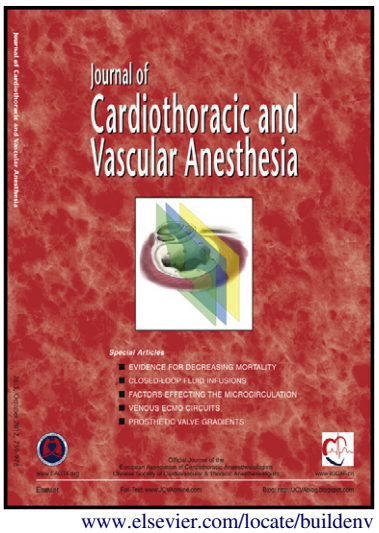

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Levosimendan Treatment for Heart failure: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Emerging studies suggest that administration of levosimendan therapy may be better than dobutamine or placebo in decompensated heart failure. We performed an updated meta-analysis of trials to obtain the best estimates of the efficacy and safety of levosimendan for the initial treatment of decompensated heart failure.

Design: A meta-analysis.

Setting: Hospitals.

Participants: A total of 5349 patients from 25 randomized controlled studies were included in the analysis.

Interventions：None.

Measurements and Main Results: We performed a meta-analysis of trials comparing levosimendan therapy with dobutamine or placebo in patients with decompensated heart failure. Twenty-five trials, involving 5349 patients, were included. Two reviewers performed independent article review and study quality assessment. Data on overall mortality, early term mortality, midterm mortality, long term mortality, efficacy outcomes, and adverse events were collected. Mortality outcomes were according to follow-up duration: early term (≤30-day), midterm (30-day to ≤ 6 -month), and long term (> 6-month). Levosimendan was performed a comparison with dobutamine or placebo, calculating pooled relatives risk (RRs) and associated 95% confidence intervals (CIs). A random effects model would be selected for meta-analysis if there were significant heterogeneity. Levosimendan significantly reduced total mortality (17.1% versus 20.8%; RR, 0.84; 95% CI, 0.75-0.94). Compared with dobutamine, levosimendan was associated with significant reduction in mortality at final follow up (RR, 0.86; 95%CI, 0.76-0.97; I^2=7%; *P*=0.02).Compared with placebo, levosimendan was associated with a nonsignificant trend in favor of placebo in mortality at final follow up (11.6% versus 16.2%, RR, 0.75; 95% CI, 0.56 to 1.01; *P*=0.06), but it was associated with a significant reduction in long term mortality (RR, 0.34; 95%CI, 0.15 to 0.76; *P*=0.009).Compared with dobutamine or placebo, levosimendan therapy was associated with improvements in haemodynamic and echocardiographic derived cardiac parameters. Levosimendan therapy increased the risks of extrasystoles (RR, 1.88; 95%CI, 1.26-2.81), hypotension (RR, 1.33; 95%CI, 1.15-1.53), and headache or migraine (RR, 1.94; 95%CI, 1.54-2.43) when compared with control therapy.

***Conclusions*:** As compared to placebo or dobutamine, Levosimendan in patients with

heart failure seems to have haemodynamic and cardiac benefits. It reduced total mortality and was associated with an increased risk of cardiovascular adverse events.

Introduction

Advanced decompensated chronic heart failure (CHF) has emerged as a complex clinical condition associated with release of oxygen-derived free radicals that promote progressive left ventricular dysfunction. It is the most frequent reason before hospital admission among patients over the age of 65 years, [1] and about 5000 hospital admissions per million population per year are attributable to heart failure.[2]

Intravenous levosimendan, a vasodilator and inotropic agent for the treatment of acutely decompensated heart failure, improves myocardial contractility and enhances the sensitivity of myofilaments to calcium thereby causing an increase in myocardial oxygen consumption.[3] It has been found to have phosphodiesterase type Ⅲ inhibitory properties at high concentrations, [4] and to produce vasodilatation by opening the ATP-sensitive potassium channels in vascular smooth muscle cells.[5]

When properly applied, meta-analysis can increase the statistical power of primary end points, clarily disagreement among studies, and estimate effect sizes to quantify outcomes from a set of individual studies.[6] In early clinical studies in patients with heart failure, levosimendan had favorable effects on cardiac symptoms, hospitalization, and risk of death.[7-9] To better assess the clinical benefit, we carried out a meta-analysis of efficacy and safety of levosimendan therapy on clinical outcome and survival in patients with heart failure.

Methods

Data Sources and Searches

We attempted to identify all relevant published randomized trials comparing levosimendan with dobutamine or placebo for the initial treatment of decompensated heart failure. We searched MEDLINE (1950-Aug, 2014), EMBASE(1980- Aug, 2014), and the Cochrane Library (2014) for English-language randomized controlled trials using the terms "heart failure," "levosimendan," "dobutamine," "placebo," "controlled clinical trial," "randomized controlled trial," and "random." We also performed manual search of references from original articles and pertinent reviews. Searches were restricted to completed trials in human beings with abstracts or full texts published in English.

Study Selection

Two investigators (B.J.G., Z.C.L.) independently evaluated studies for inclusion, and any disagreements were resolved by discussion. Criteria for inclusion were (1) proper randomization, (2) inclusion of patients with objectively diagnosed heart failure, (3) comparison of levosimendan with dobutamine or placebo and dobutamine versus placebo for the initial treatment of heart failure, and (4) use of objective methods to assess one or more clinical outcomes.

Outcomes

Study outcomes were analyzed comparing the results from trials with levosimendan versus dobutamine , the results from trials with levosimendan versus placebo, and the results from trials with dobutamine versus placebo.

The hemodynamic and cardiac parameters of levosimendan were measured by the mean arterial pressure(MAP), pulmonary artery pressure(PAP), pulmonary vascular resistance(PVR), systemic vascular resistance (SVR), cardiac index(CIN), stroke

volume (SV), left ventricular ejection fraction(LVEF), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension（LVEDD）, and ratio of E-wave and A-wave peak velocities of the mitral flow profile(E/A).

