

The Efficacy and Safety of Levosimendan on Patients with Refractory Heart Failure (ReHF): A systematic review and meta-analysis

Jiayan Zhang^{a,1}, Yanyan Li^{b,1}, Yafang Zha^a, Yuheng Jiao^a, Song Zhang^{a,*}

- Department of Cardiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, 160 Pujian Road, Shanghai 200127, China
- Department of Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 1665 Kongjiang Road, Shanghai 200092, China

Corresponding Author

Song Zhang
Address: Renji Hospital, School of Medicine, Shanghai Jiao Tong University, 160 Pujian Road, Shanghai 200127, China
Tel: +86-021-25077291
E-mail : Zhangsong3961@xinhumed.com.cn (S.Zhang)

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Highlights

- This meta-analysis focused on patients with ReHF for the first time;
- Included 20 RCTs across 20 years with contradictory results;
- Evaluation of several indicators, including all-cause mortality in 180 days, BNP, NT-Pro-BNP, hemodynamic indicators (including HR, LVEF, PCWP), and adverse events, providing evidence for the clinical application of levosimendan.

ABSTRACT

The object of the meta-analysis is to compare the efficacy and safety of levosimendan with both dobutamine and placebo in patients with refractory heart failure (ReHF). Databases, mainly Pubmed, Embase, Cochrane Library, Scopus, and Google Scholar, were searched for randomized controlled trials (RCTs) regarding ReHF treatment, including levosimendan,

dobutamine, and placebo. Mean difference (MD) was generated as effect size by meta-analysis for continuous variables while odds ratios (ORs) for binary variants. All the analyses were performed with Review Manager 5.4. A total of 20 RCTs reporting 3059 patients were enrolled in our analysis. Compared with placebo, levosimendan significantly reduced B-type natriuretic peptide (BNP) (MD=-409.38, 95% CI: -504.81 to -313.95), N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) (MD=-626.45, 95% CI: -1097.97 to -154.93), and pulmonary capillary wedge pressure (PCWP) (MD=-5.04, 95% CI: -5.61 to -4.47) and significantly increased the left ventricular ejection fraction (LVEF) (MD=4.83, 95% CI: 3.99 to 5.67). In summary, levosimendan showed comparable results regarding the above indicators with dobutamine. However, levosimendan failed to reduce all-cause mortality in 180 days compared with either placebo (OR=0.75, 95% CI: 0.54 to 1.04) or dobutamine (OR=0.85, 95% CI: 0.68 to 1.07). This meta-analysis showed that levosimendan significantly improved hemodynamics indices and cardiac function in ReHF patients. However, levosimendan failed to reduce the long-term mortality compared with either dobutamine or placebo.

Keywords

Refractory heart failure; Levosimendan; Dobutamine; Placebo; Meta-analysis

INTRODUCTION

Refractory heart failure (ReHF) refers to patients with devastating reduced cardiac output who have exacerbated symptoms or hemodynamic indices despite optimized treatment[1, 2, 3, 4, 5, 6]. The current guideline mainly recommends diuretics, vasodilators, and non-invasive positive end-expiratory pressure (PEEP) for ReHF[1]. Recently, positive inotropic agents have been widely used to relieve symptoms and ensure that the vital organs get enough blood supply when ReHF fails to respond to conventional treatment[2]. Dobutamine is a traditional inotropic agent used to treat acute decompensated heart failure (ADHF), congestive HF, and ReHF. As a β -adrenergic agonist, it enhances myocardial contractility by increasing intracellular calcium and elevating myocardial energy consumption, leading to an increased risk of death and other adverse events[7].

Lately, levosimendan has been used to treat ADHF for at least two of its mechanisms. On the one hand, as a calcium sensitizer, it increases myocardial contractility without

increasing oxygen consumption[3]. On the other hand, levosimendan causes dilation of peripheral blood vessels (including small arteries and veins) and coronary arteries[3]. Therefore, levosimendan can increase the patients' cardiac output (CO) and improve the symptoms of circulatory congestion. Moreover, levosimendan has a third mechanism involving an inhibition effect towards phosphodiesterase 3 (PDE3), which may have a negative effect on the heart rate (HR) control of patients with HF; however, only a few researchers have reported this negative effect on the HR of levosimendan[4, 5].

Many studies have compared the efficacy of the two positive inotropic drugs on HF patients, but the results were controversial. Therefore, we conducted this updated meta-analysis to evaluate the efficacy and safety of levosimendan on ReHF patients by including more randomized controlled trials.

METHOD

This study was designed according to the Preferred Reporting Project Guide for Systematic Reviews and Meta-analysis (PRISMA).

Literature search

Databases including PubMed, Embase, Cochrane Library, Scopus, and Google Scholar were searched. The MeSH terms were: ('levosimendan' or 'simendan') and ('heart failure' or 'refractory heart failure' or 'HF').

Inclusion Criteria

- (a) Randomized controlled trials (RCTs);
- (b) Patients diagnosed with New York Heart Association (NYHA) class III to IV symptoms and/or severe low left ventricular ejection fraction (LVEF) \leq 40%;
- (c) Intervention included intravenous infusion of levosimendan (with or without a loading dose);
- (d) The control group was treated with dobutamine or placebo;
- (e) One or more clinical outcomes of interest.

