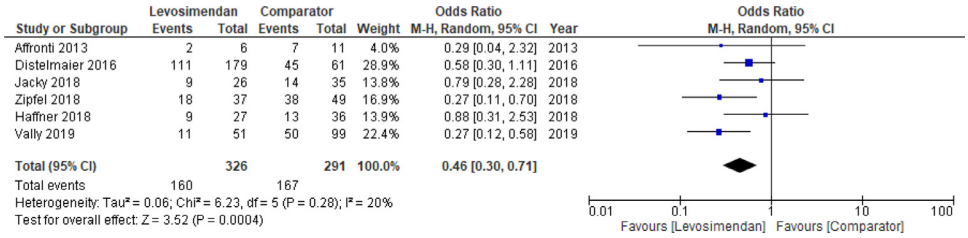

Fig 3. Forest plot—mortality.

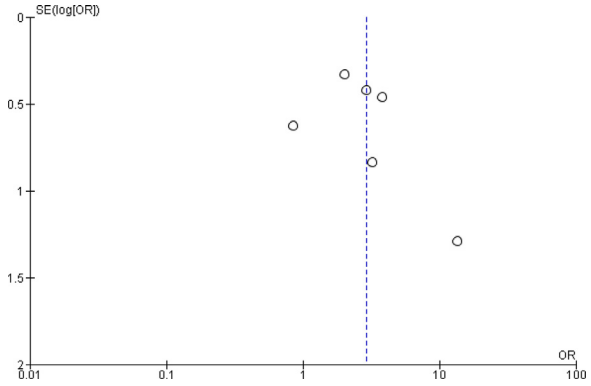

Fig 4. Funnel plot—veno-arterial extracorporeal membrane oxygenation weaning success.

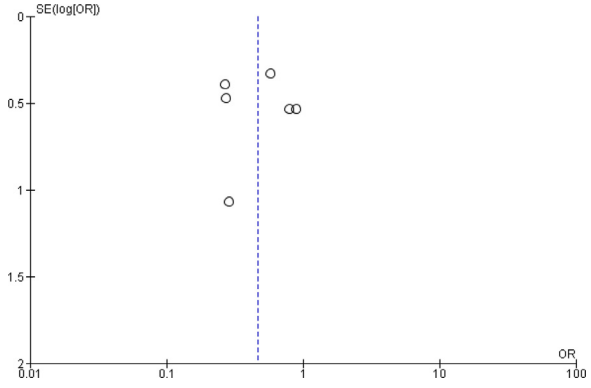

Fig 5. Funnel plot—mortality.

successful VA-ECMO weaning or mortality. Patients on levosimendan had longer ICU and hospital lengths of stay. However, there were more patients with sepsis and liver failure.[37] Recently, Vally et al. conducted a study in which levosimendan was administered within 3.2 ± 2.8 days after VA-ECMO cannulation and included surgical and nonsurgical patients. The inotropes in both arms were administered at the physicians' discretion. Levosimendan had a beneficial effect on weaning but not on mortality after propensity score matching, which may be attributed to the lack of study power.[39]

Silvestri et al. published a poster for a meta-analysis of four studies[34,35,37,39] (n = 471) in August 2019, and suggested that levosimendan use improves weaning success in cardiogenic shock. They reported a success rate of 82% versus 65% (OR 1.27, CI, 95% 1.13-1.4; $p < 0.01$, $I^2 = 26\%$) as compared with the control group.[46] While writing the manuscript of this systematic review, Burgos et al. published their systematic review and meta-analysis (n = 557)[47] to answer a similar question. They included all the studies selected in this systematic review except two recent studies.[36,38] To the best of the authors' knowledge, these two meta-analyses were the first full reports that pooled data to investigate the effectiveness of levosimendan in VA-ECMO weaning. Prior meta-analyses examined the efficacy and/or safety of levosimendan use in various medical settings and conditions, such as low-cardiac-output syndrome,[12] acute heart failure,[48] cardiac surgery,[49-51] cardiogenic shock,[52] and coronary revascularization.[53] Levosimendan, in this systematic review and the recent one,[47] was associated with successful VA-ECMO weaning (OR 2.89, 95% CI, 1.53-5.46; $p_{\text{overall effect}} = 0.001$, $I^2 = 49\%$) and (risk ratio [RR] 1.42, 95% CI, 1.12-1.8; $p_{\text{for effect}} = 0.004$, $I^2 = 71\%$, respectively) and much lower risk of mortality (OR 0.46, 95% CI, 0.30-0.71; $p_{\text{overall effect}} = 0.0004$, $I^2 = 20\%$) and (RR 0.62, 95% CI, 0.44-0.88; $p_{\text{for effect}} = 0.007$, $I^2 = 36\%$, respectively). Furthermore, levosimendan improved hemodynamic and echocardiographic parameters. Due to the suspicion of bias, that is, methodologicissue and dubious eligibility, the two posters[36,40] were excluded from the second meta-analysis of this study, resulting in improved overall effects for both VA-ECMO weaning and mortality. This systematic review presented other important surrogate endpoints. However, pooling their data was not feasible.