The safety outcomes were adverse events, such as ventricular tachycardia, extrasystoles, hypotension, constipation, diarrhea, hypokalemia, nausea, vomiting, urinary track infection, dizziness, headache or migraine, angia pectoris, chest pain or myocardial ischaemia, and mortality. Mortality outcomes were according to their follow-up duration: early term (≤30 days), midterm (30 days to ≤ 6 months), and long term (> 6 months).

Statistical Analyses

We determined pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for mortality in heart failure patients who received levosimendan or treatment with dobutamine or placebo. Furthermore, the pooled RR of any adverse event was calculated. Data were pooled by use of a fixed-effects model (Mantel– Haenszel method).[10] Results obtained with a fixed-effects model were also compared with those obtained with a random effects model. Heterogeneity was assessed by visual inspection of the forest plots and by the Q-statistic.All analyses were performed using Review Manager software 5.1.

Results

Study Selection and Characteristics

There were 25 studies[11-35] (as shown in Figure1) with 5349 patients in the present meta-analysis (study characteristics are listed in Table 1), among which 7[11-14, 22, 23, 25]were double-blind, 3[26, 27, 31]were single-blind, 8[19, 20, 24, 28-30, 34, 35]were

intention-to-treat, and 7[15-18, 21, 32, 33] had concealed allocation. The dose of levosimendan varied between 0 and 24 μg/kg (as an intravenous bolus) or between 0.05 and 0.6 μg/kg/min (as a continuous infusion). Follow-up durations were ≤30days in 12 trials,[14-16, 21,24-29, 31, 33,34]1 month in 2 trials, [22, 23] 3 months in 2 trials, [13, 28] 4 months in 1 trial, [32]5 months in 1 trial, [30] 6 months in 6 trials, [11, 12, 17, 18, 20, 35] and 12 months in 1 trial.[19]

Methodological quality

We summarized the methodological quality of jadad score of the reported studies in Table 1.The bias assessments were shown in Figure 10 according to the risk of bias.

Meta-Analysis

Mortality Outcomes

Death occurred in 407 of 2380 patients (17.1%) treated with levosimendan and in 502 of 2411 patients (20.8%) treated with controls. Use of levosimendan was associated with a significant reduction in total death (RR, 0.84; 95%CI, 0.75-0.94; I^2=19%; *P*=0.003; Fig 2). Reanalysis with an random effects model did not change this result (RR, 0.81; 95%CI, 0.69-0.95; *P*=0.009). As shown in Fig 3, the total number of events in levosimendan group was 52(16.7%) versus 95(22.5%) in dobutamine group, and there was no significant difference between the two groups regarding early mortality (RR, 0.61; 95% CI, 0.26 to 1.45; I^2=63%; *P*=0.26). Compared with dobutamine, pooled analysis of levosimendan indicates no reduction in midterm mortality, with an RR of 0.85 (95%CI, 0.64 to 1.11; *P*=0.23; Fig 4). Reanalysis with an random effects model did not change this result (RR, 0.85; 95%CI, 0.64-1.12; *P*=0.24). Compared with placebo, pooled analysis of levosimendan indicates no

reduction in midterm mortality, with an RR of 0.85 (95%CI, 0.62 to 1.16; *P*=0.31; Fig 4). Reanalysis with an random effects model did not change this result (RR, 0.85; 95%CI, 0.64-1.17; *P*=0.32). Levosimendan therapy was associated with a significant reduction in long term mortality as compared with placebo (RR, 0.34; 95%CI, 0.15 to 0.76; *P*=0.009; Fig 5). Reanalysis with an random effects model did not change this result (RR, 0.35; 95%CI, 0.15-0.81; *P*=0.01). Levosimendan therapy was not associated with a reduction in long term mortality as compared with dobutamine (RR, 0.89; 95%CI, 0.76 to 1.04; *P*=0.15; Fig 5). Reanalysis with an random effects model did not change this result (RR, 0.83; 95%CI, 0.63-1.11; *P*=0.21).Compared with dobutamine, levosimendan was associated with significant difference in mortality at final follow up (RR, 0.86; 95%CI, 0.76-0.97; I^2=7%; *P*=0.02; Fig 6). Reanalysis with an random effects model did not change this result (RR, 1.39; 95%CI, 0.46-4.21; *P*=0.56). Compared with placebo, levosimendan was associated with a nonsignificant trend in favor of placebo in mortality at final follow up (11.6% versus 16.2%, RR, 0.75; 95% CI, 0.56 to 1.01; *P*=0.06, Fig 7). Reanalysis with an random effects model did not change this result (RR, 0.64; 95%CI, 0.39-1.07; *P*=0.09). Compared with placebo, dobutamine was associated with a nonsignificant trend in favor of placebo in mortality at final follow up (RR, 1.44; 95% CI, 0.48 to 4.33; *P*=0.51, Fig 8). Reanalysis with an random effects model did not change this result (RR, 1.39; 95%CI, 0.46- 4.21; *P*=0.56). Funnel plot analysis did not show evidence of small study bias for the risk of mortality in levosimendan group versus dobutamine group and levosimendan group versus placebo (Fig 9).

Hemodynamic parameters

The effect of levosimendan versus dobutamine or placebo on haemodynamic

parameters are shown in Table 2.

Comparing levosimendan vs dobutamine or placebo, SBP, DBP, MAP, PVR, and SVR were reduced more with levosimendan, but PAP, CIN, and SV were increased more with levosimendan.

Echocardiographic derived cardiac parameters

Combing data from studies comparing levosimendan with dobutamine infusion, the results showed significant differences in LVESD, LVEDD, and E/e, but no differences were observed in LVEF and E/A. When we compared levosimendan with placebo, there were significant differences in LVEF, LVESD, and E/A (Table 2).