Exclusion criteria

- (a) Republished literature;
- (b) Case reports, animal studies, children studies, reviews, and meta-analysis;
- (c) Literature with no relevant outcomes;
- (d) Full text was unavailable.

Quality assessment:

All randomized controlled trials were assessed for any risk of bias based on the Cochrane Collaboration tool.

Data extraction:

The extracted data included: (a) first authors; (b) publication year; (c) sample size (percentage of males vs. females); (d) patients' baseline characteristics; (e) delivery details of levosimendan and dobutamine or placebo; (f) the duration of follow-up.

Two investigators independently searched, assessed, and collected data from each study. Any discrepancy was adjudicated by a senior investigator.

Statistical analysis:

Review Manager software 5.4 was used for the analysis. Mean difference (MD) was generated as effect size by meta-analysis for continuous variables while odds ratios (ORs) for binary variants. If $I^2 \leq 50\%$ and $p > 0.01$, a fixed-effects model would be implemented, otherwise a random-effects model would be performed. If there were obvious heterogeneity, a sensitivity analysis would be carried out. $p < 0.05$ was considered statistically significant.

RESULTS

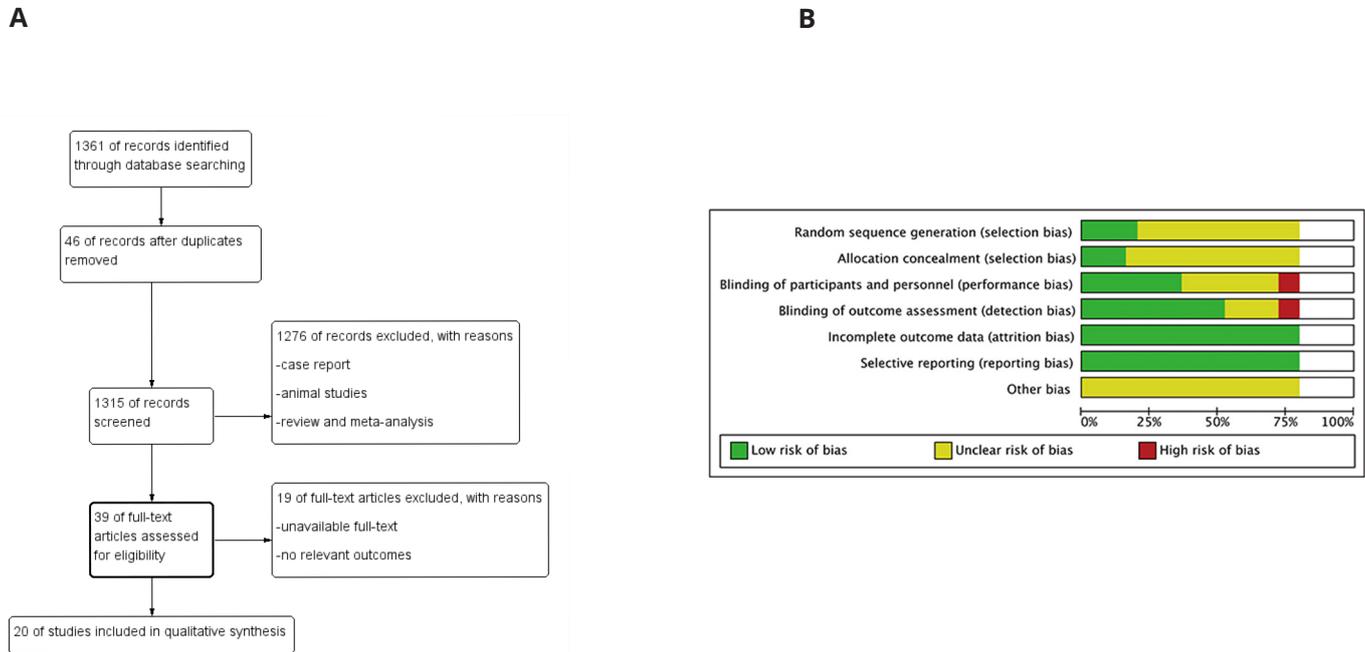
Eventually, a total of 20 RCTs, including 3059 patients, were eligible. Figure 1A shows the flow gram of the screening process and the reasons for exclusion. Table 1 presents the basic characteristics of the included trials. All patients in this study had ReHF (NYHA III-IV) and LVEF $<$ 40% with mean age ranging from 50 to 71, and the proportion of male patients exceeded 50% except for two studies. Levosimendan was injected at least for 24h at a dose of 0.1 or 0.2 $\mu\text{g}/\text{kg}/\text{min}$. The follow-up period was at least 1 day to 180 days. All included RCTs had a low risk of bias and homogeneous quality, as shown in Figure 1B.

Table 1. Basic characteristics of the included trials.

