OPEN

Repeated Levosimendan Infusions in the Management of Advanced Heart Failure: Review of the Evidence and Meta-analysis of the Effect on Mortality

Simona Silvetti, MD, PhD, Piero Pollesello, PhD,† and Alessandro Belletti, MD‡*

Abstract: In the latest years, several studies described the impact of repetitive/intermittent i.v. levosimendan treatment in the management of advanced heart failure. For this updated review, we systematically searched the literature for clinical trials, registries, and real-world data and identified 31 studies that we commented in a narrative review: 3814 patients were described, of whom 1744 were treated repetitively with levosimendan. On the basis of the nature of the study protocols and of the end points, out of those studies, we further selected 9 that had characteristics, making them suitable for a meta-analysis on mortality. This short list describes data from 680 patients (of whom 399 received repeated doses of levosimendan) and 110 death events (of which 50 occurred in the levosimendan cohort). In the meta-analysis, repetitive/intermittent therapy with i.v. levosimendan was associated with a significant reduction in mortality at the longest time point available: 50 of 399 (12.5%) versus 60 of 281 (21.4%) in the control arms, with a risk ratio of 0.62 (95% confidence interval, 0.42–0.90; $P < 0.01$). In a sensitivity analysis, removing each trial and reanalyzing the remaining data set did not change the trend, magnitude, or significance of the results. A visual inspection of the funnel plot did not suggest publication bias. The results provide a very strong rationale for continuing to investigate the repetitive use of levosimendan in patients with advanced heart failure by properly powered regulatory clinical trials. Meanwhile, it seems that the use of repetitive/intermittent i.v. levosimendan infusions has become one of the few effective options for preserving the hemodynamic and symptomatic balance in such patients.

Key Words: advanced heart failure, repetitive treatment, inodilator, mortality, levosimendan

Received for publication August 25, 2023; accepted October 23, 2023.

From the *Neonatal and Pediatric Intensive Care Unit, Department of Critical Care and Perinatal Medicine, IRCCS Istituto Giannina Gaslini, Genova, Italy; †Content and Communication, Orion Pharma, Espoo, Finland; and ‡Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy.

P. Pollesello is full-time employee of Orion Pharma where the inotrope levosimendan was discovered and developed. The remaining authors report no conflicts of interest.

Correspondence: Piero Pollesello, PhD, Content and Communications, Branded Products, Orion Pharma, Espoo, Finland (e-mail: piero.pollesello@orionpharma.com).

(*J Cardiovasc Pharmacol*™ 2024;83:144–157)

INTRODUCTION

Advanced heart failure (AdHF) may be characterized as a condition in which patients have severe and persistent symptoms of heart failure (broadly corresponding to New York Heart Association [NYHA] class IIIb or IV) with severe functional impairment, end-organ involvement, and recurrent hospitalizations for decompensation despite being maintained on optimized heart failure (HF)-related medical therapy, including (but not limited to) diuretics, beta-blockers, angiotensin-focused therapies, and mineralocorticoid antagonists. A full exposition of the diagnostic criteria for AdHF has recently been published by the Heart Failure Association of the European Society of Cardiology.[1]

AdHF is a condition characterized by considerable clinical instability and risk. Recurrent unplanned hospitalizations is a common feature, and intravenous inotropic therapy has an established role in the restoration of hemodynamic stability in these episodes.[2] Beyond that, there has been a notable expansion in the use of intermittent intravenous therapy either for prolonged symptom relief, as a "bridge" to heart transplantation (HTx) or the installation of a mechanical left ventricular assistance device (LVAD), or as part of a palliative regimen for patients who are ineligible for transplantation or an LVAD.[3–6]

Levosimendan is primarily indicated for the management of acute decompensated heart failure but—in the 20 years since it was first approved for clinical use—a series of clinical studies have examined the impact of recurrent intermittent infusions in AdHF. As recently discussed by Altenberger et al,[7] this inodilator drug enhances cardiac contractility through a calcium sensitization action exerted on cardiac troponin C, although its action in opening ATP-dependent potassium channels in vascular smooth muscle causes vasodilatation. This combination of actions produces a well-characterized hemodynamic response that includes enhancement of cardiac index/output and reductions in systemic blood pressure and pulmonary capillary wedge pressure. Use of repetitive/intermittent levosimendan in AdHF to prevent reacutization events has also been encouraged by the fact that the drug hemodynamic effects may persist for >7 days after a 12–24 hours of infusion because of the formation of a pharmacologically active metabolite (designated OR-1896) with a longer half-life.

In the latest years, a considerable number of new trials described the impact of repetitive/intermittent i.v.

levosimendan treatment in the management of AdHF. Therefore, we considered it appropriate to update a previous meta-analysis we had published some years ago[8] and consolidate the experiences of the latest studies to identify trends and general principles that can guide the use of repeated infusions of levosimendan in AdHF.

For this review, we systematically searched for clinical trials, registries, and real-world clinical studies in which repetitive levosimendan was used in adult patients with a diagnosis of AdHF, identified those suitable for a narrative review, and on the basis of the nature of the study protocols and of the end points, further select the ones to introduce in a meta-analysis on the mortality data. We then performed such analysis at the longest available period described in the included studies.

METHODS

Search Strategy

Pertinent studies were independently searched for in CENTRAL, Google Scholar, MEDLINE/PubMed, Scopus, and the Cochrane Central Register of clinical trials (updated August 30, 2023) by 2 of the authors. Our primary search strategy aimed to include any study ever performed in which levosimendan was intermittently administered in patients with AdHF. In addition, we employed backward snowballing (ie, scanning of references from the retrieved articles and other pertinent reviews) to obtain further studies. The search strategy on PubMed was broad and encompassed all articles on "levosimendan" with a filter applied on "clinical." No language restriction was enforced. This systematic review and meta-analysis was registered on June 15 in the international prospective register of systematic reviews PROSPERO at the National Institute for Health and Care Research (identifier CRD42023429364).

Study Selection for the Narrative Review and for the Meta-analysis

References obtained from database and literature searches were first independently examined at a title/abstract level by 2 authors, with divergences being resolved by consensus. Then, if potentially pertinent, they were retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: studies describing the use of intravenous repetitive administration performed in AdHF patients, with no restrictions either on dose or time of administration, or on the nature of the protocol (prospective, retrospective, blinded, presence of a control arm, registry, case series). The exclusion criteria were duplicate publications either acknowledged or not (in this case we referred to the article with the longest follow-up period available); non-adult patients; case reports with 3 patients or less; and oral administration of levosimendan. In the further selection of the studies to be included in the meta-analysis, the following inclusion criteria were used: prospective study, random allocation to treatment; mortality as end point; and comparison of levosimendan versus any control. Two investigators independently assessed compliance with selection criteria and selected studies for the final analysis, with divergences being resolved by consensus.

Data Abstraction and Study

Baseline and outcome data were independently abstracted by the 2 authors, with divergences being resolved by consensus. Specifically, we extracted potential sources of significant clinical heterogeneity, such as study design, sample size, clinical setting/indication, bolus and infusion doses of levosimendan and duration of treatment, control treatment, and follow-up duration, as well as rehospitalization data. The primary end point of our meta-analysis was the mortality at the longest available checkpoint in the study.

Internal Validity and Risk of Bias Assessment

The internal validity of and risk of bias in the included trials was appraised by 2 independent investigators according to the latest version of the "Risk of bias assessment tool" developed by The Cochrane Collaboration,[9] with divergences being resolved by consensus. Visual inspection of a funnel plot was performed to assess the presence of publication bias.

Data Analysis and Synthesis

Dichotomous data were extrapolated to compute the individual and pooled risk ratio (RR) with pertinent 95% confidence interval (CI) using the Mantel–Haenszel method. We used a fixed-effects model since in the presence of low statistical inconsistency ($I^2 \leq 25\%$). Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing. The hypothesis of statistical heterogeneity was tested by means of the Cochran Q test, with statistical significance set at the 2-tailed 0.10 level, whereas the extent of statistical consistency was measured with I^2, defined as $100\% \times (Q - df)/Q$, where "Q" is Cochran heterogeneity statistic and "df" is the degrees of freedom.

Sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining data set (performing a new analysis after the removal of each study).

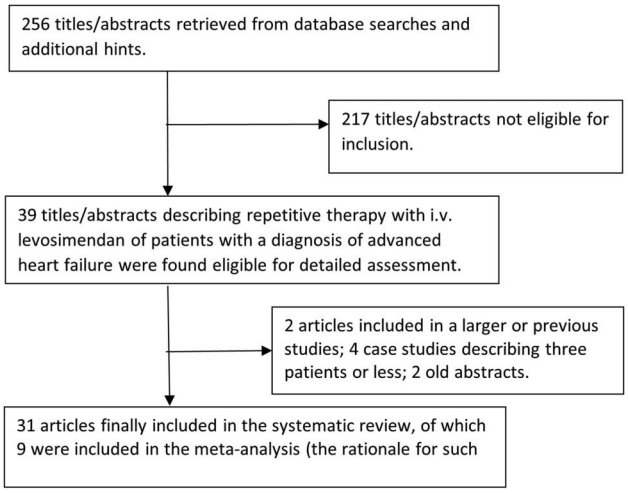

FIGURE 1. Flow diagram for selection of the relevant data from the literature.

