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ORIGINAL ARTICLE

Levosimendan in acute decompensated heart failure: Systematic review and meta-analysis

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Fatigue;
Mexico

Abstract
Objectives: To assess the risks and benefits of levosimendan in acute decompensated heart failure compared to dobutamine or placebo.
Methods: Pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL), the European Heart Journal, and the Journal of the American College of Cardiology and Circulation were searched for randomized clinical trials of a 24 h IV infusion of levosimendan compared to dobutamine or a placebo in patients ≥18 years old admitted with a diagnosis of acute decompensated heart failure of any etiology with a NYHA class III and IV heart failure, a left ventricular ejection fraction <0.35, pulmonary catheter wedge pressure >15 mmHg or cardiac index <2.5 ml/min/m^2.
Results: Eleven clinical trials (2747 patients) met the inclusion criteria for this review. Levosimendan was associated with a significant increase in NYHA class OR 3.06 (95% CI 1.23–7.59; $p = 0.02$), and a tendency to improve fatigue OR 1.80 1.53 (IC95% 0.99–2.39, $p = 0.06$) and clinical improvement composite OR 1.20 (IC95% 0.99–1.46; $p = 0.06$), as compared to dobutamine or a placebo.
Conclusions: Levosimendan in acute decompensated heart failure improves NYHA functional class, LVEF and BNP levels when compared to dobutamine or a placebo, with an increase in side effects.

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Introduction

Heart failure (HF) is a clinical syndrome derived from any structural alteration or cardiac function which leads to the inability of the heart to deliver oxygen at the rate metabolically active tissue require unless it does so at the expense of an increase in ventricular inflow pressure.[1,2] Thus, HF has been divided into heart failure with preserved ejection fraction or diastolic heart failure (HFpEF), and heart failure with reduced ejection fraction or systolic heart failure (HFrEF), although it would also always be possible to differentiate it based on the time of onset or evolution (acute or chronic), severity, clinical stage or symptom direction (anterograde or retrograde) whichever predominates in the syndrome. HFpEF prevalence varies from 40 to 71%; nonetheless, this depends on the great variability of the ejection fraction cut-off criteria to classify it.[1,2] Close to 1–2% of adult population have HF, with a prevalence which may be greater than 10% in people over 70 years of age.[3]

Heart failure decreases quality of life by increasing morbidity and mortality due to frequent hospitalizations caused by acute decompensation or intensification. It can also be the main cause of hospitalization in individuals over 65 years of age. This not only represents an increase in the cost of heart failure treatment, but it is also a prognosis marker in the course of the disease, since mortality linked to acute decompensation may be up to 10% at 60 days, with a rate of new hospitalizations in the following 6 months of 50% and a mortality of 30% at 1 year.[2,4,5]

Acute decompensated heart failure is defined as the sudden or gradual onset of the signs and symptoms of heart failure, which requires an unplanned visit to the doctor's office or the emergency unit, or in some cases, hospitalization. Regardless of the precipitating causes of the exacerbation, the universal finding in decompensated HF is the rise in intracavitary filling pressure, with the resulting systemic and pulmonary congestion.[6]

There is no widely accepted nomenclature for HR syndromes which require hospitalization. ''Acute HF'' or ''acute HF syndrome'' or ''acutely decompensated HF'' have been used indistinctly. Even though the latter term has a greater acceptance, its main limitation is that it does not distinguish between a first timer or a previously stable HF with acute worsening. Patients who are hospitalized due to HF may be classified depending on their etiology in those with acute myocardial ischemia, accelerated arterial hypertension, acutely decompensated HF, cardiogenic shock and decompensated right heart failure.[2]

Most patients with decompensated HF admitted to the hospital suffer a worsening of their chronic HF. Between 15 and 20% represent new HF diagnoses. Close to 50% have an ejection fraction $\leq$40%. This group has a high prevalence of the atheromatous coronary disease (60%), fibrillation or atrial flutter (30–46%), valvular heart disease (44%) and dilated cardiomyopathy (25%), all according to the chronicity of the subjacent disease.[7]

Treatment goals for decompensated HF are an improvement of symptoms and hemodynamic deterioration and the reduction of morbidity and mortality. Modern treatments have improved prognosis, reducing the risk of a new hospitalization by up to 30–50%, with significant changes in mortality.[8] In this sense, calcium sensitizers, unlike adrenergic agonists, increase myocardial contractility with a minimal energy consumption and a lower risk of arrhythmias, with an improvement in mortality and hemodynamic parameters.[9,10] Levosimendan, an agent in the group of calcium sensitizers, has inotropic and vasodilator (inodilator) effects which improve myocardial work without a change in oxygen consumption. This is produced by the opening of ATP-dependent K^+ channels in the myocyte and smooth vascular muscle cells, thus causing vasodilation with pre-charge and post-charge reduction and an increase in coronary flow.[11] Moreover, it has a positive chronotropic effect caused by the increase of Ca^{2+} sensitivity on behalf of contractile proteins, a characteristic which determines an increase in myocardial force without alteration, ventricular diastolic relaxation or induced cell death.[12,13]

There are different publications comparing Levosimendan with other inotropic drugs which have been proven to show an improvement in mortality, hemodynamic parameters and biochemical parameters in favor of levosimendan; however, not much is known about the change in parameters of symptom improvement as the main objective of HF treatment. The main objective of this systemic review and meta-analysis is to evaluate whether or not levosimendan offers a benefit in symptomatic improvement versus dobutamine and/or a placebo.

Methods

Patients

Adults $\geq$18 years of age, admitted to the hospital due to decompensated heart failure of any etiology, in the NYHA (New York Heart Association) III or IV functional class, a left ventricular ejection fraction (LVEF) <0.35, a pulmonary wedge pressure (PWP) $\geq$ 15 mmHg or a cardiac index <2.5 L/min/m^2.

Included studies

Randomized clinical trials (control or placebo) with a priori well-defined primary outcome which did not have more than a 10% loss during follow up.

Intervention

Intravenous infusion of levosimendan for 24 h, compared with placebo and/or dobutamine.

Objectives

- Primary: Clinical improvement of dyspnea, fatigue, NYHA functional class and combined terminal point of clinical improvement (dyspnea, fatigue, and NYHA functional class).
- Secondary: Improvement of hemodynamic parameters (LVEF, heart index or cardiac output [CO]) and pulmonary wedge pressure, brain natriuretic peptide (BNP), total mortality, adverse effects and the use of rescue

