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Levosimendan versus dobutamine in critically ill patients: a meta-analysis of randomized controlled trials

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Abstract: Objective: To evaluate the clinical efficacy of levosimendan versus dobutamine in critically ill patients requiring inotropic support. Methods: Clinical trials were searched in PubMed, EMBASE, and the Cochrane Central Registry of Clinical Trials, as well as Web of Science. Studies were included if they compared levosimendan with dobutamine in critically ill patients requiring inotropic support, and provided at least one outcome of interest. Outcomes of interest included mortality, incidence of hypotension, supraventricular arrhythmias, and ventricular arrhythmias. Results: Data from a total of 3052 patients from 22 randomized controlled trials (RCTs) were included in the analysis. Overall analysis showed that the use of levosimendan was associated with a significant reduction in mortality (269 of 1373 [19.6%] in the levosimendan group, versus 328 of 1278 [25.7%] in the dobutamine group, risk ratio (RR)=0.81, 95% confidence interval (CI) 0.70–0.92, P for effect=0.002). Subgroup analysis indicated that the benefit from levosimendan could be found in the subpopulations of cardiac surgery, ischemic heart failure, and concomitant β-blocker therapy in comparison with dobutamine. There was no significant difference in the incidence of hypotension, supraventricular arrhythmias, or ventricular arrhythmias between the two drugs. Conclusions: In contrast with dobutamine, levosimendan is associated with a significant improvement in mortality in critically ill patients requiring inotropic support. Patients having cardiac surgery, with ischemic heart failure, and receiving concomitant β-blocker therapy may benefit from levosimendan. More RCTs are required to address the questions about no positive outcomes in the subpopulation in a cardiology setting, and to confirm the advantages in long-term prognosis.

Key words: Heart failure, Levosimendan, Mortality, Survival, Dobutamine
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1 Introduction

Acute heart failure (AHF) frequently happens in critically ill patients due to myocardial injury, cardiac dysfunction, arrhythmias, and inflammatory activation. First of all, the underlying cardiac disease and precipitating factors should be managed. Clinicians must treat acute coronary syndromes, arrhythmias, hypertension or severe infection as soon as possible when such present. Secondly, vasodilators and/or diuretics are usually administrated to improve symptoms. When AHF is severe and not responding to first line treatments above, inotropic agents may be applied (Bayram *et al*., 2005). Unfortunately, a situation like that is common in hospitals. Positive inotropic agents are usually used to relieve the symptoms of tissue hypoperfusion and ensure the vital organs blood supply. Thus, inotropes are suitable for low cardiac output syndrome (LCOS), and are particularly effective in patients with lower blood pressure, and intolerance or poor response to vasodilators and diuretics (McMurray *et al*., 2012). Vasodilators reduce ventricular filling pressure and systemic vascular resistance, and decrease cardiac

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load and ease breathing difficulties. Therefore, recommendations from guidelines show that vasodilators can be used in the early stages of AHF, especially in patients with systolic blood pressure >110 mmHg (McMurray *et al*., 2012). In clinical settings, inotropes are commonly used for critically ill patients with AHF, acute worsening of a pre-existing decompensated chronic heart failure (ADCHF), and end stage decompensated heart failure (HF). They are frequently administrated to patients in cardiology and cardiac surgery settings. Inotropes also should be considered when patients with severe sepsis or septic shock present cardiac dysfunction after sufficient fluid resuscitation, according to the international guidelines for management of severe sepsis and septic shock (Dellinger *et al*., 2008). However, it is still controversial to use inotropes in HF treatment, because almost all of the large randomized controlled trials (RCTs) and meta-analyses indicate that use of intravenous conventional inotropes may bring about an increasing risk of death.

In spite of their expected beneficial effect on cardiac output, most inotropes carry the risk of increased incidence of myocardial ischemia and arrhythmias, resulting in a detrimental effect on short-term outcome (Thackray *et al*., 2002; Abraham *et al*., 2005; Costanzo *et al*., 2007; Singer, 2007; Dickstein *et al*., 2008) and a worsened long-term prognosis (Thackray *et al*., 2002; Abraham *et al*., 2005; Bayram *et al*., 2005; Mebazaa *et al*., 2011). However, relevant data are still inadequate. In fact, positive inotropic agents are usually administered to the most severe cases of HF patients who already carry a high risk of death. Therefore, inotropes are usually clinicians' last resort, and selecting an appropriate inotropic drug is very important and pivotal to clinicians. Currently, qualified data on comparing inotropic agents are still insufficient and the challenge for clinicians in selecting the proper inotropes has been emphasized in a few reports (de Backer *et al*., 2010; Mebazaa *et al*., 2010; Parissis *et al*., 2010).

As a new calcium sensitizer, levosimendan has inotropic and vasodilatory actions mediated by the sensitization of contractile proteins to calcium, the opening of potassium channels and inhibition of phosphodiesterase-3. It has been used in many developed countries and is recommended in the European Society of Cardiology guidelines for treatment of AHF (Dickstein *et al*., 2008). In fact, levosimendan is the first inotropic drug found to establish a positive effect on patient survival time for any inotropic drug in contrasted with placebo. Nevertheless, levosimendan has not been approved by the Federal Drug Administration in the United States. Thus, more evidence for levosimendan is required to confirm its advantages. Dobutamine has been the most common choice in the treatment of AHF in recent decades, with an expected effect on short-term improvement of symptoms, though there is concern about an increased risk of death. In clinical settings, it is still confusing to select between levosimendan and dobutamine for patients requiring inotropic support.

Up to now, outcomes of RCTs comparing levosimendan with dobutamine are controversial and ambiguous. We performed an updated meta-analysis of all the RCTs in which levosimendan and dobutamine were compared to reach a conclusion about the better choice in the treatment of critically ill patients requiring inotropic drugs. In addition, we analyzed mortality in different settings (i.e., cardiology, cardiac surgery, and other subpopulations) to evaluate which is more suitable for some particular kinds of patients and which method of administration will be better. The side effects of levosimendan and dobutamine were also evaluated.

2 Materials and methods

2.1 Search strategy

We performed a primary search for RCTs in PubMed, EMBASE, and the Cochrane Central Registry of Clinical Trials, as well as Web of Science. The search terms used were levosimendan and dobutamine. We also used sensitive filters to identify RCTs in the PubMed database (Haynes *et al*., 2005) and the EMBASE database (Wong *et al*., 2006). There was no limitation on language, publication status, or study year, but only those conducted in humans were considered. Two authors independently conducted the search and the search was finalized on February 1st, 2012. To identify other unrecognized publications, backward snowballing was used by reviewing the bibliographies of included RCTs and review articles. This study did not require ethical approval.