Study	Year	Population	N	Mean age(-years)	% Male	Levo bolus(ug/kg)	Levo infusion(ug/kg/min)	Levo duration(h)	Control	Control dose(ug/kg/min)	Control duration(h)	Duration of follow-up(-days)
1Slawsky	2000	NYHA III/IV; EF≤30%;	146	57	82.0	6	0.1 to 0.4	6h	Placebo	NA	6h	6h
Moiseyev	2002	HF due to AMI	504	67	51.6	6	0.1	6h	Placebo	NA	6h	180
						12	0.2	6h	Placebo	NA	6h	180
						24	0.2	6h	Placebo	NA	6h	180
Follath	2002	EF<35%	203	59	86.7	24	0.1 to 0.2	24h	Dobu	5	24h	180
Avgeropoulou	2005	NYHA IV	29	71	7.6	12	0.1	24h	Dobu	5	24h	5
Adamopoulos	2006	NYHA III/IV; EF≤30%;	69	70	84.1	6	0.1	24h	Dobu placebo	5 NA	24h 24h	120 120
Mebazaa	2007	EF≤30%	1327	67	72.0	12	0.1 to 0.2	24h	Dobu	5 to 40	24h	180
Parissis	2006	NYHA III/IV; EF<35%	54	63	92.6	NR	0.1 to 0.2	24h	Placebo	NA	24h	3
Parissis ¹	2007	NYHA III/IV; EF<30%	63	65	82.5	NR	0.1	24h	Placebo	NA	24h	3
Parissis ²	2007	EF<35%	39	64	84.6	NR	0.1	24h	Placebo	NA	24h	3
Lilleberg	2007	NYHA III-IV; EF<35%	22	55	18	12	0.1 to 0.2	24h	Placebo	NA	24h	14
Duygu ¹	2008	NYHA III/IV; EF<40%	40	53	52.5	6 to 12	0.1	24h	Dobu	5 to 20	24h	30
Duygu ²	2008	NYHA III-IV	60	65	58.3	6 to 12	0.1	24h	Dobu	5 to 20	24h	1
Duman	2009	NYHA III-IV; EF<35%	74	64	69.5	NR	0.2	24h	Dobu	10	24h	1
Duygu	2009	NYHA III-IV; EF<40%	40	60	70.0	6 to 12	0.1	24h	Dobu	5	24h	1
Yilmaz	2009	NYHA III-IV; EF<35%	40	65	75.0	NR	0.1 to 0.2	24h	Dobu	5	6h	1
Bergh	2010	NYHA III-IV; EF<35%	60	70	85.0	12	0.1 to 0.2	24h	Dobu	5 to 10	48h	30
Farmakis	2010	NYHA III-IV; EF<35%	98	64	90.9	NR	0.1	24h	Standard therapy	NR	NR	180
Jia	2014	EF<40%	160	63	60.0	24	0.1	24h	Placebo	NR	24h	180
Mushtaq	2015	NYHA III-IV; EF<35%	42	69	83.3	NR	0.05 to 0.2	24h	Placebo	NA	24h	1
Gencer	2017	EF≤35%	122	66	76.2	6 to 12	0.1 to 0.2	24h	Dobu	10	48h	1

N= total number of patients, Levo= levosimendan, EF= ejection fraction, NYHA= New York Heart Association classification, NA= not applicable, NR=not reported.

Figure 1

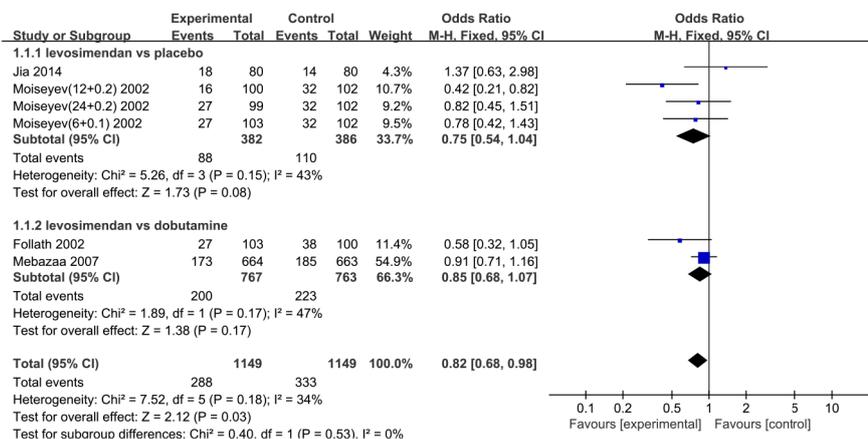


All-cause mortality in 180 days:

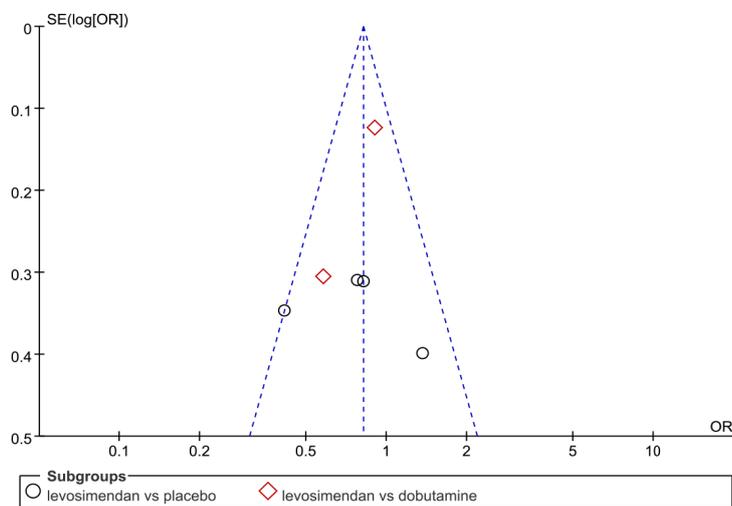
Four out of 20 studies with a total of 2298 patients reported all-cause mortality in 180 days[7, 8, 9, 10]. Compared with the placebo group, the levosimendan group showed no statistical significance in reducing all-cause mortality in 180 days (OR=0.75, 95% C: 0.54 to 1.04). Compared with the dobutamine group, the levosimendan group showed no statistical significance (OR=0.85, 95% CI: 0.68 to1.07), either (Figure 2A). The Funnel plot analysis showed no publication bias (Figure 2B).

