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SYSTEMATIC REVIEW

The Efficacy and Safety of Levosimendan in Patients with Advanced Heart Failure: An Updated Meta-Analysis of Randomized Controlled Trials

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Abstract

Background Intermittent ambulatory levosimendan administration has been shown in several small randomized controlled trials to benefit patients with advanced heart failure, preventing heart failure rehospitalization and mortality. We aim to investigate the totality of high-quality evidence regarding the efficacy and safety of intermittent levosimendan in advanced heart failure patients.

Methods Up to September 2023, we systematically reviewed the randomized controlled trials indexed in PubMed, Embase Cochrane, SCOPUS, and Web of Science. We used mean difference (MD) to estimate the continuous outcomes, and risk ratio (RR) for the dichotomous outcomes with a 95% confidence interval (CI), using the random-effects model. Ultimately, a trial sequential analysis was employed to enhance the reliability of our findings and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework for certainty leveling.

Results Fifteen randomized controlled trials with 1181 patients were included. Intermittent levosimendan was significantly associated with an improved left ventricular ejection fraction compared with placebo (MD 6.39 [95% CI 3.04–9.73], $P = 0.002$; $I^2 = 75$, $P = 0.0005$), with cumulative z-score of change after ≤ 1 week passing the monitoring boundaries, favoring the levosimendan, but did not cross the required information size. Additionally, levosimendan reduced the all-cause mortality rate (RR 0.60 [95% CI 0.40–0.90], $P = 0.01$; $I^2 = 9$, $P = 0.36$). However, we found no difference between levosimendan and placebo in all-cause rehospitalization rate (RR 0.75 [95% CI 0.46–1.22], $P = 0.25$; $I^2 = 70$, $P = 0.04$), event-free survival rate (RR 0.97 [95% CI 0.72–1.30], $P = 0.84$; $I^2 = 63$, $P = 0.03$), or any adverse event (RR 1 [95% CI 0.73–1.37], $P = 1.00$, $I^2 = 0\%$, $P = 0.70$).

Conclusion In patients with advanced heart failure, intermittent levosimendan significantly improved left ventricular ejection fraction, brain natriuretic peptide values, and all-cause mortality rate. Levosimendan use is not associated with a change in rehospitalization or event-free survival.

Registration PROSPERO identifier number (CRD42023487838).

Ahmed Saad Elsaeidy and Mohamed Abuelazm have equal contributions and are co-first authors.

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Key Points

Levosimendan significantly enhanced heart performance and lowered death rates in patients with severe heart failure.

Despite its benefits for heart function and survival, levosimendan did not reduce the frequency of hospital readmissions or overall survival without events.

The use of levosimendan did not lead to an increase in adverse side effects compared with placebo.

1 Introduction

Heart failure is a severe pandemic affecting an estimated 64 million individuals in 2017 [1]. The prevalence rate of heart failure ranges from 1 to 3%, and the lifetime risk of heart failure has increased to one in four individuals. The 1-year mortality risk associated with index diagnosis is 15–30%. Mortality risk is increased dramatically following acute heart failure hospitalization, at approximately 11% over the next 90 days post-discharge [2]. Moreover, the projected increase in heart failure prevalence from 2012 to 2030 is 46%, and the total cost is expected to rise from $30.7 billion to $69.8 billion (US dollars) between 2012 and 2030 [3, 4]. The current guideline-directed medical therapy (GDMT) aims to reduce heart failure mortality and hospitalizations [5]. However, targeted interventions decreasing morbidity and mortality during the vulnerable post-discharge period are still lacking [6].

Levosimendan is an inodilator calcium-sensitizing agent with the following effects: (1) inotropic effect via increasing troponin C sensitivity to calcium without increasing intracellular calcium, (2) vasodilator effect via opening potassium channels in vasculature smooth muscles, and (3) cardioprotection against ischemia via the activation of potassium channels in cardiac mitochondria. It is also postulated that levosimendan possesses cardioprotective properties as a calcium sensitizer offering a neutral effect on myocardial oxygen consumption and modulating a favorable oxidative balance [7]. These properties may lead to protection against arrhythmias and cardiac remodeling [8], as opposed to inotropic agents that increase myocardial oxygen demand and promote arrhythmias [9].

The hemodynamic effects of intravenous (IV) levosimendan encompass a dose-dependent stroke volume and cardiac output elevation while cardiac filling pressures are reduced [10]. Finally, the neurohormonal effects of IV levosimendan include a reduction in natriuretic peptides, interleukin-6, and high-sensitivity C-reactive protein (hs-CRP) [11–13].

Levosimendan is available in Europe and South America but is not approved in the USA. IV inotropes (e.g., dobutamine and milrinone) are largely limited to inpatient settings and palliative efforts due to studies suggesting increased mortality and lack of improved clinical outcomes with long-term use [14]. Furthermore, although milrinone may exert favorable hemodynamic effects, short-term use did not improve cumulative days of hospitalization for cardiovascular cause or mortality within 60 days of administration [15]. A great unmet need exists to improve outcomes in high-risk heart failure patients; levosimendan may meet that need. However, evidence is sparse regarding the clinical benefits of intermittent levosimendan use, with several randomized controlled trials (RCTs) investigating its potential effect on advanced heart failure outcomes [6, 11, 13, 16–27].

To thoroughly evaluate the existing evidence, this systematic review and meta-analysis investigates levosimendan's efficacy and safety in advanced heart failure management.

2 Methods

2.1 Registration

The PROSPERO registration ID of this study is (CRD42023487838). We conducted this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [28] and the Cochrane Handbook for Systematic Reviews and Meta-Analyses [29].

2.2 Data Sources and Search Strategy

A.S.E. and B.A. conducted a comprehensive search across multiple databases including PubMed, SCOPUS, CENTRAL, Web of Science, and Embase, without imposing any restrictions, until September 2023. Further information regarding the search methodology is detailed in Table S1 (see the electronic supplementary material).

2.3 Eligibility Criteria

We included RCTs that met our predefined criteria: population (P) consisted of advanced chronic heart failure patients; intervention (I) involved the administration of levosimendan, regardless of the treatment regimen; comparison (C) was standard of care without levosimendan administration or placebo. Outcomes (O) were as follows: our primary outcome was the change in left ventricular ejection fraction (LVEF), while secondary outcomes were event-free survival/time to first hospitalization, change in brain natriuretic peptide

(BNP), all-cause rehospitalization, all-cause mortality, hypotension, and any adverse event.

2.4 Study Selection

A.M.A., A.R.S., S.E., and M.E. conducted individual screening of titles and abstracts using Covidence. After duplicate removal, the four reviewers independently screened the full texts according to our eligibility criteria. Any conflicts were resolved by consensus.

2.5 Data Extraction

A.M.A., S.E., M.E., and A.R.S. independently conducted data extraction from the included trials using Excel sheets. Any discrepancies were resolved through consensus. This sheet encompassed the following: (1) a summary section (including study design, country, total participants, inclusion and exclusion criteria, details of levosimendan prescription, and follow-up period); (2) baseline characteristics (such as gender, age, body mass index, medical history including diabetes, hypertension, coronary artery disease, and clinical parameters); and (3) study outcomes (including event-free survival/time to first event, change in BNP, change in LVEF, all-cause mortality, all-cause rehospitalization, hypotension, and any adverse events). Conflicts were resolved through consensus.