2.2 Study selection

All abstracts were reviewed to identify potentially eligible RCTs in a standardized manner by two authors. If the abstract indicated that the study potentially met the inclusion criteria, authors would retrieve and review full text articles. Disagreements were resolved through discussion.

The inclusion criteria were defined as: (1) RCTs, (2) study design that included a levosimendan group and a dobutamine group, and (3) evaluation of efficacy or side effects, including one or more outcomes such as mortality, incidence of hypotension and arrhythmia during study. The exclusion criteria were defined as: (1) repeated articles, (2) incomplete data, (3) non-adult studies, (4) oral administration of levosimendan, (5) baseline data that were not similar to those in other articles, and (6) lack of data on relevant outcomes. Compliance to selection criteria was evaluated independently and qualified studies were selected for the final analysis by two authors. Divergences were resolved by consensus.

2.3 Data abstraction and study characteristics

Two authors assessed all included trials for internal validity and risk of bias in the light of the Cochrane Collaboration methods. Potential sources of significant clinical heterogeneity were extracted, including clinical setting, follow-up duration, study design, sample size, infusion dose and duration, and so on. We took mortality at the longest follow-up available as the primary end point in the analysis. Each report was also assessed for the adequacy of allocation concealment, adequate sequence generation, blinding, and other methodological quality item.

Two authors collected specific data for analysis. Data collected included: mortality, incidence of side effects (hypotension, supraventricular arrhythmia, and ventricular arrhythmia), patient baseline characteristics, study definition of HF, and details of administration. When data and information in these papers were inadequate or missing, we contacted the authors by email.

2.4 Data synthesis and analysis

Computations were performed with RevMan 5. We assessed statistical heterogeneity and inconsistency by using Cochran Q and I^2 tests, respectively (Higgins *et al*., 2003). Data from individual studies were analyzed to compute individual and pooled risk ratios (RRs) with pertinent 95% confidence intervals (CIs). The primary analysis was conducted by means of the Peto fixed effects model when $I^2 \leq 25\%$ and with the random effects model when $I^2 > 25\%$. In addition, the number needed to treat (NNT) was also computed for the primary end point. We conducted a sensitivity analysis by sequentially excluding each study and recalculating the pooled estimates on remaining studies. Visual inspection of funnel plots was used to assess the risk of small study bias. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing and 0.10 for heterogeneity testing.

3 Results

We identified a total of 175 potentially relevant publications by database searches and snowballing. Sixty-three full-text articles were assessed after excluding 112 articles on the basis of title and abstract (Fig. 1). Sixteen studies were excluded because of lacking interest outcome data and further details, thirteen because there was no dobutamine as a control, three because they were not randomized, six because of duplicate publication, one because there was no levosimendan alone as intervention, one involving a healthy population, and one performing analyses only on patients on-treatment instead of intention-to-treat principle. We finally identified 22 eligible RCTs for inclusion in the analysis (Follath *et al*., 1999; 2002; Nieminen *et al*., 2000; Alvarez *et al*., 2005; 2006; Morelli *et al*., 2005; Adamopoulos *et al*., 2006; Mebazaa *et al*., 2007; Duygu *et al*., 2008a; 2008b; Levin *et al*., 2008a; 2008b; 2009; Samimi-Fard *et al*., 2008; Alhashemi *et al*., 2009; Vaitsis *et al*., 2009; Yilmaz *et al*., 2009; Bergh *et al*., 2010; Iyisoy *et al*., 2010; Wang *et al*., 2010; Yontar *et al*., 2010; Bonios *et al*., 2012).

3.1 Study characteristics

In total, 22 studies enrolling 3 052 patients (1 587 to levosimendan and 1 465 receiving dobutamine) fulfilled all eligibility criteria (Table 1). Nineteen studies reported data on mortality, nine studies reported data on hypotension, and eleven studies reported data on arrhythmias. Fourteen studies used

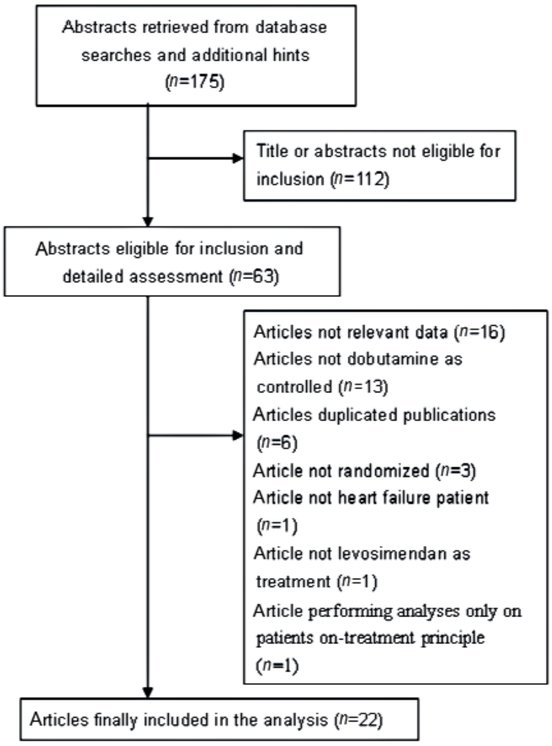

Fig. 1 Flow diagram of the study selection process

levosimendan in a cardiology setting, which was defined as patients with HF originating from various kinds of heart diseases except cardiac surgery; one of these studies used weekly intravenous infusions of levosimendan 0.3 μg/(kg·min) for 6 h over a 6-month period (Bonios *et al*., 2012); one of these studies was performed in ST-segment elevation myocardial infarction (STEMI) patients with cardiogenic shock related to percutaneous coronary intervention (PCI); in six studies of cardiology setting all patients had ischemic HF, which was defined as HF originating from ischemic cardiomyopathy; in eight studies of cardiology setting some patients had ischemic HF and more than a half patients in most of these studies had ischemic HF except one (Follath *et al*., 2002). Three studies in cardiology setting did not report outcomes of mortality, and in these studies some patients had ischemic HF (Yilmaz *et al*., 2009; Iyisoy *et al*., 2010; Wang *et al*., 2010). In eleven studies which reported outcomes of mortality in cardiology setting, six studies included patients with left ventricular ejection fraction (LVEF) <40%, five studies included patients with pulmonary capillary wedge pressure (PCWP) >15 mmHg, and four studies included patients with cardiac index <2.5 L/(min·m^2). Five studies used levosimendan in cardiac surgery, which was defined as patients with LCOS after heart surgery; two studies in cardiac surgery included patients who all underwent coronary artery bypass grafting (CABG) (Levin *et al*., 2008b; 2009); two studies in cardiac surgery included patients undergoing either CABG or cardiac valve replacement (Alvarez *et al*., 2005; 2006); one study in cardiac surgery included patients all undergoing cardiac valve replacement (Levin *et al*., 2008a). All studies in cardiac surgery included patients with cardiac index <2.2 L/(min·m^2) plus a PCWP >15 mmHg. Three trials were performed in sepsis, which was defined as patients with myocardial dysfunction due to severe sepsis or septic shock. Twelve studies included patients who received concomitant β-blocker therapy. Two of them included all patients who received concomitant β-blocker therapy. All twenty-two authors used a continuous infusion, and eighteen of them followed bolus. Dose of levosimendan varied from 3 to 36 μg/kg as intravenous bolus and from 0.05 to 0.6 μg/(kg·min) as a continuous infusion. Five studies were multicentered. Detailed information of study characteristics can be seen in Tables 1 and 2. Study quality of the included studies was of variable (Table 3) and four of them had a low risk of bias.