Figure 2

A



B

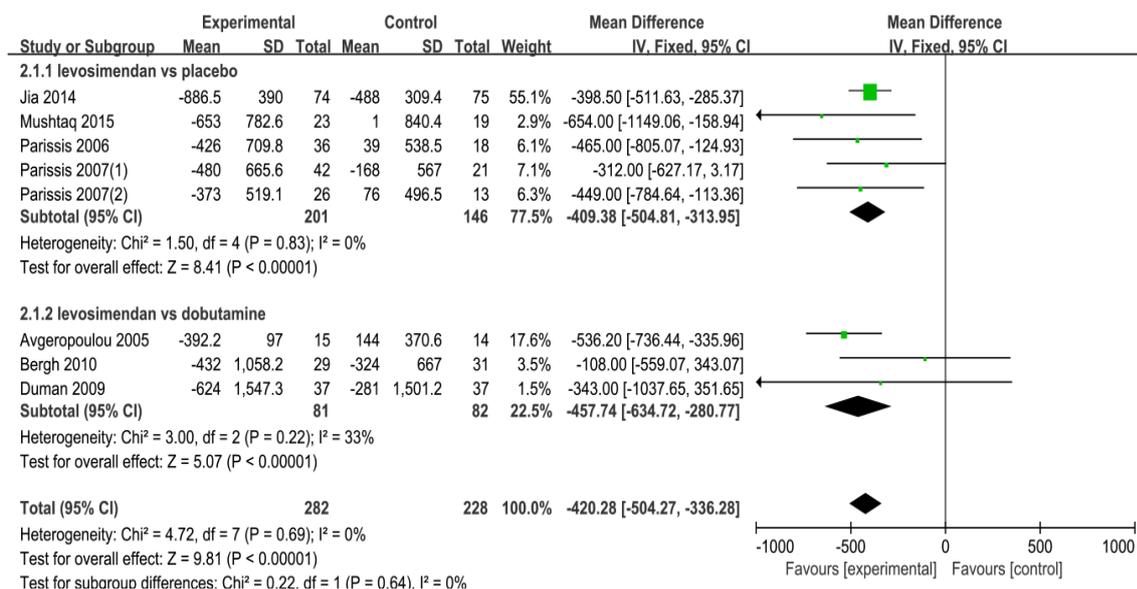


**Cardiac function:
BNP change**

Eight out of 20 studies with a total of 608 patients reported BNP change from the start of infusion[6, 7, 11, 12, 13, 14, 15, 16]. Compared with the placebo group, levosimendan showed a significant benefit in decreasing BNP (MD=-409.38, 95% CI: -504.81 to -313.95) and compared with the dobutamine group, levosimendan also significantly reduced the BNP level (MD=-457.74, 95% CI: -634.72 to -280.77) (Figure 3A).

Figure 3

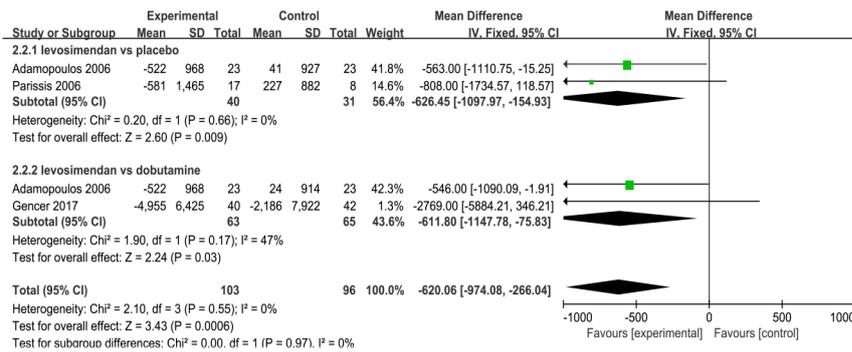
A. BNP pg/ml



NT-Pro BNP change:

Three out of 20 studies with a total of 176 patients reported NT-Pro BNP change from the start of infusion [6, 17, 18]. Compared with the placebo group, the levosimendan group had a significantly reduced NT-Pro BNP level (MD=-626.45, 95% CI: -1097.97 to -154.93). Compared with the dobutamine group, levosimendan also significantly reduced the NT-Pro BNP level (MD=-611.80, 95% CI: 1147.78 to -75.83) (Figure 3B).