2.6 Risk of Bias and Certainty of Evidence

A.M.A., S.E., M.E., and A.R. used ROB-II to assess the quality of the included studies. ROB-II investigates the risk of bias according to five domains (randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result). Any conflict was handled through discussion or by inviting A.S.E. to make a final decision [30]. Furthermore, M.A. applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines to appraise the quality of evidence [31, 32].

2.7 Statistical Analysis

We used Review Manager (RevMan) software to pool the data of the included trials [33]. We calculated the risk ratio (RR) for the dichotomous outcomes and mean difference (MD) for the continuous outcomes, along with a 95% confidence interval (CI). To handle differences in the study settings and participant demographics, we used a random-effects model to address potential heterogeneity [34]. To determine between-study variance (tau-squared) within the random-effects model, we applied the DerSimonian and Laird method. We assessed heterogeneity using the I^2 statistic, which gauges the part of total variability due to heterogeneity instead of random chance. As per the Cochrane Handbook [35], the Chi-squared test was evaluated as significant heterogeneity if the alpha level was less than 0.1, while the I^2 test was interpreted as follows: not significant was indicated by 0–40%, moderate heterogeneity was indicated by 30–60%, and substantial heterogeneity was indicated by 50–90% [35]. We carried out a leave-one-out sensitivity analysis to assess the robustness of the pooled results. Also, leave-one-out analysis is useful to investigate the influence of each study on the overall effect-size estimate and to identify influential studies. If the P value was less than 0.05, the total effect size was regarded as statistically significant. Furthermore, considering the relatively small number of studies included in some outcomes and to improve the reliability of our results, we implemented a trial sequential analysis (TSA) to balance type I and type II errors and provide an estimate of when the effect size would be substantial enough to withstand the impact of additional studies [36, 37].

3 Results

3.1 Search Results and Study Selection

Initially, 7021 records were identified after extensive searches across databases. Following removal of duplicate entries, 3993 studies were deemed eligible for title and abstract screening. Among these, 3932 studies were excluded as they did not align with our research objectives. Subsequently, 61 articles underwent full-text screening. Ultimately, we included 15 eligible RCTs [6, 11, 13, 16–27]. Figure 1 illustrates the PRISMA flow diagram.

3.2 Baseline Characteristics

Fifteen eligible RCTs involving 1181 patients were included [6, 11, 13, 16–27]. The levosimendan treatment regimen varied significantly among the trials, as outlined in Table 1. Treatment duration and follow-up periods ranged from 24 h to 12 months. Approximately 76% of the enrolled patients were males, with mean ages spanning from 50.2 to 80.8 years. Also, about 51.4% of the included patients had a history of hypertension, and 18.5% had a history of coronary disease, with a mean LVEF range from 20 to 33.4%. Additional baseline characteristics of the enrolled participants are provided in Table 2. Moreover, Table S2 in the electronic supplementary material provides detailed inclusion and exclusion criteria of the trials.

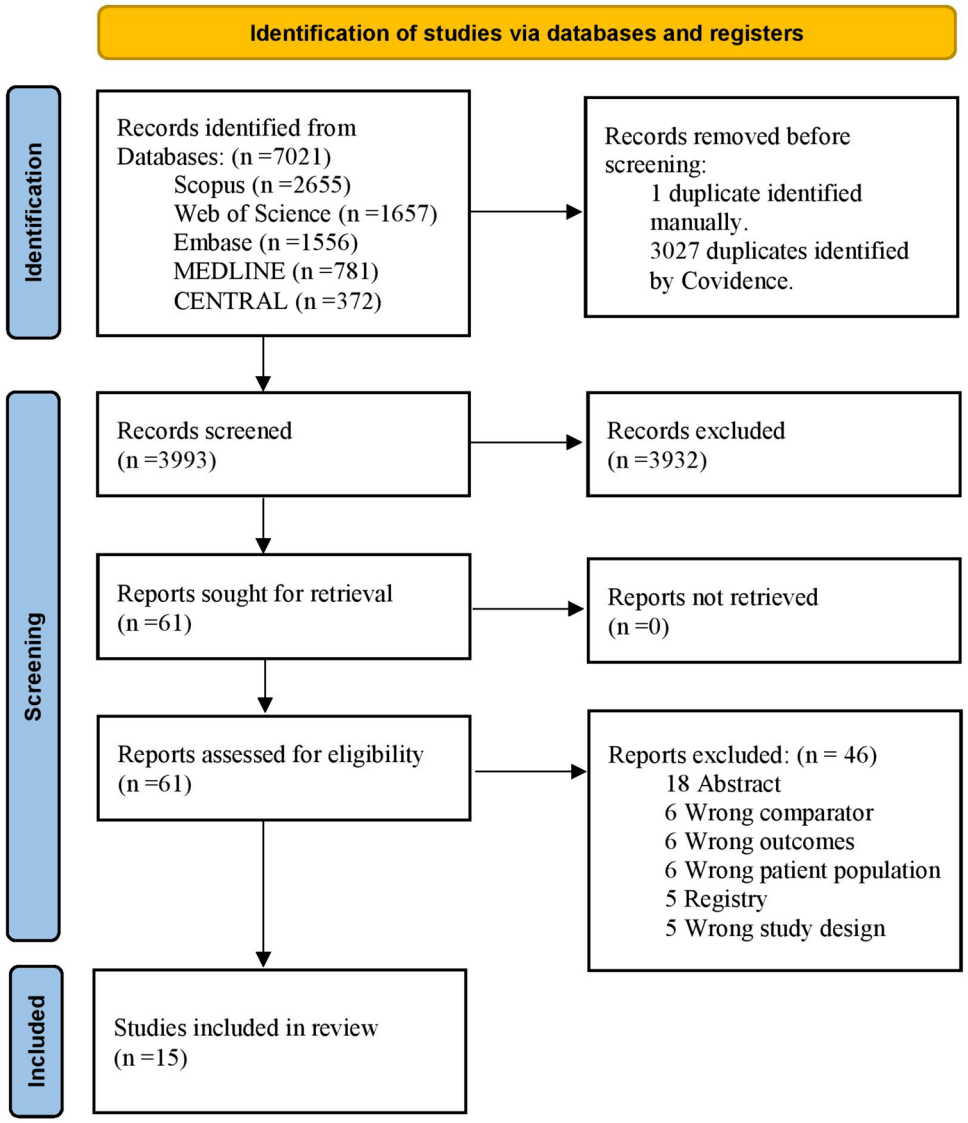

Fig. 1 PRISMA flow chart of the screening process. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analysis

3.3 Risk of Bias and Certainty of Evidence

ROB-II revealed that only one study exhibited a high risk of bias, while four studies exhibited a low risk of bias. Conversely, the others raised some concerns of bias across various domains (Fig. 2). The evidence certainty level is elaborated in a GRADE framework profile in Table 3. Across the included trials, there was a very low level of certainty for all pooled outcomes, except for all-cause mortality, which was assessed to have a low certainty level.