Unadjusted *P* values are reported throughout. All data were analyzed according to the intention-to-treat principle whenever possible. Data were analyzed using Review Manager version 5.4.1 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2020). This study was performed in non-Cochrane mode but in compliance with Appendix S1 of The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10–12]

RESULTS

Study Selection

Our search strategy yielded a total of 256 articles. After exclusion of the nonpertinent titles or abstracts, 31 data sets were retrieved and assessed according to the selection criteria (Fig. 1). For the purposes of the systematic review, we further differentiated them between (1) randomized control trial (RCT) (n = 9) that report comparative data for levosimendan versus other interventions, including mortality effects and (2) reports of studies (n = 22) that provided data about the efficacy and safety of repetitive use of levosimendan but used noncomparative/unblinded/unrandomized protocols and/or did not report mortality data.

All 31 studies were considered for the systematic review, whereas only the RCT were used for the meta-analysis. Within each category, we addressed and reviewed the studies in chronological order, starting with the earliest. The selected studies are listed in Tables 1 and 2, stratified according to the classification as described.

Review of the RCT Reporting Mortality Data

Mavrogeni et al[13]

In this 6-month, prospective, randomized, open-label study, 50 patients with AdHF (NYHA class III or IV, with established left ventricular [LV] dysfunction) were randomized to levosimendan or a usual-care control group. Levosimendan was given monthly as a 24-hour infusion (6 μg/kg as a 10-minute i.v. bolus and then as a continuous infusion varying from 0.1 μg/kg initially to 0.2 μg/kg if tolerated).

Mortality at the end of the study was significantly lower in the levosimendan group (2 deaths vs. 8; $P < 0.05$), and a larger proportion of patients in the levosimendan group reported improvement in symptoms (dyspnea and fatigue) at that time (65% vs. 20%; $P < 0.001$). The levosimendan group also had a significant increase in LV ejection fraction versus controls (28% ± 7% vs. 21% ± 4%; $P = 0.003$) and significant improvements in other metrics of LV function.

Berger et al[14]

Using selection criteria guided by the findings of the COPERNICUS trial,[15] 75 patients with AdHF (left ventricular ejection fraction [LVEF] <35%; NYHA class IIIb or IV) who were intolerant to bisoprolol titration to the target dose of 20 mg/day were randomized to a monthly 24-hour infusion of levosimendan (0.1 μg/kg/min/24 hours, with or without loading dose according to initial systolic blood pressure [SBP]; n = 39) or a chronic infusion with PGE_1 (2.5 ng/kg/min, titrated according to SBP; n = 36) for 3 months.

During 12 weeks of treatment, the mean dosage of bisoprolol increased from 4 to 10 mg/day in all patients who completed the study (levosimendan, n = 27; PGE_1, n = 32; $P < 0.0001$). The combined end point of death or urgent HTx or implantation of a ventricular assist device was reached by 12 levosimendan patients (31%) and 4 PGE_1 patients (11%; $P = 0.04$), and more patients in the levosimendan group experienced worsening of HF status (29 vs. 16; $P = 0.008$). However, at the 1-year follow-up, the combined end point was no longer statistically significant (levosimendan, n = 2; PGE_1, n = 15), and in both groups, there were significant improvements in LVEF ($P < 0.05$) and NYHA clinical status ($P < 0.0001$).

TABLE 1. Summary Listing of RCTs Reporting the Effect of Repetitive Levosimendan in AdHF With Mortality as an Outcome

References	Publication Date	Study Acronym	Total Patients	Treated With Repeated Levosimendan	Mortality as an Outcome/ Longest Time-Point	Comparator	NCT Trial Identifier
Mavrogeni et al[13]	2007		50	25	Yes/6 mo	Yes/standard treatment	
Berger et al[14]	2007		75	39	Yes/1 y	Yes/PGE1	
Kleber et al[16]	2009		28	18	Yes/8 wk	Yes/placebo	
Malfatto et al[17]	2012		33	22	Yes/1 y	Yes/furosemide	
Bonios et al[18]	2012		63	21*	Yes/6 mo	Yes/dobutamine	
Altenberger et al[19]	2014	LevoREP	120	63	Yes/24 wk	Yes/placebo	01065194
Comin-Colet et al[20]	2018	LION-HEART	69	48	Yes/150 d	Yes/placebo	01536132
Garcia-Gonzalez et al[21]	2021	LAICA	97	70	Yes/1 y	Yes/placebo	00988806
Pölzl et al[22]	2023	LeoDOR	145	93	Yes/180 d	Yes/placebo	03437226
Sum of Table 1			**680**	**399**			

The numbers in bold represents sums of entries.
*Levosimendan-only group versus dobutamine ± levosimendan.

TABLE 2. Summary Listing of Studies of Repetitive Levosimendan in AdHF That Were Nonblinded, Nonrandomized, or Noncontrolled or Which did Not Explore Mortality as an Outcome

References	Publication Date	Total Patients	Patients Treated With Repeated Levosimendan	Mortality as a Specified Outcome	Comparator	Protocol§
Spargias et al[24]	2003	20	9	Yes	Yes*	Prospective
Nanas et al[25]	2005	36	18	Yes	Yes	Consecutive
Parissis et al[26]	2006	25	17	No	Yes	RCT
Parle et al[27]	2008	44	44	No†	No	Prospective
Papadopoulou et al[28]	2009	20	20	No	No	Prospective
Drakos et al[29]	2009	162	29‡	Yes	Yes	Prospective
Tuomainen et al[30]	2013	13	13	No	No	Prospective
Tasal et al[31]	2014	29	13	No	Yes*	Consecutive
Hübner et al[32]	2015	86	15	Yes	No	Consecutive
Ortis et al[33]	2017	50	25	Yes	Yes	Retrospective
Oliva et al[34]	2018	185	185	Yes	No	Registry
Masarone et al[35]	2020	15	15	No	No	Consecutive
Wawrzyniak et al[37]	2021	4	4	No	No	Case series
Masarone et al[36]	2022	30	30	Yes	No	Prospective
Barras et al[38]	2022	84	42	Yes	Yes	Retrospective
Wechsler and Schwinger[39]	2022	178	19	No	No	Retrospective
Dobarro et al[40]	2023	403	403	Yes	No	Registry
Reis et al[41]	2023	24	24	Yes	Yes	Consecutive
Książczyk et al[42]	2023	46	16	Yes	Yes	Registry
Wang et al[43]	2023	63	63	No	No	Prospective
Bagudá et al[44]	2023	1015	238	Yes	Yes	Registry
Cholley et al[45]	2023	602	103	No	No	Registry
Sum of Table 1		**3134**	**1345**			
Sum of Tables 1 and 2		**3814**	**1744**			

The numbers in bold represents sums of entries.
*Comparator group received a single course of levosimendan.
†Death recorded.
‡Arm receiving only repetitive levosimendan.
§Nature of the study protocol: RCT, prospective, retrospective, consecutive, case series, data from registry.

Kleber et al[16]

This randomized, placebo-controlled, double-blind, parallel-group study conducted at centers in Germany and Sweden, which explored hemodynamic effects of levosimendan in patients (n = 28) who had symptoms consistent with NYHA class III–IV HF because of pulmonary hypertension despite optimized medical therapy.

Levosimendan was delivered as a loading dose of 12 μg/kg over 10 minutes and then infused for 24 hours at a rate of 0.1–0.2 μg/kg/min. Treatment was subsequently repeated for 4 cycles at 2-week intervals (0.2 μg/kg/min/6 hours).

The primary end point of the study was the intergroup difference in pulmonary vascular resistance between baseline and 24 hours. There was a mean decrease in pulmonary vascular resistance of 12% ± 9% in the levosimendan group and a mean increase of 25% ± 11% in the placebo group ($P = 0.009$).

Malfatto et al[17]

In this randomized, open-label study, 33 patients with AdHF who had been hospitalized for heart failure at least twice in the past 6 months were assigned to either levosimendan (n = 22) or furosemide (n = 11) group. Levosimendan was administered at a rate of 0.1 μg/kg/min (to a total dose of 12.5 mg) with 4 cycles of treatment being delivered at 4-week intervals. Furosemide infusions were started at a rate of 2 mg/h and then titrated according to urinary output and other criteria to a maximum dose of 250 mg/24 hours.

Levosimendan infusion improved left ventricular performance (measured by echocardiography) and favorably modulated neurohormonal activation (primarily brain natriuretic peptide [BNP] levels). No similar trends were seen in the furosemide group. One-year mortality was higher in furosemide-treated patients (4/11 [36.4%]) than in the levosimendan group (4/22 [18.2%]).