Adverse events

Table 3 summarizes the adverse events identified in this meta-analysis. In trials, levosimendan therapy increased risk of extrasystoles recurrence (RR, 1.88; 95%CI, 1.26-2.81; P=0.002), headache or migraine(RR, 1.94; 95%CI, 1.54-2.43; P<0.00001), and hypotension (RR,1.33;95%CI, 1.15-1.53; P=0.0001) in patients with heart failure, as compared with the combined control therapy. The pooled data revealed a nonstatistically significant difference in ventricular tachycardia, constipation, diarrhea, hypokalemia, nausea, vomiting, urinary track infection, dizziness, and angia pectoris, chest pain or myocardial ischaemia.

Discussion

The objective of our meta-analysis was to assess the effect of levosimendan on cardiac and haemodynamic parameters, adverse events , and mortality, nearly 14 years after its approval for clinical use. We therefore compiled 25 clinical studies that

compared levosimendan with dobutamine or placebo in patients with decompensated heart failure. In this meta-analysis of 25 studies involving 5349 patients, we have demonstrated a significant reduction in the incidence of both total mortality and long term mortality. However, we observed no significant differences in either incidence of early term mortality or rate of midterm mortality. We found all-cause mortality to be significantly lower with levosimendan than with dobutamine. Importantly, in our analysis, incidence of mortality in patients treated with levosimendan was certainly not lower than in patients treated with placebo.

Short-term results following levosimendan treatment in acute heart failure syndromes have found a reduction in mortality rates.[11, 36] Results for long term outcome in two large-scale randomized clinical trials (SURVIVE and REVIVE-II) has reported no reduction in mortality rates, when compared with placebo or dobutamine, at 90 and 180 days, respectively.[12] A meta-analysis of 5 RCTs of intravenous levosimendan found no statistically significant reduction in mortality.[37] However, a recent meta-analysis of 23 trials in mortality rates in mortality rates updated in 2012 reported a significant reduction in the risk of all-cause mortality in levosimendan-treated patients.[38] In 2015, in critically ill patients with low cardiac output syndrome not having cardiac surgery, Koster etal. [39]showed that levosimendan was associated with mortality (RR 0.83, TSA-adjusted 95 % CI 0.59-0.97). Our meta-analysis also demonstrated a significant reduction in the incidence of total mortality. In adult cardiac surgery patients, when compared with placebo, levosimendan was associated with a decrease in mortality (OR=0.48, 95% CI 0.28 to 0.80).[40]However, in our meta-analysis, compared with placebo, levosimendan was associated with a nonsignificant trend in favor of placebo in mortality at final follow up. A large randomized controlled study is warranted.

To the best of our knowledge, previous studies have shown that levosimendan provides not only rapid effects which is itself mediate but also sustained influences what is mediated by its active metabolite OR-1896.[41, 42] Levosimendan has a half-life of 1.3 h, however, the plasma concentration level of OR-1896 and OR-1855 have long have-life at 48 and 72 h after levosimendan infusion. It also demonstrated that hemodynamic effects sustained for at least 48 h without any tolerance to levosimendan.[42]

Literature demonstrates that heart failure is a systemic condition. Furthermore, neurohormonal activation mediates clinical progression and cardiac remodelling.[43] During the process of human heart disease, a family of natriuretic peptides with diuretic, potent natriuretic, and vasorelaxant activity was detected.[44] Natriuretic peptides, such as BNP and NT-proBNP, correlated with symptomatic LV dysfunction, influence the severity of symptoms and prognosis, and reflect diastolic dysfunction.[45, 46] Many previous studies have shown that a significant reduction in plasma BNP or NT-proBNP concentrations in response to levosimendan.[12, 18, 22, 30, 47-51] The E/A and E/e ratio have been proposed as reliable markers of diastolic function, while LVEF has been established to be an marker of systolic function.Recent studies have found that levosimendan produces a beneficial effects over the E/e ratio, the E/A ratio, LVEF, tissue Doppler imaging tricuspid annulus early diastolic velocity, left ventricular wall stress, and left atrium performance.[26, 29, 34, 52-54] Consistent with these findings, the present meta-analysis has come to similar conclusions on the effect on cardiac parameters.

It is noteworthy that levosimendan improves hemodynamic parameters.[8, 55, 56] Recently, studies have been documented that levosimendan might cause dose dependent decreases in pulmonary arterial, right atrial, pulmonary capillary wedge

pressure, mean arterial pressure, and a concomitant increase in cardiac index.[11, 24] This meta-analysis is in accordance with the results of these studies.

Earlier studies have reported adverse events with cardiac disorders, vascular disorders, gastrointestinal disorders, infections, metabolism and nutrition disorders, nervous system disorders, and renal disorders in patients with heart failure receiving levosimendan.[11-14, 23] Nieminen etal[14] showed that hypotension, nausea, and headache happened more frequently in the high concentration levosimendan group. In the SURVIVE trial, [12] levosimendan showed higher risks of headache, hypokalemia, and atrial fibrillation. As compared to other comparators, the incidence of hypokalemia was consistently higher in the levosimendan groups .[11,14] However, the specific mechanism need to be explored. What's more, Bergh etal[22] reported that there was no significant differences in both atrial fibrillation and ventricular tachycardia in levosimendan or dobutamine group. In 2007, a study reported that levosimendan had an effect on improving long-term renal function in patients with advanced chronic heart failure, and this improvement was superior to controls.[57] A recent meta-analysis of 10 trails updated in 2010 and including 440 patients receving levosimendan treatment during coronary atery bypass graft surgery found statistically significant differences in acute renal function and atrial fibrillation.[58] Our pooled meta-analysis demonstrated that levosimendan was associated with cardiovascular events, including extrasystoles and hypotension.

