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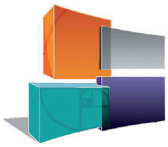

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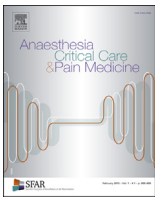

Original Article

Levosimendan in patients with low cardiac output syndrome undergoing cardiac surgery: A systematic review and meta-analysis

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ABSTRACT

Levosimendan is an inotropic agent that has been shown in small studies to treat low cardiac output syndrome in cardiac surgery. However, large randomised controlled trials (RCTs) have been recently published and presented neutral results. We sought to determine the effect of levosimendan on mortality in adults with low ejection fraction undergoing cardiac surgery. We searched different databases: Medline, Embase, Cochrane Central Register of Controlled Trials, and clinical trial registries. We included RCTs comparing events in the levosimendan versus placebo in adult patients with ejection fraction $\leq$ 35% undergoing cardiac surgery. Outcomes were mortality at 30-day, mortality beyond 30−day, acute kidney injury and myocardial infarction. Five trials with a total of 1519 patients were selected. Four trials were rated as low risk of bias. Our meta-analysis showed no significant difference between levosimendan versus placebo mortality at 30-day [odds radio (OR): 0.62; 95% confidence intervals (CI): 0.32 to 1.20; I^2 = 33%; high quality evidence] and mortality beyond 30-day (OR: 0.71; 95% CI: 0.46 to 1.11; I^2 = 0%). Similarly, there were no significant differences between the levosimendan versus placebo in the incidence of acute kidney injury (OR: 0.61, 95% CI: 0.33−1.13) and myocardial infarction (OR: 0.41, 95% CI: 0.08 to 1.22). The current evidence suggests that levosimendan is not associated with significantly reduced mortality in patients with reduced ejection fraction undergoing cardiac surgery.

1. Introduction

More than 1 million patients undergo annually cardiac surgery in Europe and the United States [1]. The low cardiac output syndrome is a common complication affecting up to 20% of such patients [2,3] and is associated with a heightened risk of perioperative death and more frequent complications, including myocardial infarction and renal failure stroke [4,5,6]. This syndrome is managed with inotropic agents, which are the cornerstone of perioperative haemodynamic support [2,7,8].

Levosimendan, a calcium-sensitizing inotrope and ATP-sensitive potassium–channel opener, increases cardiac output with minimal effect on myocardial oxygen consumption [9,10]. It is currently used in more than 60 countries for the prevention and treatment of the low cardiac output syndrome [11–14]. Also, it has been ranked as the most efficient inotrope to improve survival [15]. Previous meta-analyses pooling small randomised controlled trials (RCTs) suggested that levosimendan could reduce morbidity and mortality in patients undergoing cardiac surgery, especially those with reduced ejection fraction (EF) [13,16–23]. However, findings from three large RCTs published did not confirm a definite survival advantage from levosimendan [14,24,25]. Moreover, previous meta-analyses combined heterogeneous populations including patients with reduced EF and patients with another cardiovascular dysfunction into one overall intervention effect estimate. Thus, given the conflicting evidence and the limitations of the previous meta-analyses prompted us to conduct an updated systematic review and meta-analysis.

In this study, we performed a systematic review and meta-analysis including complete results from recently published large RCTs to determine the effect of levosimendan on mortality in patients with low cardiac output syndrome undergoing cardiac surgery.

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2. Methods

We developed and followed a protocol that is not registered on PROSPERO. The present systematic review was conducted in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [26].

2.1. Information sources and search strategy

Medline, EMBASE, and the Cochrane Library at the CENTRAL Register of Controlled Trials were searched from database inception to January 1, 2018 with the assistance of a professional librarian. We also searched grey literature and clinical trial registries. We cross checked the references of potentially eligible RCTs. There were no restrictions on language.

For the search strategy, we used in various relevant combinations, MeSH terms and keywords pertinent to the intervention of interest: ''levosimendan'', ''placebo'', ''cardiac surgery'', ''randomised controlled trial'' (Appendix data).

2.2. Study selection

Two authors performed the study selection independently. They screened titles and abstracts for initial study inclusion. They screened the full text of potentially relevant trials. Disagreements between the two reviewers were resolved by consensus, and if necessary, consultation with a third reviewer.

Eligible studies met the following PICOS criteria:

- population: adult cardiac surgery patients had a left ventricular ejection fraction of 40% or less;
- intervention: levosimendan;
- comparison intervention: placebo;
- outcome: any primary or secondary endpoint of the present systematic review;
- study design: RCT.