Bonios et al[18]

Sixty-three patients with treatment-refractory NYHA class IV HF and histories of recent hospitalization for cardiac decompensation were enrolled in this open-label study. After initial hemodynamic stabilization and weaning from dobutamine (where used), patients were assigned at random to intermittent infusions of either (a) levosimendan (0.3 μg/kg/

min); (b) dobutamine (10 mg/kg/min); or (c) levosimendan (0.2 μg/kg/min) plus dobutamine (10 mg/kg/min). Six-hour infusions of assigned therapies were administered weekly over a 6-month period. Patients also received regular administrations of amiodarone to suppress possible inotrope-related proarrhythmic effects.

Patients were followed for a mean of 11.1 ± 12.0 months after the initiation of study therapy. At 3 months, event rates for the primary end point of death or urgent implantation of an LVAD were 10% in the levosimendan group, 38% in the dobutamine group ($P = 0.047$ vs. levosimendan), and 49% in the levosimendan+ dobutamine group ($P = 0.006$ vs. levosimendan). The respective rates at 6 months were 20%, 52% ($P = 0.037$ vs. levosimendan), and 57% ($P = 0.009$ vs. levosimendan), respectively. No significant intergroup differences were noticed for the 6-month event rates of the secondary end point of death, elective or urgent LVAD implantation, or hospitalization for HF decompensation.

Altenberger et al[19] (LEVO-Rep Study)

This prospective, randomized, double-blind, placebo-controlled, 3-country study enrolled patients with chronic HF (NYHA class III or IV) diagnosed at least 3 months previously. Patients had to have an LVEF of ≤35%, a walking distance of <350 m in the 6-minute walk test (6MWT), and had to be in receipt of individually devised neurohormonal therapy. The total study period was 6 months, which comprised a 6-week treatment period and a further 18 weeks of follow-up. During the treatment period, 63 of120 patients received 4 cycles of levosimendan (infused on an ambulatory basis for 6 hours at 0.2 μg/kg/min) at 2-week intervals. Response to therapy was assessed at the conclusion of follow-up.

No treatment effect was seen on the primary combined end point of proportion of patients showing a ≥20% improvement in the 6MWT and a ≥15% increase in Kansas City Cardiomyopathy Questionnaire score or on either component of that end point.

Comin-Colet et al[20] (LION-HEART Study)

Sixty-nine patients enrolled at 12 centers in Spain were randomly assigned at a 2:1 ratio to levosimendan or placebo groups. Levosimendan was given as a 6-hour i.v. infusion (0.2 μg/kg/min without bolus) every 2 weeks for 12 weeks. Sixty-one patients (88%) received all the scheduled drug infusions, with a cumulative mean levosimendan dose per patient of 30.3 ± 8.9 mg.

The primary end point was the treatment effect on serum NT-proBNP compared with placebo, considered as the area under the curve of the NT-proBNP values (expressed as pg/day/mL) throughout treatment. Calculations based on 826 measurements identified that the proportion of patients experiencing a clinically relevant reduction in NT-proBNP levels (defined as >25% reduction from baseline) was significantly higher in the levosimendan group (48% vs. 9%; $P = 0.002$ by Fisher exact test), that the baseline-adjusted area under the curve of NT-proBNP levels over time was significantly smaller in patients treated with levosimendan (344×10^3 vs. 535×10^3 pg/day/mL; $P = 0.003$), and that the percentage of intergroup change in baseline-adjusted NT-proBNP was highly statistically significant ($P < 0.001$).

Among secondary end points, there was a marked and highly significant reduction in the rate of HF hospitalization among patients treated with levosimendan (hazard ratio [HR] 0.25; 95% CI, 0.11–0.56; $P = 0.001$ vs. placebo).

Garcia-Gonzalez et al[21] (LAICA Study)

A total of 97 patients with AdHF were randomized in this multicenter, randomized, double-blind, placebo-controlled, clinical trial. Levosimendan was administered to 70 patients as a continuous 24-hour i.v. infusion (0.1 μg/kg/min) once monthly for 1 year. The mean cumulative dose of levosimendan per patient was 110 ± 79 mg delivered in a median of 13 doses.

Treatment with levosimendan was associated with an overall event rate of 33% for the primary end point (rehospitalization for acute decompensated HF requiring admission to an emergency department or hospital ward for >12 hours, or clinical deterioration of underlying HF) compared with a rate of 44% in the placebo group ($P = 0.286$). The intergroup difference in the incidence of hospital readmissions for acute decompensated HF remained >12% at follow-up to 6 months (25.7% vs. 40.7%; $P = 0.147$) and 12 months (32.8% vs. 44.4%; $P = 0.28$).

For the aggregated end point of acute decompensation of HF and/or death, the cumulative event incidences followed a similar trajectory, with significatively lower rates in the levosimendan group at 1 and 3 months (5.7% vs. 25.9%; $P = 0.004$% and 17.1% vs. 48.1%; $P = 0.001$, respectively); similar trends were also recorded up to 1-year follow-up (34.2% vs. 59.2% at 6 months; $P = 0.025$% and 41.4% vs. 66.6% at 12 months; $P = 0.022$).

Time-to-event analysis (Kaplan–Meier curves) showed benefits from levosimendan throughout the study for the outcomes of time from randomization to first hospitalization for acute decompensated HF and time from randomization to death, but only the latter was statistically significant (log rank: 4.06; $P = 0.044$). The cumulative incidence of death at each time point was lower in the levosimendan group than in the placebo group but did not achieve statistical significance at any time or overall (8.5% vs. 22.2%; $P = 0.08$).

No clinically relevant differences in tolerability or adverse events were noted between the 2 treatment groups, and no new safety signals for levosimendan were observed.

Pölzl et al[22] (LEODOR Study)

LEODOR was a multicenter, randomized, double-blind, placebo-controlled study (see protocol in Pölzl et al[23]), and the results have been very recently published.[22] The premise of the study was that repetitive administration of levosimendan in the discharge period immediately following hospitalization for cardiac decompensation in AdHF will be associated with greater clinical stability compared with placebo over the course of 14 weeks. Patients were randomized into 3 arms and received either a 6-hour infusion of levosimendan every

2 weeks or a 24-hour infusion every 3 weeks, over the course of 12 weeks, or matching placebo. The 2 levosimendan arms could be coanalyzed versus placebo.

A global rank end point was developed in which all participants were ranked across 3 hierarchical groups, that is, (1) time to death or urgent HTx or implantation of LVAD, (2) time to any nonfatal HF event requiring i.v. vasoactive therapy, and (3) time-averaged proportional change in NT-proBNP from baseline to 14 weeks. A follow-up visits was scheduled also at week 26 after the commencement of therapy.

Due to an interim interruption of the study as a result of the COVID-19 pandemic, the planned number of patients could not be recruited. The final mITT analysis included 145 patients, 93 in the combined levosimendan arms and 52 in the placebo arm. Patient characteristics were similar between treatment and placebo arms, but no statistical difference was recorded in the composite primary end point (mean rank score of 72.9 for the levosimendan group vs. 73.1 for the placebo group; $P = 0.99$), making analysis of the secondary end points aleatory.

From the safety perspective, the number of investigator-reported adverse events during and immediately after drug application was 12.4% in the levosimendan group versus 11.8% in the placebo group (NS, $P = 0.9$), and the cumulative mortality data at the longest available time (end of week 26) in the treated patients of the combined levosimendan arms was 13 of 93 and 5 of 52 in the placebo arm (NS, $P = 0.6$).

Review of the Noncomparative/ Nonrandomized/Nonmortality Studies

Spargias et al[24]

The first contribution to the literature in this category involved treating 20 patients with acute decompensation of end-stage heart failure with a single course of levosimendan (0.1 μg/kg/min/24 hours; no bolus) and then repeating the treatment up to 7 more times at 4- to 8-week intervals in the 9 patients who showed what were described as a "markedly favorable clinical response" to the first course of therapy.

Pre- versus postanalyses showed improvement in NYHA status ($P = 0.007$) and in some hemodynamic indices. There was 1 unplanned hospital admission in patients who received multiple courses of therapy, compared with 4 in the 11 patients who did not receive more than the initial course of levosimendan. There were 3 deaths in the repetitive subgroup versus 4 in the nonrepetitive subgroup, but 2 of the 3 deaths in the repetitive subgroup were in patients whose later course(s) of levosimendan were unplanned and given in response to unplanned admission for decompensated HF. The 3 patients who received most courses of levosimendan (4, 7, or 8 infusions) had a dramatic improvement in symptomatic status and remained stable during follow-up.

Nanas et al[25]

This study enrolled 36 patients with systolic dysfunction and AdHF (NYHA class IV) refractory to standard therapy who were admitted for cardiac decompensation. Standard therapy was continued in all patients. Eighteen patients were treated with continuous dobutamine—10 μg/kg/min i.v. for 48 hours (longer if needed)—and then with an 8-hour daily infusion for the next 3 days and with weekly infusions thereafter. The other 18 patients were treated similarly but with the further addition, after the initial 24-hour infusion of dobutamine, of a 6-mg/kg i.v. bolus of levosimendan, followed by a 24-hour infusion at 0.2 μg/mg/kg, then similar levosimendan infusions (without bolus) every 2 weeks thereafter.