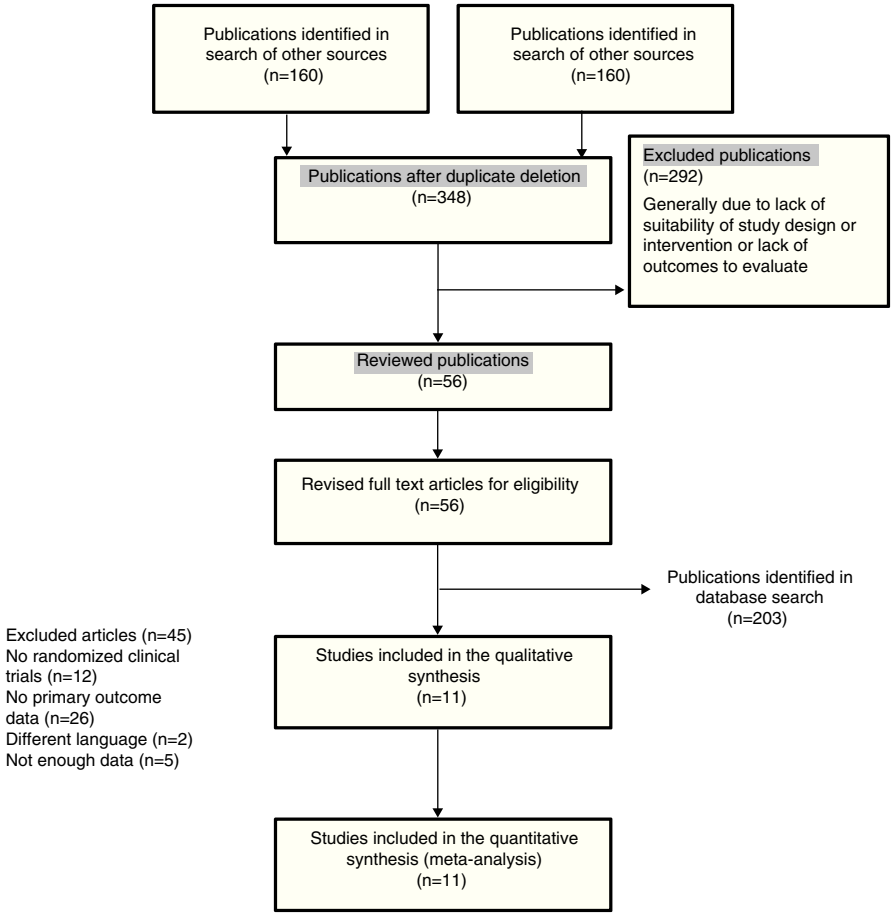

Figure 1 Flowchart of the trials included in the systematic review.

Table 1 Search terms.

Source	Terms used
PubMED	''simendan''[Supplementary Concept] AND (''heart failure''[MeSH Terms] OR (''heart''[All Fields] AND ''failure''[All Fields]) OR ''heart failure''[All Fields]) OR (Decompensated[All Fields] AND (''heart failure''[MeSH Terms] OR (''heart''[All Fields] AND ''failure''[All Fields]) OR ''heart failure''[All Fields])) NOT (''paediatrics''[All Fields] OR ''pediatrics''[MeSH Terms] OR ''pediatrics''[All Fields]) NOT (''infant''[MeSH Terms] OR ''infant''[All Fields] OR ''infants''[All Fields]) AND (Clinical Trial[ptyp] AND (''load free full text''[sb] AND has abstract[text]))
CENTRAL[a]	''Levosimendan AND decompensated heart failure''
European Heart Journal	''Levosimendan''
Journal of the American College of Cardiology	''Levosimendan''
Circulation	''Levosimendan''

[a] Cochrane Central Register of Controlled Trials.

treatment, defined as use of positive inotropes or intravenous vasodilators, which were not part of the analyzed medications (i.e. dopamine or norepinephrine).

Exclusion criteria

Duplicated trials, trials which were in a language other than Spanish or English, trials that did not have relevant information to measure the primary outcome, non-randomized clinical trials and articles that were not available in full text format were excluded.

Search parameters to identify the studies

Relevant clinical trials were found by electronic search in MEDLINE (1966 to August 2013), in the platforms of Pubmed,

Table 2 Characteristics of included trials.

Study	No. of patients	Multicentric	Follow-up (days)	Severity of heart failure
Bergh 2010[15]	60	Yes	30	NYHA III and IV, LVEF $\leq$ 0.35, PWP $\geq$ 15 mmHg and CI < 2.5 L/min/m^2
Flevari 2006[16]	34	No	150	NYHA III or IV, LVEF $\leq$ 0.35 and CI $\leq$ 2.5 L/min/m^2
Kivikko 2003[17]	146	Yes	14	NYHA III and IV, LVEF $\leq$ 0.3, PWP $\geq$ 15 mmHg and CI $\leq$ 2.5 L/min/m^2
Kurt 2010[18]	59	Yes	5	NYHA III and IV
LIDO 2002[19]	203	Yes	180	FEVI < 0.35, PWP > 15 mmHg and CI < 2.5 L/min/m^2
Parissis 2005[20]	45	No	90	NYHA III or IV, LVEF $\leq$ 0.3
Parissis 2006[21]	25	Yes	114	NYHA III and IV, LVEF $\leq$ 0.3
REVIVE I 2013[22]	100	Yes	90	LVEF < 0.35 and presence of dyspnea despite management with diuretic IV
REVIVE II 2013[22]	600	Yes	90	LVEF < 0.35 and presence of dyspnea despite management with diuretic IV
Slawsky 2000[23]	148	Yes	6 h	NYHA III and IV, LVEF $\leq$ 0.3, PWP $\geq$ 15 mmHg and CI $\leq$ 2.5 L/min/m^2
SURVIVE 2007[24]	1327	Yes	180	LVEF $\leq$ 0.3, PWP $\geq$ 18 mmHg and CI <2.2 L/min/m^2

NYHA: New York Heart Association functional class, LVEF: left ventricular ejection fraction, PWP: pulmonary wedge pressure, CI: cardiac index.

EBSCOhost, ProQuest, the Cochrane Central Registry of Clinical Trials (CENTRAL), the European Heart Journal, the Journal of the American College of Cardiology and Circulation, the Mexican Journal of Cardiology, the Mexican Cardiology Archives and the Spanish Journal of Cardiology. No non-indexed sources were searched. The search terms can be found in Table 1. The search was limited to human subjects, with languages limited to Spanish and English, as well as those conducted by a single author and ending on August 30, 2013.

Selection and extraction of studies

Two authors reviewed the abstracts to identify potential clinical trials. If the summary met the inclusion criteria, the study was considered for a full-text review. Full-text articles were extracted and evaluated for validity and quality by both authors to determine if they met the eligibility criteria specified. When one of these was unclear, the study was not accepted for review.

Statistics

Meta-analytic techniques were used to increase the power of hypothesis testing and also to obtain information not available in individual trials. Using the effect methods for each model, we calculated the value of their statistical association and their corresponding chi-square. The chi-square of homogeneity, calculated as the difference between the total chi-square and the association of the chi-square, allowed us to measure the degree of homogeneity among the association values to be evaluated. The results were expressed as relative risk, odds ratio or difference from the standardized mean, with a 95% confidence interval. To carry out the statistical calculations and the meta-analytical graphs, we used Review Manager version 5.2, which provided us with the Cochrane Collaboration.[14]

Level of significance

Association: Only the least significant p-value of the association test should be taken into consideration; for the conclusion, the level of significance was proposed at $p = 0.05$.

Heterogeneity: Because statistical tests lack the power to measure heterogeneity in a meta-analysis, a level of statistical significance of $p = 0.10$ was used.

Results

Description of the studies

The main features of the included studies and patients are summarized in Tables 2 and 3.[15–24] The description of the data of each included trial can be consulted in Tables 5–15.[15–24] Of the 363 references to potential clinical trials initially selected, only 11 randomized clinical trials met the inclusion criteria and were included in the qualitative and quantitative analysis, including a total of 2747 patients in the analysis (Fig. 1). The reasons for excluding the 45 full-text references are summarized in Table 16.[31–75]

Table 3 Characteristics of patients included in the trials.