3.4 Primary Outcomes: LVEF

Levosimendan demonstrated a statistically significant enhancement in LVEF compared with placebo (MD 6.39 [95% CI 3.04–9.73], $I^2 = 75\%$) (Fig. 3A). Excluding Zhang et al. 2015 from the subgroup analysis for the ≤ 1-week revealed a consistent statistically significant difference between the study groups (MD 4.09 [95% CI 1.41–6.67], $I^2 = 27\%$) (Table S3, see the electronic supplementary material). A TSA for LVEF change at ≤ 1 week declared that the cumulative z-curve surpassed the traditional and TSA boundaries, establishing sufficient and conclusive evidence (Fig. 3B).

3.5 Secondary Efficacy Outcomes

Levosimendan was associated with a significant decrease in all-cause mortality compared with placebo (RR 0.60 [95% CI 0.40–90], $I^2 = 9\%$) (Fig. 4). Additionally, levosimendan demonstrated a significant reduction in BNP level (SMD −0.42 [95% CI −0.74 to −0.09], $I^2 = 0\%$) without any heterogeneity (Fig. 5A). A TSA for BNP change at ≤ 1 week

Table 1 Summary of the included studies

Study ID	Country	Study design	Sample size	Levosimendan dosage			Follow-up duration
				Bolus dose	Maintenance dose	Treatment duration	
Pölzl et al. 2023 [6]	Austria	RCT	148	No bolus dose	6-h infusion: 0.2 µg/kg/min over 6 h every 2 weeks for 12 weeks 24-h infusion: 0.1 µg/kg/min over 24 h every 3 weeks for 12 weeks	12 weeks	180 ± 14 days
García-González et al. 2021 [16]	Spain	RCT	97	No bolus dose	0.1 µg/kg/min, IV over 24 h once every 30 days	12 months	12 months
Cui et al. 2020 [26]	China	RCT	49	12 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over 24 h	24 h	1 month
Comín-Colet et al. 2018 [25]	Spain	RCT	69	No bolus dose	0.2 µg/kg/min, IV over 6 h	12 weeks	25 weeks
Zhang et al. 2015 [24]	China	RCT	42	12 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over an hour. Then, 0.2 µg/kg/min, IV over 23 h	24 h	4 weeks
Shah et al. 2014 [23]	India	RCT	50	12.5 mg/mL, IV	200 µg/kg dose in 50 mL of normal saline at the rate of 2 mL/h for 24 h, IV	24 h	2 months
Altenberger et al. 2014 [27]	Austria, Greece, and Germany	RCT	120	No bolus dose	0.2 µg/kg/min, IV over 6 h Four cycles of levosimendan at 2-week intervals	6 weeks	18 weeks
Llorens et al. 2012 [19]	Spain	RCT	45	In patients with SBP > 120 mmHg: 6 µg/kg, IV for 10 min In patients with SBP = 90: 120 mmHg: No bolus dose	0.1 µg/kg/min, IV over 24 h In patients who experienced a decline of SBP below 90 mmHg, the dose was reduced by half, and nitroglycerin tapered gradually to withdrawal if necessary	24 h	6 months
Kurt et al. 2010 [17]	Turkey	RCT	60	12 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over 24 h	24 h	NA
Nieminen et al. 2008 [21]	Finland, Estonia, Latvia, Lithuania, and Russia	RCT	307	No bolus dose	LS-1: 1-mg capsule once daily LS-2: 1-mg capsule twice daily	180 days	180 days

Table 1 (continued)

Study ID	Country	Study design	Sample size	Levosimendan dosage			Follow-up duration
				Bolus dose	Maintenance dose	Treatment duration	
Mavrogeni et al. 2007 [20]	Greece	RCT	50	6 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over an hour. Then, 0.2 µg/kg/min, IV over 23 h	8 months	6 months
Parissis et al. 2007 [22]	Greece	RCT	63	No bolus dose	0.1 µg/kg/min, IV over 24 h	24 h	NA
Lilleberg et al. 2007 [18]	Finland	RCT	22	12 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over an hour. Then, 0.2 µg/kg/min, IV over 23 h	25 h	14 days
Parissis et al. 2006 [11]	Greece	RCT	25	6 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over an hour. Then, 0.4 µg/kg/min, IV over 23 h	15 weeks (5 repetitive infusions)	1 month
Parissis et al. 2005 [13]	Greece	RCT	34	6 µg/kg, IV for 10 min	0.1 µg/kg/min, IV over an hour. Then, 0.4 µg/kg/min, IV over 23 h	24 h	5 months

IV intravenous, *LS-1* 1-mg capsule of levosimendan once daily group, *LS-2* 1-mg capsule of levosimendan twice daily group, *NA not available, RCT* randomized controlled trial, *SBP* systolic blood pressure

declared that the *z*-curve surpassed the traditional and TSA boundaries, establishing sufficient and conclusive evidence (Figure S1, see the electronic supplementary material).

However, no significant difference was observed between levosimendan and placebo in terms of event-free survival (RR 0.97 [95% CI 0.72–1.30], $I^2 = 63\%$) (Fig. 5B). Subgroup analysis was also done according to the time point; all subgroups had no significant differences (Figure S2). Heterogeneity in the 5-month subgroup was resolved by excluding the study Parissis et al. (2005) ($I^2 = 32\%$, $P = 0.23$), and the results remained insignificant (RR 1.34 [95% CI 0.92–1.95]) (Table S4). Furthermore, no distinction was found between levosimendan and placebo concerning all-cause rehospitalization (RR 0.75 [95% CI 0.46–1.22], $I^2 = 70\%$) (Fig. 5C). Subgroup analysis was consistent according to the time points, with no significant difference in all subgroups (Figure S3). Heterogeneity in the 6-month subgroup was resolved by excluding the study Llorens et al. (2012) ($I^2 = 0\%$), and the results became statistically significant (RR 0.54 [95% CI 0.37–0.79]) (Table S5).

3.6 Safety Outcomes

While levosimendan did not show an overall elevated risk of any adverse events (RR 1 [95% CI 0.73–1.37], $I^2 = 0\%$) (Fig. 6A), it was associated with a statistically significant increase in the risk of hypotension (RR 2.01 [95% CI 1.06–3.82], $I^2 = 0\%$) (Fig. 6B). There was no statistically significant difference in tachycardia events between groups (RR 0.86 [95% CI 0.38–1.96], $I^2 = 3\%$) (Fig. 6C). Additionally, the requirement for renal replacement therapy/dialysis was investigated by Shah et al. 2014, with an event rate of 16% observed in both groups.

4 Discussion

The key findings are summarized as follows: (1) intermittent levosimendan is associated with a statistically significant increase in LVEF; (2) levosimendan is associated with a statistically significant reduction in BNP; (3) levosimendan is associated with a statistically significant reduction in all-cause mortality; (4) levosimendan is not associated with a reduction in all-cause rehospitalization; (5) levosimendan is not associated with increased adverse events apart from hypotension.