We excluded observational, non-controlled, or non-randomised interventional studies, emergency surgery, duplicate publications, studies with non-intravenous administration of levosimendan and studies without reporting of mortality as an outcome.

2.3. Data collection process

Two investigators independently extracted data from the included RCTs using a standardised form. We contacted the investigators of all unpublished studies and published studies to obtain additional study details. Disagreements between the two reviewers were resolved by consensus, and if necessary, consultation with a third reviewer. Another reviewer double-checked the extracted data.

2.4. Outcomes

The primary outcome was mortality at 30 days. We considered a reduction of mortality to be the most important potential benefit of levosimendan in cardiac surgery.

The secondary outcomes were mortality beyond 30 days, acute kidney injury (AKI) and myocardial infarction.

2.5. Quality assessment

Two reviewers independently assessed the risk of bias (low risk of bias, high risk of bias, or unclear risk of bias) using the Cochrane risk of bias instrument, which deals with random sequence generation and allocation concealment (selection bias), blinding of study participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. They resolved any disagreements by discussion and consensus or by consulting a third reviewer.

We used the GRADE approach to rate the quality of evidence and generate absolute estimates of effect for the outcomes [27].

2.6. Data synthesis

The meta-analysis and systematic review was performed according to PRISMA guidelines [26]. Reporting of statistical data followed SAMPL guidelines [28]. Computations were performed with RevMan 5.3.3 software (The Cochrane Collaboration). The meta-analysis was done using random effect models regardless of the level of heterogeneity because the included RCTs differed meaningfully in clinical and methodological features. We used Mantel–Haenszel (M–H) method as the primary analysis to estimate odds ratio (OR) and 95% confidence intervals (CI). We assessed heterogeneity with the Cochran Q test and the I^2 test, with I^2 values exceeding 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [29]. Forest plots were constructed to provide a graphical representation of the analysis. We generated a funnel plot to examine publication bias.

We conducted sensitivity analyses to examine the impact of using:

- alternative effect measures (risk ratio);
- pooling methods (Peto or Inverse Variance);
- statistical models (fixed).

3. Results

3.1. Study selection and study characteristics

The search strategy yielded 791 manuscript abstracts (Fig. 1). Five trials [14,25,30–32] were included in the final analysis. The 5 trials included randomised 1519 patients (Table 1). Clinical heterogeneity was mostly due to dose, setting, and follow-up. Indeed, two studies [31,32] used levosimendan in coronary artery bypass grafting (CABG) surgery only and 3 [14,25,30] in combined cardiac surgery. Two trials administered a bolus. Follow-up varied between 30 days and 6 months.

The Cochrane Collaboration's tool indicated that trials were of variable quality (Fig. 2), and that four trials were rated as low risk of bias, whereas three were considered moderate. Table 2 is GRADE summary findings for all outcomes.

3.2. Outcome: mortality

The associations between levosimendan and mortality are shown in Fig. 3. Our meta-analysis showed no significant difference between levosimendan versus placebo mortality at 30-day [OR: 0.62; 95% (CI): 0.32 to 1.20; I^2 = 33%; high quality evidence] and mortality beyond 30−day (OR: 0.71; 95% CI: 0.46 to 1.11; I^2 = 0%).

Sensitivity analyses using an alternative statistical method (Peto; OR: 0.66; 95% [CI]: 0.42 to 1.02) (Inverse Variance; OR: 0.62; 95% [CI]: 0.32 to 1.20), effect measure (risk ratio: 0.65; 95% [CI]: 0.35 to 1.18), and analysis model (fixed effects; OR: 0.66; 95% [CI]: 0.42 to 1.03) at a time showed similar results of 30-day mortality.

The funnel plot for 30-day mortality did not show a publication bias in the analysis (Appendix Fig. 1).