B. NT-Pro BNP pg/ml



Hemodynamics index

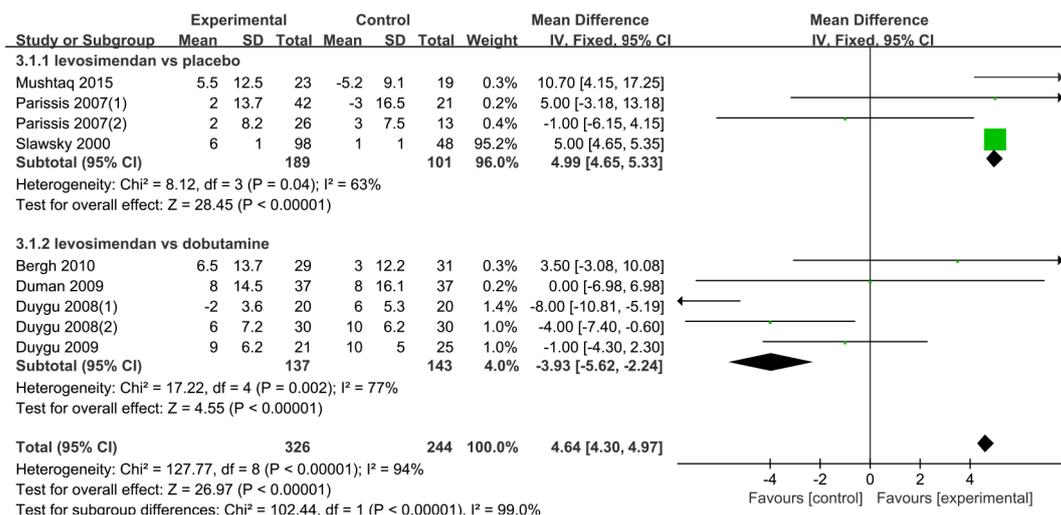
HR change

Nine out of 20 studies with 570 patients reported HR changes from the start of infusion [12, 13, 14, 15, 16, 19, 20, 21, 22]. Compared with the placebo group, levosimendan significantly raised the HR of patients (MD=4.99, 95% CI: 4.65 to 5.33). Compared with the dobutamine group, levosimendan could remarkably slow down HR (MD=-3.93, 95% CI: -5.62 to -2.24) (Figure 4A).