Study	Age (median, SD)	Sex (% male)	LVEF % (median, SD)	Etiology (%)	NYHA (%)	Treatment (%)
Bergh 2010[15]	70 ± 10	90	21.2 ± 5.8	Ischemic: 66.6 Not ischemic: 26.6	III: 17 IV 12	Not described
Flevari 2006[16]	65 ± 1.3	87	22 ± 1.4	Ischemic: 77 Not ischemic: 23	–	ACEI/ARB: 89 β-Blockers: 86 Diuretics: 100 Digitalis: 46 AA: 75 Amiodarone: 58
Kivikko 2003[17]	57 ± 2	83	21 ± 1	Ischemic: 62 Not ischemic: 29	III: 67 IV: 33	ACEI/ARB: 95 Diuretics: 98 Digitalis: 88
Kurt 2010[18]	64 ± 10.7	68.6	25.4 ± 4.3	Ischemic: 32.3 Not ischemic: 67.7	III: 72 IV: 28	Not described
LIDO 2002[19]	59 ± 11	86	–	Ischemic: 47 Not ischemic: 53	–	Digoxin: 75 Diuretics: 92 ACEI: 88 β-Blockers: 38 Nitrates: 40 Anticoagulants: 43 Antiarrhythmics III: 14 CCB: 4
Parissis 2005[20]	66 ± 5	94	20 ± 5	Ischemic: 85 Not ischemic:15	–	ACEI/ARB: 88 β-Blockers: 64 Diuretics 100 Digitalis 46 AA: 41 Amiodarone 41
Parissis 2006[21]	67 ± 6	92	22 ± 4	Ischemic: 85 Not ischemic: 15	III: 44 IV: 66	ACEIs: 100 β-blockers: 80 Diuretics: 100 AA: 52 Amiodarone: 40
REVIVE I 2013[22]	59 ± 15	75	20 ± 6	Ischemic: 48 Not ischemic: 52	–	ACEI/ARB: 64 β-Blockers: 44 Digoxin: 58 Spironolactone: 35 IV Vasodilator: 7 IV Inotropic: 20 IV Vasodilator + Inotropic: 2
REVIVE II 2013[22]	63 ± 15	72	23 ± 7	Ischemic: 53 Not ischemic: 47	–	ACEI/ARB: 85 β-Blockers: 78 Digoxin 60 Spironolactone: 41 IV Vasodilator: 13 IV Inotropic: 11 IV Vasodilator + Inotropic: 2
Slawsky 2000[23]	58 ± 1	82	21 ± 1	Ischemic: 59 Not ischemic: 41	III: 66.5IV: 33.5	Not described
SURVIVE 2007[24]	66 ± 12	72	24 ± 5	Ischemic: 76 Not ischemic: 24	IV: 86	ACEI/ARB: 69 Diuretics IV: 79 β-Blockers: 51 AA: 53 Nitrates IV: 37 Dopamine IV: 7

SD: standard deviation, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association functional class, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, AA: aldosterone antagonist, IV: intravenous.

Table 4 Levosimendan vs control comparisons.

Clinical improvement				
	Studies	Participants	Statistical method	Estimation of effect
Outcome				
1.1 Dyspnoea	4	1683	Odds ratio (M–H, Fixed, CI 95%)	1.04 [0.82, 1.33]
1.2 Fatigue	3	364	Odds ratio (M–H, Fixed, CI 95%)	1.53 [0.99, 2.39]
1.3 NYHA class	3	145	Odds ratio (M–H, Fixed, CI 95%)	3.06 [1.23, 7.59]
1.4 Composite	8	2468	Odds ratio (M–H, Fixed, CI 95%)	1.20 [0.99, 1.46]
Mortality				
2.1 Total mortality	8	2541	Odds ratio (M–H, Random, CI 95%)	0.92 [0.74, 1.14]
Hemodynamic parameters				
3.1 LVEF	3	130	Odds ratio (IV, Random, CI 95%)	4.07 [2.36, 5.77]
Biochemical parameters				
4.1 BNP	6	1551	Odds ratio (IV, Random, CI 95%)	−325.61 [−358.32, −292.89]
Adverse effects				
5.1 Headache	5	2422	Odds ratio (M–H, Fixed, CI 95%)	1.88 [1.51, 2.34]
5.2 Hypotension	6	952	Odds ratio (M–H, Fixed, CI 95%)	1.38 [1.17, 1.64]
5.3 Heart failure	4	2073	Odds ratio (M–H, Fixed, CI 95%)	0.83 [0.70, 0.97]
5.4 Hypokalemia	4	2073	Odds ratio (M–H, Fixed, CI 95%)	1.23 [0.94, 1.62]
5.5 Non-sustained ventricular tachycardia	4	877	Odds ratio (M–H, Fixed, CI 95%)	1.43 [1.08, 1.89]
5.6 Atrial fibrillation	3	2013	Odds ratio (M–H, Fixed, CI 95%)	0.04 [0.02, 0.06]
Rescue				
6.1 Rescue treatment	4	888	Odds ratio (M–H, Fixed, CI 95%)	0.63 [0.48, 0.82]

M–H: Mantel–Haenszel, CI: confidence interval, IV: instrumental variable.

Table 5 Characteristics of a study by Bergh, 2010.[a]

Methods	Randomized, multicenter, double-blind, double-dummy, parallel group phase IV trial. A randomized, stratified study with respect to the use of Carvedilol and random assignment to the infusion of levosimendan for 24 h (group 1) or dobutamine for 48 h (group 2) with a 1:1 ratio, each with placebo of the alternate infusion. Follow up: 30 days
Participants	>18 years with decompensated ischemic and non-ischemic HF Severity of cardiac failure: NYHA III or IV functional class, LVEF $\leq$ 0.35, PWP $\geq$15 mmHg and CI <2.5 L/min/m^2 Group 1: No. of patients: 29 Group 2: No. of patients: 31
Interventions	Group 1. Levosimendan bolus of 12 μg/kg in 10 min, followed by infusion at 0.1 μg/kg/min for 50 min with increments at 0.2 μg/kg/min for 23 h. Possibility of reduction to 0.05 0 0.1 μg/kg/min if adverse effects were present. Group 2: Dobutamine in continuous infusion without loading dose, starting at 5 μg/kg/min for 1 h and increasing to 10 μg/kg/min for 47 h. Possibility of reduction to 2.5 or 5 μg/kg/min if adverse effects were present.
Outcomes	Changes in hemodynamic measures, symptoms, β-blocker therapy, serum BNP level, adverse effects and death.
Notes	Primary or secondary outcomes were not differentiated

Risk of bias		
Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''Patients...were randomly allocated...in a 1:1 ratio'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information

[a] Bergh CH, Andersson B, Dahlström U, et al. Intravenous levosimendan vs dobutamine in acute decompensated heart failure patients on beta-blockers. Eur J Heart Fail. 2010; 12, 404–10.