3.2 Quantitative data synthesis

In the overall population, levosimendan showed a significant reduction in mortality at the longest follow-up available (269 of 1373 [19.6%] in the levosimendan group vs. 328 of 1278 [25.7%] in the dobutamine group, RR=0.81, 95% CI 0.70–0.92, *P* for effect=0.002, *Q*=19.05, *P* for heterogeneity=0.39, I^2=6%, NNT=16 with 2651 patients and 19 studies included) in comparison with dobutamine (Fig. 2). Studies with at least 30 d of follow-up showed a significant reduction in mortality (Table 4). A reduction in mortality was also found when studies with short-term follow-up (<30 d) were analyzed (Table 4). The studies with at least 90 d of follow-up demonstrated no significant reduction in mortality, but a trend in favor of levosimendan, so did the studies with at least 180 d of follow-up (Table 4).

Furthermore, the reduction in mortality was confirmed in the cardiac surgery setting (12 of 175 [6.9%] in the levosimendan group vs. 28 of 175 [16.0%] in the dobutamine group, RR=0.43, 95% CI

0.23–0.81, P=0.009, Q=4.73, P for heterogeneity=0.32, I^2=15%, NNT=11 with 5 studies included) (Fig. 3). However, the advantages were not found in the cardiology setting (219 of 1042 [21.0%] in the levosimendan group vs. 246 of 954 [25.8%] in the dobutamine group, RR=0.88, 95% CI 0.75–1.03, P=0.11, Q=7.81, P for heterogeneity=0.65, I^2=0%) (Fig. 4). No difference in mortality was found in a subgroup of sepsis including only three studies.

In addition, the studies including patients with ischemic HF also indicated a significant reduction in mortality (236 of 1278 [18.5%] in the levosimendan group vs. 284 of 1188 [23.9%] in the dobutamine group, RR=0.82, 95% CI 0.71–0.95, P=0.01, Q=15.53, P for heterogeneity=0.34, I^2=10%, NNT=14 with 15 studies included) (Fig. 5), so did the studies including patients who had totally ischemic HF (26 of 398 [6.5%] in the levosimendan group vs. 46 of 310 [14.8%] in the dobutamine group, RR=0.54, 95% CI 0.34–0.84, P=0.007, Q=6.72, P for heterogeneity=0.46, I^2=0%, NNT=13 with 8 studies included) (Fig. 6).

We performed a lot of other subanalyses on mortality and reported it in Table 4. A significant reduction in mortality was found in a subanalysis including studies with patients receiving concomitant β-blocker therapy (231 of 1229 [18.8%] in the levosimendan group vs. 280 of 1138 [24.6%] in the dobutamine group, RR=0.82, 95% CI 0.70–0.95, P=0.008, Q=14.69, P for heterogeneity=0.20, I^2=25%, NNT=17 with 12 studies included) (Fig. 7), but no significant reduction in a subanalysis including studies without patients receiving concomitant β-blocker therapy (Table 4). A significant reduction in mortality was found in those with levosimendan bolus or with infusion rate ≤0.1 μg/(kg·min), but no significant difference in mortality was found in those without levosimendan bolus or with infusion rate >0.1 μg/(kg·min) (Table 4).

Table 1 Clinical data of 22 included articles

Study	n_L	n_D	Levo bolus (μg/kg)	Levo infusion (μg/(kg·min))	t_L (h)	Dobu dose (μg/(kg·min))	t_D	Duration of follow-up
Adamopoulos *et al*., 2006	23	23	6	0.1	24	5 to 10	24 h	120 d
Alhashemi *et al*., 2009	21	21	0	0.05 to 0.2	24	5 to 20	7 d	End of ICU stay
Alvarez *et al*., 2006	25	25	12	0.2	24	7.5	24 h	15 d
Alvarez *et al*., 2005	15	15	18	0.2	24	7.5	24 h	1 d
Bergh *et al*., 2010	29	31	12	0.1 to 0.2	24	5 to 10	48 h	30 d
Bonios *et al*., 2012	21	21	0	0.3	6*	10	6 h*	180 d
Duygu *et al*., 2008a	20	20	6 to 12	0.1	24	5 to 20	24 h	30 d
Duygu *et al*., 2008b	30	32	6 to 12	0.1	24	5 to 10	24 h	180 d
Follath *et al*., 2002	103	100	24	0.1 to 0.2	24	5 to 10	24 h	180 d
Follath *et al*., 1999	9	10	12	0.2 to 0.6	24	8 to 16	24 h	14 d
Iyisoy *et al*., 2010	20	20	12	0.1	24	5 to 10	24 h	1 d
Levin *et al*., 2009	127	126	10	0.1	24	≥5	24 h	End of hospitalization
Levin *et al*., 2008a	36	35	10	0.1	24	≥5	24 h	30 d
Levin *et al*., 2008b	69	68	10	0.1	24	5 to 12.5	24 h	30 d
Mebazaa *et al*., 2007	664	663	12	0.1 to 0.2	24	5 to 40	≥24 h	180 d
Morelli *et al*., 2005	15	15	0	0.2	24	5	24 h	30 d
Nieminen *et al*., 2000	95	20	3 to 36	0.05 to 0.6	24	6	24 h	2–9 d
Samimi-Fard *et al*., 2008	11	11	24	0.1	24	5	24 h	365 d
Vaitsis *et al*., 2009	23	19	0	0.1	24	5 to 10	24 h	30 d
Wang *et al*., 2010	119	106	12	0.1 to 0.2	24	2 to 4	24 h	1 d
Yilmaz *et al*., 2009	27	13	0	0.1 to 0.2	24	≥5	≥24 h	1 d
Yontar *et al*., 2010	37	23	3 to 6	0.1 to 0.2	24	2.5 to 5	24 h	1 d

Levo: levosimendan; Dobu: dobutamine; n_L: number of Levo patients; n_D: number of Dobu patients; t_L: Levo duration; t_D: Dobu duration.
* Once a week for 180 d