Forty-five-day survival rates were 6% in the dobutamine-only group and 61% in the patients who also received levosimendan ($P = 0.0002$; log-rank test). The median duration of survival was 16 days in the dobutamine-only group and 45 days in the dobutamine plus levosimendan group; 1 in 18 patients in the dobutamine-only group survived to 45 days compared with 11 in 18 in the combination treatment group ($P = 0.0002$; log-rank test).

Parissis et al[26]

In this open-label study, AdHF patients were randomized to 5 repetitive infusions with levosimendan (n = 17) or placebo (n = 8) at 3-week intervals. Sixteen of the 18 patients assigned to levosimendan received infusions at a rate of 0.1 μg/kg/min and 2 received them at a rate of 0.2 μg/kg/min. Patients were assessed before and 24 hours after each infusion cycle and again 30 days after the final infusion. Patients were well matched at baseline for demographic indices.

Responses to levosimendan were consistent with the drug being associated with improvements in multiple indices of left ventricular geometry and performance and with corresponding improvements in biomarkers of myocardial injury and neurohormonal and immune activation. At the final assessment, improvement in NYHA functional status was apparent only in the levosimendan group. By contrast, 6 of the 8 patients in the control group required increased doses of furosemide in response to deterioration of clinical symptoms.

Parle et al[27]

Forty-four patients with AdHF (LVEF ≤35% plus BNP ≥150 ng/L) who failed to respond to other medical measures were treated by levosimendan infusion (optional 10-minute i.v. bolus of 6–12 μg/kg then a continuous 24-hour infusion started at a rate of 0.1 μg/kg/min and titrated hourly up to 0.4 μg/kg/min according to hemodynamic response and to a total dose of 12.5 mg). Six of the 156 infusions were coadministered with dobutamine. All patients were reported to have received maximally tolerated doses of all established HF medications. Most patients (n = 21) received 2 infusions of levosimendan and most of the rest received 3 or 4 infusions. (1 patient received 26 infusions over 2 years.)

The distribution of NYHA class at the outset was class IV, 58% and class III, 41%. At the completion of 48 months of observation, the distribution had changed to class IV, 19%; class III, 43%; and class II, 37%. A patient who received 4 infusions improved sufficiently to be removed from the transplant list. Average BNP levels 5 days after an infusion fell from 1081.1 ± 176.0 to 703.3 ± 84.8 ng/L ($P < 0.01$).

Levosimendan was judged to be well tolerated: 130 of 156 infusions were completed without an adverse event. Symptomatic hypotension was recorded in 12 infusions and resolved upon discontinuation in 7. Three of the 7 patients who died had received no other inotropes. The minimum time between last infusion of levosimendan and death in these 3 cases was 22 days.

Papadopoulou et al[28]

This study in 20 patients with AdHF examined the effect of levosimendan (0.1 mg/kg/min/24 hours monthly for 6 months) on patient-assessed quality of life measured by the Left Ventricular Dysfunction-36 (LVD-36) questionnaire, the Minnesota Living with Heart Failure Questionnaire (LIhFE), and the Specific Activity Questionnaire. Compared with pretreatment baseline, the LIhFE score improved (ie, reduced) from 35.4 ± 18.6 to 22.2 ± 13.0 ($P < 0.0001$). Similarly, the LVD-36 score improved (ie, reduced) during levosimendan treatment (52.6 ± 26.2 at baseline vs. 27.4 ± 17.3 at 6 months; $P < 0.0001$). Improvement in Specific Activity Questionnaire score was also statistically significant (4.2 ± 1.6 at baseline vs. 4.7 ± 1.3 at 6 months; $P < 0.05$), although that scale addresses strenuous activity of a kind unusual for patients with severely symptom-limited physical function.

Drakos et al[29]

This study included 162 patients presenting with decompensated end-stage chronic HF who were refractory to standard therapy but could be weaned from an initial 24- to 72-hour infusion of an inotropic agent. One hundred forty participating patients were then assigned in a nonrandomized manner to inotropic therapy with dobutamine (10 mg/kg/min/8 hours; n = 83) or levosimendan (0.3 μg/kg/min also over 8 hours; n = 29) or a combination of both (n = 29), at weekly intervals for 6 months. Oral amiodarone (40 mg thrice daily for 3 days at the outset; 200 mg twice daily thereafter) was given throughout the study to both those sets of patients. The remaining 22 patients, acting as controls, were treated with optimal conventional therapy. Mean duration of follow-up was 12 ± 17 months.

Six-month and 1-year survival rates were significantly higher in patients assigned to inotropes than to optimal conventional therapy (51% vs. 18% and 36% vs. 9%, respectively; $P = 0.001$ for both). No significant differences were apparent in 1-year survival rates for patients assigned to dobutamine, levosimendan, or combination inotrope therapy (35.4% vs. 48.3% vs. 32.1%, respectively).

Tuomainen et al[30]

The effects of 3 intermittent 24-hour infusions of levosimendan (0.2 μg/kg/min; no bolus) were explored in 13 patients with what was described as "moderate to severe congestive HF" (NYHA class II–III). Blinding and randomization were not reported and are assumed not to have occurred. There was an improvement in patient-assessed quality of life after the first treatment that persisted but did not increase with further infusions but no statistically significant improvement in objective physical exercise capacity (VO_2). Plasma natriuretic peptide levels fell during each infusion, but the reductions were not sustained.

Tasal et al[31]

A series of 29 patients with an average age of 60.2 ± 7.4 years were recruited to this study. Participants had acute decompensated HF, with LVEF <35% and conspicuous H-related symptomatology (NYHA III/IV) despite use of i.v. diuretics and vasodilators. All patients received levosimendan as 6 μg/kg bolus followed by a continuous infusion of 0.1 μg/kg/min/24 hours. This treatment was repeated at 1 and 3 months in 13 patients, and pre-versus-post comparisons were made between those patients and the 16 patients who received only a single dose of levosimendan. All measurements were made 3 days after treatment, with the final set of measurements made at 6 months.

A significant enhancement of baseline NYHA functional status and myocardial performance was apparent only in the patients who received multiple courses of levosimendan treatment ($P = 0.03$ and $P < 0.001$ respectively). Similarly, significant reductions in brain natriuretic peptide ($P < 0.01$) and plasma interleukin-6 ($P = 0.05$) levels were also achieved only in the patients given repeated levosimendan treatment. No patient died in either group.

Huebner et al[32]

These authors described a retrospective, single-center registry exercise in which data on 117 patients who were high-urgent candidates for heart transplant were examined. The authors concluded that "intermittent inotropes in high-urgent patients are an adequate strategy as a bridge to transplant" but did not give details of inotrope usage beyond noting that levosimendan was mostly infused at a rate of 0.1 μg/kg/min/24 hours (without a loading dose) at 2-month intervals.

Ortis et al[33]

This was a retrospective study in which outcomes were assessed over 12 months in 25 AdHF patients who were eligible for levosimendan but did not receive it and in 25 others for whom intermittent levosimendan was initiated as a continuous infusion at 0.1–0.2 mg/kg/min, to a total dose of 12.5 mg. The mean infusion time for levosimendan was 32.8 hours. Patients underwent a mean of 4.12 infusions at a mean interval of 56 days and with a mean interval between baseline and last infusion of 7.1 months. Use of intermittent levosimendan was associated with biochemical, hemodynamic, and clinical stability, whereas patients who did not receive it continued on a trajectory of rising serum NT-proBNP levels, declining left ventricular function, deteriorating NYHA status, and increased frequency of hospitalizations (43 vs. 17 during 12 months of follow-up; $P < 0.009$).

Oliva et al[34] (RELEVANT-HF Study)

RELEVANT-HF was a registry study conducted at 7 high-volume cardiovascular centers. The enrolled cohort comprised 185 patients with AdHF (NYHA class III–IV with ≥2 HF hospitalizations/emergency visits in the previous 6 months and systolic dysfunction; INTERMACS score ≥4) despite optimal medical management who were treated with levosimendan infusions (0.05–0.2 μg/kg/min/24 hours with no initial bolus) every 3–4 weeks for 6 months. The average

total administered dose of levosimendan was 62 ± 29 mg, with 44% of infusions administered either at home or in a hospital day-case setting.

Prespecified clinical outcomes were favorably influenced by levosimendan in a pre-versus-post comparison. An ancillary analysis suggested that direct costs based on infusion setting were on average lower by €1157 ± 8676 during the 6 months of levosimendan therapy compared with the preceding 6 months ($P = 0.053$).

One year after the start of levosimendan therapy, 141 patients were alive and 128 were still receiving repeated scheduled infusions. Twelve had stopped treatment, and 26 had died. One-year overall survival was 86%, whereas event-free survival (meaning free from death or urgent HTx or LVAD installation) was 76%.

Masarone et al 2020[35] and 2021[36]

These 2 studies were designed to evaluate the effects of levosimendan in AdHF patients after infusions of relatively short duration (6–8 hours). In both of these investigations, levosimendan was infused at a rate of 0.2 μg/kg/min to a total dose of 6.25 mg. The duration of infusion was thus 6–8 hours depending on patient body weight. Infusions were repeated at 2-week intervals.