Table 6 Characteristics of a study by Flevari, 2006.[a]

Methods	Randomized trial comparing the efficacy of levosimendan (Group 1) infusion against placebo (control group) in patients with chronic left ventricular systolic dysfunction decompensated by coronary artery disease or NYHA III or IV dilated cardiomyopathy Follow up: 90 days
Participants	>18 years with chronic systolic heart failure hospitalized for advanced decompensation with NYHA class III and IV for coronary artery disease or dilated cardiomyopathy Severity of cardiac failure: NYHA class III and IV with LVEF $\leq$0.3 Group 1: No. of patients: 30 Group 2: No. of patients: 15
Interventions	Group 1: Levosimendan infused at 0.1 μg/kg/min continuous for 24 h.
Outcomes	Symptomatic improvement at 6 h and 48 h later, walk test at 6 min. Echocardiographic parameters. BNP, electrocardiographic Holter 24 h before and 24 h during infusion.
Notes	Primary and secondary outcomes are not differentiated

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''Patients were randomized (in a 2:1 design)'' Comment: Not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: Not enough information
Blinding (performance bias)	High risk	Comment: It is not said if there was blinding, but the outcome can be influenced by the absence of it.

[a] Flevari P, Parissis JT, Leftheriotis D, et al. Effect of levosimendan on ventricular arrhythmias and prognostic autonomic indexes in patients with decompensated advanced heart failure secondary to ischemic or dilated cardiomyopathy. Am J Cardiol. 2006; 98(12): 1641–5.

Table 7 Characteristics of a study by Kivikko, 2003.[a]

Methods	Double-blind, placebo-controlled clinical trial. A continuation study from a previous study to compare levosimendan (group 1) against placebo (group 2) for 24 h, with group 1 being re-randomized to receive levosimendan or placebo for an additional 24 h. Follow up: 14 days
Participants	>18 years hospitalized for acutely decompensated heart failure of ischemic or non-ischemic origin Severity of cardiac failure: Class NYHA III, IV, LVEF $\leq$ 0.3, PWP $\geq$15 mmHg and CI $\leq$2.5 L/min/m^2. Group 1: No. patients first 24 h: 98 per 6 h, 85 per 24 h; Remaining 24 h: 42 Group 2: No. patients first 24 h: 48; Remaining 24 h: 43
Interventions	Levosimendan with bolus of 6 μg/kg, infusion of 0.1 μg/kg/min per 1 h. Hourly boluses of 6 μg/kg and infusion titration of 0.1 μg/kg/min every hour up to 0.4 μg/kg/min. At the end of 6 h, half of the dose was continued for 24 h and at the end of 24 h, it was re-randomized 1: 1 for infusion for the remaining 24 h.
Outcomes	Changes in hemodynamic measures, symptoms, plasma concentration of metabolites of levosimendan, adverse effects and death.
Notes	The primary outcome is not established, the losses of group 1 during the first 24 h are not commented.

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''...patients were randomized 1:1'' Comment: Not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: Not enough information
No loss report (attrition bias)	Unclear risk	Quote: ''98 patients received levo for 6 h and 48 received placebo. After 6 h, 85 patients in the levo group were continued for a total of 24 h on open-label Levo'' Comment: There is insufficient information on 13/98 patients in the levosimendan group prior to the new randomization
Lack of data (reporting bias)	High risk	Comment: The complete results of the dyspnea and fatigue outcome are not described

[a] Kivikko M, Lehtonen L, Colucci W. Sustained hemodynamic effects of Intravenous Levosimendan. Circulation. 2003; 107:81–86.

Table 8 Characteristics of a study by Kurt, 2010.[a]

Methods	Randomized 2-group trial to receive levosimendan plus standard treatment without a diuretic (Group 1) or single standard treatment with a diuretic (Control group) for 24 or 48 h. Standard treatment consisted of Furosemide, ACEI, ARB, spironolactone, β-blockers Follow up: 5 days.
Participants	>18 years with decompensated chronic heart failure Severity of Heart Failure: NYHA Class III and IV Group 1: No. of patients: 31 Control group: No. patients: 29
Interventions	Levosimendan IV with a bolus of 12 μg/kg for 10 min, followed by infusion at 0.1 μg/kg/min for 24 h, unless there were adverse events, in which the dose divided and the infusion left for 48 h.
Outcomes	Changes in hemodynamic parameters, LVEF by echocardiography, NYHA functional class, and serum levels of BNP, Troponin I, Myoglobin, D-dimer, BUN, Creatinine, uric acid, potassium, sodium, hematocrit, and free light chains − κ and λ
Notes	Outcomes and follow-up time are not established

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''Randomized into two groups'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information
Blinding (performance bias)	Unclear risk	Comment: No comment, probably not performed

[a] Kurt IH, Yavuzer K, Batur MK. Short-term effect of levosimendan on free light chain kappa and lambda levels in patients with decompensated chronic heart failure. Heart Vessels. 2010; 25(5): 392–9.

Table 9 Characteristics of a study by LIDO, 2002.[a]

Methods	Randomized, multicenter, double-blind, double-dummy, parallel-group trial comparing one group of patients on levosimendan infusion for 24 h (Group 1) vs. one control group on dobutamine infusion for 24 h (Control group). Follow up: 180 days
Participants	>18 years admitted to the hospital for low-cost heart failure: deterioration of severe chronic heart failure, cardiac failure after cardiac surgery and recent acute heart failure. Severity of cardiac failure: LVEF <0.35, CI <2.5 L/min/m^2 and PWP > 15 mmHg Group 1: No. of patients: 103 Control group: No. patients: 100
Interventions	Group 1: Levosimendan with bolus of 24 μg/kg in 10 min, followed by continuous infusion for 24 h of 0.1 μg/kg/min with a double increase every 2 h until reaching goal of improvement of the cardiac index > 30% with possibility to decrease to the half or suspend for major limiting or cardiovascular events Control group: Continuous infusion of 5 mcg/kg/min for 24 h without loading dose, with an increase in dose twice every 2 h until reaching goal of improvement of the cardiac index >30% with the possibility of halving or suspending by events Limiting or cardiovascular diseases
Outcomes	Primary: Proportion of patients with improvement of hemodynamic parameters at the end of 24 h (Improvement of >30% in cardiac index or decrease of ≥25% in PWP) Secondary: Changes in hemodynamic parameters other than cardiac index and PWP from baseline to 24 h, changes in symptoms of heart failure (dyspnea and fatigue) assessed by the patient on a scale of four (much better, slightly better, unchanged, worse) from baseline up to 24 h, proportion of patients requiring rescue therapy with positive inotropes, vasodilators or diuretics, number of days alive and out of hospital and without intravenous drugs in the first month, time to develop worsening of heart failure and death. Safety: Spontaneous reports of adverse reactions, laboratory tests and all-cause mortality at 31 and 180 days.

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Low risk	Quote: ''Assigned randomly... in blocks of four according to a computer-generated code'' Comment: Probably was performed
Allocation concealment (selection bias)	Low risk	Quote: ''Treatment allocation and size of the randomization blocks were concealed from the investigators'' Comment: Probably was performed
Blinding (performance bias)	Low risk	Quote: ''Double-blind, double dummy'' Comment: Probably was performed

[a] Follath F, Cleland JGF, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double-blind trial. Lancet. 2002; 360:196–202.