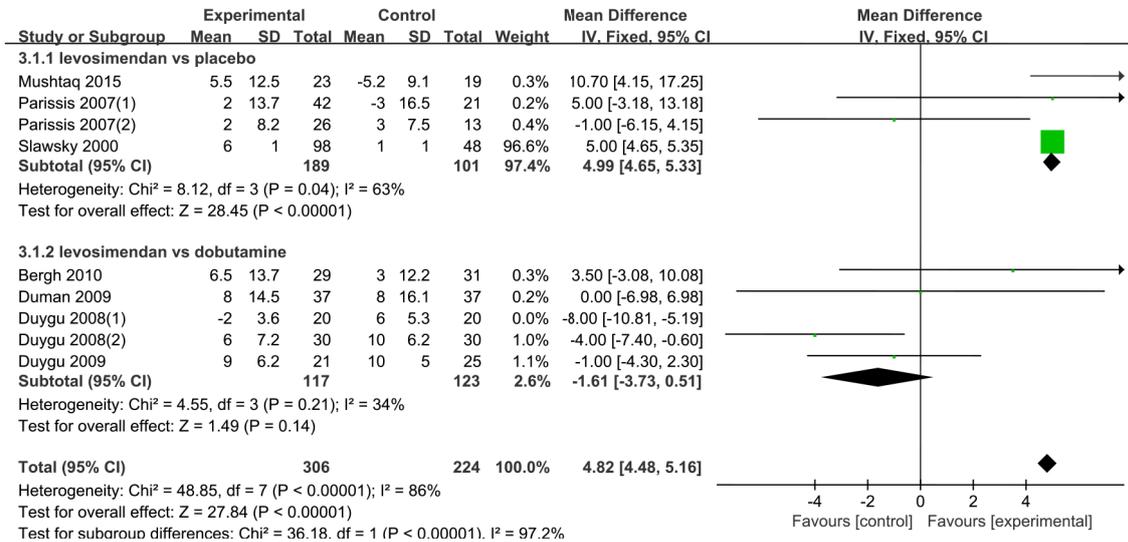
Figure 4

A. HR beats/minute

Before sensitive analysis



After sensitive analysis

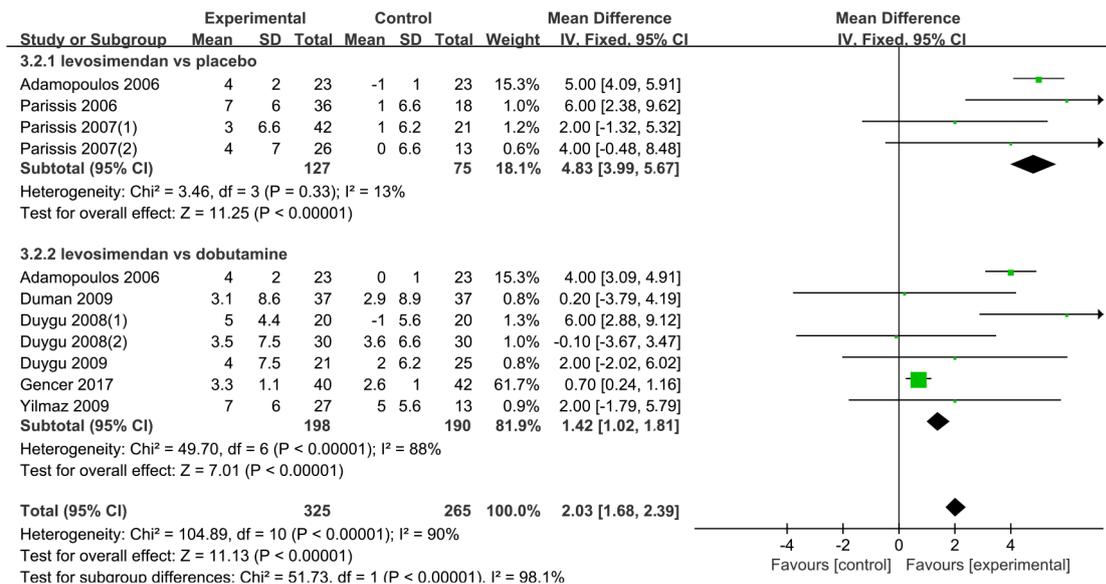


LVEF change:

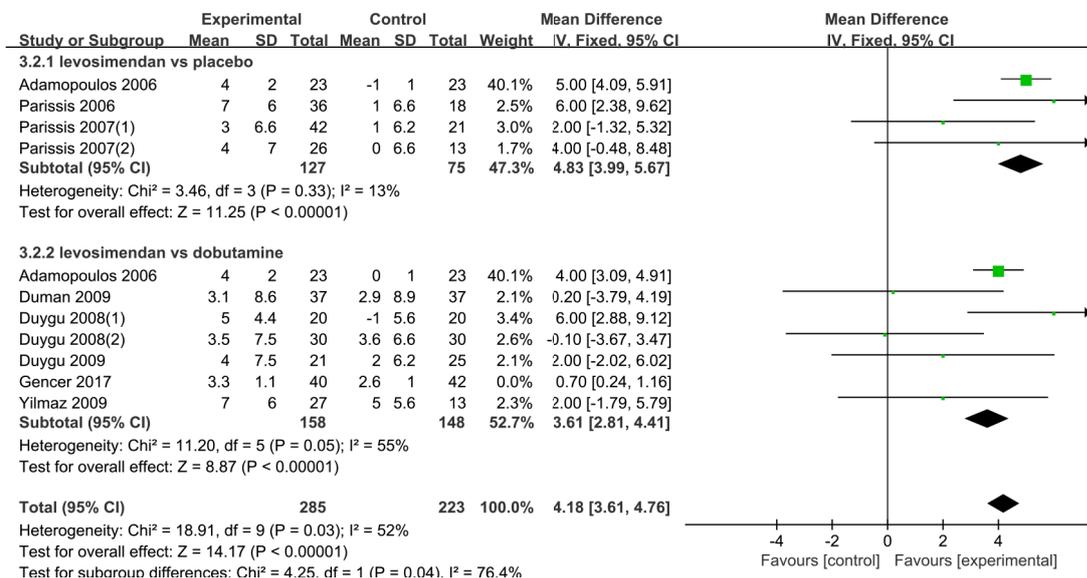
Eleven out of 20 studies with a total of 688 patients reported changes in LVEF from the start of the infusion[6, 11, 13, 15, 16, 17, 18, 19, 20, 21, 23]. Compared with the placebo group, levosimendan significantly increased LVEF (MD=4.83, 95% CI: 3.99 to 5.67). Compared with the dobutamine group, levosimendan also showed significantly more benefits in increasing LVEF (MD=1.42, 95% CI: 1.02 to 1.81) (Figure 4B).