In the 2020 study[38] conducted in 15 patients with confirmed systolic AdHF, there were 3 hospitalizations during 12 months of follow-up, compared with 12 in the 12 months before treatment ($P < 0.05$). There were no deaths during that time and no indication that repeated use of levosimendan was associated with an increased burden of ventricular arrhythmias. Performance in the 6MWT was modestly enhanced (Δ40 m; $P < 0.05$).

In their later research,[39] the same investigators explored the hemodynamic effects of a median of 18 infusions per patient in 30 patients with AdHF.

Echocardiographic data indicated significant ($P < 0.05$) improvements in multiple indices of contractile function, including (but not limited to) stroke volume, cardiac output, and cardiac index. There were accompanying signs of improvement (ie, reductions) in various indices of congestion, including left atrial pressure, mean pulmonary artery pressure, and inferior vena cava diameter ($P < 0.01$ for all).

Wawrzyniak et al[37]

In this case series, aimed to show indications for the use of levosimendan in various settings, repetitive levosimendan infusions were found to be safe and effective in 4 patients and seemed to prolong the time of clinical stability, although they did not alter the eventual natural history of HF, with increasing frequency of hospitalizations and rising natriuretic peptide levels.

Barras et al[38]

This retrospective study examined the impact of repeated infusions of levosimendan at the lowest recommended dose (0.05 μg/kg/min/24 hours) in 42 patients who received an average of 4 cycles of therapy at approximately monthly intervals. Responses were compared with a propensity-matched cohort of control patients identified from >400 candidates. The study end point of event-free survival was attained by 28 levosimendan-treated patients compared with 11 controls (HR 0.31; 95% CI, 0.17–0.59; $P < 0.001$), principally as a result of greater hospitalization-free survival with levosimendan (HR 0.25; 95% CI, 0.11–0.6; $P = 0.002$). No baseline variables were statistically associated with 1-year clinical outcome, but at 3 months, survivors in the levosimendan group who were event-free at 1 year were more likely to be taking beta-blockers (96.4% vs. 60%; $P = 0.012$) and to be doing so at the target dosage (33% ± 20% vs. 18% ± 20% target dose; $P = 0.036$). They also had lower heart rates (71.6 ± 10.4 vs. 81 ± 14 beats/min; $P = 0.039$).

Wechsler and Schwinger[39]

Data from 178 patients (mean age of 73 ± 13 years) were collected and grouped according to whether levosimendan was given once or repetitively. Repetitive dosing was given to 19 patients (between 2 and 11 applications for a total of 47 applications, mean time between the repetitive dosing 133 days), with a total of 225 applications (178 once + 47 repetitive applications). The ejection fraction measured by echocardiography improved significatively more in the repetitive group ($P < 0.05$). Levosimendan treatment was associated with significant reduction of NT-BNP, NYHA class, and bodyweight in all groups. No adverse side effects (eg, rhythm disorder, hypotension, electrolyte disorder) were seen.

Dobarro et al[40] (LEVO-D Registry)

This multicenter retrospective study analyzed data from 403 patients with an average age of 71 years diagnosed with advanced heart and considered by attending physicians to need optimal medical therapy. Patients who were candidates for transplantation or LVAD were excluded, as were patients with de novo HF or who underwent any procedure, which might improve prognosis. Most patients (77.9%) recorded at least 1 admission for HF during the year before the first use of levosimendan.

Three strategies for levosimendan use were identified: bailout (40.2% of patients, defined as levosimendan administration after clinical judgement of deterioration without a prespecified protocol); fixed number (33.3% of patients, defined as a fixed number of doses during a prespecified period) and "sine die" (26.5% of patients, when the drug was started and given intermittently within a prespecified period between doses but with no declared stopping point). Most patients remained within the same strategy during follow-up.

Two hundred ninety-five patients survived 1 year after the start of levosimendan therapy, and 176 patients (43.7% of the total cohort) were classified as responders to levosimendan. Compared with the previous year, the period of levosimendan therapy was associated with significant reductions in HF admissions (38.7% vs. 77.9%; $P < 0.0001$), unplanned HF visits (22.7% vs. 43.7%; $P < 0.0001$), or combined HF events including deaths (56.3% vs. 81.4%; $P < 0.0001$). It is not clear from the original report if this finding related only to a before-and-after comparison among patients classified as levosimendan responders or was a whole-cohort comparison. No influence of levosimendan dosing strategy on outcome was identified, leading the authors to surmise that "a bailout

approach might be enough for this population." The authors also developed a score to predict likely response to levosimendan, based on beta-blocker and amiodarone use, prior transcatheter edge-to-edge repair, HF visit in the previous year, heart rate >70 bpm, and hemoglobin >12 g/dL.

Reis et al[41]

These authors documented single-center experience with 24 consecutive advanced HF patients referred for intermittent, intravenous, outpatient administration of levosimendan over 3.25 years ending in March 2021. Their central conclusion was that "repeated levosimendan administration in advanced HF patients is a safe procedure and was associated with a reduction in HF hospitalizations."

Most of the patients, who had mean LVEF 24% and >1 (median) HF-related hospitalizations in the preceding 6 months, received levosimendan as a bridge to transplantation or in response to clinical deterioration. At 6-month follow-up, there was a large and significant reduction in the proportion of patients classifies as NYHA class IV (down from 52.2% to 12.5%, $P = 0.025$) and an improvement of average LVEF (from 24.0% to 29.7%, $P = 0.008$). The median number of HF-related hospitalizations per patients fell to 0.4 ± 0.7 ($P < 0.001$ vs. prelevosimendan). NT-proBNP levels were also reduced significantly (from 8812.5 to 3807.4 pg/mL, $P = 0.038$) and whole enhancements recorded various dimensions of exercise capacity, including peak oxygen uptake ($P = 0.043$) and VE/VCO2 slope ($P = 0.040$).

Książczyk et al[42]

This prospective observational study at cardiology centers in Lodz and Gdansk, Poland was conducted between 2015 and 2018. The 46 inpatients enrolled fulfilled the following criteria for AdHF: (1) symptomatically NYHA class III or IV; (2) LVEF ≤30%; (3) (a) congestion requiring i.v. diuretics or (b) low output requiring inotropes or vasoactive drugs or (c) malignant arrhythmias causing >1 visit or hospitalization in the past 12 months. All patients received i.v. levosimendan (0.1 μg/kg/min) over 24–48 hours to 12.5 mg or the maximum-tolerated dose. Most patients (n = 30) received single infusion (the "nonrepetitive" subgroup), and 16 patients (the "repetitive" subgroup) received >1 infusion (to a maximum of 4, delivered at 2–4 weeks of intervals [n = 4]).

The end point of death or HTx or left ventricular assist device (LVAD) therapy within 1 year of follow-up occurred in 16 patients (53%) in the nonrepetitive contingent and 6 patients (38%) in the repetitive subgroup; hospitalizations occurred in 10 patients (33%) versus 4 patients (25%), respectively. In Kaplan–Meier analysis, the nonrepetitive subgroup was characterized by a markedly higher risk of death compared with the repetitive subgroup (HR, 6.63; 95% CI, 1.96–22.41; $P = 0.002$). The median survival time for the 2 subsets was respectively 57 (38–64) days and 145 (82–185) days.

Wang et al[43]

A group of 63 patients with advanced HF with reduced ejection fraction (LVEF <40%) were stratified according to sinus rhythm (SR, n = 34) or atrial fibrillation (AF, n = 29) status. All patients received 6 cycles of intermittent repeated levosimendan infusion, delivered according to center-approved protocol (total dose 12.5 mg, delivered i.v. at 0.05–0.2 μg/kg/min over 24–48 hours, and repeated every 2–4 weeks for 3 months).

After completing levosimendan treatment, LVEF, BNP, and resting HR were significantly decreased ($P < 0.05$) in both patient subgroups with no significant differences between the 2 groups. Further before and after comparisons revealed that after 6 cycles of levosimendan infusion, NYHA classification and left ventricular end-diastolic diameter were significantly improved in the SR subgroup only ($P < 0.05$).

There was no significant difference between patients with different resting HR either in the SR group or in the AF group. Wang et al interpreted these data as indicating that the absence of SR (or more specifically the presence of AF) need not limit the use of repetitive levosimendan in advanced HF with reduced ejection fraction patients and nor, a priori, prejudice the clinical response to such therapy.

Bagudá et al[44] (LEVO-T Registry)

This registry on repetitive ambulatory levosimendan as a bridge to HTx retrospectively examined data from all patients listed for elective heart transplant over a 5-year period in 14 centers in Spain. Of the 1015 patients included, 238 received levosimendan more than once (the average was 6 cycles per patient).

The proportion of patients experiencing HF hospitalizations were similar for patients who started levosimendan in the first 30 days after listing (33.6%) and those who did not (34.5%), but among those not treated with levosimendan, 102 patients were switched to levosimendan after an HF admission and thereafter had a marked reduction in hospitalization frequency (from 0.57 admissions per month before levosimendan and 0.21 afterward).