Table 2 Characteristics of 22 included articles

Study	Setting	C1	C2	C3	C4	C5	C6	C7	C8	C9
Adamopoulos *et al.*, 2006	Cardiology	Yes	No	No	No	Part	Part	Yes	No	No
Alhashemi *et al.*, 2009	Sepsis	Yes	Yes	No	No	No	No	No	No	No
Alvarez *et al.*, 2006	Cardiac surgery	Yes	Yes	Yes	No	Part	No	Yes	No	No
Alvarez *et al.*, 2005	Cardiac surgery	Yes	No	No	No	Part	No	Yes	No	No
Bergh *et al.*, 2010	Cardiology	Yes	Yes	Yes	Yes	Part	All	Yes	Yes	No
Bonios *et al.*, 2012	Cardiology	Yes	No	No	No	Part	Part	No	No	No
Duygu *et al.*, 2008a	Cardiology	Yes	No	No	No	All	All	Yes	No	No
Duygu *et al.*, 2008b	Cardiology	Yes	No	No	No	All	Part	Yes	No	No
Follath *et al.*, 2002	Cardiology	Yes	Yes	Yes	Yes	Part	Part	Yes	Yes	Yes
Follath *et al.*, 1999	Cardiology	Yes	No	Yes	No	All	No	Yes	No	No
Iyisoy *et al.*, 2010	Cardiology	No	No	Yes	No	Part	Part	No	No	No
Levin *et al.*, 2009	Cardiac surgery	Yes	No	No	No	All	Part	Yes	No	Yes
Levin *et al.*, 2008a	Cardiac surgery	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Levin *et al.*, 2008b	Cardiac surgery	Yes	No	Yes	Yes	All	Part	Yes	Yes	Yes
Mebazaa *et al.*, 2007	Cardiology	Yes	Yes	Yes	Yes	Part	Part	Yes	Yes	Yes
Morelli *et al.*, 2005	Sepsis	Yes	No	Yes	No	No	No	No	No	No
Nieminen *et al.*, 2000	Cardiology	Yes	Yes	Yes	No	All	Part	Yes	No	Yes
Samimi-Fard *et al.*, 2008	Cardiology	Yes	No	No	No	All	Part	No	No	No
Vaitsis *et al.*, 2009	Sepsis	Yes	No	No	No	No	No	No	No	No
Wang *et al.*, 2010	Cardiology	No	Yes	Yes	Yes	Part	No	No	Yes	Yes
Yilmaz *et al.*, 2009	Cardiology	No	Yes	No	No	Part	Part	No	No	No
Yontar *et al.*, 2010	Cardiology	Yes	No	No	No	All	Part	Yes	No	No

C1: report data on mortality; C2: report data on hypotension; C3: report data on supraventricular arrhythmias; C4: report data on ventricular arrhythmias; C5: ischemic heart failure; C6: concomitant β-blocker therapy; C7: levosimendan bolus; C8: multicentered; C9: studies with >100 patients

Table 3 Review of authors' judgments about each methodologic quality item of 22 included articles

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Adamopoulos *et al.*, 2006	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Alhashemi *et al.*, 2009	Unclear	Unclear	No	Unclear	Unclear	yes	Unclear	Yes	High
Alvarez *et al.*, 2006	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Alvarez *et al.*, 2005	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Bergh *et al.*, 2010	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Low
Bonios *et al.*, 2012	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Duygu *et al.*, 2008a	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Duygu *et al.*, 2008b	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Follath *et al.*, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Follath *et al.*, 1999	Unclear	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Moderate
Iyisoy *et al.*, 2010	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Levin *et al.*, 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	High
Levin *et al.*, 2008a	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	High
Levin *et al.*, 2008b	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Mebazaa et *al.*, 2007	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Morelli *et al.*, 2005	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Nieminen *et al.*, 2000	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Samimi-Fard *et al.*, 2008	Unclear	Unclear	No	Yes	Unclear	No	Yes	Yes	Moderate
Vaitsis *et al.*, 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	High
Wang *et al.*, 2010	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	Yes	Moderate
Yilmaz *et al.*, 2009	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Yontar *et al.*, 2010	Unclear	Unclear	No	Yes	Unclear	yes	Yes	Yes	Moderate

Q1: adequate sequence generation; Q2: allocation concealment used; Q3: blinding; Q4: concurrent therapies similar; Q5: incomplete outcome data addressed; Q6: uniform and explicit outcome definitions; Q7: free from selective outcome reporting; Q8: free from other bias; Q9: overall risk of bias

Table 4 Subanalysis on mortality

Subgroup of interest	n_s	Event of Levo group	Event of Dobu group	RR [95% CI]	P	I^2 (%)	NNT
Studies with sepsis patients	3	31 of 59 (52.5%)	35 of 55 (63.6%)	0.82 [0.60–1.12]	0.21	0	
Studies including patients receiving concomitant β-blocker therapy	12	231 of 1229 (18.8%)	280 of 1138 (24.6%)	0.82 [0.70–0.95]	0.008	25	17
Studies not including patients receiving concomitant β-blocker therapy	7	38 of 144 (26.4%)	48 of 140 (34.3%)	0.75 [0.55–1.02]	0.07	0	
Studies with the longest follow-up of at least 30 d	12	243 of 1044 (23.3%)	289 of 1036 (27.9%)	0.83 [0.72–0.96]	0.01	23	22
Studies with the longest follow-up of at least 90 d	6	211 of 852 (24.8%)	238 of 848 (28.1%)	0.88 [0.75–1.03]	0.12	13	
Studies with the longest follow-up of at least 180 d	5	209 of 829 (25.2%)	233 of 825 (28.2%)	0.89 [0.76–1.05]	0.16	15	
Studies with short-term follow-up (<30 d)	7	26 of 329 (7.9%)	39 of 240 (16.2%)	0.64 [0.42–0.97]	0.04	0	11
Studies with more than 100 patients	5	216 of 1058 (20.4%)	261 of 977 (26.7%)	0.64 [0.43–0.95]	0.03	60	16
Blinded studies	7	213 of 956 (22.3%)	237 of 881 (26.9%)	0.89 [0.76–1.04]	0.14	0	
Multicentered studies	5	208 of 865 (24.3%)	241 of 862 (28.0%)	0.74 [0.50–1.10]	0.14	55	
Studies with Levo infusion ≤0.1 μg/(kg·min)	8	39 of 339 (11.5%)	68 of 334 (20.4%)	0.57 [0.34–0.96]	0.03	39	12
Studies with Levo infusion >0.1 μg/(kg·min)	11	230 of 1034 (22.2%)	260 of 944 (27.5%)	0.88 [0.75–1.02]	0.08	0	
Studies with Levo bolus	15	234 of 1293 (18.1%)	285 of 1202 (23.7%)	0.81 [0.70–0.94]	0.007	22	18
Studies without Levo bolus	4	35 of 80 (43.8%)	43 of 76 (56.6%)	0.76 [0.56–1.03]	0.08	0	

n_s: number of studies; RR: risk ratio; CI: confidence interval; NNT: number needed to treat; Levo: levosimendan; Dobu: dobutamine