B. LVEF %

Before sensitive analysis



After sensitive analysis

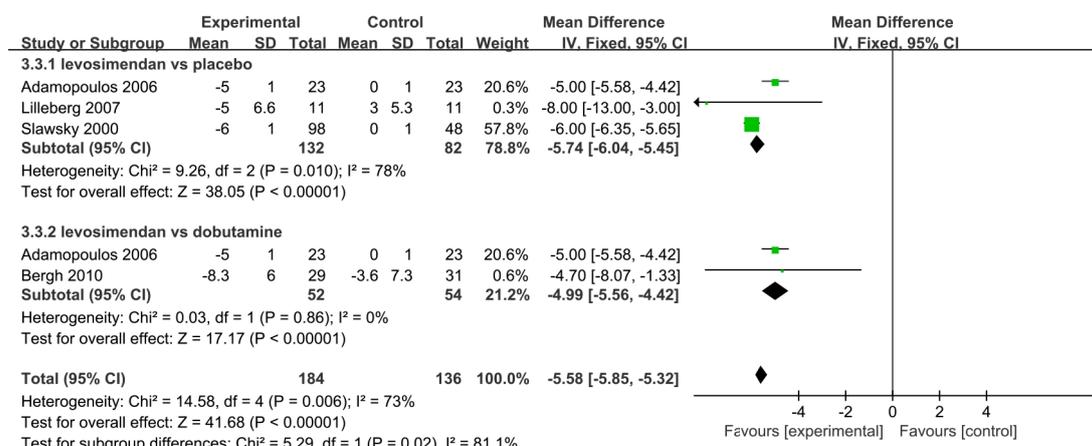


PCWP change

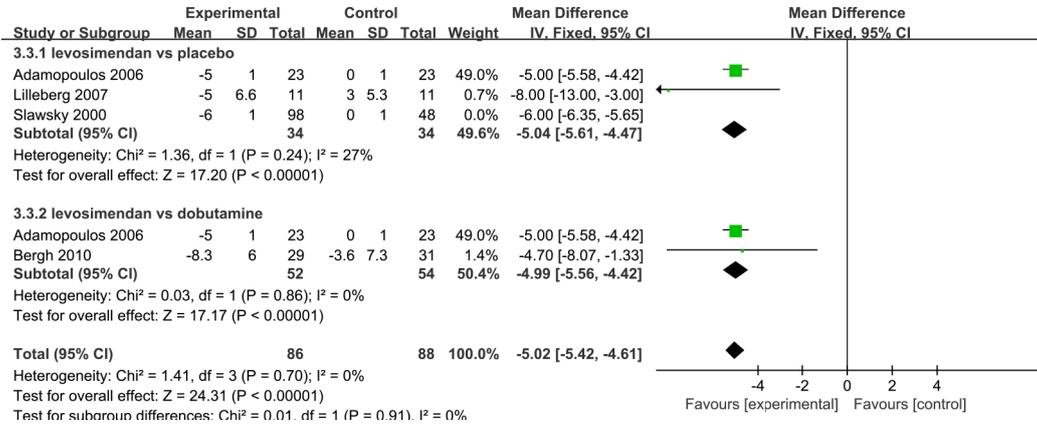
Four out of 20 studies with 320 patients reported changes in PCWP[12, 17, 22, 24]. Compared with placebo group, levosimendan significantly decreased PCWP (MD=-5.74, 95% CI: -6.04 to -5.45). However, compared with the dobutamine group, levosimendan was significantly inferior in reducing PCWP (MD=-4.99, 95% CI: -5.56 to -4.42) (Figure 4C).

C. PCWP mmHg

Before sensitive analysis



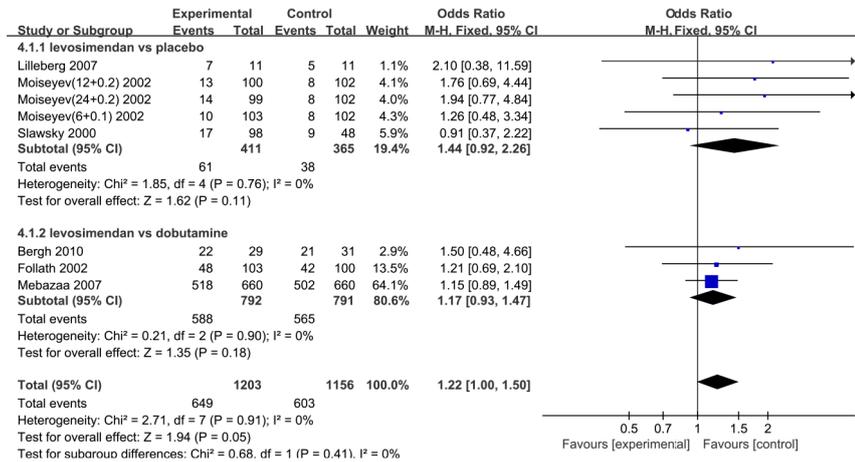
After sensitive analysis



Adverse events:

The reported adverse events comprised hypotension, nausea, headache, atrial fibrillation, arrhythmia, and so on. Six out of 20 studies with a total of 2359 patients reported changes in AD [8, 9, 10, 12, 22, 24]. Compared with the placebo group, levosimendan did not reduce the AD rate (OR=1.44, 95% CI: 0.92 to 2.26), and this result was comparable between levosimendan (OR=1.17, 95% CI: 0.93 to 1.47) and dobutamine (Figure 5).

Figure 5



Sensitive analysis

Significant heterogeneity existed in the HR, LVEF, and PCWP groups, so sensitivity analyses were performed to investigate the causes of heterogeneity.

As for the HR outcome, we found that Duygu's[25] study contributed immensely to the heterogeneity in the pairwise comparison between levosimendan and dobutamine, presumably owing to its small sample and poor quality. After excluding this article, the heterogeneity was eliminated. However, the significance disappeared between the two groups.

As for the LVEF outcome, in the comparison between levosimendan and dobutamine, we found that Gencer's[18] article contributed immensely to the heterogeneity. The duration of dobutamine injection in Gencer's[18] study was 48h, which was different from other studies. After excluding that article, the heterogeneity was eliminated, and the results resembled the former.

As for the PCWP outcome, in the comparison between levosimendan and placebo, Slawsky's [22] article was verified to contribute immensely to the heterogeneity. The duration of following-up in that study was 6h, making it different from other studies. After excluding the article, the heterogeneity was eliminated, and the result resembled the former.

DISCUSSION

To our knowledge, this is the first meta-analysis comprehensively evaluating the efficacy and safety of levosimendan on ReHF regarding multiple indicators (all-cause mortality, cardiac function, hemodynamics indices, and adverse event).