Outcome analysis based on matched propensity scores found no differences in survival at 1 year after listing between patients receiving levosimendan and those who did not (HR, 1.03; 95% CI, 0.36–2.97; $P = 0.958$) or in survival after hypertension (HR, 0.97; 95% CI, 0.60–1.56; $P = 0.958$). The authors concluded that levosimendan seems to be safe in transplant-listed patients, despite their poor clinical profile and might therefore be used to promote clinical stability while waiting for a transplant.

Cholley et al[45] (France-Levo Registry)

FRANCE-levo is a prospective, observational, cohort study created to profile the current indications, dosing regimens, and side effects of levosimendan, as well as patient outcomes over a year in French cardiology centers. The 602 enrolled patients represented more than one-quarter of national annual levosimendan use in France. To be noticed that the study included 36 patients (6%) younger than 18 years. Patients were being treated with levosimendan for cardiogenic shock (n = 250), decompensated heart failure (n = 127), for prevention of treatment cardiac surgery–related low cardiac output prophylaxis or treatment (n = 86), and weaning

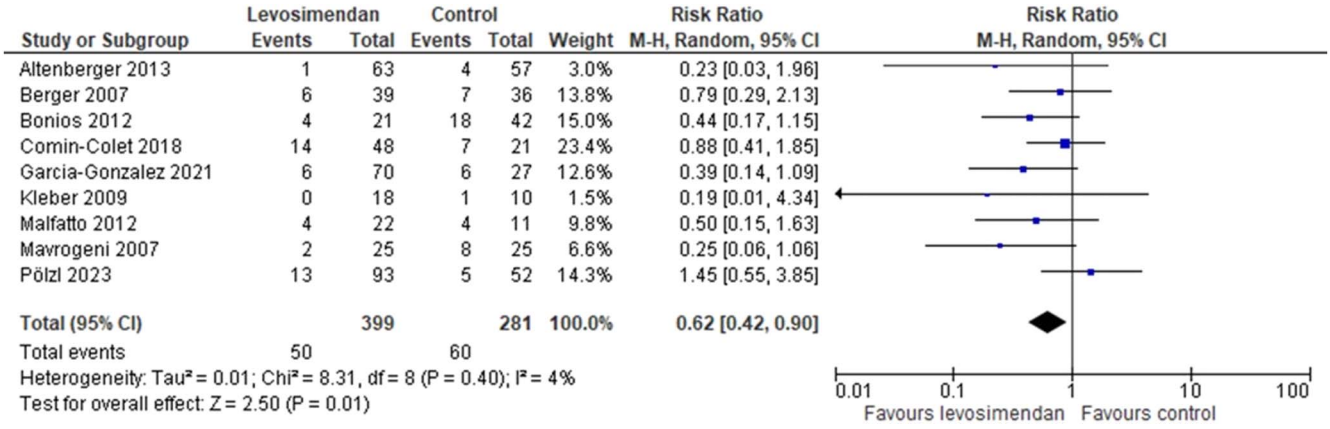

FIGURE 2. Forest plot of the mortality data at the longest period available for levosimendan-treated versus comparator-treated patients.

from venoarterial extracorporeal membrane oxygenation (n = 82).

Use of levosimendan bolus was limited (n = 45; 7.5%). A minority of patients (n = 103; 17.1%) received repeated infusions; the median number of infusions was nevertheless recorded as 4 with a median dose interval of 21 days (range, 4–96 days) and an average dose per infusion of 18.1 ± 6.4 mg. Of note, only 20% of patients admitted for decompensated heart failure had repeated levosimendan infusions (no patient in this group was <18 years of age), with only 4% electively readmitted for that purpose. Most patients (n = 461; 76.6%) also received inotropes and/or vasoactive agents. Use of these drugs, as represented by the vasoactive inotrope score tended to increase in the weeks preceding levosimendan treatment and decrease afterward, suggesting a favorable effect of levosimendan on hemodynamic stability.

Hypotension was recorded in 218 patients (36.2%), being most conspicuous among patients with cardiogenic shock (108; 43.2%), and AF in 85 patients (14.1%, including 45 [18%] with cardiogenic shock and 14 [17.1%] weaning from extracorporeal membrane oxygenation); 17 unspecified serious adverse events were recorded in 14 patients (2.3% of the population). In all, 136 patients (22.6%) died in hospital, with cardiogenic shock with multiorgan failure being the most common cause (n = 66; 11%). A further 26 patients died between hospital discharge and day 90.

Meta-analysis of the Mortality Data

The overall pooled analysis shows that the use of levosimendan was associated with a significant reduction in mortality at the longest time point available in the 9 studies considered (ranging from 8 weeks to 1 year, see Table 1): 50 of 399 (12.5%) in the levosimendan arms versus 60 of 281 (21.4%) in the control arms, RR 0.62; 95% CI, 0.42–0.90; $P = 0.01$, $I^2 = 4\%$ (Fig. 2).

Removing each trial and reanalyzing the remaining data set did not change the direction, magnitude, or significance of the results (Table 3). Visual inspection of the funnel plot (Fig. 3) did not suggest the presence of publication bias.

DISCUSSION

Commentary on the non-comparative/non-randomized/non-mortality Studies

The size, design, and nature of several of these trials are illustrative of the ways in which investigators working in a robust ethical framework seek to explore possible new therapeutic applications of a relatively new drug approved for a specialized or niche indication, as levosimendan was at the time. The lack of blinding, randomization, and a comparator treatment (either active or placebo) in various of these studies is to be expected, but the limitations on analysis arising from these design features has to be acknowledged. Therefore, it is appropriate to regard these studies as exploratory and experimental.

Despite those limitations, some general principles may be extracted from these early investigations in AdHF. It is, for example, a recurring finding that repeated infusions of levosimendan leads to clinical stabilization of patients with AdHF and that the drug was well tolerated in that application. Moreover, trends in clinical status, indices of left ventricular function and hemodynamics, and biochemistry/neuropeptide profiles altered in directions consistent with the pathophysiology model of AdHF then extant. This consistency of trend

TABLE 3. Sensitivity Analysis: Significance and Magnitude of the Result When Removing Each Trial One by One and Reanalyzing the Remaining Data set

Study Removed [Ref.]	RR	95% CI	*P*	I^2 (%)
Mavrogeni et al[13]	0.68	0.45–0.97	0.03	0
Berger et al[14]	0.60	0.38–0.90	0.02	13
Kleber et al[16]	0.62	0.42–0.93	0.02	10
Malfatto et al[17]	0.62	0.40–0,95	0.03	14
Bonios et al[18]	0.65	0.42–0.99	<0.05	9
Altenberger et al[19]	0.64	0.43–0.94	0.02	6
Comin-Colet et al[20]	0.56	0.36–0.86	0.008	3
Garcia-Gonzalez et al[21]	0.66	0.44–0.99	<0.05	5
Pölzl et al[22]	0.54	0.36–0.80	0.002	0

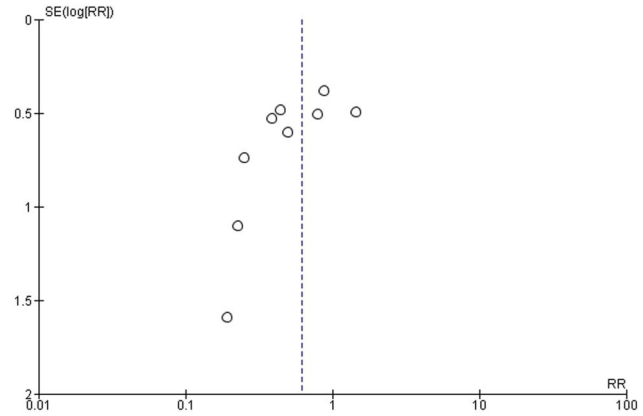

FIGURE 3. Funnel plot of the mortality data at the longest period available for levosimendan-treated versus comparator-treated patients.

supports a cause–effect relation between the use of levosimendan and the outcomes recorded.

Given that it is numerically the largest study in this section of our analysis, RELEVANT-HF[34] is a notable contribution to levosimendan research in AdHF and produced encouraging results. The RELEVANT-HF investigators conceded, however, that without a control arm, it was impossible to exclude the possibility that their results may have been a function of frequent clinical visits, strict monitoring, and constant therapy adjustments, rather than an explicit direct effect of levosimendan. Adverse events data in RELEVANT-HF were somewhat at variance with other experience from the same era (see, eg, Parle et al[27]), in that infusion-related adverse events occurred in a relatively high proportion of patients (n = 23 [12.4%]), with ventricular arrhythmias (n = 16 [8.6%]) rather than with hypotension (n = 4 [2.2%]), the preponderant finding. Overall, however, the reported tolerability profile was consistent with experience in other studies and broadly reassuring, especially given the parlous general health status of the patients.

Interesting is the profiling of a subset of levosimendan "super responders" (patients in whom LVEF increased by ≥20% during treatment) by Ortis et al.[33]

Clinical and biomarker findings from the 2 studies of Masarone et al[35,36] add to an overall picture of improved ventricular function, plus relief of congestion and enhancement of physical functioning. Recently, larger registries[40,44,45] collected safety data, confirming the overall tolerability of levosimendan in HF patients.