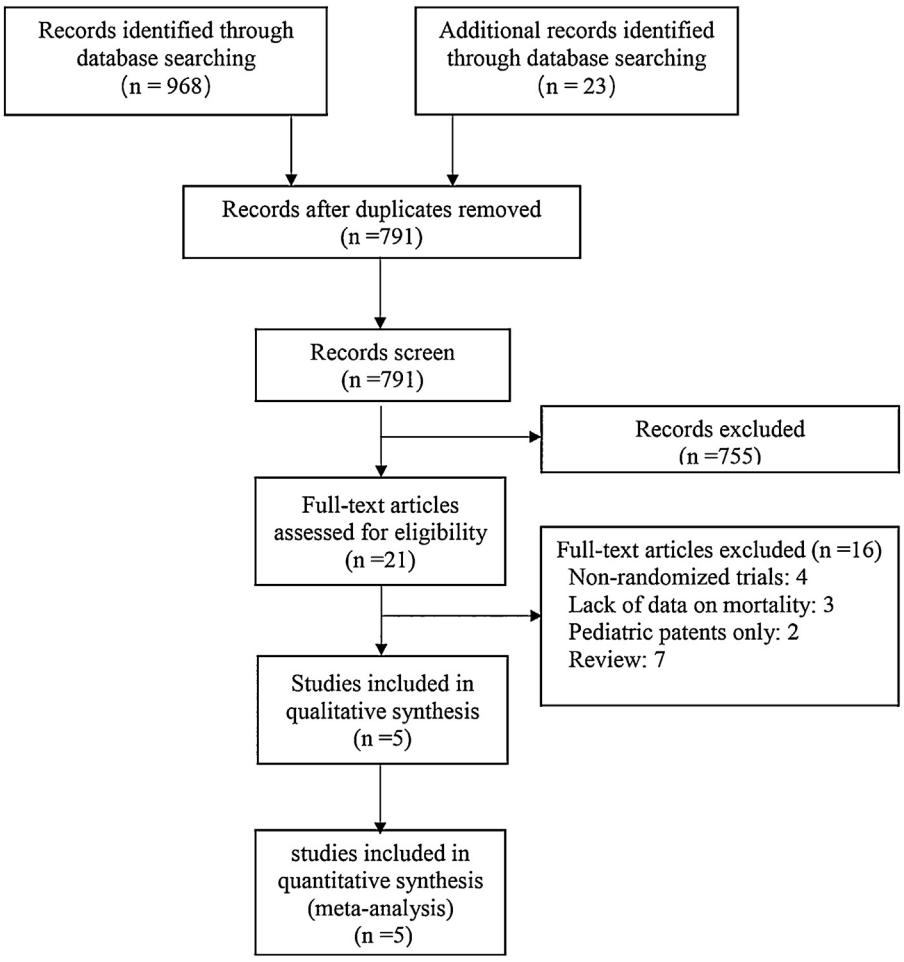

Fig. 1. Study selection for inclusion in a meta-analysis of levosimendan in cardiac surgery.

Table 1
Characteristics of included studies.

Author	Year	Patients	Surgery	Mean ejection fraction (SD)		Time of levosimendan administration	Dose of levosimendan	Follow-up
				Levosimendan	Control			
Cholley	2017	335	CABG with CPB, with or without valve	33 (6)	33 (6)	Preoperative	Bolus: none Inf: 0.1 μg/kg/min Duration: 24 h	6 months
Erb	2014	33	CABG with or without valve	22.0 (4.5)	22.4 (5.5)	Preoperative	Bolus: none Inf: 0.1 μg/kg/min Duration: unknown	6 months
Levin	2012	252	CABG	18 (3)	19 (2)	Preoperative	Bolus: 10 μg/kg Inf: 0.1 μg/kg/min Duration: 24 h	30 days
Mehta	2017	849	CABG with CPB with or without valve, or isolated valve surgery	26 (24–32)[a]	27 (22–31)[a]	Preoperative	Bolus: 12 μg/kg Inf: 0.1 μg/kg/min Duration: 24 h	3 months
Shah	2014	50	CABG	22 (4)	22 (3)	Preoperative	Bolus: none Inf: 200 μg/kg dose Duration: 24 h	30 days

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass.
[a] Median (IQR).

3.3. Outcome: AKI and myocardial infarction

AKI was reported in four trials. There was no difference in incidence of AKI between levosimendan versus placebo (OR: 0.61, 95% CI: 0.33–1.13) (Fig. 4).

Myocardial infarction was reported in three studies. The analysis including trials found similar incidence of postoperative myocardial infarction with levosimendan or placebo (OR: 0.41, 95% CI: 0.08–1.22) (Fig. 4).