Table 10 Characteristics of a study by Parissis, 2005.[a]

Methods	Randomized, open trial to compare efficacy of levosimendan infusion (Group 1) versus placebo (Control group) in patients with LV systolic dysfunction Follow up: 150 days
Participants	>18 years with advanced cardiac failure hospitalized for NYHA III and IV functional class Severity of cardiac failure: NYHA class III or IV, LVEF <0.30 Group 1: No. of patients: 17 Control group: No. of patients: 17
Interventions	Group 1: Levosimendan bolus of 6 μg/kg for 10 min, followed by continuous infusion of 0.1 μg/kg/min titrated up to 0.4 μg/kg/min or up to limiting event.
Outcomes	Change in symptoms by NYHA class, echocardiographic parameters, changes in serum BNP and IL-6, IL-10.
Notes	The primary outcome was not defined.

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''...patients were randomized immediately after their hospital admission...'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information
Blinding (performance bias)	High risk	Quote: ''open-label study'' Comment: The outcome can be influenced by the absence of blinding

[a] Parissis JT, Panou F, Farmakis D, et al. Effects of Levosimendan on Markers of Left Ventricular Diastolic Function and Neurohormonal Activation in Patients with Advanced Heart Failure. Am J Cardiol. 2005; 96: 423–26.

Table 11 Characteristics of a study by Parissis, 2006.[a]

Methods	Randomized, open-label, placebo-controlled trial. Randomized 2: 1 study of two groups to receive 5 infusions of levosimendan every 3 weeks (Group 1) or placebo (Group 2) Follow up: 114 days
Participants	>18 years with decompensated chronic heart failure Severity of cardiac failure: NYHA class III, IV and LVEF ≤0.3 Group 1: No. of patients: 17 Group 2: No. of patients: 8
Interventions	Levosimendan with bolus of 6 μg/kg in 10 min, followed by infusion at 0.1 μg/kg/min for 24 h, titrating up to 0.4 μg/kg/min every 3 weeks for 5 doses.
Outcomes	Changes in echocardiographic measures, symptoms, NYHA class, hemodynamics, serum pro-BNP level, troponin T, high sensitivity CRP of IL-6
Notes	The primary outcome is not established.

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''Randomly allocated 2:1'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information, probably not performed
Blinding (performance bias)	High risk	Quote: ''Open-label study'' Comment: The outcome can be influenced by the absence of blinding

[a] 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;92:1768–72.

Table 12 Characteristics of a study by REVIVE I, 2013.[a]

Methods	A randomized, multicenter, double-blind, placebo-controlled, parallel group trial in patients hospitalized for acute decompensated heart failure to compare effectiveness of levosimendan IV (Group 1) versus placebo (control group). Follow up: 90 days
Participants	>18 years admitted for acute decompensated heart failure Severity of cardiac failure: LVEF <0.35 Group 1: No. of patients: 51 Control group: No. of patients: 49
Interventions	Group 1: 12 μg/kg bolus in 10 min (6 μg/kg in patients with concomitant use of inotropes or vasodilators or both at the start of infusion), followed by infusion at 0.1 μg/kg/min for 50 min in increments of 0.2 μg/kg/min for 23 h. Possibility of reduction or at 0.05 or 0.1 μg/kg/min or suspension if adverse effects occur
Outcomes	Primary: Distribution of the clinical compound as ''improvement'', ''unchanged'' or ''worse'' Secondary: Change in BNP concentration to 24 h, Global assessment by patient at 6 h, assessment of dyspnea by patient at 6 h, duration of initial hospitalization after infusion start (days alive and out of hospital) by 14 days, time to death or worsening of heart failure at 31 days after infusion start, NYHA class 5 days after infusion, all cause mortality within 90 days of infusion start. Safety: Heart rate, blood pressure, 12-lead electrocardiogram, general laboratory, adverse events.
Notes	NYHA class is not reported at baseline, only reported without significant change in outcome

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''...patients were randomly assigned...'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information
Blinding (performance bias)	Low risk	Quote: ''double-blind'' Comment: Was probably performed
No complete report (report bias)	Low risk	Quote: ''The NYHA functional class at 5 days was not significantly different between treatment groups ($p = 0.196$). Comment: The complete data were not commented to be analyzed in the meta-analysis

[a] Packer M, Colucci W, Fisher L, et al. Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure. J Am Coll Cardiol HF. 2013;1:103–11.

Table 13 Characteristics of a study by REVIVE II, 2013.[a]

Methods	A randomized, multicenter, double-blind, placebo-controlled, parallel group trial in patients hospitalized for acute decompensated heart failure to compare the effectiveness of levosimendan IV (Group 1) versus placebo (control group). Follow up: 90 days
Participants	>18 years admitted for acute decompensated heart failure Severity of cardiac failure: LVEF <0.35 Group 1: No. of patients: 299 Control group: No. patients: 301
Interventions	Group 1: 12 μg/kg bolus in 10 min (6 μg/kg in patients with concomitant use of inotropes or vasodilators or both at the start of infusion), followed by infusion at 0.1 μg/kg/min for 50 min in increments of 0.2 μg/kg/min for 23 h. Possibility of reduction or at 0.05 or 0.1 μg/kg/min or suspension if adverse effects occur
Outcomes	Primary: Distribution of the clinical compound as ''improvement'', ''unchanged'' or ''worse'' Secondary: Change in BNP concentration to 24 h, Global assessment by patient at 6 h, assessment of dyspnea by patient at 6 h, duration of initial hospitalization after infusion start (days alive and out of hospital) by 14 days, time to death or worsening of heart failure at 31 days after infusion start, NYHA class 5 days after infusion, all cause mortality within 90 days of infusion start. Safety: Heart rate, blood pressure, 12-lead electrocardiogram, general laboratory, adverse events.
Notes	NYHA class is not reported at baseline, only reported without significant change in outcome

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''...patients were randomly assigned...'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information
Blinding (performance bias)	Low risk	Quote: ''double-blind'' Comment: Was probably performed
Incomplete result (reporting bias)	High risk	Quote: ''The NYHA functional class at 5 days was not significantly different between treatment groups ($p = 0.196$). Comment: The complete data were not commented to be analyzed in meta-analysis

[a] Packer M, Colucci W, Fisher L, et al. Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure. J Am Coll Cardiol HF. 2013;1:103–11.

Table 14 Characteristics of a study Slawsky 2000.[a]

Methods	Multicenter, randomized, double-blind, placebo-controlled trial with levosimendan infusion 2: 1 (Group 1) or placebo (control group) for 6 h with blinding. Follow-up: Not mentioned, although there are no measurements beyond 6 h.
Participants	>18 years with LV systolic dysfunction admitted for management of decompensated heart failure Severity of cardiac failure: NYHA class III and IV with LVEF $\leq$0.3, PWP $\geq$15 mmHg and CI $\leq$2.5 L/min/m^2 Group 1: No. patients: 98 Group 2: No. patients: 48
Interventions	Levosimendan with a bolus of 6 μg/kg, followed by continuous infusion, initially at 0.1 μg/kg/min. A bolus of 6 μg/kg was repeated every hour at the rate of infusion, increasing 0.1 μg/kg/min until 0.4 μg/kg/min or until some limiting event
Outcomes	Changes in hemodynamic parameters, symptoms (dyspnea and fatigue) and adverse events.
Notes	The primary outcome is not established.

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Unclear risk	Quote: ''Patients were randomized 2:1'' Comment: There is not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information, probably not performed

[a] Slawsky MT, Colucci WS, Gottlieb SS, et al. Acute Hemodynamic and Clinical Effects of Levosimendan in Patients With Severe Heart Failure. Circulation. 2000; 102:2222–27.