Commentary on the RCTs Reporting Mortality Data

The array of benefits identified in these studies fortifies interest in the use of intermittent levosimendan as an inotropic therapy for AdHF. Nevertheless, these investigations were individually too small to confirm conclusively many of the benefits reported: researchers involved in these investigations were quick to acknowledge the limitations of their work. Points of interest to emerge from these investigations included the apparent facilitation of beta-blocker use in the work of Berger et al[14] and the potential of a levosimendan–dobutamine combination recorded by Bonios et al.[18] A case remains for a trial of this intervention to avert full decompensation and the associated hospitalizations and loss of cardiac contractile reserve.[46]

Also of note is the verdict by Berger et al[14] that administration of levosimendan was more convenient than the use of PGE_1 and that safety and tolerability data also favored levosimendan. With imminent patent expiry likely to erode cost differentials, the time may be right, therefore, to revisit this use of levosimendan in a larger trial.

Across these studies, safety and tolerability data for levosimendan were in line with expectation, with event rates within the usual ranges and no new or unexpected findings. It deserves repetition that all patients in these studies were a priori in a fragile state of health and usually recipients of multiple HF-related medications (as well, in many instances, as an array of other medications). The consistent and predictable tolerability and safety findings with levosimendan are thus an important aspect of the drug's suitability for use in AdHF.

The controlled studies described are among the most searching assessments of levosimendan in AdHF to be completed to date. However, it will be apparent from the descriptions of each that they were conducted when there was still no settled view about the optimal dose, frequency and timing of levosimendan in this indication, or about whether distinct and clinically identifiable subsets of patents were particularly promising (or unpromising) candidates for this therapy. The plurality of end points selected for these studies is in part a reflection of those uncertainties. As a result, each study produced indications of possible benefit across a range of outcomes without delivering statistically compelling evidence of benefit.

Specific methodological or technical issues sometimes militated against conclusive outcomes. For example, LAICA[21] recruited fewer than 100 of a planned 213 patients, leaving the study substantially underpowered. Despite that limitation, the intergroup differences in event rates and the significant improvement in survival during 12 months of treatment are striking findings supportive of the use of levosimendan.

LION-HEART[20] provides a clear demonstration of the practicality and feasibility of intermittent levosimendan therapy. The NT-proBNP data may be seen as a signal of possible therapeutic benefit from levosimendan. The HF hospitalization data are compatible with that view, but HF hospitalization was a secondary end point. More generally, proper consideration must be given to the circumspection of the LION-HEART investigators themselves, who characterized their research as a "small pilot study." The results are therefore perhaps best considered as indicative and/or hypothesis generating, albeit that they conform to, and corroborate, trends seen in other studies.

The average dosage of levosimendan administered in LEVO-Rep[19] was only 14 mg—considerably less than that in LION-HEART[20] and LAICA.[21] This may explain the lack of a robust effect on the primary end point (which trended in favor of levosimendan but not significantly so). Lacking an effect on the primary end point, caution is appropriate when

assessing the difference in event-free survival at 24 weeks (17.4% in the levosimendan group vs. 35.1% placebo group; OR 0.39; 95% CI, 0.15–0.98; $P = 0.037$).

We express regret that the ambitious international study LEODOR[22] was cut short by the COVID-19 pandemic. The involvement of 30 centers in 10 European countries (Austria, Italy, Spain, Germany, Slovenia, Hungary, Sweden, Finland, Denmark, and Switzerland) has certainly been a laudable effort to collect evidence in a properly powered and innovative study. The results of this study were not supportive of the study hypothesis, albeit with no significant effect on the primary end point, leaving many questions unanswered.

Limitations of the Meta-analysis

Several limitations must be considered when assessing our investigation: First, the heterogeneous population described in the 9 selected studies should be taken into consideration when interpreting the results of the meta-analysis.

Second, the heterogeneous selection of comparators in the studies is of some concern: placebo was used in 5 studies, and dobutamine, furosemide, and PGE1 in 1 study each. In 1 study, levosimendan was compared with standard treatment. As an additional note of caution to the reader, we highlight that in all the studies considered, levosimendan was used in the context of the prevailing standard of care, which itself may have evolved during the years under review.

Third, the different time point of the collection of mortality data (from 8 weeks to 1 year) is a limitative factor in the interpretation of the mortality effect of repetitive levosimendan. Four, the heterogeneous dosing and intervals of administration of levosimendan must be seen as a limitation.

Fifth, the assessment of the patients was nonblinded in some studies: Bonios et al[18] and Malfatto et al[17] adopted randomized assignment but open-label protocols, whereas Mavrogeni et al[13] conducted an open-label study. On the positive side, the remaining 6 RCTs, which in aggregate accounted for 79% of the patients and 65% of the mortality events in our meta-analysis, were double-blind trials.

As it regards the meta-analysis methodology, quality appraisal of the studies and risk of bias were not systematically evaluated but a complete descriptive analysis of the quality of each study is reported in the text. However, because the results of a meta-analysis are meant to shed light on the overall safety and efficacy of a drug and to help in powering future clinical trials,[47] we consider our results useful as providing a strong rationale for a properly powered study on the effect of levosimendan on mortality in patients with AdHF.

CONCLUSIONS

Our literature search identified 31 studies that were reviewed and commented in this systematic analysis: a total of 1744 AdHF patients were treated with repetitive i.v. levosimendan. From our initial selection, we further identified 9 studies that had characteristics making them suitable for a meta-analysis on mortality. In the 680 patients included in those 9 studies, repetitive/intermittent therapy with i.v. levosimendan (n = 399) was associated with a significant reduction in mortality at the longest time point available (RR = 0.62; 95% CI, 0.42–0.90; $P < 0.01$). This central finding was robust in sensitivity analysis, and a visual inspection of the funnel plot identified no indications of publication bias.

A recent clinical trial on the use of repetitive levosimendan infusions in patients with pulmonary hypertension in the presence of heart failure with preserved ejection fraction (PH-HFpEF)[48] was not included because this diagnosis does not match with AdHF. Not included were also the data supporting the "bridge-to-transplant" use of levosimendan (see recent update by Masarone et al[49]). As it regards the future, a new RCT is ongoing on the repetitive use of levosimendan in ambulatory heart failure patients: we noticed that the study protocol is already published.[50]

Finally, it should be noted that although clinical trials of interventions in AdHF have tended to focus on reducing mortality and/or rehospitalisation,[51] many patients value quality of life and symptom relief over longevity,[52] and the use of levosimendan in this context is supported by results from any of the investigations examined in this review. In a recent article, Elsherbini et al[53] meta-analyzed studies on intermittent levosimendan infusions in ambulatory patients with end-stage HF and described the association of this therapy with less frequent cardiovascular death alongside with improved NYHA class, quality of life, BNP levels, and LV function.

Repetitive/intermittent i.v. levosimendan infusions appear to be one of the few effective options for AdHF patients with frequent hospitalization for hemodynamic and symptomatic imbalance,[54] and it has been adopted in clinical practices across the world.[55,56] Despite some methodological limitations, our results therefore encourage continued investigation of the repetitive use of levosimendan in AdHF patients in properly powered regulatory clinical trials. Such studies should focus not only on the decrease of long-term mortality but also on the quality-of-life parameters such as symptom relief and reduction of rehospitalization. This could be of overall importance—in general—for the future of inotropes as treatment for heart failure.[57]

In a recent report, in fact, encouraging data were described, which support the use of continuous inotropic infusion in AdHF patients to reduce hospitalizations and improve quality of life.[58]

ACKNOWLEDGMENTS

The authors thank Peter Hughes (Hughes associates, Oxford, United Kingdom) for editing the language of the manuscript.

REFERENCES

1. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20:1505–1535.
2. Farmakis D, Agostoni P, Baholli L, et al. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: an expert panel consensus. *Int J Cardiol*. 2019;297:83–90.