Ambulatory use of intermittent levosimendan in advanced heart failure is under investigation. Advanced heart failure patients often tolerate GDMT with disease-modifying drugs poorly. Tomasoni et al. demonstrated that a minority of advanced heart failure patients in the HELP-HF registry were able to tolerate target doses of GDMT

Table 2 Baseline characteristics of the included studies

Study ID	General characteristics						Medical history					
	Sex (male)		Age (years)		BMI		Hypertension		Diabetes		Coronary disease	
	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo
Pölzl et al. 2023 [6]	72 (77.5)	41 (78.8)	69.3 ± 9.6	67.8 ± 10.1	26.9 ± 4.9	29.6 ± 5.8	59 (63.4)	33 (63.5)	38 (40.9)	26 (50.0)	NA	NA
Cui et al. 2020 [26]	22 (85)	19 (83)	50.2 ± 13.4	54.4 ± 13.2	NA	NA	9 (34.6)	11 (47.8)	5 (19.2)	7 (30.4)	4 (15.4)	9 (39.1)
Shah et al. 2014 [23]	15 (60)	16 (64.0)	59.9 ± 8.8	61.3 ± 7.6	NA	NA	18 (72)	20 (80)	16 (64.0)	13 (52.0)	NA	NA
Zhang et al. 2015 [24]	10 (48)	10 (48)	74.8 ± 4.5	74.5 ± 4.3	NA	NA	8 (38)	7 (33)	5 (25)	6 (29)	8 (38)	8 (38)
Altenberger et al. 2014 [27]	50 (79)	45 (79%)	69.5 ± 11.5	69.5 ± 10.5	NA	NA	36 (57.1)	37 (64.3)	22 (34.9)	24 (42.9)	39 (61.9)	32 (57.1)
Kurt et al. 2010 [17]	17 (54.8)	17 (58.6)	63.3 ± 11.9	64.87 ± 10.4	NA	NA	9 (29)	12 (41.4)	9 (29)	6 (20.7)	NA	NA
Nieminen et al. 2008 [21]	LS-1: 77 (75) LS-2: 84 (82)	86 (84)	LS-1: 65 ± 10 LS-2: 62 ± 12	63 ± 1	LS-1: 28 ± 5.2 LS-2: 29 ± 5.4	30 ± 5.7	LS-1: 71 (70) LS-2: 64 (62)	63 (62)	LS-1: 27 (27) LS-2: 24 (23)	23 (23)	LS-1: 61 (60) LS-2: 64 (62)	64 (63)
García-González et al. 2021 [16]	62 (88.6)	20 (74.1)	68.1 ± 11.1	71.33 ± 9	NA	NA	47 (67.1)	17 (63)	36 (51.43)	14 (51.9)	33 (47.1)	13 (48.2)
Mavrogeni et al. 2007 [20]	20 (80)	20 (80)	62 ± 20	61 ± 19	NA	NA	NA	NA	NA	NA	NA	NA
Parissis et al. 2007 [22]	35 (83.3)	17 (81)	65 ± 8	66 ± 8	NA	NA	NA	NA	NA	NA	NA	NA
Lilleberg et al. 2007 [18]	11 (100)	7 (63.6)	55 ± 9	55 ± 8	NA	NA	NA	NA	NA	NA	5	2
Comín-Colet et al. 2018 [25]	41 (85.4)	16 (76)	68 ± 10	63 ± 9	27 ± 4	27 ± 5	32 (67)	13 (62)	24 (50)	11 (52)	NA	NA
Parissis et al. 2006 [11]	16 (94.1)	7 (87.5)	67 ± 6	70 ± 8	NA	NA	NA	NA	NA	NA	NA	NA
Parissis et al. 2005 [13]	16 (94.1)	15 (82.3)	66 ± 5	68 ± 5	NA	NA	NA	NA	NA	NA	NA	NA

Table 2 (continued)

Study ID	General characteristics						Medical history					
	Sex (male)		Age (years)		BMI		Hypertension		Diabetes		Coronary disease	
	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo
Llorens et al. 2012 [19]	6 (24)	7 (35)	80.8 ± 7.9	77.6 ± 9.9	NA	NA	24 (96)	17 (85)	14 (56)	7 (35)	5 (20)	4 (20)

Study ID	Clinical parameters											
	LVEF		Heart rate (bpm)		SBP (mm Hg)		DBP (mm Hg)		NYHA functional class		NT-proBNP (pg/mL)	
	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo
Pölzl et al. 2023 [6]	24 ± 5	24 ± 5	69 ± 20.7	66.4 ± 22.4	101.3 ± 28.7	101.4 ± 29.1	NA	NA	II: 4 (4.3) IIa: 59 (63.4) IIb: 26 (28.0) IV: 4 (4.3)	II: 5 (9.6) IIa: 29 (55.8) IIb: 17 (32.7) IV: 1 (1.9)	5330.3 ± 5106.3	5290.3 ± 4511.4
García-González et al. 2021 [16]	24.6 ± 7.9	26 ± 9.9	NA	NA	NA	NA	NA	NA	III: 64 (91.43) IV: 5 (7.14)	III: 25 (92.59) IV: 1 (3.7)	7963 ± 1564.3	14232 ± 5373
Cui et al. 2020 [26]	30.2 ± 7.2	33.4 ± 4.7	86.2 ± 13.1	82.7 ± 16.6	121.9 ± 14.51	126.7 ± 24.55	80.4 ± 11.91	83.7 ± 14.9	III: 14 (53.8) IV: 12 (46.2)	III: 12 (52.2) IV: 11 (47.8)	4715.6 ± 6881.2	4380.4 ± 4350.1
Comín-Colet et al. 2018 [25]	27 ± 9	25 ± 6	73 ± 12	74 ± 13	114 ± 17	107 ± 10	NA	NA	II: 46 (96) IV 2 (4)	II: 19 (91) IV: 2 (9)	5678 ± 4847	5419 ± 5331
Zhang et al. 2015 [24]	30.6 ± 6	30.9 ± 6.3	115 ± 53	117 ± 56	133 ± 49	132 ± 47	86 ± 24	185 ± 24	I: II 0 0 III: IV 21	I–II: 0 0 III–IV: 21	2895.7 ± 1497.5	2910.5 ± 1490.4
Shah et al. 2014 [23]	22.5 ± 4.1	22.6 ± 3.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Altenberger et al. 2014 [27]	24 ± 5	24 ± 5	73 ± 12	73 ± 12	120 ± 14	120 ± 18	NA	NA	IIIb: 61 (96.8) IV: 2 (3.2)	IIIb: 53 (92.9) IV: 4 (7.1)	3230.7 ± 2955.1	3593 ± 1172.3
Llorens et al. 2012 [19]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5482 ± 4711	5988 ± 6027
Kurt et al. 2010 [17]	25.4 ± 4.3	25.4 ± 4.5	93.8 ± 23	96.6 ± 23.7	128.3 ± 20.6	116.3 ± 21.3	71.1 ± 10.7	78.8 ± 20.2	III: 21 (72.4) IV: 8 (27.6)	III: 24 (80) IV: 6 (20)	NA	NA
Nieminen et al. 2008 [21]	LS-1: 25 ± 4.9 LS-2: 25 ± 5.3	25 ± 4.9	LS-1: 75 ± 13 LS-2: 74 ± 12	78 ± 13	LS-1: 123 ± 18 LS-2: 124 ± 17	124 ± 15	NA	NA	LS-1: IIIB: 4 (82) IV: 18 (18) LS-2: IIIB: 6 (93) IV: 7 (7)	IIIB: 87 (85) IV: 15 (15)	LS-1: 7557 ± 6680 LS-2: 5414.3 ± 4961.7	5809.3 ± 6489