Table 15 Characteristics of a study by SURVIVE, 2007.[a]

Methods	A randomized, double-blind, multicenter, parallel-group trial comparing the efficacy and safety of infusion of levosimendan (Group 1) or dobutamine (Group 2) in patients over 18 years of age hospitalized for decompensated heart failure requiring therapy Inotrope. Follow up: 180 days
Participants	>18 years hospitalized for decompensated heart failure Severity of cardiac failure: NYHA class III and IV with LVEF $\leq$0.3, PWP $\geq$18 mmHg and CI <2.2 L/min/m^2 Group 1: No. patients: 664 Group 2: No. patients: 663
Interventions	Group 1: Levosimendan with bolus of 12 μg/kg in 10 min, followed by 0.1 μg/kg/min for 50 min, increasing the dose to 0.2 μg/kg/min for a further 23 h. Group 2: Dobutamine infused at 5 μg/kg/min, with discretionary increments up to 40 μg/kg/min as maximum dose for at least 24 h.
Outcomes	Primary: Mortality from any cause to 180 days. Secondary: Mortality from any cause at 31 days, change in baseline BNP level at the first 24 h, number of days of life, and out of hospital during 180 days, change in dyspnea and patient-rated global assessment at 24 h and cardiovascular mortality at 180 days. Adverse events at 31 days.
Notes	None

Risk of bias

Bias	Judgment of the author	Support of the judgment
Random sequence (selection bias)	Low risk	Quote: ''Randomization was performed by a 2-step procedure...vials were assigned a number using randomly permuted blocks...patients were randomized centrally using an interactive voice response system'' Comment: Was probably performed
Allocation concealment (selection bias)	Unclear risk	Comment: There is not enough information, probably not performed
Blinding (performance bias)	Low risk	Quote: ''Double-blind'' Comment: Was probably performed

[a] Mebazaa A, Nieminen M, Packer M, et al. Levosimendan vs Dobutamine for Patients with Acute Decompensated Heart Failure. The SURVIVE Randomized Trial. JAMA. 2007; 297(17): 1883–91.

Table 16 Characteristics of excluded studies.

Study	Reason for exclusion
Adamopoulos 2006[31]	There was no relevant clinical data for the primary outcome
Álvarez 2006[32]	Insufficient data
Antila 2004[33]	Non-randomized clinical trial
Arutiunov 2010[34]	There was no relevant clinical data for the primary outcome
Avgeropoulou 2005[35]	There was no relevant clinical data for the primary outcome
BELIEF 2008[36]	No blinding or randomization
Böhm 2011[37]	There was no relevant clinical data for the primary outcome
Despas 2010[38]	There was no relevant clinical data for the primary outcome
Duman 2009[39]	There was no relevant clinical data for the primary outcome
Duygu 2008a[40]	Insufficient data
Duygu 2008b[41]	There was no relevant clinical data for the primary outcome
Duygu 2008c[42]	There was no relevant clinical data for the primary outcome
Duygu 2009[43]	There was no relevant clinical data for the primary outcome
Farmakis 2010[44]	Non-randomized clinical trial
Feola 2001[45]	Non-randomized clinical trial
Follath 2003[46]	There was no relevant clinical data for the primary outcome
Iyosoy 2010[47]	There was no relevant clinical data for the primary outcome
Jonsson 2003[48]	Not a clinical study
Karth 2003[49]	There was no relevant clinical data for the primary outcome
Kasikcioglu 2005[50]	There was no relevant clinical data for the primary outcome
Kirlidis 2009[51]	Non-randomized clinical trial
Llorens-Soriano 2007[52]	Non-randomized clinical trial
Mavrogeni 2007[53]	There was no relevant clinical data for the primary outcome
Mebazza 2009[54]	There was no relevant clinical data for the primary outcome
Michaels 2005[55]	Non-randomized clinical trial
Michalopoulou 2007[56]	There was no relevant clinical data for the primary outcome
Moertl 2005[57]	There was no relevant clinical data for the primary outcome
Nieminen 2000[58]	Insufficient data
Nieminen 2003[59]	Not a clinical study
Nieminen 2008[60]	Insufficient data
Paksoy 2012[61]	In a language other than Spanish or English
Papazoglou 2003[62]	There was no relevant clinical data for the primary outcome
Parissis 2004[63]	There was no relevant clinical data for the primary outcome
Parissis 2007[64]	There was no relevant clinical data for the primary outcome
Parle 2007[65]	Non-randomized clinical trial
Poelzl 2008[66]	There was no relevant clinical data for the primary outcome
Silva-Cardoso 2004[67]	Non-randomized clinical trial
Silva-Cardoso 2009[68]	Non-randomized clinical trial
Sundberg 2000[69]	Insufficient data
Tziakas 2005[70]	There was no relevant clinical data for the primary outcome
Tek 2010[71]	There was no relevant clinical data for the primary outcome
Ukkonen 2000[72]	There was no relevant clinical data for the primary outcome
Wang 2010[73]	In a language other than Spanish or English
Yilmaz 2007[74]	There was no relevant clinical data for the primary outcome
Yilmaz 2009[75]	There was no relevant clinical data for the primary outcome

As in most of the studies on HF we analyzed, the inclusion criteria were that patients be in the NYHA III or IV functional class, with an LVEF below 35% measured by two-dimensional echocardiography or radionuclide ventriculography, a PWP > 15 mmHg and a cardiac index < 2.5 L/min/m^2. The mean age of the patients was 63 ± 4.2 years, 81.9 ± 8.8% were men and the mean LVEF was 21 ± 1.7%. The etiology of heart failure was ischemic in 62.9 ± 16.9% and non-ischemic in 35.7 ± 17.4%. The most common concomitant treatments were ACE inhibitors, angiotensin II receptor antagonists (ARBs), β-blockers and diuretics.

Risk of bias in included studies

We included 7 double-blind clinical trials and 4 open-label studies.[16,18,20,21] The randomization method was described