The authors of this review and Burgos et al. have evaluated the RoB using different assessment tools ie, ROBIN-I tool[27,28] and Newcastle-Ottawa scale (NOS), respectively.[54] In this systematic review, the RoB assessment of the included studies ranged from moderate to critical for both VA-ECMO weaning and mortality (Tables S5 and S6). The overall RoB was rated as critical for both outcomes due to the critical bias of confounding (Table 5). Burgos et al. assessed the methodologic strength of the studies using the NOS. They developed a "star system" to rate each study on three broad perspectives. The studies' quality ranged from 6six-to-nine stars, with nine stars representing the highest level and six stars representing high quality.[47] It is not surprising to reach an opposite conclusion, which is explained by using tools with different approaches for RoB assessment. The disagreement is more overt specifically when at low and high levels of RoB, as was shown in one study that compared the performance of different tools in 28 cohort studies.[55] The frequently used NOS[54] is a composite scoring scale that assesses the quality of cohort and case-control studies. The Cochrane-proposed ROBIN-I[27,28] is a domain-based tool to assess RoB in nonrandomized studies of interventions and a wide variety of observational designs. The

agreement between the two tools in the previously mentioned study[55] did not show a good correlation for overall RoB. Although 86% of the studies can be considered at serious RoB according to ROBINS-I, 75% of the studies would be at low RoB when the NOS was applied. Both tools differ in most aspects of usability such as scoring time, coverage of the tool, loss of information, and ease of consensus. For example, NOS requires shorter scoring time, which may explain its common use, although ROBIN-I is more demanding about the information and the details needed to be assessed. In addition, it has a broader scope, which means a more comprehensive analysis of the studies as compared with NOS. The detailed algorithm of ROBIN-I probably was the reason for its better performance in the overall RoB judgment as compared with other tools.[55] Finally, another study[56] concluded that numeric rating scales could not identify studies at increased risk of bias and may have led to imprecise estimates of treatment effect. The domain-based RoB assessment is gaining more popularity over the use of numeric scales,[55] as it provides a more structured framework for qualitative decision-making on the overall quality, and for the detection of possible sources of bias within the studies and the body of evidence under review. This is necessary as the quality of evidence may differ across the reported outcomes of the same study, with some being more subject to bias than other outcomes.[56] Additionally, in this systematic review, the certainty in the body of evidence was rated as very low for both outcomes on the GRADE system (Table 6). The quality of evidence in a systematic review is essential as it is a reflection of the extent of confidence that an estimate of effect is correct.[57]

This systematic review had some limitations. The observational aspect of the included studies with their inherent methodologic limitations subjected them to bias and confounding.[58] In a conservative approach, random effect model was used to reduce the impact of this limitation and the potential bias in the estimates. Publication and selection biases affect the small studies, which usually have lower methodologic quality; thus leading to the so-called small-study effects that cause larger treatment effects, that is, overestimate of the true effect.[57,59] This precludes having definitive conclusions. Although the funnel plots in this review were almost symmetrical, suggesting a low probability of reporting bias, there were fewer than ten included studies. In addition, this meta-analysis pooled data of a heterogeneous population, surgical and nonsurgical, into one overall effect estimate. However, data from the Extracorporeal Life Support Organization (ELSO) registry showed equal proportions of both patients' groups, about 50% each.[60] Other heterogeneous aspects included lack of universal VA-ECMO weaning definition or protocol across the included studies; improvement of VA-ECMO experience during recent years; various dosing regimens and timing of administration of levosimendan; and failure in describing details of inotropes or IABP use. For example, as previously mentioned, VA-ECMO weaning outcome was defined in only three studies,[35,37,39] two of them[35,39] defining weaning failure as death during VA-ECMO support or death 24 hours after VA-ECMO removal, whereas one[37] defined successful weaning as 24-hour survival after VA-ECMO removal without the need for repeat VA-ECMO. Thus, the discrimination between mortality on VA-ECMO and after VA-ECMO weaning was not be conclusive. Due to the limitations of this systematic review, the results and conclusions of the analysis must be taken with caution. Well-designed randomized trials are awaited to support the favorable effects of levosimendan in VA-ECMO weaning. Randomized trials also are needed to address other aspects of VA-ECMO weaning, such as optimal dosing and timing of inotrope administration. A registered, randomized controlled, double-blind, multicenter trial (NCT04158674) investigating weaning failure, but not survival, in patients with severe chronic heart failure in acute decompensation is under way.

Conclusion

Levosimendan may offer a valid option to facilitate successful weaning from VA-ECMO and to lower the risk of mortality. The currently available evidence suggests the advantages of levosimendan use in improving endothelial function, hemodynamics, and echocardiographic parameters, especially in the absence of major adverse effects. However, the results should be considered to establish a hypothesis for adequately powered randomized controlled trials to confirm the conclusions of these results.

Acknowledgments

The authors thank Dr Klaus Distelmaier and Dr Georg Goliasch for their support in providing additional data of their published study.

Conflict of Interest

All the authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.01.019.

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