Table 2 (continued)

Study ID	Clinical parameters									
	LVEF		Heart rate (bpm)		SBP (mm Hg)		DBP (mm Hg)		NYHA functional class		NT-proBNP (pg/mL)	
	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo	Levosimendan	Placebo
Mavrogeni et al. 2007 [20]	22 ± 6	22 ± 5	78 ± 13	80 ± 13	NA	NA	NA	NA	III or IV: 25 (100)	III or IV: 25 (100)	NA	NA
Parissis et al. 2007 [22]	23 ± 6	22 ± 5	83 ± 15	86 ± 17	99 ± 11	100 ± 12	NA	NA	3.3 ± 0.7	3.4 ± 0.6	NA	NA
Lilleberg et al. 2007 [18]	25 ± 5	28 ± 6	63 ± 9	66 ± 10	116 ± 11	125 ± 17	71 ± 8	74 ± 9	NA	NA	8524.7 ± 8862.9	5353.3 ± 4702.1
Parissis et al. 2006 [11]	22 ± 4	23 ± 4	74 ± 9	73 ± 8	117 ± 14	110 ± 15	73 ± 8	71 ± 8	III: 7 (41.1) IV: 10 (58.9)	III: 4 (50%) IV: 4 (50%)	1547 ± 347	1302 ± 302
Parissis et al. 2005 [13]	20 ± 5	23 ± 6	NA	NA	103 ± 13	109 ± 13	65 ± 8	68 ± 6	3.7 ± 0.5	3.5 ± 0.5	NA	NA

Data are reported as *n* (%) or mean ± SD

BMI body mass index, *DBP* diastolic blood pressure, *LS-1* 1-mg capsule of levosimendan once daily group, *LS-2* 1-mg capsule of levosimendan twice daily group, *LVEF* left ventricular ejection fraction, *NA* not available, *NT-proBNP* N-terminal-pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *SBP* systolic blood pressure

[38]. The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) recommend against ambulatory use of IV inotropic agents such as dobutamine and milrinone, except in palliative care or bridging to advanced therapy settings due to lack of survival benefit [14, 39, 40]. Novel agents such as the myosin activator omecamtiv mecarbil were developed as adjunct therapies to reduce severe heart failure patient risk. However, the Food and Drug Administration (FDA) declined approval due to lack of survival benefit [41]. A great unmet need exists for a therapeutic option to prevent disease progression, decrease hospitalizations, lower mortality, and enhance the quality of life in advanced heart failure patients. Given its distinct mechanism of action as an inodilator calcium-sensitizing agent with cardioprotective properties, intermittent ambulatory levosimendan holds promise for enhancing cardiovascular outcomes and improving quality of life in advanced heart failure patients.

Despite mixed evidence in several relatively small RCTs, our findings suggest that intermittent levosimendan may improve cardiovascular outcomes in heart failure patients, primarily by reducing all-cause mortality. These positive clinical outcomes might stem from improving hemodynamic and neurohormonal profiles, as manifested by increased LVEF and reduced natriuretic peptides in our results. Our results align with a study including eight RCTs and seven observational studies, which showed decreased cardiovascular mortality, improved New York Heart Association (NYHA) class, and health-related quality of life with ambulatory levosimendan use; however, that study was limited by heterogeneity and the small size of included studies [42]. In keeping with our findings, Cui et al. (2021) also found that levosimendan reduced BNP levels and increased LVEF in patients with advanced heart failure [43]. Moreover, the RELEVANT-HF registry, designed to acquire real-world data for patients with advanced heart failure receiving levosimendan, also demonstrated that patients experienced a shorter length of hospital stay in the 6 months following the initiation of treatment compared with the 6 months prior to treatment [43].

Levosimendan may also exert a positive impact on the pulmonary circulation and the right ventricle, which can contribute to improved cardiovascular outcomes. A systematic review and meta-analysis involving 390 patients showed a significant increase in right ventricular (RV) fractional area change, tricuspid annular plane systolic excursion, and tricuspid annular peak systolic velocity and a significant decrease in pulmonary pressures with levosimendan use [44]. These findings are of particular importance in the advanced heart failure population that may seek durable left ventricular assist device (LVAD) options, as up to 24%