4. Discussion

In this meta-analysis of five randomised controlled trials involving 1519 adult cardiac surgery patients with low EF, we

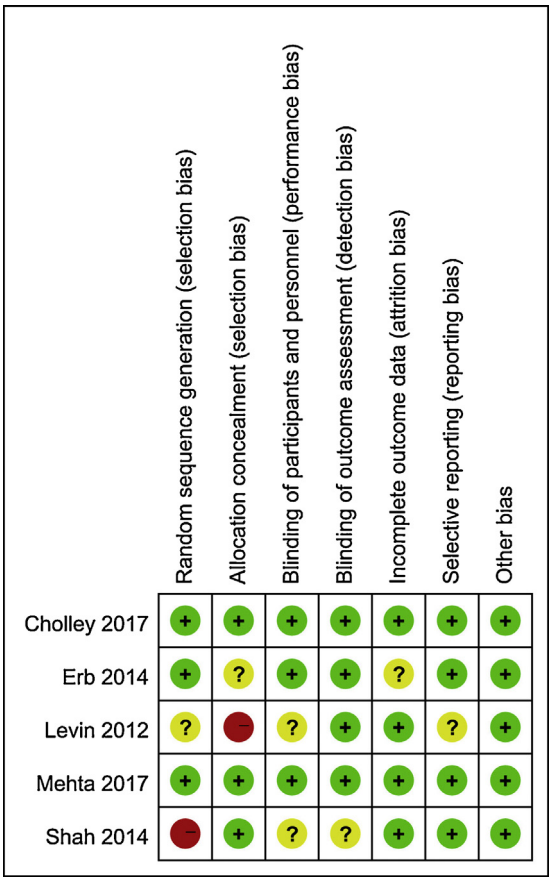

Fig. 2. Risk of bias summary.

found that perioperative administration of levosimendan did not significantly reduce the risk for clinical events including death, AKI, and myocardial infarction. In numerous sensitivity analyses, our finding did not change.

4.1. Compared with other studies

Several systematic reviews and meta-analyses have been published so far on the topic [13,16–21,33]. Most of them, published before 2017, provide the general message of significant benefits for levosimendan regarding patient mortality, without differences in the overall population and the patients with reduced EF [13,16,17,21,22]. The most recent meta-analyses have stated that levosimendan reduces mortality in patients with preoperative reduced EF but does not affect overall mortality [18–20,33].

In this meta-analysis, we come to different conclusions from those of authors of previous meta-analyses. Various reasons might explain differences and strengthen our study. First, previous meta-analyses combined heterogeneous populations, including patients with reduced EF, and patients with another cardiovascular dysfunction into one overall intervention effect estimate [18,20]. Second, comparisons to placebo or another inotrope are so fundamentally different; however, previous meta-analyses combined heterogeneous comparison in the same meta-analysis [18,20,33]. Third, we could include two large studies [14,26] published in 2017, which accounted for more than half of the total number of patients, which made it possible to provide improved precision concerning the effects of levosimendan. Fourth, our meta-analysis separately assessed mortality according to various time points of follow-up, which avoided bias of pooling date of different time points. Fifth, previous meta-analyses [17,18,21,22,34,35] pooled the 2008 study [36] and the 2012 study [31] by Levin et al., in one analysis. The recruitment period of the 2012 study (between December 1, 2002 and June 1, 2008) encompasses that of the 2008 study (between December 1, 2003 and December 1, 2006); results of both studies were positive and made up a relatively significant weight of many positive meta-analyses. Possible duplicate publications of Levin et al., strongly influenced results of the meta-analyses. Thus, we eliminate the first study and kept only the 2012 study in our study.

Additionally, we have provided a rigorous assessment of the quality of evidence and absolute as well as relative risks.

4.2. Limitations

Our study also has limitations. First, although the statistical heterogeneity was low in all outcomes, our analysis is limited by clinically relevant heterogeneity among trails. Those variabilities included dose of levosimendan, timing of levosimendan administration, whether using bolus, surgical population, length of follow-up, and definition of outcomes. These diversities may have influenced the effect of levosimendan. However, we were unable to assess all important variables for lack of adequate data. For example, second outcomes of this study were AKI and myocardial infarction. However, the definitions for AKI and myocardial infarction were to some extent different in the included trials. Levin et al..'s study and Shah et al.'s study defined renal failure as elevated creatinine ($>$ 50% from baseline) with or without oliguria (urine output $<$ 0.5 mL/kg/h) or requiring dialysis. Cholley et al.'s study and Mehta et al.'s study only reported data of renal

Table 2
GRADE evidence profile of outcomes, levosimendan versus placebo.