Limitations

Sereval limitations of the present meta-analysis should be considered. Firstly, the primary limitation of this meta-analysis is the lack of complete mortality data. Not all the studies in this report have reported total mortality and long term mortality.

Secondly, nearly all the studies lasted less than 12 weeks, limiting our assessment of long term mortality. Finally, we only included English language studies.

Conclusions Levosimendan therapy was effective in reducing the risk of total mortality in patients with heart failure. Compared with dobutamine, levosimendan was associated with significant difference in mortality at final follow up. It was associated with a significant reduction in long term mortality when compared with placebo. Levosimendan treatment was associated with improvements in haemodynamic and cardiac parameters, when compared with dobutamine or placebo. Significant differences of adverse events for infusion of levosimendan in extrasystoles, hypotension, and headache or migraine were observed.

Disclosures The authors have no conflicts of interest to disclose.

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Figure captions:

Figure 1. PRISMA flow diagram for study selection.

Figure 2. Total mortality during levosimendan treatment.

Figure 3. Meta-analysis for the comparison of early term mortality in levosimendan group versus dobutamine group.

Figure 4. Meta-analysis for the comparison of midterm mortality in levosimendan group versus dobutamine group and levosimendan versus placebo group.

Figure 5. Meta-analysis for the comparison of long term mortality in levosimendan group versus dobutamine group and levosimendan versus placebo group.

Figure 6. Meta-analysis for the comparison of mortality in levosimendan group versus dobutamine group.

Figure 7. Meta-analysis for the comparison of mortality in levosimendan group versus placebo group.

Figure 8. Meta-analysis for the comparison of mortality in dobutamine group versus placebo group.

Figure 9. Funnel plots of studies assessing the comparison of mortality in levosimendan group versus dobutamine group (A) and levosimendan group versus placebo (B). RR, risk ratio; SE, standard error.

Figure 10. Methodological quality of included studies according to the Cochrane Collaboration's tool for assessing risk of bias.

Table captions:

Table 1. Summary of patient characteristics from the 25 studies included in the Meta-Analysis.

Table 2. Measures of hemodynamic and cardiac parameters after levosimendan intervention.

Table 3. Summary risk ratios for safety outcomes with levosimendan versus control treatment.

Table 1 . Summary of Patient Characteristics from the 25 Studies Included in the Meta-Analysis

Author	Enrollment, y	Year of Publication	Country and Centers	Blinding	Patients Included	Age, y	Male, %	Population	Intervention drug	Control drug	Levosimendan infusion, μg/kg/min	Control drug infusion, μg/kg/min	Levosimendan duration, h	Control duration, h	Follow-Up duration, months	Jadad score
Follath[11]	NA	2002	Europe, 26 centers	Double-blind	203	59(11)	87	Admitted to hospital with low-output heart failure	Levosimendan	Dobutamine	0.1 to0.2	5	24	24	6	5
Mebazaa[12]	2003-2004	2007	Worldwide, 75 centers	Double-blind	1328	67(12)	80	Hospitalized with acutely decompensated heart failure	Levosimendan	Dobutamine	0.1 to0.2	5 to 40	24	24	6	5
Packer[13]	2001-2004	2013	Worldwide, 103 centers	Double-blind	700	61(15)	73	Hospitalized with acutely decompensated heart failure	Levosimendan	Placebo	0.1 to0.2	NA	24	24	3	5
Nieminen[14]	1994-1996	2000	Worldwide, 12 centers	Double-blind	151	64(15)	87	Admitted with stable chronic heart failure	Levosimendan	Dobutamine	0.05 to 0.6	6	24	24	1 day	5
Tasal[15]	2011-2013	2014	Turkey, multi-center	UNK	553	63(2)	67	Hospitalized with acutely decompensated heart failure	Levosimendan	Dobutamine	NA	NA	24	24	Hosp	3
Cavusoglu[16]	NA	2008	Turkey, multi-center	UNK	44	NA	NA	NYHA class IV admitted with decompensated heart failure	Levosimendan	Dobutamine	0.2	10	24	24	2 day	2
Qarawani[17]	2007-2011	2013	Israel, multi-center	UNK	84	73(9)	63	Ischemic decompensated heart failure	Levosimendan	Placebo	0.1 to 0.2	NA	24	24	6	3
Farmakis[18]	NA	2010	Greece, single center	UNK	98	64(10)	91	Admitted for acutely decompensated heart failure	Levosimendan	Placebo	0.1	NA	24	24	6	4
Dominguez-Rodriguez[19]	NA	2008	Spain, multi-center	Open	22	64(14)	77	Cardiogenic shock with severe left ventricular systolic dysfunction	Levosimendan	Dobutamine	0.1	5	24	24	12	4
Bonios[20]	NA	2012	Greece, multi-center	Open	63	56(12)	94	Hospitalized for decompensated, end stage chronic heart failure	Levosimendan	Dobutamine	0.3	10	6	6	6	4
Avgeropoulou[21]	2002-2003	2005	Greece, multi-center	UNK	29	71(10)	76	NYHA IV admitted with advanced decompensated heart failure	Levosimendan	Dobutamine	0.1	5 to 10	24	24	5 days	4
Bergh[22]	2002-2005	2010	Europe, 13 centers	Double-blind	60	71(11)	85	Admitted to hospital with acutely decompensated heart failure	Levosimendan	Dobutamine	0.1 to 0.2	5 to 10	24	48	1	5
Mebazaa[23]	NA	2009	Multi-center	Double-blind	1327	67(12)	72	Hospitalized with acute heart failure	Levosimendan	Placebo	0.1 to 0.2	NA	24	NA	1	5
De Luca[24]	2003-2004	2005	Italy, single center	Open	26	57(5)	69	AMI with left ventricular dysfunction	Levosimendan	Placebo	0.1	NA	24	NA	1 day	3
Tritapepe[25]	2005-2007	2009	Italy, single center	Double-blind	106	66	80	Recruited with coronary artery disease undergoing elective CABG surgery	Levosimendan	Placebo	NA	NA	24	NA	30 days	5
Parissis[26]	NA	2008	Greece, multi-center	Single-blind	26	62(11)	65	Hospitalized for advanced chronic heart failure	Levosimendan	Placebo	0.1	NA	24	NA	2 days	3
Parissis[27]	NA	2007	Greece, multi-center	Single-blind	39	63(11)	85	Advanced chronic heart failure	Levosimendan	Placebo	0.1	NA	24	NA	2 days	3
Flevari[28]	NA	2006	Greece, multi-center	Open	45	65(1)	87	NYHA III/IV admitted with decompensated advanced heart failure	Levosimendan	Placebo	0.1	NA	24	NA	3	3
Parissis[29]	NA	2006	Greece, multi-center	Open	54	63(10)	93	Hospitalized for NYHA III/IV symptoms of advanced heart failure	Levosimendan	Placebo	0.1 to 0.2	NA	24	NA	2 days	3
Parissis[30]	NA	2005	Greece, single center	Open	34	67(5)	91	Hospitalized for NYHA III/IV symptoms of advanced heart failure	Levosimendan	Placebo	0.1 to 0.4	NA	24	NA	5	3
Parissis[31]	NA	2004	Greece, multi-center	Single-blind	27	71(3)	NA	NYHA III/IV admitted with decompensated advanced heart failure	Levosimendan	Placebo	0.1 to 0.4	NA	24	NA	2 days	3
Adamopoulos[32]	NA	2006	Multi-center	UNK	69	70(2)	84	NYHA III/IV dmitted for acute decompensated heart failure	Levosimendan	Dobutamine, Placeobo	0.1 to 0.4	Dobutamine(5), Placebo(NA)	24	Dobutamine(24), Placebo(NA)	4	3
Levin[33]	2003-2006	2008	Multi-center	UNK	137	62	59	Low cardiac output syndrome	Levosimendan	Dobutamine	0.1	5 to 12.5	24	24	Hosp	3
Duman[34]	NA	2009	Turkey, multi-center	Open	74	65(9)	70	NYHA III or IV admitted with decompensated heart failure	Levosimendan	Dobutamine	0.2	10	24	24	1 day	4
Mavrogeni[35]	NA	2007	Greece, single center	Open	50	62(20)	80	Hospitalized for NYHA III/IV advanced heart failure	Levosimendan	Placebo	0.1 to 0.2	NA	24	NA	6	4