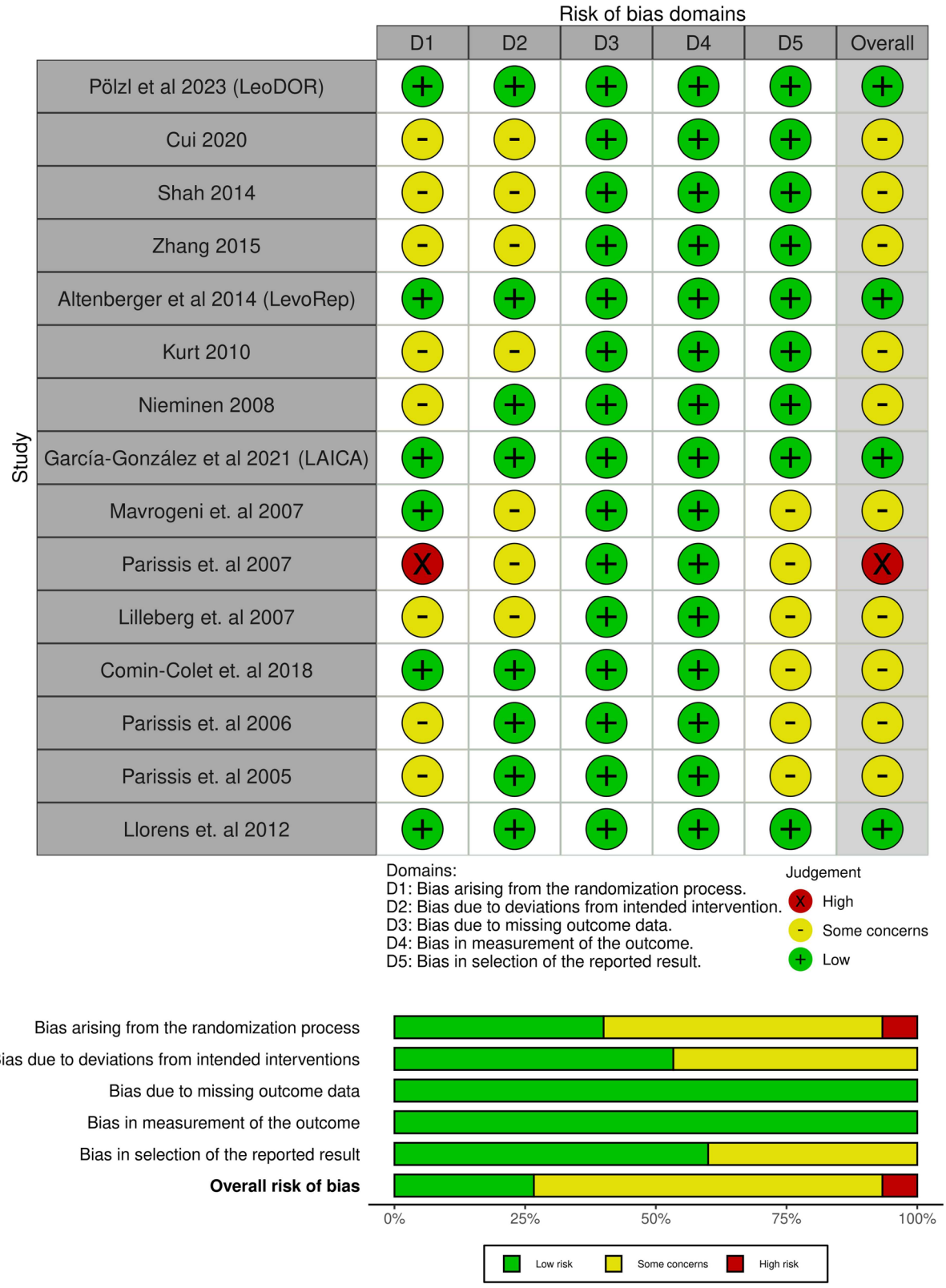

Fig. 2 Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each study in the review. The lower panel presents risks (low = green, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review

Table 3 GRADE evidence profile

Certainty assessment						
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
LVEF change						
323 (7 RCTs)	Serious[a]	Very serious[b]	Not serious	Very serious[c]	None	⨁◯◯◯ Very low
All-cause mortality						
636 (7 RCTs)	Serious[a]	Not serious	Not serious	Serious[d]	None	⨁⨁◯◯ Low
BNP change						
157 (3 RCTs)	Serious[a]	Not serious	Not serious	Very serious[c]	None	⨁◯◯◯ Very low
Event-free survival						
465 (5 RCTs)	Serious[a]	Serious[e]	Not serious	Very serious[d]	None	⨁◯◯◯ Very low
All-cause re-hospitalization						
260 (4 RCTs)	Serious[a]	Serious[e]	Not serious	Very serious[d]	None	⨁◯◯◯ Very low
Any adverse event						
462 (7 RCTs)	Serious[a]	Not serious	Not serious	Very serious[d]	None	⨁◯◯◯ Very low
Hypotension						
327 (5 RCTs)	Serious[a]	Not serious	Not serious	Very serious[d]	None	⨁◯◯◯ Very low
Tachycardia						
463 (4 RCTs)	Serious[a]	Not serious	Not serious	Very serious[d]	None	⨁◯◯◯ Very low

BNP brain natriuretic peptide, *CI* confidence interval, *GRADE* Grading of Recommendations Assessment, Development, and Evaluation, *LVEF* left ventricular ejection fraction, *RCT* randomized controlled trial

[a]All the included trials showed an overall some concerns of bias

[b]*I*-squared > 75%

[c]A wide CI that does not exclude the appreciable harm/benefit, with total participants less than 400

[d]A wide CI that does not exclude the appreciable harm/benefit, with low number of events

[e]*I*-squared > 50%

develop right heart failure following LVAD implantation, leading to worse cardiovascular outcomes [45].

Furthermore, there is evidence that levosimendan improves long-term kidney function in patients with advanced heart failure. Studies showed increased glomerular filtration rate and decreased creatinine with levosimendan use [46–48]. This effect may be explained by favorable cardiac effects or potential extra-cardiac mechanisms. That said, Shah et al. failed to demonstrate a reduction in the need for renal replacement therapies with the use of levosimendan.

Our results suggest that levosimendan is well tolerated in patients with advanced heart failure with no increased risk of adverse events apart from an increase in hypotensive events. However, increased hypotension with levosimendan did not correspond to a rise in all-cause mortality. Despite its inotropic properties, levosimendan did not exhibit a significant increase in tachycardic events in our results. This finding can be explained within the context that levosimendan does not increase intracellular calcium or oxygen consumption, leading to less likely ventricular arrhythmias during treatment [49]. We may demonstrate that intermittent ambulatory levosimendan use leads to improvements in LVEF, BNP, and all-cause mortality without an increased hazard of overall adverse events.

However, this study cannot demonstrate the risk–benefit ratio of intermittent levosimendan for patients with advanced heart failure as there was not enough data to pool and discuss the whole safety profile of the treatment (Table S6, see the electronic supplementary material).