As a calcium sensitizer, the mechanism of action of levosimendan is different from traditional inotropic drugs such as dobutamine which has been widely used in ReHF[26]. Some studies have attempted to compare the two drugs on HF patients before.

Cui's[27] meta-analysis, which included 9 RCTs, focused on the clinical indicators in advanced HF patients. Gong's[28] meta-analysis, which included 25 articles, focused on mortality in the ADHF population. Zhou's[2] meta-analysis included 7 articles reporting BNP, LVEF, and HR changes in ADHF patients. However, these studies showed conflicting results. BNP and NT-Pro BNP are natriuretic peptide biomarkers that are increasingly implemented to determine the presence and severity of HF[29]. In our study, levosimendan significantly reduced both BNP and NT-Pro BNP levels compared with dobutamine and placebo. This result was consistent with many previous studies. This beneficial effect of levosimendan could be due to systemic small vessels' dilation, which substantially reduced ventricular anterior and posterior load[3, 30, 31, 32, 33].

Rife precedent studies have reported that levosimendan improved hemodynamic parameters. Two meta-analyses[2, 27] reported a significant increment in LVEF and reduction of PCWP after levosimendan administration compared with the control group, consistent with our study. However, we found that levosimendan could increase HR compared with placebo but showed a similar effect compared with dobutamine in the sensitive analysis[34]. These results were incongruity with Zhou's[2] study.

There was no significant difference between the levosimendan and control group on all-cause mortality at 180 days. A large-scale RCT (LIDO)[10] revealed that levosimendan showed more benefits in reducing mid to long-term mortality than placebo. However, Mebazee's[8] study (SURVIVE) revealed that levosimendan did not reduce all-cause mortality in 180 days compared with dobutamine. Gong's[28] study showed that all-cause mortality was significantly lower with levosimendan than dobutamine rather than placebo. In addition, Gong's[28] study found that compared with placebo, dobutamine did not reduce mortality significantly. The hemodynamic effects of

dobutamine could be compromised by β -blockers, while the mechanism of levosimendan was independent of β -blockers. However, most patients with ReHF require β -blockers for treatment. Under this circumstance, levosimendan seems to be more suitable for the treatment of ReHF patients. Judging from the previous results, short-term injection with levosimendan could reduce BNP, NT-Pro BNP, and PCWP and increase LVEF after 3 days of injection. However, the all-cause mortality in 180 days did not decrease. Recently, several studies have recommended intermittent injection of levosimendan for discharged patients, which can reduce cardiovascular deaths in patients with ReHF and reduce the rate of rehospitalization[35, 36]. Therefore, intermittent levosimendan injection for ReHF rather than short-term treatment could be the key to reducing long-term mortality.

As for AD, our study showed no significant difference between levosimendan and placebo or dobutamine. Bergh[37] reported no statistical difference in the incidence of AE (including atrial fibrillation, ventricular tachycardia, and hypotension) between levosimendan (0.1-0.2ug/kg/min for 24h) and dobutamine in patients, which was consistent with our findings. However, a large RCT[10] reported that levosimendan caused fewer adverse events than dobutamine. A meta-analysis[2] demonstrated that levosimendan increased the risk of extrasystoles and hypotension. In addition, Moiseyev[9] reported that levosimendan infusion for 6h (0.1-0.2ug/kg/min) did not significantly increase hypotension or ischemia, but sinus tachycardia occurred in the high-dose levosimendan group (24 ug/kg+0.4 ug/kg/min) compared with placebo. Due to the inconsistent results, we cannot fully disclose that levosimendan is safe.

We infer that the occurrence of AD is related to the PDE3 inhibition exerted by levosimendan when used in large doses (up to 0.4 ug/kg/min). Some studies revealed that using PDE3 inhibitors such as milrinone increased mortality due to sudden cardiac death linked to increased arrhythmia[38]. Dobutamine could cause catecholamine-induced damage to a proportion of cardiac myocytes leading to an increased risk of death. It's worth noting that levosimendan's as a PDE3 inhibitor results in cAMP accumulation and the occurrence of arrhythmia and hypotension. Thus, the safety of levosimendan needs further investigation.

There are wide concerns on HF with preserved ejection fraction since there is currently no effective treatment for this disease.

Recently, the HELP trial[39] showed that compared with placebo, levosimendan could effectively improve the hemodynamic parameters of PH-HFpHF patients, especially for PCWP, which seemed to improve the patient's exercise endurance. Our findings provide new clinical evidence for the treatment of HFpHF and an opportunity for wider application of levosimendan in the future.

LIMITATIONS

Firstly, most of the included studies had a sample size of less than 100. Secondly, we failed to make a subgroup analysis according to the different dosages of levosimendan and whether patients were given a loading dose.

Thirdly, we did not include RCTs with an oral administration of levosimendan since it is not widely used in clinical practice.

CONCLUSION

Levosimendan has been proven to improve cardiac function by reducing BNP and NT-Pro BNP. In terms of hemodynamics indices, it could significantly increase LVEF and reduce PCWP while showing no more benefits on HR than the control group. Additionally, levosimendan didn't significantly reduce all-cause mortality and AD rate. Thus, more clinical studies are needed to resolve these disputes.

Disclosure of interest:

The authors report no conflict of interest.

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