Outcome	No. of patients (Studies)		Study results (95% CI) and measurements	Absolute effect estimates (per 1000)			Quality	Importance
	Levosimendan	Placebo		Levosimendan	Placebo	Absolute risk (95% CI)		
Mortality at 30 days	34/764 (3.8%)	50/755 (6.6%)	OR: 0.62 (0.32 to 1.2)	42	66	24 fewer (from 44 fewer to 12 fewer)	⊕⊕⊕⊕ high	Critical
Mortality beyond 30days	38/615 (6.2%)	51/605 (8.4%)	OR: 0.71 (0.46 to 1.18)	61	81	23 fewer (from 44 fewer to 8 more)	⊕⊕⊕⊖ high	Important
Myocardial infarct	69/722 (9.6%)	73/714 (10.2%)	OR: 0.41 (0.08 to 2.16)	44	102	58 fewer (from 93 fewer to 95 more)	⊕⊕⊕⊕ moderate[a]	Important
Acute kidney injury	23/733 (3.1%)	78/738 (5.2%)	OR: 0.61 (0.33 to 1.13)	32	52	20 fewer (from 34 fewer to 6 more)	⊕⊕⊕⊖ high	Important

CI: confidence interval; OR: odds ratio; high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.

[a] Serious imprecision.

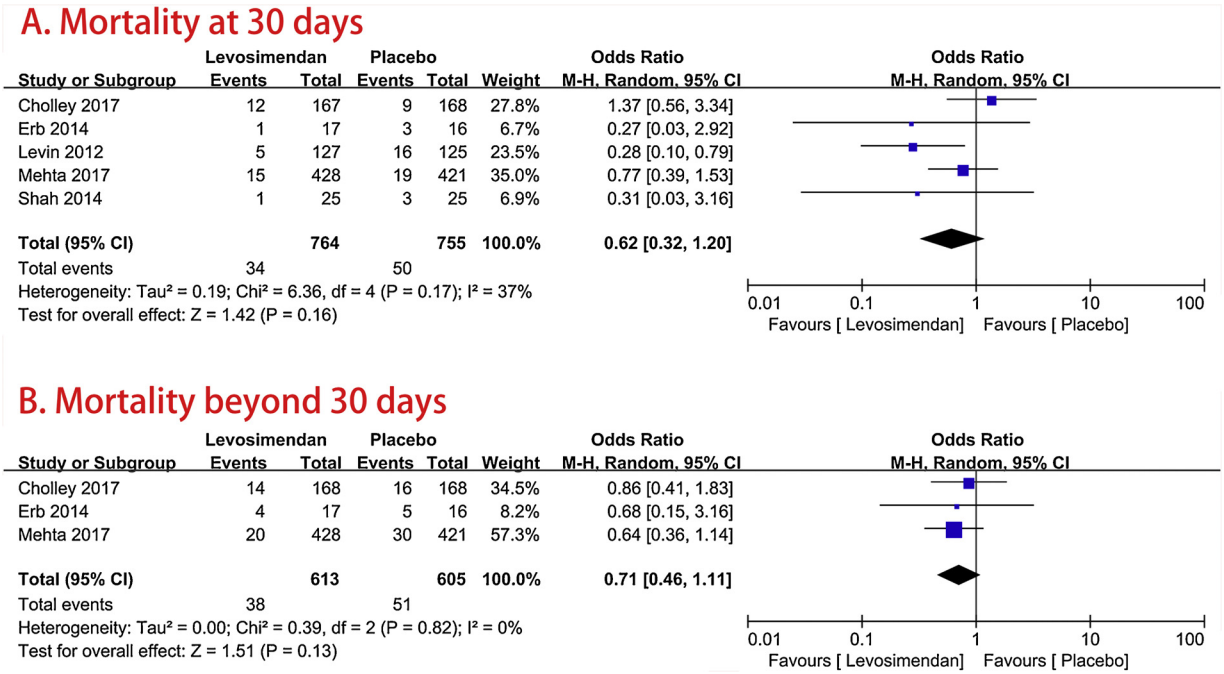

Fig. 3. Association of levosimendan vs. placebo with mortality at 30 days and beyond 30 days.