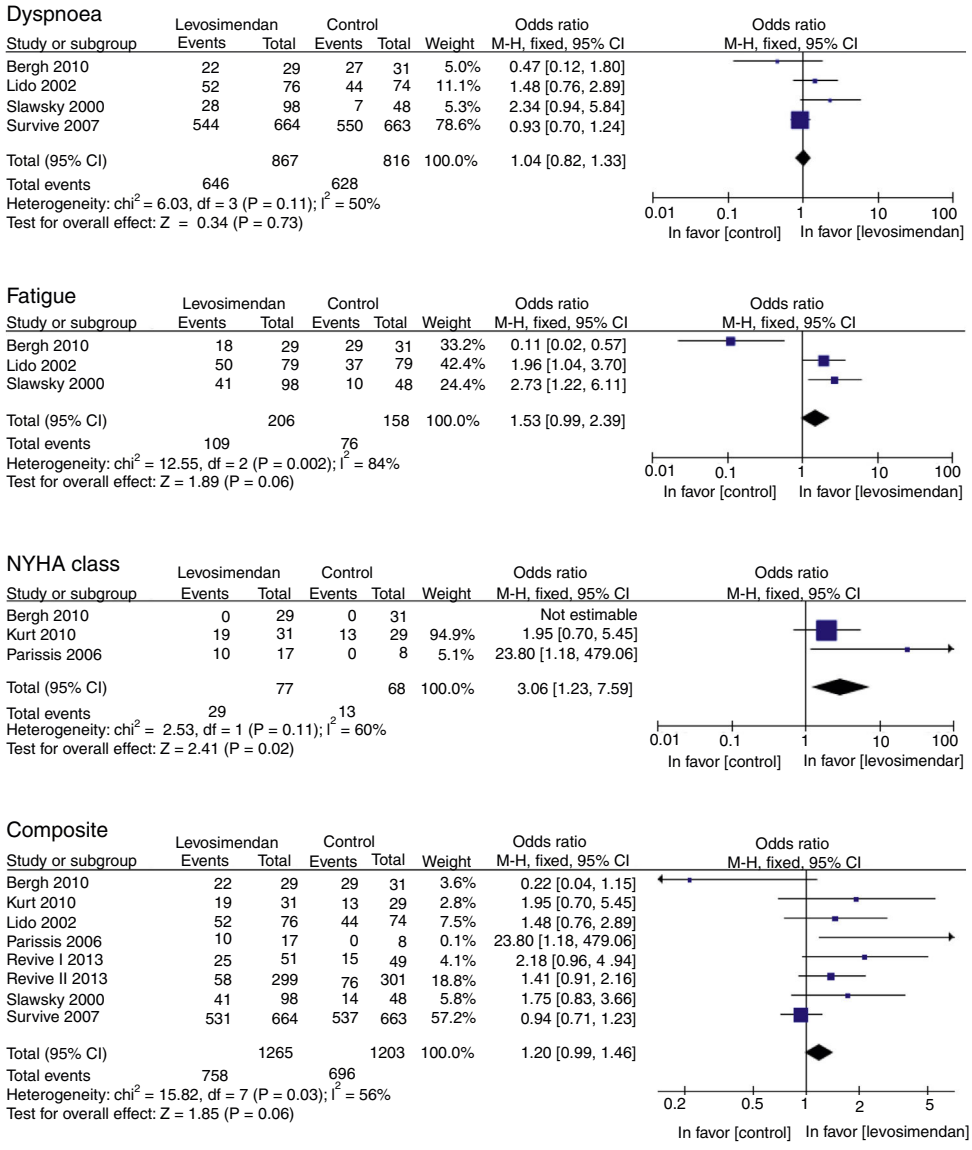

Figure 2 Primary outcomes.

in 2 clinical trials involving 1530 patients (55.6% of all patients).[19,24] The primary outcome was described in 4 trials, including 2230 patients (79.7% of all patients).[19,22,24]

Results of the meta-analysis

Outcomes of clinical improvement

There was no difference in dyspnea (RM 1.04, 95% CI 0.82–1.33, $p = 0.73$), although there was a tendency to reduce fatigue (RM 1.53, 95% CI 0.99–2.39, $p = 0.06$). There was a significant improvement in the NYHA functional class with levosimendan compared to that with placebo or dobutamine (RM 3.06, 95% CI 1.23–7.59, $p = 0.02$), although at the combined endpoint of clinical improvement, there was only a marginal reduction of 20% (RM 1.20, IC 95% 0.99–1.46, $p = 0.06$) (Table 4). There was substantial heterogeneity ($p < 0.10$) in all primary outcomes (Fig. 2).

Secondary outcomes

There was no difference in mortality between the levosimendan group and the placebo or dobutamine groups (RR 0.92, 95% CI 0.74–1.14, $p = 0.43$), although there was a significant improvement in LVEF (RR of 4.07, 95% RR = 95% CI −358.32 to −292.89; $p < 0.00001$), in the incidence of new episodes of heart failure (RR 0.83, 95% CI 0.70–0.97, $p = 0.02$) and in the use of rescue treatment (RR 0.63 95% CI 0.48–082, $p = 0.0007$) (Fig. 3). The following adverse events were more commonly observed in the levosimendan group compared to the placebo or dobutamine groups: headache (RR 1.88, 95% CI 1.51–2.34, $p < 0.00001$), hypotension (RR 1.38, 95% CI 1.17–1.64; RR 1.43, 95% CI 1.08–1.89, $p = 0.01$),

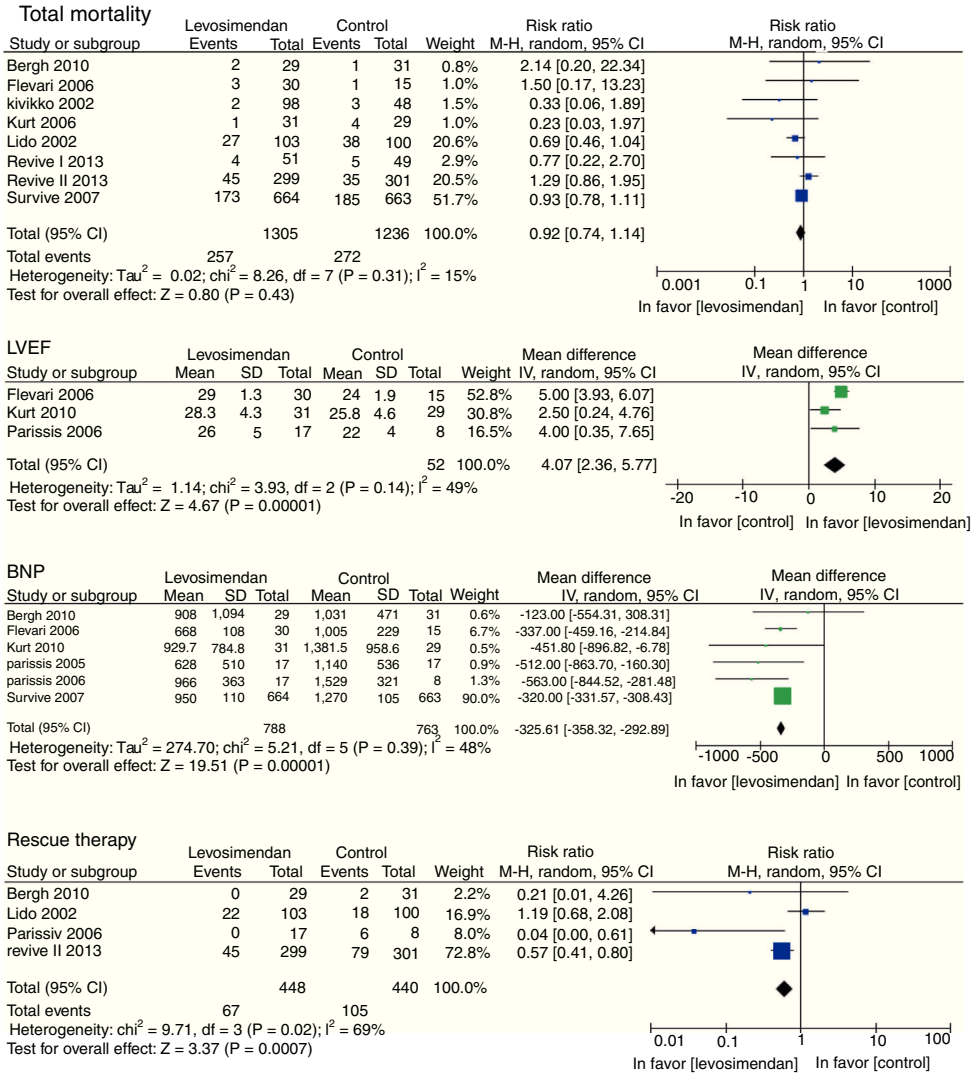

Figure 3 Secondary outcomes.

and atrial fibrillation (RR 0.04, 95% CI 0.02–0.06, $p = 0.0002$), as well as non-sustained ventricular tachycardia. There was no difference in the development of hypokalemia (RR 1.23, 95% CI 0.94–1.62, $p = 0.13$) (Fig. 4).