Abbreviations: NA, not available; UNK, unknown; Hosp, during hospitalization.

Table 2 . Measures of Hemodynamic and Cardiac Parameters after Levosimendan Intervention

Control group	Outcomes	Studies,n	WMD	95% CI	*P* Value
Dobutamine	SBP(mmHg)	2	-7.08	-13.05 to -1.10	0.02
	DBP(mmHg)	2	-4.75	-5.36 to -4.15	<0.00001
	MAP(mmHg)	1	-2.5	-4.52 to -0.48	0.02
	PAP(mmHg)	1	7	3.72 to 10.28	<0.0001
	PVR(dyne x s)/cm^5	1	-104	-177.45 to -30.55	0.006
	SVR(dyne x s)/cm^5	1	-300	-531.81 to -68.19	0.01
	CIN(L/m^2/min)	2	0.57	0.08 to 1.06	0.02
	SV(ml)	1	9.02	1.36 to 16.68	0.02
	LVEF(%)	3	-0.01	-0.90 to 0.88	0.98
	LVESD(cm)	3	-2.26	-2.95 to -1.56	<0.00001
	LVEDD(cm)	1	3.6	0.38 to 6.82	0.03
	E/A	2	0.27	0 to 0.55	0.05
	E/e	1	-1.7	-3.07 to -0.33	0.01
Placebo	SBP(mmHg)	5	-4.76	-7.91 to -1.61	0.003
	SVR(dyne x s)/cm^5	1	-254	-497.89 to -10.11	0.04
	LVEF(%)	7	3.15	2.38 to 3.93	<0.00001
	LVESD(cm)	3	-2.35	-3.27 to -1.42	<0.00001
	E/A	4	-0.52	-1.01 to -0.03	0.04

Abbreviations :WMD, weighted mean difference; CI, confidence interval; DBP , diastolic pressure; SBP, systolic pressure; MAP , mean arterial pressure; PAP, pulmonary artery pressure; PVR , pulmonary vascular resistance; SVR, structural vascular resistance; CIN , cardiac index; SV=,stroke volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD ,left ventricular end-diastolic dimension.

Table 3．Summary Risk Ratios for Safety Outcomes with Levosimendan vs Control Treatment

Adverse events	Studies, n	Levosimendan group, n	Control group, n	Risk ration(95%CI)	I^2,%	*P* Value
Ventricular tachycardia[11-13, 33]	4	1176	1170	1.13(0.91-1.42)	63	0.27
Extrasystoles[11-13]	3	1107	1102	1.88(1.26-2.81)	52	0.002
Hypotension[11-13, 22, 25, 35]	6	1206	1208	1.33(1.15-1.53)	51	0.0001
Constipation[12, 13]	2	1004	1002	0.98(0.71-1.36)	0	0.91
Diarrhea[12, 13]	2	1004	1002	1.31(0.88-1.93)	0	0.18
Hypokalemia[12, 13, 22]	3	1033	1033	1.23(0.94-1.62)	48	0.13
Nausea[12, 13, 22]	3	1033	1033	1.12(0.88-1.43)	42	0.36
Vomiting[12, 33]	2	1004	1002	1.02(0.70-1.47)	0	0.93
Urinary track infection[12, 13, 22]	3	1033	1033	-0.01(-0.03-0.01)	0	0.41
Dizziness[11-13]	3	1107	1102	1.24(0.89-1.73)	0	0.2
Headache or migraine[11-13, 22]	4	1136	1133	1.94(1.54-2.43)	0	<0.00001
Angia pectoris,chest pain or myocardial ischaemia[11-13, 25, 33]	5	1228	1220	0.59(0.32-1.11)	44	0.1

Abbreviation: CI,confidence interval.