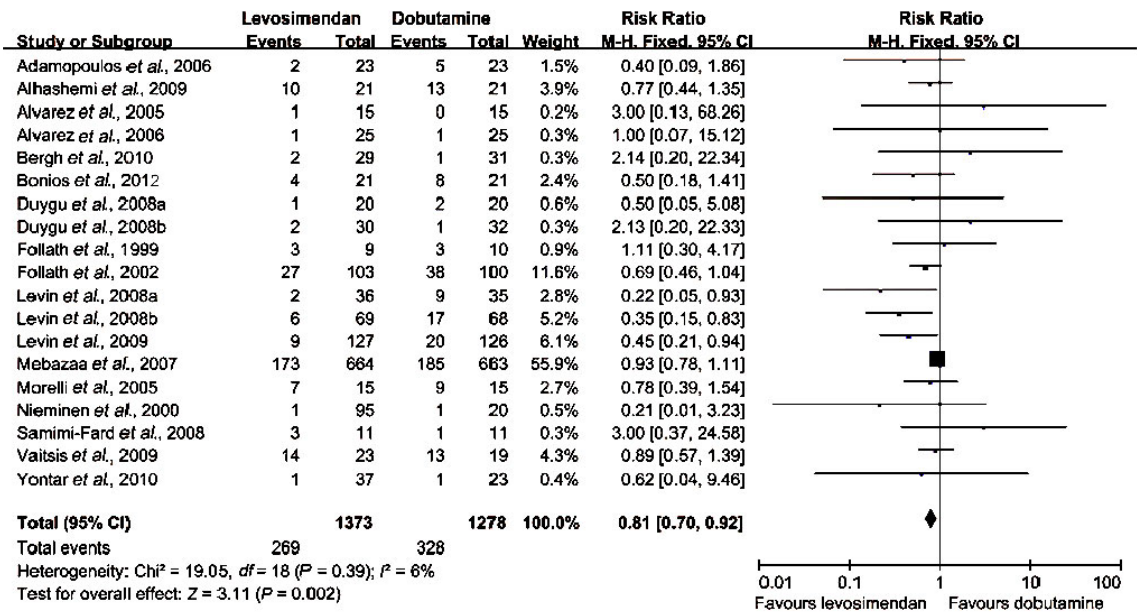

Fig. 2 Forest plot for the risk of mortality in the overall population

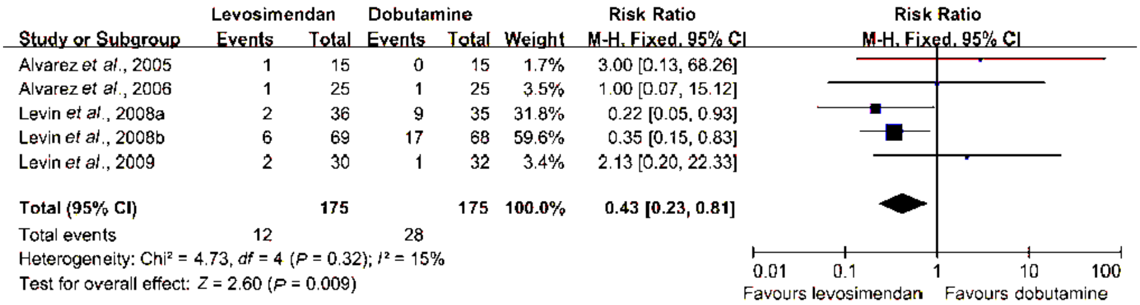

Fig. 3 Forest plot for the risk of mortality in the cardiac surgery setting

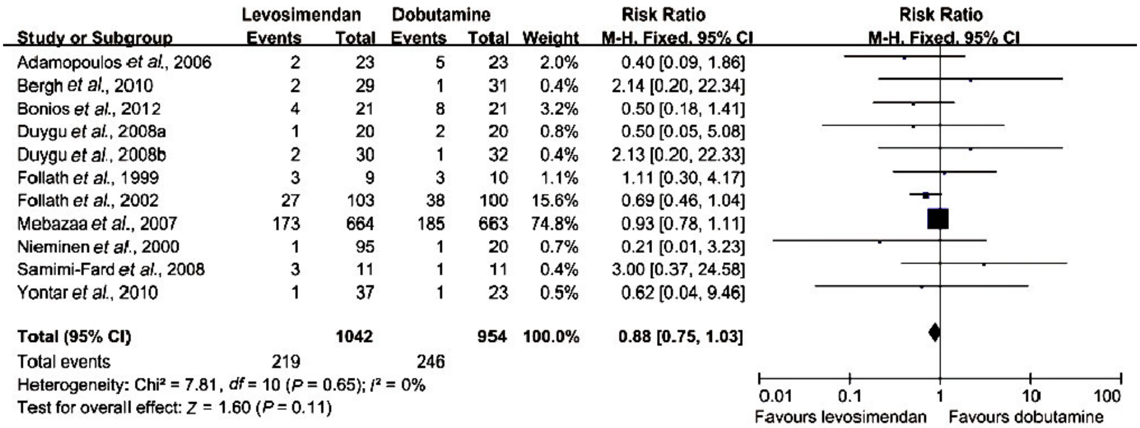

Fig. 4 Forest plot for the risk of mortality in the cardiology setting

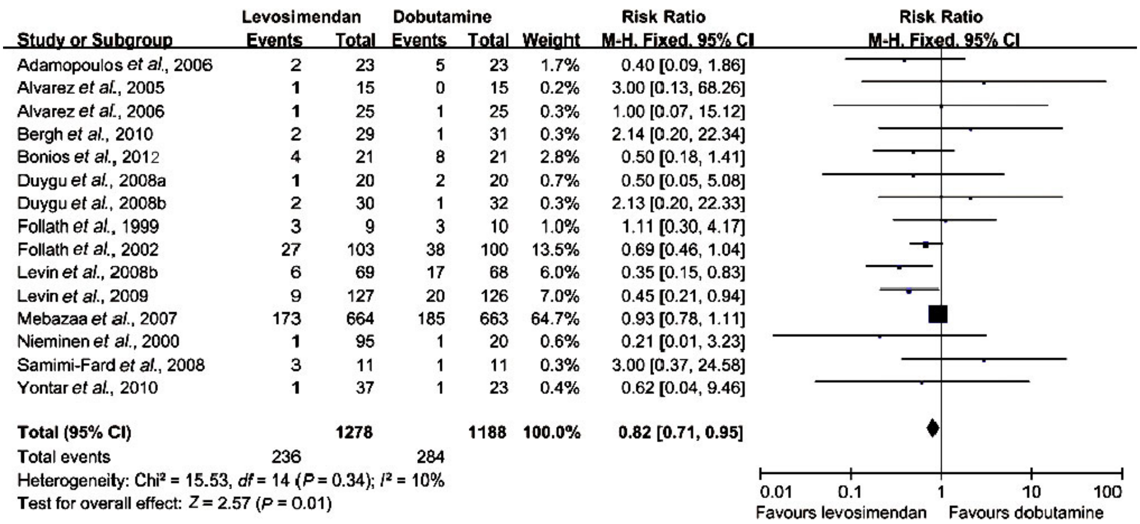

Fig. 5 Forest plot for the risk of mortality in the studies including some patients with ischemic HF