Discussion

There are few randomized clinical trials that report the outcomes of symptomatic improvement, and among them, the majority only report the NYHA functional class. However, it is important to note that they do not consider the limitations associated with fatigue, palpitations, dyspnea or angina, and therefore, there are no reports of the improvement of these individual symptoms in the trials. Thus, because patients with HF most often present a pivotal symptom, it is important to know if an intervention, in this case, levosimendan, will improve a specific symptom to a certain extent. In this meta-analysis evaluating the intermittent administration of levosimendan against placebo in chronic HF, we conclude that NYHA functional class $\geq$ 3 is similar in survivors of both groups.[24] Contrary to previous findings, the present meta-analysis demonstrates a statistically significant improvement in the NYHA functional class, although only through a trend toward improvement in fatigue outcomes and the combined endpoint of clinical improvement in favor of levosimendan when compared to placebo or dobutamine. To this extent, a larger sample is required to reduce the confidence interval of the outcomes.

In a systematic review with a meta-analysis, Ribeiro, et al. concluded that there was no significant difference in mortality in patients with decompensated HF treated with a levosimendan infusion when compared to dobutamine or placebo.[25] However, there are other meta-analyses that report a benefit in mortality in favor of levosimendan in critically ill patients, patients undergoing cardiac surgery with an ejection fraction <0.40 and in acute heart failure.[26–29] The present meta-analysis did not show a significant difference in mortality when comparing levosimendan with placebo or dobutamine. However, an improvement in LVEF,

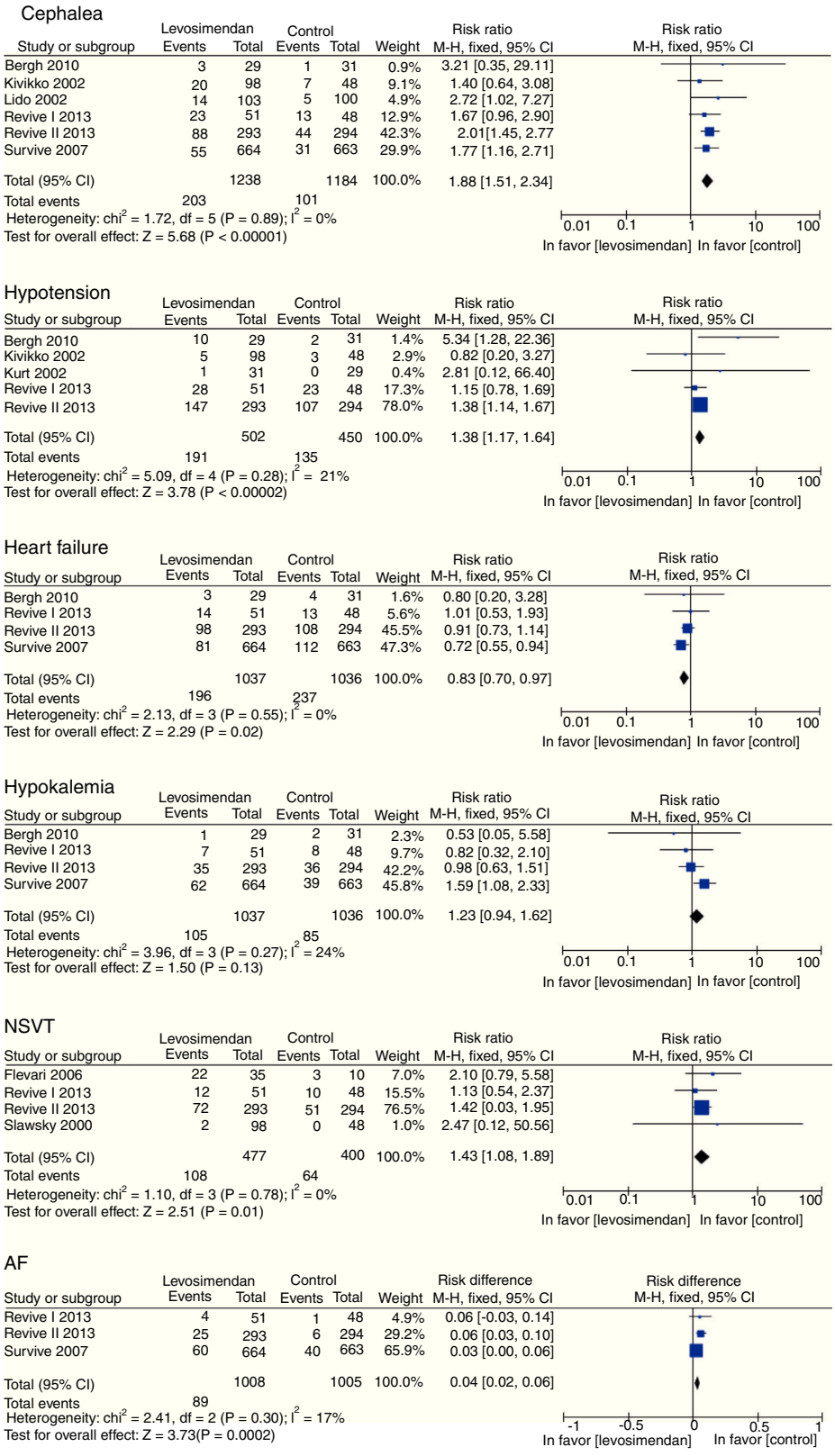

Figure 4 Adverse events outcomes

B-type natriuretic peptide (BNP) levels and a decrease in new heart failure events and the use of salvage therapy in favor of levosimendan was shown, with a statistically significant difference.

Regarding the adverse effects analyzed, some reports of meta-analyses show no difference between levosimendan and dobutamine in hypotension, supraventricular arrhythmias, and ventricular arrhythmias.[29,30]

Although other systematic reviews have reported a trend toward hypotension against levosimendan and a reduction of postoperative atrial fibrillation in favor of levosimendan, in the present meta-analysis there were fewer headaches, cases of hypotension, non-sustained ventricular tachycardia, and atrial fibrillation in favor of placebo or dobutamine, with significant differences.[27,28]

Conclusions

This systematic review and meta-analysis showed an improvement of the NYHA functional class and other combined points of clinical improvement, but not of the simple outcomes of dyspnea or fatigue in patients with decompensated heart failure when levosimendan was used compared to placebo or dobutamine. In addition, it demonstrated an improvement in other prognostic markers of HF, such as LVEF, serum BNP level and reduction in the use of rescue treatments during the exacerbation of HF. However, it is important to mention that the side effects associated with levosimendan may limit its use.

The main limitation of this review was the lack of standardization of the reporting of outcomes of clinical improvement, adverse effects, and follow-up times in the controlled trials used for the meta-analysis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare no conflicts of interest.

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