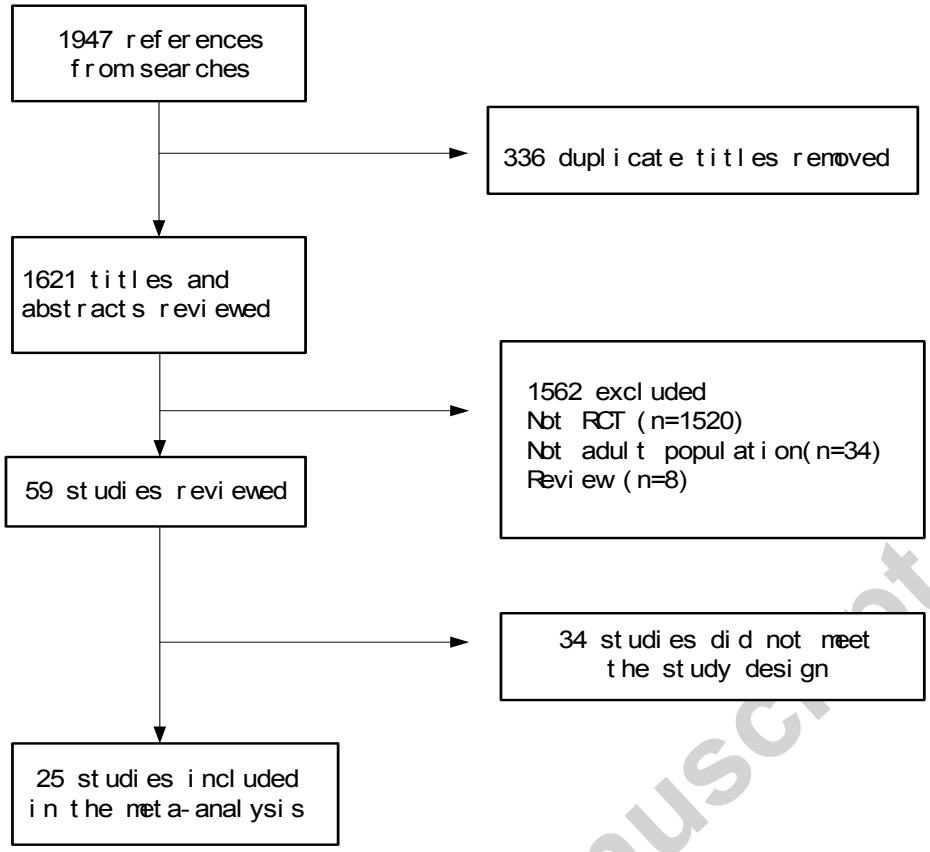

Fig 1. PRISMA flow diagram for study selection.

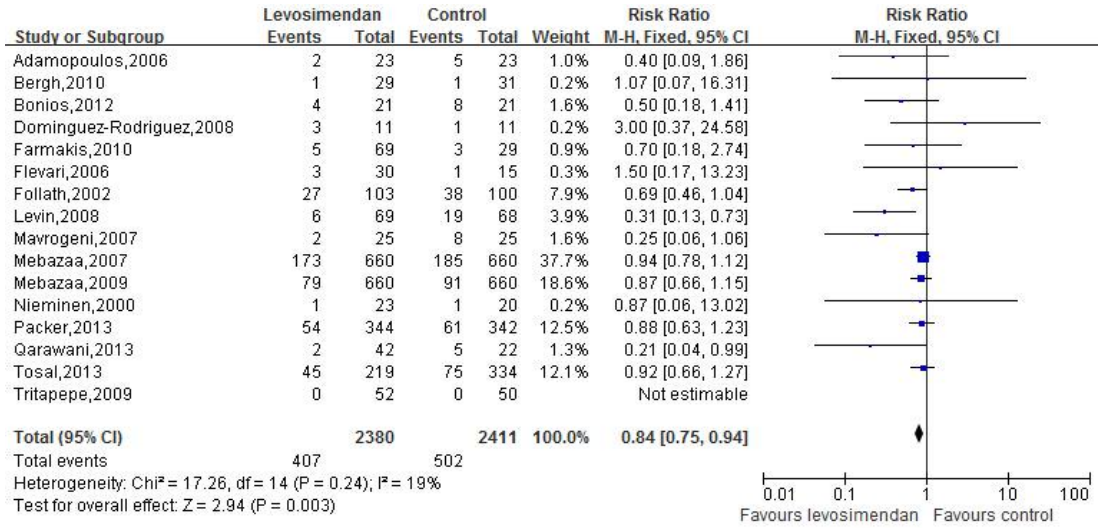

Figure 2. Total mortality during levosimendan treatment.

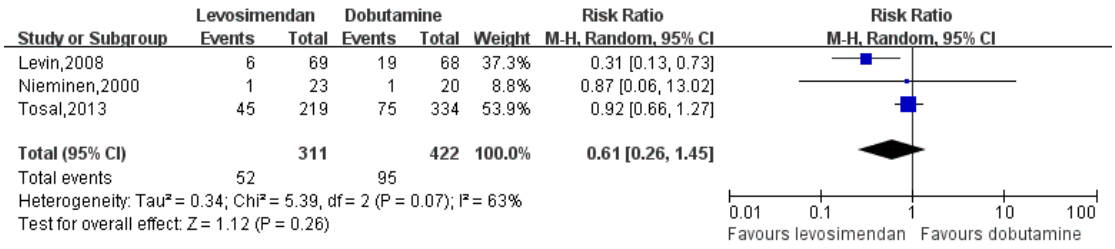

Figure 3. Meta-analysis for the comparison of early term mortality in levosimendan group versus dobutamine group.