3. Bouchez S, Fedele F, Giannakoulas G, et al. Levosimendan in acute and advanced heart failure: an expert perspective on posology and therapeutic application. *Cardiovasc Drugs Ther*. 2018;32:617–624.
4. Masarone D, Melillo E, Gravino R, et al. Inotropes in patients with advanced heart failure: not only palliative care. *Heart Fail Clin*. 2021; 17:587–598.
5. Agostoni P, Farmakis DT, García-Pinilla JM, et al. Haemodynamic balance in acute and advanced heart failure: an expert perspective on the role of levosimendan. *Card Fail Rev*. 2019;5:155–161.
6. Fruhwald S, Pollesello P, Fruhwald F. Advanced heart failure: an appraisal of the potential of levosimendan in this end-stage scenario and some related ethical considerations. *Expert Rev Cardiovasc Ther*. 2016;14:1335–1347.
7. Altenberger J, Gustafsson F, Harjola VP, et al. Levosimendan in acute and advanced heart failure: an appraisal of the clinical database and evaluation of its therapeutic applications. *J Cardiovasc Pharmacol*. 2018;71:129–136.
8. Silvetti S, Greco T, Di Prima AL, et al. Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials. *Clin Res Cardiol*. 2014;103:505–513.
9. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
10. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). Cochrane*; 2011. Available from: http://handbook.cochrane.org. Accessed August 20, 2023.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1–e34.
13. Mavrogeni S, Giamouzis G, Papadopoulou E, et al. A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure. *J Card Fail*. 2007;13:556–559.
14. Berger R, Moertl D, Huelsmann M, et al. Levosimendan and prostaglandin E1 for uptitration of beta-blockade in patients with refractory, advanced chronic heart failure. *Eur J Heart Fail*. 2007;9:202–208.
15. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
16. Kleber FX, Bollmann T, Borst MM, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study. *J Clin Pharmacol*. 2009;49:109–115.
17. Malfatto G, Della Rosa F, Villani A, et al. Intermittent levosimendan infusions in advanced heart failure: favourable effects on left ventricular function, neurohormonal balance, and one-year survival. *J Cardiovasc Pharmacol*. 2012;60:450–455.
18. Bonios MJ, Terrovitis JV, Drakos SG, et al. Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure. *Int J Cardiol*. 2012;159:225–229.
19. Altenberger J, Parissis JT, Costard-Jaeckle A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. *Eur J Heart Fail*. 2014;16:898–906.
20. Comín-Colet J, Manito N, Segovia-Cubero J, et al. 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;20:1128–1136.
21. García-González MJ, Aldea Perona A, Lara Padron A, et al. Efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients: the LAICA study. *ESC Heart Fail*. 2021;8:4820–4831.
22. Pölzl G, Altenberger J, Comín-Colet J, et al. 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;6:174–181.
23. Pölzl G, Allipour Birgani S, Comín-Colet J, et al. Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period. *ESC Heart Fail*. 2019;6:174–181.
24. Spargias KS, Anifantakis A, Papadakis M, et al. Preliminary clinical experience with the repetitive administration of levosimendan in patients with end-stage heart failure. *Ital Heart J*. 2003;4(suppl 2):45S–49S.
25. Nanas JN, Papazoglou P, Tsagalou EP, et al. Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone. *Am J Cardiol*. 2005;95:768–771.
26. Parissis JT, Adamopoulos S, Farmakis D, et al. Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. *Heart*. 2006;92:1768–1772.
27. Parle NM, Thomas MD, Dembo L, et al. Repeated infusions of levosimendan: well tolerated and improves functional capacity in decompensated heart failure—a single-centre experience. *Heart Lung Circ*. 2008; 17:206–210.
28. Papadopoulou EF, Mavrogeni SI, Dritsas A, et al. Assessment of quality of life using three activity questionnaires in heart failure patients after monthly, intermittent administration of levosimendan during a six-month period. *Hellenic J Cardiol*. 2009;50:269–274.
29. Drakos SG, Kanakakis JV, Nanas S, et al. Intermittent inotropic infusions combined with prophylactic oral amiodarone for patients with decompensated end-stage heart failure. *J Cardiovasc Pharmacol*. 2009;53:157–161.
30. Tuomainen PO, Magga J, Timonen P, et al. Intermittent levosimendan treatment in patients with severe congestive heart failure. *Clin Res Cardiol*. 2013;102:485–493.
31. Tasal A, Demir M, Kanadasi M, et al. Comparison of single-dose and repeated levosimendan infusion in patients with acute exacerbation of advanced heart failure. *Med Sci Monit*. 2014;20:276–282.
32. Hübner T, Nickel T, Steinbeck G, et al. A single German center experience with intermittent inotropes for patients on the high-urgent heart transplant waiting list. *Clin Res Cardiol*. 2015;104:929–934.
33. Ortis B, Villani A, Oldani M, et al. Intermittent levosimendan infusions in advanced heart failure: a real world experience. *J Int Med Res*. 2017; 45:361–371.
34. Oliva F, Perna E, Marini M, et al. Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration. *Int J Cardiol*. 2018;272:255–259.
35. Masarone D, Valente F, Verrengia M, et al. Efficacy and safety of repeated infusion of levosimendan in outpatients with advanced heart failure: a real-world experience. *J Cardiovasc Med (Hagerstown)*. 2020;21:919–921.
36. Masarone D, Melillo E, Errigo V, et al. Hemodynamic effects of levosimendan in outpatients with advanced heart failure: an echocardiographic pilot study. *J Cardiovasc Pharmacol*. 2022;79:e36–e40.
37. Wawrzyniak M, Migaj J, Straburzyńska-Migaj E, et al. Repetitive use of levosimendan in clinical practice: a case series. *Cardiovasc J Afr*. 2021; 32:339–342.
38. Barras N, Sotiropoulos K, Regamey J, et al. Intermittent scheduled low-dose levosimendan infusions improves event-free survival in advanced chronic heart failure: a propensity score matching analysis. *Eur J Heart Fail*. 2017;19(suppl S1):378.
39. Wechsler M, Schwinger RHG. Association of repetitive dosing of levosimendan with reduction of NYHA class and NT-proBNP levels in decompensated heart failure: a retrospective cohort study. *Drugs Real World Outcomes*. 2022;9:529–537.
40. Dobarro D, Donoso-Trenado V, Solé-González E, et al. Intermittent inotropic support with levosimendan in advanced heart failure as destination therapy: the LEVO-D registry. *ESC Heart Fail*. 2023;10:1193–1204.
41. Ferreira Reis J, Valentim Gonçalves A, Ilhão Moreira R, et al. Levosimendan in outpatients with advanced heart failure: single-center experience of 200 intermittent perfusions. *Rev Port Cardiol*. 2023;42: 335–343.
42. Ksiązczyk M, Gruchała M, Stopczyńska I, et al. A favorable alliance between repetitive use of levosimendan and advanced heart failure: Polish two-centered inpatient perspective in need of validation. *Kardiol Pol*. 2023;81:287–289.
43. Wang W, Li F, Huang H, et al. Is there any difference in the therapeutic effects of levosimendan on advanced HFrEF patients with sinus rhythm or atrial fibrillation? *Front Cardiovasc Med*. 2023;10:1084300.

44. Bagudá JDJ, Frutos FD, López-Vilella R, et al. Repetitive ambulatory levosimendan as a bridge to heart transplantation. *Rev Esp Cardiol (Engl Ed)*. 2023. [in press]. doi: 10.1016/j.rec.2023.07.002.
45. Cholley B, Bojan M, Guillon B, et al. Overview of the current use of levosimendan in France: a prospective observational cohort study. *Ann Intensive Care*. 2023;13:69.
46. Oliva F, Comin-Colet J, Fedele F, et al. Repetitive levosimendan treatment in the management of advanced heart failure. *Eur Heart J Suppl*. 2018;20(suppl I):I11–I20.
47. Greco T, Zangrillo A, Biondi-Zoccai G, et al. Meta-analysis: pitfalls and hints. *Heart Lung Vessel*. 2013;5:219–225.
48. Burkhoff D, Borlaug BA, Shah SJ, et al. Levosimendan improves hemodynamics and exercise tolerance in PH-HFpEF: results of the randomized placebo-controlled HELP trial. *JACC Heart Fail*. 2021;9:360–370.
49. Masarone D, Kittleson M, Pollesello P, et al. Use of levosimendan in patients with advanced heart failure: an update. *J Clin Med*. 2022;11:6408.
50. Tycińska A, Gierlotka M, Bartuś S, et al. Repetitive use of LEvosimendan in Ambulatory Heart Failure patients (LEIA-HF)—the rationale and study design. *Adv Med Sci*. 2022;67:18–22.
51. Silvetti S, Belletti A, Fontana A, et al. Rehospitalization after intermittent levosimendan treatment in advanced heart failure patients: a meta-analysis of randomized trials. *ESC Heart Fail*. 2017;4:595–604.
52. Nieminen MS, Dickstein K, Fonseca C, et al. The patient perspective: quality of life in advanced heart failure with frequent hospitalisations. *Int J Cardiol*. 2015;191:256–264.
53. Elsherbini H, Soliman O, Zijderhand C, et al. Intermittent levosimendan infusion in ambulatory patients with end-stage heart failure: a systematic review and meta-analysis of 984 patients. *Heart Fail Rev*. 2022;27:493–505.
54. Pollesello P, Ben Gal T, Bettex D, et al. Short-term therapies for treatment of acute and advanced heart failure-why so few drugs available in clinical use, why even fewer in the pipeline? *J Clin Med*. 2019;8:1834.
55. Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and outcomes in the acute heart failure global Survey of standard treatment (ALARM-HF). *Intensive Care Med*. 2011;37:619–626.
56. Kong X, Hu X, Hua B, et al. Levosimendan in Europe and China: an appraisal of evidence and context. *Eur Cardiol*. 2021;16:e42.
57. Pollesello P, Papp Z. The future for inotropes in heart failure. Do not throw the baby out with the bathwater. *J Cardiovasc Pharmacol*. 2023;81:1–3.
58. Gentile P, Masciocco G, Palazzini M, et al. Intravenous continuous home inotropic therapy in advanced heart failure: insights from an observational retrospective study. *Eur J Intern Med*. 2023;116:65–71.