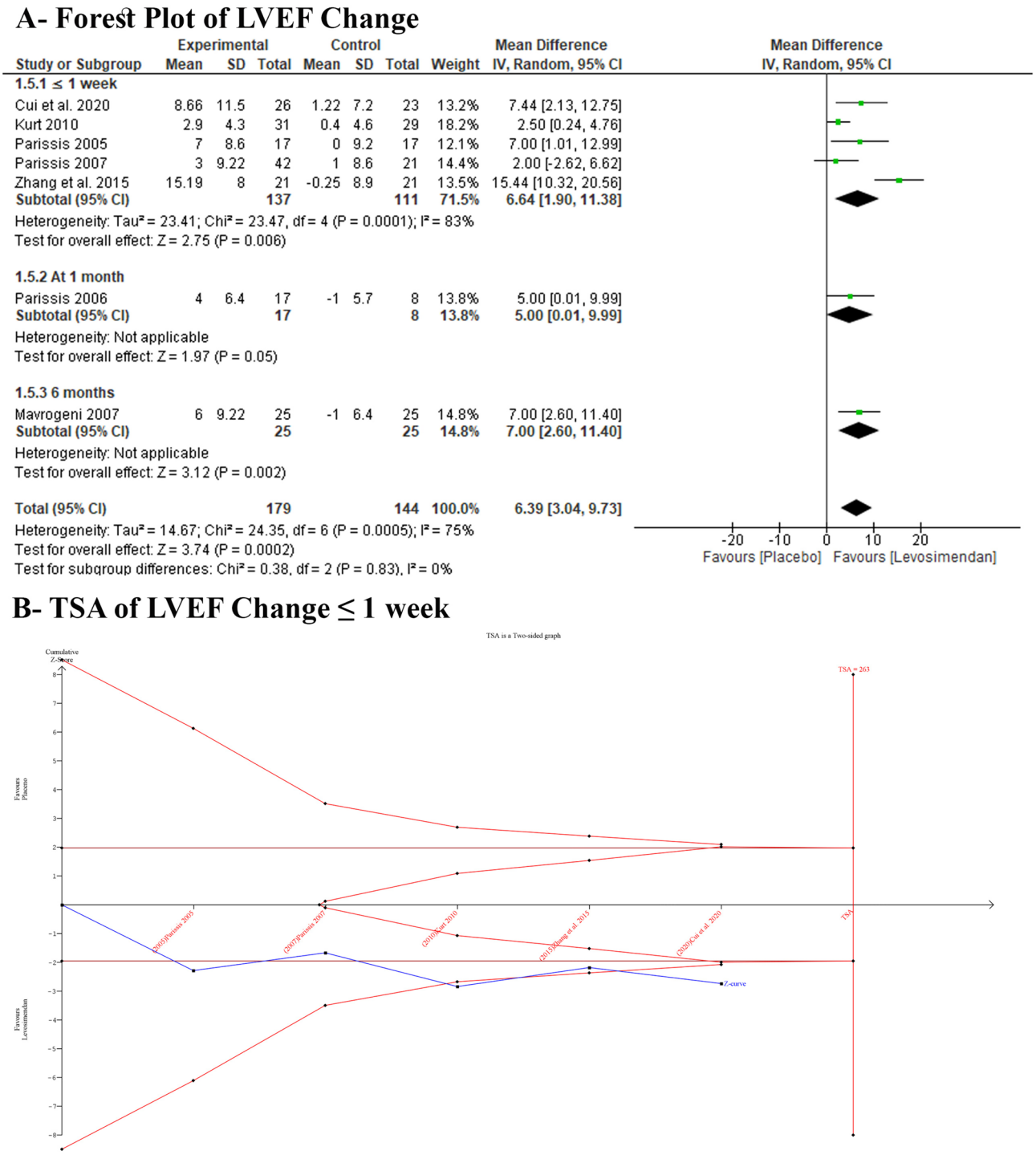

Fig. 3 Forest plot and TSA of LVEF change: **A** forest plot; **B** TSA LVEF change ≤ 1 week. *CI* confidence interval, *LVEF* left ventricular ejection fraction, *TSA* trial sequential analysis

4.1 Limitations

This study resolved some of the limitations of Cui et al. (2021) as we unified the comparator arm.

However, this review should be interpreted considering several limitations. (1) There were heterogeneous baseline patient characteristics. (2) There was predominantly male representation (76% of included patients). (3) There was variation in dosing regimens across different RCTs; some

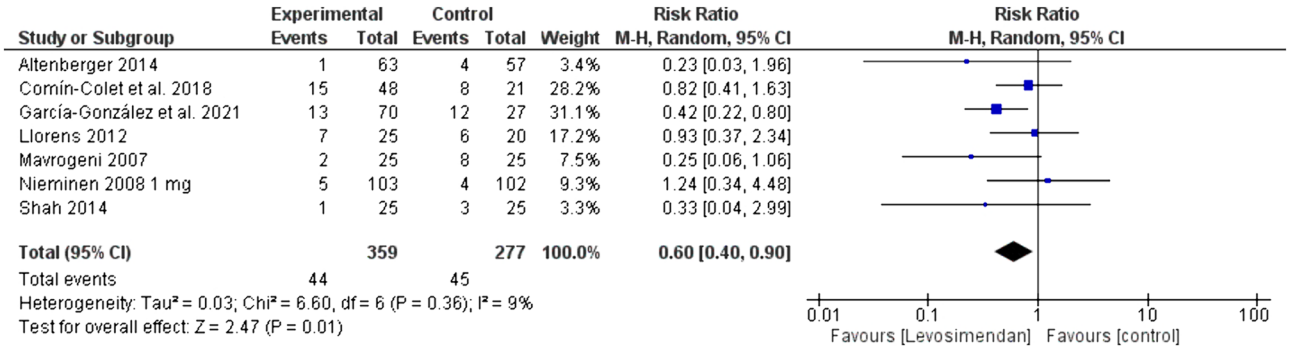

Fig. 4 Forest plot of all-cause mortality. *CI* confidence interval

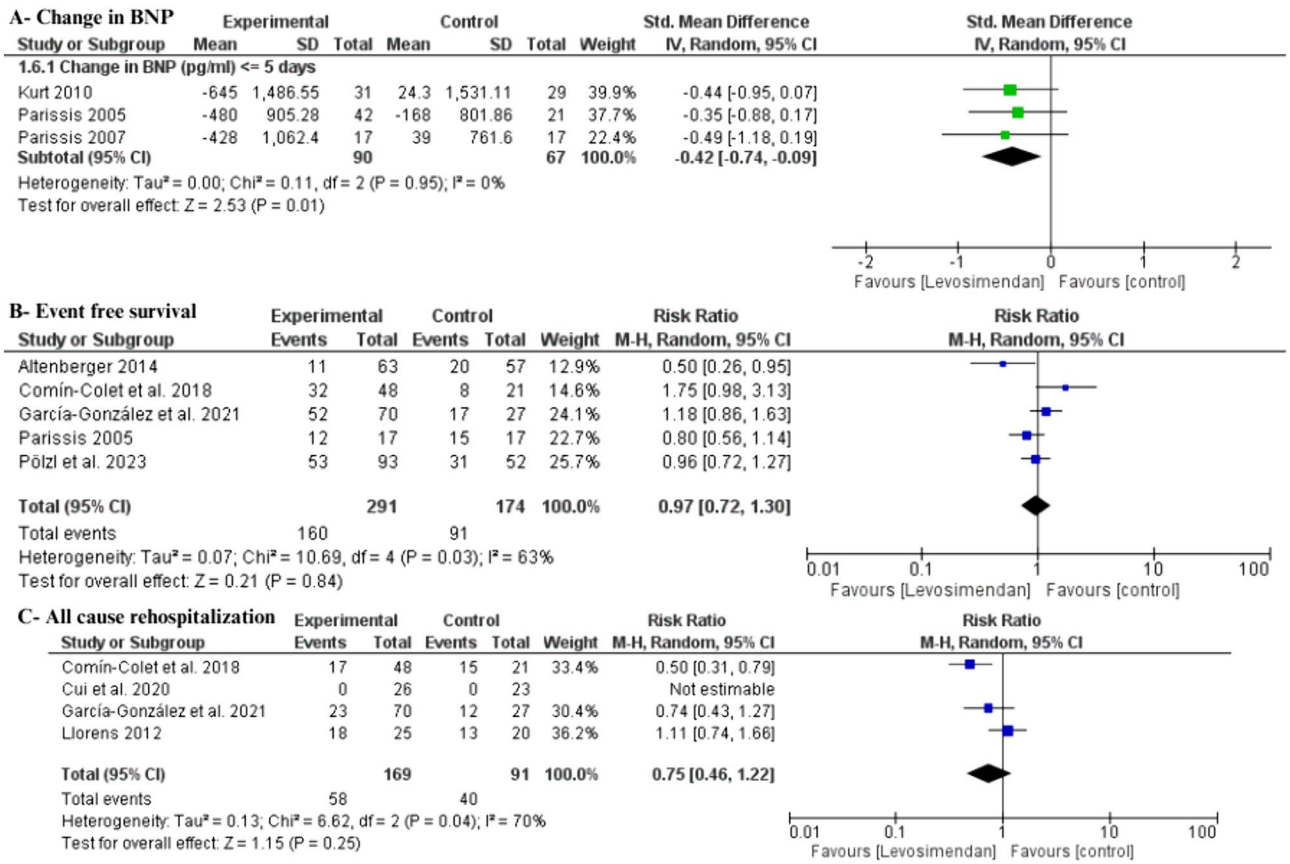

Fig. 5 Forest plot of secondary efficacy outcomes: **A** change in BNP; **B** event-free survival; **C** all-cause rehospitalization. *BNP* brain natriuretic peptide, *CI* confidence interval, *Std.* standardized

studies used a bolus dose while others did not, and different studies used different maintenance dosing. (4) Although all other studies used IV levosimendan, in the study by Nieminen et al., patients received oral levosimendan. (5) There was noted heterogeneity among some outcomes, including change in LVEF, event-free survival, and all-cause rehospitalization. (6) There was limited investigation into the effect of levosimendan on patient-reported quality of life in most studies.