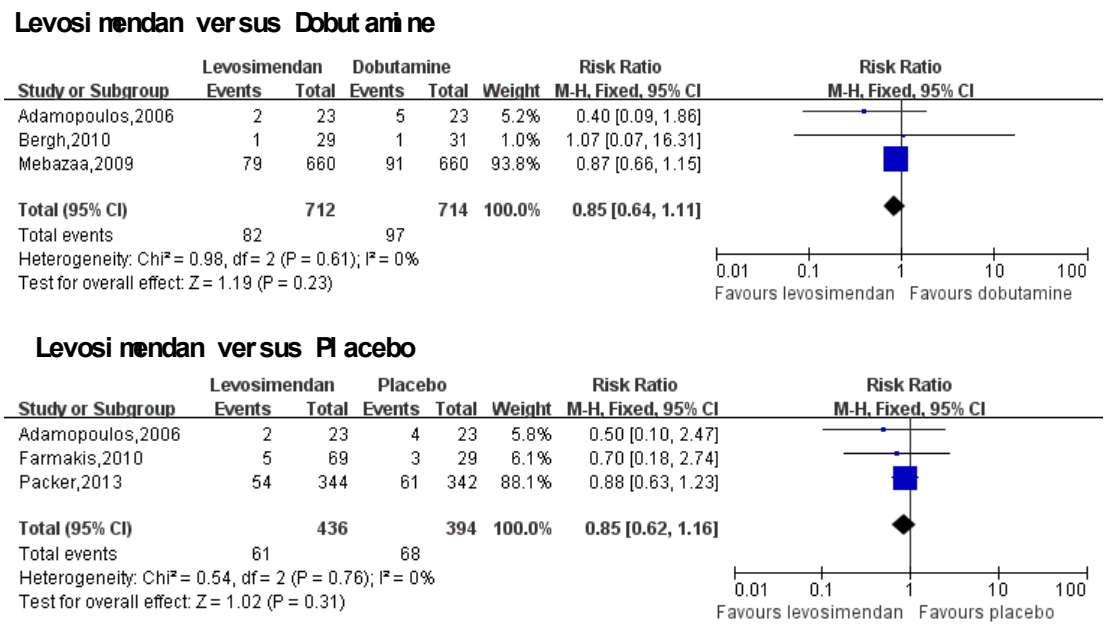

Figure 4. Meta-analysis for the comparison of midterm mortality in levosimendan group versus dobutamine group and levosimendan versus placebo group.

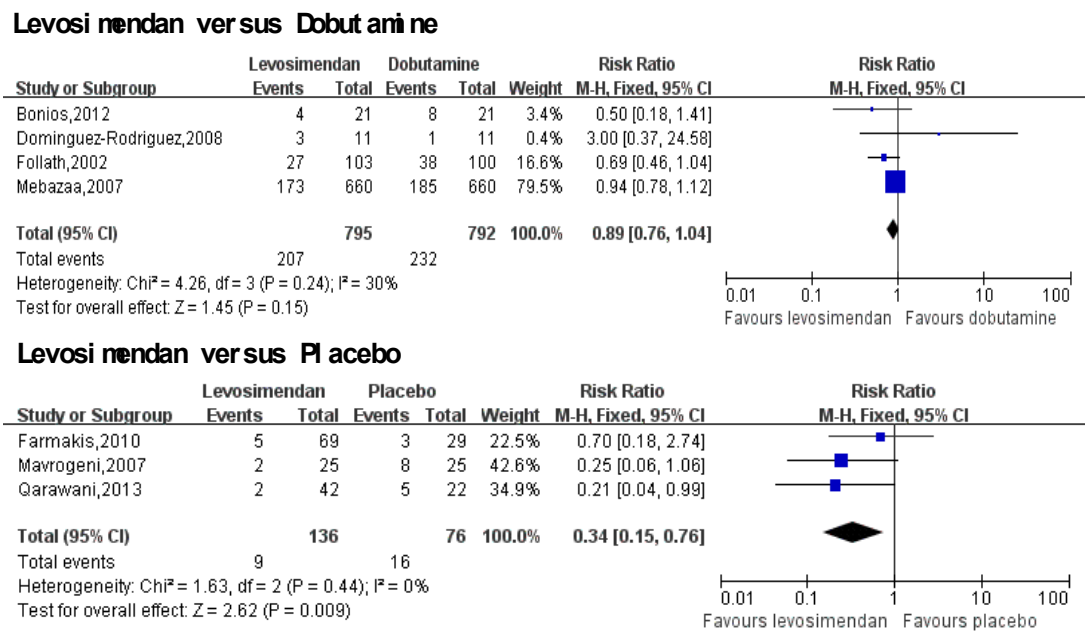

Figure 5. Meta-analysis for the comparison of long term mortality in levosimendan group versus dobutamine group and levosimendan versus placebo group.