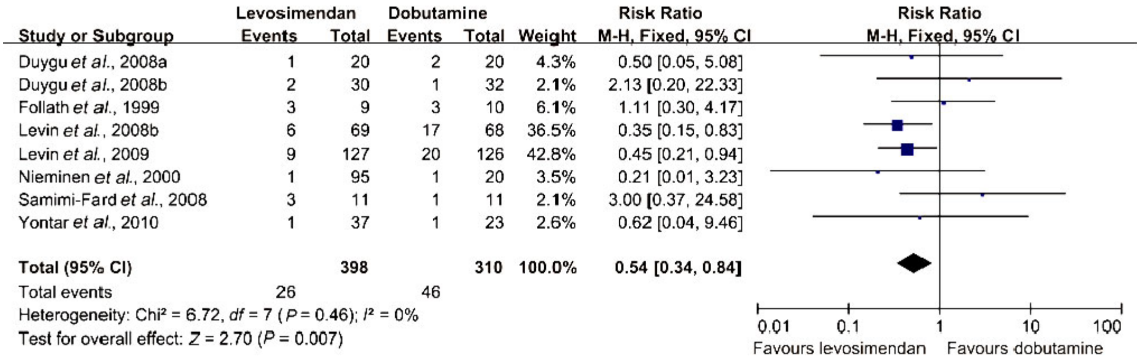

Fig. 6 Forest plot for the risk of mortality in the studies including all patients who had ischemic HF

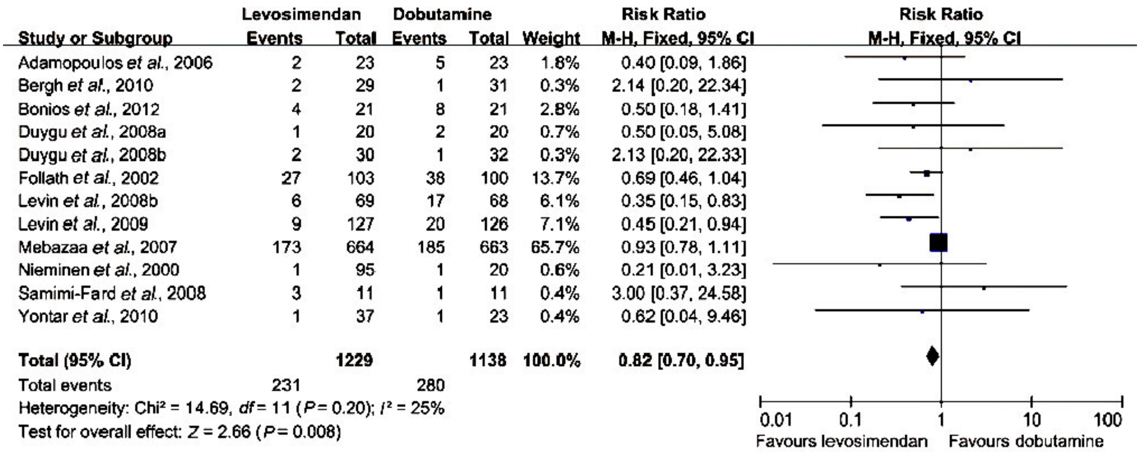

Fig. 7 Forest plot for the risk of mortality in the studies with patients receiving concomitant β-blocker therapy

An analysis of adverse events was conducted and is summarized in Table 5. We found no significant difference in the incidence of hypotension, supraventricular arrhythmias (including atrial fibrillation/flutter, sinus tachycardia, and other kinds of supraventricular tachycardia), or ventricular arrhythmias (including ventricular tachycardia and ventricular fibrillation/flutter) between levosimendan and dobutamine groups.

Sensitivity analysis by sequentially excluding each study and recalculating the pooled estimates on remaining studies confirmed the overall robustness of the results. Small study bias was not found by inspection of the funnel plot (Fig. 8). The results were also robust when studies with more than 100 patients were evaluated (Nieminen *et al.*, 2000; Follath *et al.*, 2002; Mebazaa *et al.*, 2007; Levin *et al.*, 2008b; 2009).

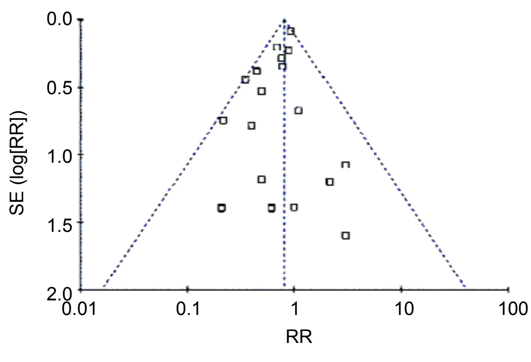

Fig. 8 Funnel plot for the risk of mortality
RR: risk ratio; SE: standard error

Table 5 Adverse events

Subgroup of interest	Number of studies	Event of Levo group	Event of Dobu group	RR [95% CI]	*P*	I^2 (%)
Composite end point of hypotension and/or norepinephrine use	9	161 of 1119 (14.4%)	143 of 1014 (14.1%)	1.06 [0.69–1.64]	0.79	66
Supraventricular arrhythmia	11	138 of 1184 (11.7%)	128 of 1093 (11.7%)	0.76 [0.49–1.19]	0.24	40
Ventricular arrhythmias	6	60 of 1020 (5.9%)	67 of 1003 (6.7%)	0.89 [0.64–1.25]	0.50	25

Levo: levosimendan; Dobu: dobutamine; RR: risk ratio; CI: confidence interval

4 Discussion

For the past 20 years, a large number of studies have shown that many inotropic agents increased mortality in critically ill patients requiring inotropic support. On one hand, use of these inotropes should be prohibited in clinical due to the increase in mortality. On the other hand, these inotropic agents really relieve symptoms and improve the patient's hemodynamics and quality of life. In treating critically ill patients with HF, especially during an emergency, inotropes are needed. To solve this contradiction, more qualified trials and reviews of inotropes are needed to evaluate the efficacy of various inotropic agents and find out which is most suitable for some particular kinds of patients.