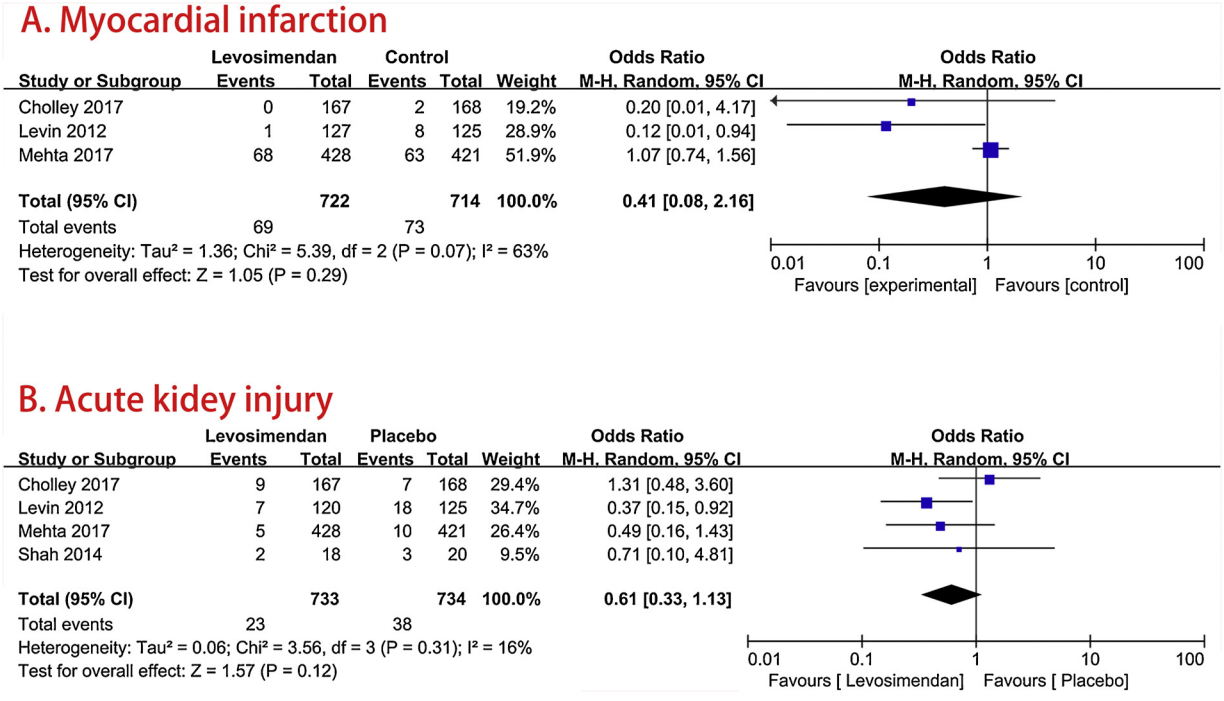

Fig. 4. Association of levosimendan vs. placebo with acute kidney injury and myocardial infarct.

replacement therapy. Also, myocardial ischaemia was not assessed similarly in all the studies.

Second, all trials included have compared active treatment with placebo. However, as to patients in the placebo group, medicine including inotrope was necessary due to the severity of patient status. For example, in Mehta et al.'s trial, more than half the patients in the placebo group postoperatively used inotropes at or beyond 24 hours after the start of the infusion of placebo. Thus, patients in the placebo group inotropes in some degree, and the definition of 'placebo' as the control varied in studies.

Third, our meta-analysis separately assessed mortality according to various time points of follow-up, 30 days and beyond 30 days. All trials reported data of mortality at 30 days. However, the effect of levosimendan on mortality beyond 30 days was unclear because only one trial [14] reported mortality at 90 days and two trails [25,30] at 180 days.

Fourth, our meta-analysis has generally reported results potentially suggestive of a protective effect of levosimendan on mortality (OR: 0.62, 95% CI: 0.32−1.20) but failed to show the statistical significance of this association. The small number of patients in our study raises the probability of a type II error. Even among those high-risk patients, an adequately powered trial assessing the effect of levosimendan on mortality would require the enrolment of approximately 3000 patients [14] Therefore, the sufficient evidence for the use of levosimendan in patients with low EF is yet to be further expanded.

4.3. Implications for clinical practice

The results of our meta-analysis seem to refute the suggestion from the previous meta-analyses [16,19,20] and challenge the previous endorsement of levosimendan use in literature [11]. Thus, adoption of levosimendan in patients with reduced EF undergoing cardiac surgery may not be recommended for routine use unless further well-powered and high quality scientific evidence shows benefit.

5. Conclusion

In summary, our meta-analysis suggests that levosimendan compared with placebo did not result in a significant difference in mortality in patients with reduced EF who were undergoing cardiac surgery. Further well-designed RCTs are needed to determine it.

Ethical approval

Not required.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.accpm.2018.08.005.

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