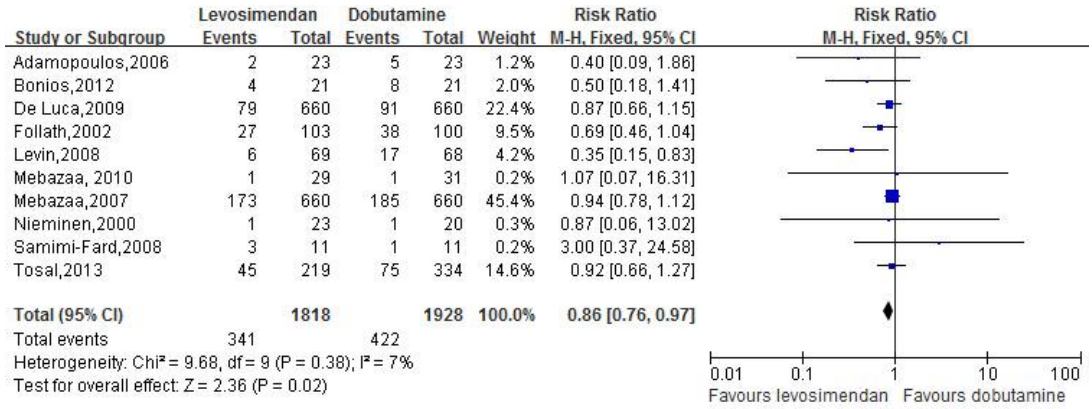

Figure 6. Meta-analysis for the comparison of mortality in levosimendan group versus dobutamine group.

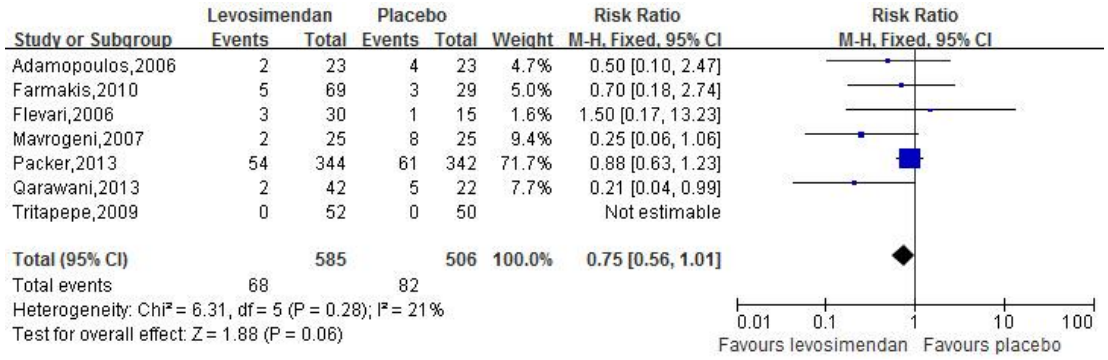

Figure 7. Meta-analysis for the comparison of mortality in levosimendan group versus placebo group.

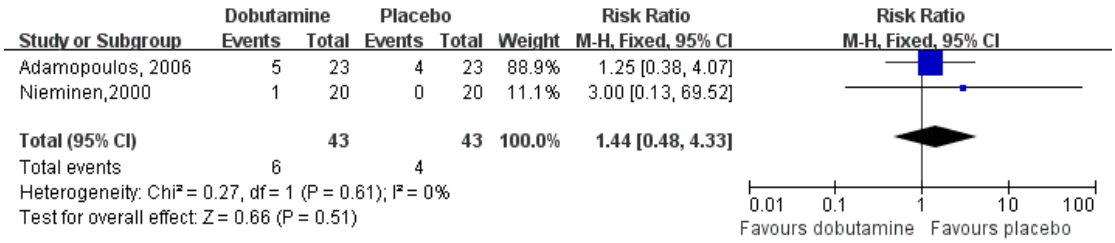

Figure 8. Meta-analysis for the comparison of mortality in dobutamine group versus placebo group.

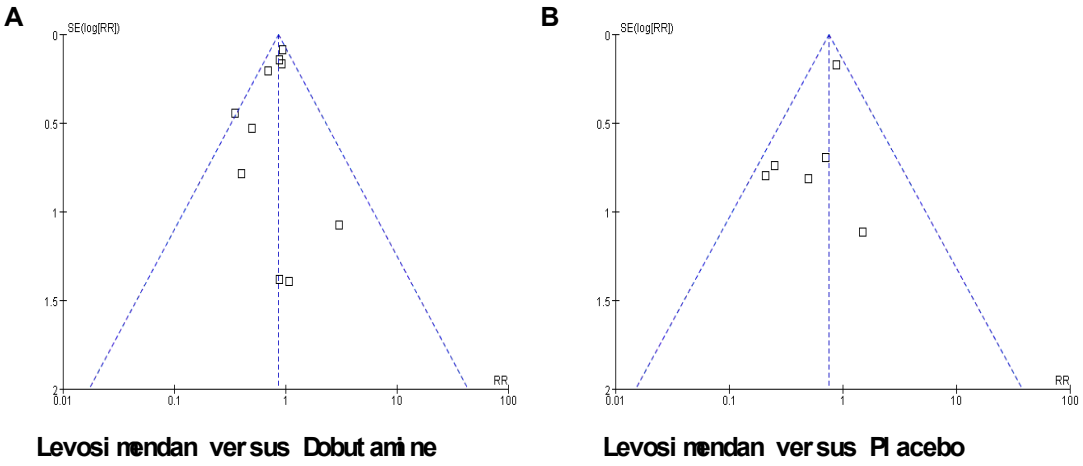

Figure 9. Funnel plots of studies assessing the comparison of mortality in levosimendan group versus dobutamine group (A) and levosimendan group versus placebo (B). RR, risk ratio; SE, standard error.

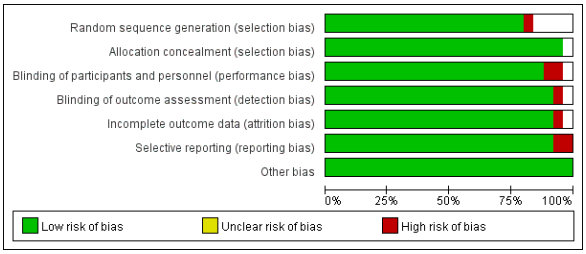

Figure 10. Methodological quality of included studies according to the Cochrane Collaboration's tool for assessing risk of bias.