Dobutamine is a typical cyclic adenosine monophosphate (cAMP)-dependent inotropic agent, which is widely applied in clinical practice. As a new calcium-sensitizing positive inotropic agent, levosimendan is similar to dobutamine with regards to their hemodynamic effects in patients requiring inotropic support. Whether or not levosimendan is better than traditional inotropes such as dobutamine is still controversial. Indeed, the similarity between the conventional inotropes and levosimendan has been demonstrated in two large clinical trials: SURVIVE (Mebazaa *et al*., 2007) and REVIVE II (Cleland *et al*., 2006). No survival benefit was found in the largest RCTs, which compared levosimendan with dobutamine in patients with acute decompensated HF (Mebazaa *et al*., 2007).

In recent years, several meta-analyses have been published and majority of which have favorable results for levosimendan (Delaney *et al*., 2010; Landoni *et al*., 2010a; 2010b; 2012; Maharaj and Metaxa, 2011) despite a negative conclusion (Ribeiro *et al*., 2010). Among the studies with favorable results, there are three studies merely comparing levosimendan with conventional inotropes and placebo adopted in the control group but without further comparing it with dobutamine (Landoni *et al*., 2010a; 2010b; 2012). The other two studies have compared levosimendan with dobutamine; however, the result of the two studies is inconsistent. One of them was in favor of levosimendan, which included 11 relevant trials (Delaney *et al*., 2010), the other meta-analysis with patients undergoing coronary revascularization found no significant difference between the two drugs, which included four relevant trials (Maharaj and Metaxa, 2011). In all three meta-analyses on mortality of levosimendan vs. dobutamine, only one was in favor of levosimendan (Delaney *et al*., 2010), two of them were negative (Ribeiro *et al*., 2010; Maharaj and Metaxa, 2011). Recently, a few new outcomes of clinical trials on levosimendan vs. dobutamine have been released. Thus, we conducted a meta-analysis of RCTs including some of the latest qualified trials to assess the effect of levosimendan compared with dobutamine on survival and side effects in critically ill patients requiring inotropic support, and tried our best to find out the new evidence for using levosimendan and dobutamine properly.

The results of our meta-analysis indicate that, when compared with dobutamine, levosimendan improved survival benefit in the overall population, as well as in the subpopulations of cardiac surgery and ischemic HF. The result in overall population is consistent with the previous study of Delaney *et al*. (2010). The number of studies on levosimendan vs. dobutamine included in the study of Delaney *et al*. (2010) was only half of that in our meta-analysis. With more cases and subjects, we increased the reliability of risk estimates and performed subanalyses to find out potential sources of heterogeneity, which finally made our results clinically more applicable. Despite the tantalizing results of survival benefit in the overall population, we suggest that more attention should be paid to the subanalyses for the mixed results of subanalyses in the study. The different results of subanalyses may be explained by the disparate mechanisms of myocardial dysfunction in cardiac surgery, cardiology setting, sepsis, and other subpopulations. Therefore, we suggest that it is not advisable to replace dobutamine with levosimendan at any time or in all patients requiring inotropic support.

In the analysis we confirmed the beneficial effect of levosimendan over dobutamine in subpopulations of cardiac surgery. Landoni *et al*. (2010b; 2012) drew similar conclusions in cardiac surgery in two previous meta-analyses. However, placebo and several conventional inotropic agents were all included in the control group in the two meta-analyses. Maharaj and Metaxa (2011) also found survival benefits in the same situation in patients after coronary revascularization, but a negative result when levosimendan was compared with dobutamine. This result in cardiac surgery is certainly worthy of clinicians' attention. Patients undergoing heart surgery often require inotropic drugs for postoperative LCOS. A β-adrenergic agonist such as dobutamine is frequently administrated under this circumstance. Although β-adrenergic agonists usually show a beneficial hemodynamic effect, they cause myocardial ischemia and arrhythmias. Levosimendan may favor the recovery of myocardial dysfunction after cardiac surgery for its anti-ischemic, cardio-protective, and vasodilatory effects. The reason for the survival benefit in subpopulation of cardiac surgery in our analysis is worth discussing. Firstly, acute myocardial ischemia and ischemia-reperfusion may be the main mechanism for LCOS after cardiac surgery with extracorporeal circulation (ECC). Meanwhile, four out of the whole five trials in cardiac surgery included patients with ischemic heart disease and undergoing CABG. Two of them included patients who were all with ischemic heart disease and underwent CABG. It implied that levosimendan may be more effective in improving myocardial ischemia and restoring myocardial function in contrast with dobutamine. Secondly, the myocardial dysfunction in cardiac surgery mainly comes from acute myocardial ischemia or other acute injury. Myocardial dysfunction in cardiac surgery may be more likely to recover than that in patients with ADCHF or chronic HF in cardiology setting.

The subanalyses in the subgroup including ischemic HF patients and in the subgroup in which all patients had ischemic HF, both indicated a favorable result to levosimendan. In fact, 15 out of the whole 19 trials on mortality are totally or partly concerning patients with ischemic HF, who account for more than half of the study population. It's an encouraging finding about ischemic HF, because with the development of global economy and improvement of living standards, there are increasing numbers of patients with coronary heart disease and ischemic HF around the world and especially in developing countries. Bayram *et al*. (2005) reported that post-discharge mortality was increased for short-term use of classical inotropes, particularly in patients with ischemic heart disease. Levosimendan may be superior to dobutamine in patients with ischemic HF for the result of many pharmacological studies and animal studies. On one hand, levosimendan demonstrates positive inotropic properties without increasing myocardial oxygen consumption (Follath, 2009) and impairing ventricular relaxation (Haikala *et al*., 1995) in failing hearts. On the other hand, levosimendan has a vasodilatory effect mediated by activation of adenosine triphosphate (ATP)-sensitive potassium channels, which reduces cardiac preload and afterload (Tavares *et al*., 2008; Follath, 2009). In addition, levosimendan can increase the diastolic coronary flow velocity through an ATP-sensitive potassium channel opening effect on coronary vasculature (Kaheinen *et al*., 2001). In contrast, one of the dobutamine's fatal weaknesses is increasing myocardial oxygen demand and further causing myocardial injury. Therefore, dobutamine can worsen myocardial ischemia in patients with ischemic cardiomyopathy, especially in the setting of acute myocardial ischemia (Pacold *et al*., 1983). In patients with acute myocardial infarction (AMI) complicated by cardiogenic shock secondary to severe left-ventricular systolic dysfunction requiring inotropic support, levosimendan increased both CI and left ventricular ejection fraction more significantly than dobutamine. However, most of studies in our analysis did not include patients with AMI. In the SUIVIVE study, which included patients with AMI, no survival benefit was found in the subpopulation of AMI. Another study including patients with AMI concluded that levosimendan did not improve long-term survival in STEMI patients revascularized by PCI who developed cardiogenic shock when compared to dobutamine. Thus, there is still no convincing evidence demonstrating that levosimendan can improve the prognosis of patients with AMI when compared with dobutamine. It should be cautious to treat AMI with levosimendan. More evidence is required to confirm the advantage of levosimendan over dobutamine in patients with AMI.