Furthermore, this meta-analysis identified some inconsistencies in its findings. While levosimendan was associated with significant improvements in LVEF, BNP levels, and overall mortality, it did not show a significant impact on all-cause rehospitalization rates, event-free survival rates, or

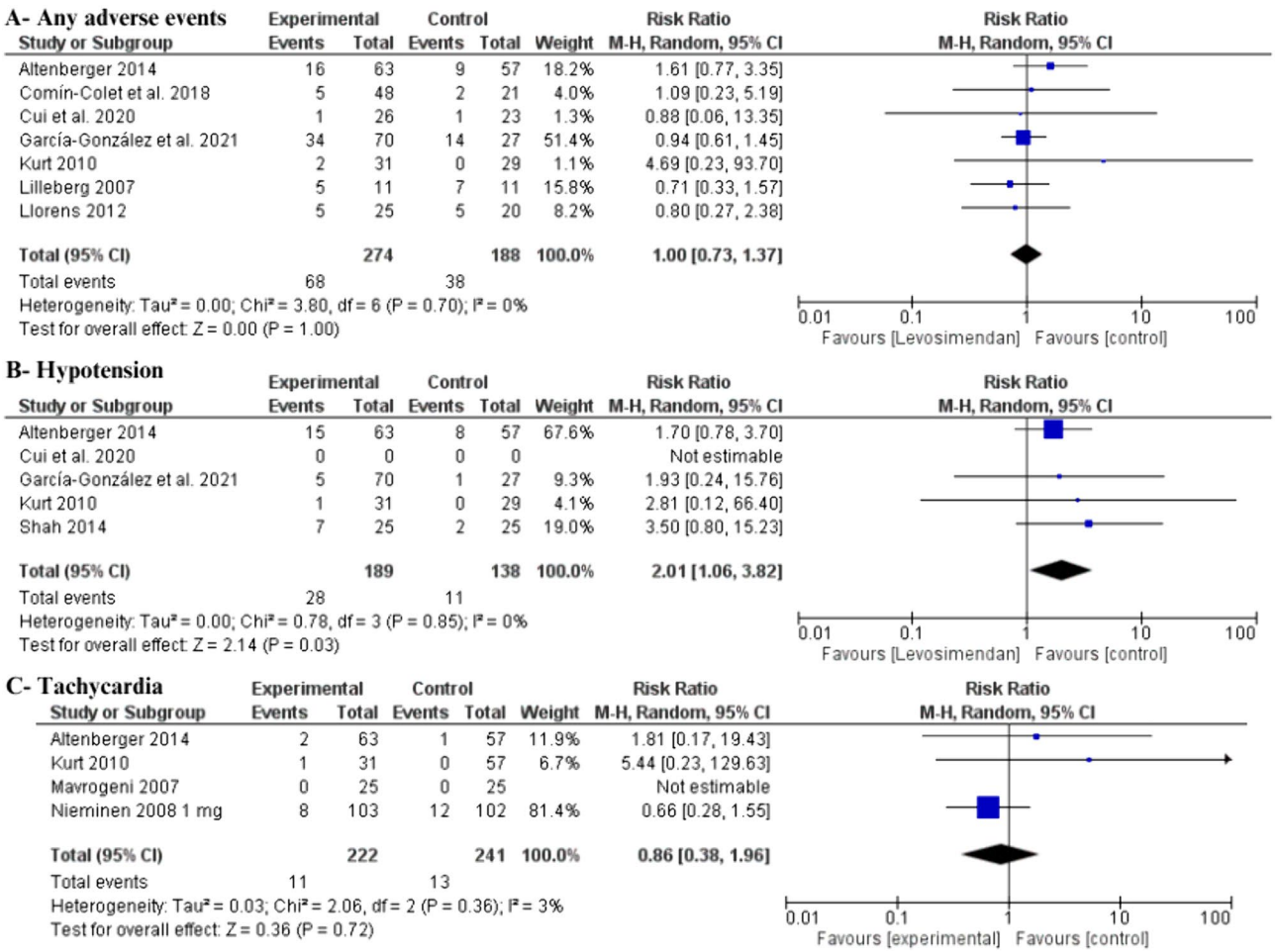

Fig. 6 Forest plot of safety outcomes: **A** any adverse events; **B** hypotension; **C** tachycardia. *CI* confidence interval

adverse events. A subgroup analysis based on the duration of follow-up for the outcomes of all-cause rehospitalization rate and event-free survival rate also revealed no significant differences between the study groups across all subgroups (Figures S2 and S3, see the electronic supplementary material). The inconsistency in these outcomes suggests that the benefits of levosimendan may be limited or context specific. However, this discrepancy in these outcomes may be attributed to the variability of the RCTs included in each outcome analysis and the absence of data related to specific follow-up time points in some studies.

4.2 Implications for Future Research

Future adequately powered trials are needed to draw definitive conclusions regarding the efficacy of ambulatory levosimendan on cardiovascular outcomes, including cardiovascular hospitalizations, cardiovascular mortality, and quality-of-life measures. Additionally, the optimal dosing regimen needs to be refined. Subsequent studies should investigate whether the effects of levosimendan are consistent across the spectrum of heart failure ejection fraction subtypes, heart failure etiologies, and different follow-up periods. Exploring levosimendan's efficacy in patients with RV heart failure is also an important area for exploration.

5 Conclusion

Our systematic review and meta-analysis suggest that intermittent levosimendan is associated with a significantly higher LVEF, lower BNP levels, and lower all-cause mortality in patients with chronic heart failure. However, levosimendan use was not associated with a reduction in all-cause rehospitalization.

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Declarations

Author contributions M.A., B.P. and C.B. conceived the idea. B.A., A.S.E. and M.A. designed the research workflow. B.A. and M.A. searched the databases. A.M.A., M.E., S.E. and A.R.S. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and B.A. and A.S.E resolved the conflicts. Y.S. performed the analysis. R.G., Y.S. and A.S.E. wrote the final manuscript. B.A., B.P., and C.B. supervised the project. All authors have read and agreed to the final version of the manuscript.

Conflict of interest The authors declare no conflict of interest.

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Ethics approval and consent to participate Not applicable.

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Availability of data and materials Not applicable.

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