Disappointingly, the research result of subgroups in a cardiology setting was not satisfactory. On one side, it may indicate levosimendan is not better than dobutamine in all kinds of patients with HF and the efficacy of levosimendan in a cardiology setting may be incomparable to those in cardiac surgery. On the other side, it may relate to removing the CASINO study (Zairis *et al*., 2004), which had a lot of problems in study quality. The CASINO study was criticized for performing analyses only on patient on-treatment instead of intention-to-treat principle. Many experts argued if the drop-outs in that study were to be included, the magnitude of the effect might be minimal to negligent. However, most of previous meta-analysis articles about levosimendan included the CAISNO study (Delaney *et al*., 2010; Ribeiro *et al*., 2010; Landoni *et al*., 2012). With the inclusion of the CASINO study, the result of analysis in cardiology setting would be in favor of levosimendan (237 of 1142 [20.8%] in the levosimendan group vs. 288 of 1054 [27.3%] in the dobutamine group, RR=0.72, 95% CI 0.53–0.96, P=0.03, Q=15.67, P for heterogeneity=0.15, I^2=30%, NNT=16 with 12 studies included), so was that in subgroup of patient's number greater than 100 and in multi-center subgroup. This also implied more large sample and multi-center clinical studies were needed to evaluate the efficacy of the two drugs, especially in cardiology setting.

Another interesting result is the subgroup analysis about the patients receiving concomitant use of β-blocker therapy. The subgroup included 12 studies. Two of them were from cardiac surgery, another ten studies were all from a cardiology setting, and none were from sepsis. The finding is encouraging, because a lot of patients with ischemic cardiomyopathy or chronic HF receive a β-blocker and β-blockers are recommended as first-line therapy by the guidelines (Hunt *et al*., 2005; Swedberg *et al*., 2005). Owing to adverse effects of β-blocker therapy on the hemodynamic response to dobutamine (Metra *et al*., 2002), patients with HF receiving β-blocker therapy usually require higher doses of dobutamine to assure its efficacy. In contrast, levosimendan still efficiently improves cardiac contractility during the concomitant use of β-blocker therapy (Lehtonen and Sundberg, 2002). Moreover, a subanalysis in the LIDO study showed that the effect of dobutamine on cardiac output was attenuated for concomitant use of β-blockers, but the effect of levosimendan was not affected (Follath *et al*., 2002). Our study firstly confirmed these results from the perspective of the prognosis, and this has not been found previously in other meta-analysis about levosimendan vs. dobutamine. Thus, levosimendan may be the better choice than dobutamine in the treatment of HF during long-term maintenance therapy with β-blockers.

Although the dataset of subanalysis on sepsis is small (only including three studies), the outcome is noteworthy. As severe sepsis usually produces low systemic vascular resistance, the beneficial effect of levosimendan may be neutralized to some extent by its vasodilator effect on critically ill patients with severe sepsis or septic shock. Clinicians should assess the cause of shock more carefully. If low systemic vascular resistance accounts for much of effects in circulatory failure, levosimendan should not be selected in patients with severe sepsis or septic shock.

The outcomes of subanalysis about different follow-up times should be paid close attention to. The survival benefit from levosimendan was only found in studies with short-term follow-up (<30 d or the longest follow-up of at least 30 d). The outcome in studies with the longest follow-up of at least 90 d or 180 d was still unsatisfactory. The effect of levosimendan vs. dobutamine on long-term prognosis has yet to be studied further.

As for the administration methods of levosimendan, a bolus dose or an infusion rate ≤0.1 μg/(kg·min) seems to be a better choice in light of our meta-analysis. However, the subgroup with no bolus dose included either patients with septic shock or patients with cardiogenic shock. The patients in this subgroup may be in a more serious condition than other patients. So, the result of subgroup with no bolus dose should be interpreted prudently. The result of subanalysis about infusion rate in our study seems to be inconsistent with that in the study of Landoni *et al*. (2012). Although Landoni *et al*. (2012) reported positive results in both subgroups of patients receiving an infusion rate ≤0.1 and >0.1 μg/(kg·min), a trend towards an increased survival was also found in the subgroup of patients receiving an infusion rate ≤0.1 μg/(kg·min). Hypotension caused by a faster infusion rate may be one of the main reasons. We did not conduct a further subanalysis on incidence of hypotension according to different infusion rates because only one trial was included in the subgroup of patients receiving an infusion rate ≤0.1 μg/(kg·min). In brief, the effect of infusion rate on blood pressure should be paid close attention to when levosimendan is used.

The most common and important adverse effects of levosimendan are hypotension and arrhythmias, so are other conventional inotropes. No significant reduction or increase for hypotension and arrhythmias was found when levosimendan was compared with dobutamine.

The present meta-analysis also has some limitations. Several enrolled trials were of suboptimal quality. Lack of clear allocation concealment was found in most studies of the analysis (20 of 22). This is likely to overstate efficacy. Only seven studies were blinded studies. Follow-up duration of two studies on mortality was only one day. We cannot draw clear conclusions about the better choice in subpopulation of cardiology and sepsis for their insufficient dataset when levosimendan was compared with dobutamine. Only one trial was included in STEMI patients with cardiogenic shock related to PCI and no long-term survival benefit was found in the study. Therefore, we cannot assume that levosimendan is better than dobutamine in these situations.

The outcomes of the analysis may be affected to some extent by publication bias. It is likely to overstate efficacy due to the smaller trials included. However, publication bias of the analysis was low because the funnel plot showed a symmetrical shape. Some trials were short of clinically relevant data. Only 2133 patients were included in the analysis of hypotension rates, 2277 patients in the analysis of supraventricular arrhythmias rates, and 2023 patients in the analysis of ventricular arrhythmias rates.

5 Conclusions

In conclusion, the present meta-analysis of RCTs suggests that levosimendan improves survival benefit in comparison with dobutamine in critically ill patients requiring inotropic support. However, the results of subanalysis on subpopulation, method of administration, and other aspects are of variable. Patients in cardiac surgery, with ischemic HF and receiving concomitant β-blocker therapy, may benefit from levosimendan. Additional large, multicentered, and powered RCTs are required to address the questions about no positive outcomes in the subpopulation of cardiology setting and to confirm the advantage in long-term prognosis.

Compliance with ethics guidelines

Xuan HUANG, Shu LEI, Mei-fei ZHU, Rong-lin JIANG, Li-quan HUANG, Guo-lian XIA, and Yi-hui ZHI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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