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REVIEW ARTICLE

The efficacy and safety of prophylactic use of levosimendan on patients undergoing coronary artery bypass graft: a systematic review and meta-analysis

Wanyu Wang[1] · Xiaoshuang Zhou[1] · Xinyang Liao[2] · Bin Liu[1] · Hai Yu[1]

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Abstract
Prophylactic use of levosimendan in cardiac surgery remains controversial and no meta-analysis has been done exclusively about that in patients undergoing coronary artery bypass graft (CABG) surgery. We conducted this systematic review and meta-analysis of levosimendan in CABG using PubMed, Embase, Scopus, and Cochrane Library (till April 20, 2018). Two-hundred and forty manuscripts were identified and 21 randomized trials (1727 patients in total) investigating the effect of levosimendan on the patients undergoing CABG surgery were finally included in this analysis. We found that levosimendan was an effective, well-tolerated inotropic agent in CABG, which was associated with a significantly reduced mortality rate [odds ratio (OR) 0.43, 95% confidence interval (CI) (0.26, 0.71), $p = 0.001$, $I^2 = 0\%$] and postoperative atrial fibrillation [OR 0.50, 95% CI (0.26, 0.97), $p = 0.04$, $I^2 = 76\%$], but a higher incidence of hypotension [OR 2.26, 95% CI (1.05, 4.85), $p = 0.04$, $I^2 = 79\%$]. Subgroup analyses revealed that such a benefit was mainly observed in the isolated CABG, the preoperative administration, with-bolus and on-pump subgroups. More high-quality and well-designed prospective studies are needed to confirm or disprove our findings in future.

Keywords Coronary artery bypass graft (CABG) · Levosimendan · Efficacy · Safety · Meta-analysis · Systematic review

Introduction

Currently, coronary artery bypass grafting (CABG) is one of the most common procedures performed by cardiac surgeons [1, 2]. In fact, more than 800,000 patients undergo CABG annually worldwide [3]. Given the insufficient cardiac function of this cohort of patients, the incidence of low cardiac output syndrome (LCOS) after isolated CABG reportedly varies from 3 to 14% [4, 5], which is associated with a 10- to 17-fold increase in mortality and markedly increased complications, including myocardial injury, stroke, renal failure, and prolonged length of stay in the intensive care unit (ICU) and hospital [5–7]. LCOS is usually managed with inotropic agents, which can increase myocardial contractility by increasing the concentration of intracellular calcium or the sensitivity of receptor proteins to calcium. However, the efficacy and safety of these traditional inotropic agents had been doubted, because the increase in myocardial contractility is reached at the expense of increased myocardial oxygen consumption, which can increase the risk of ischemia, arrhythmias, and even death after cardiac surgery [8, 9]. Levosimendan {[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenyl] hydrazono} is a newly discovered inotropic drug that can increase the cardiac output without significantly increased myocardial oxygen consumption [10–12]. It was reported to provide cardio-protective [13], anti-ischemic [14], and renal protective effects [15] and had been gaining attention during last two decades because of its efficacy in improving the prognosis of patients undergoing cardiac surgery [16].

The efficacy and safety of levosimendan in cardiac surgeries has been discussed by several randomized controlled trials (RCTs) [17–19] and meta-analyses [20, 21] in the past 15 years. Previous research had found that levosimendan

✉ Bin Liu
liubinhxyy@163.com

✉ Hai Yu
yuhaishan117@yahoo.com

[1] Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

[2] Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

decreased the incidence of mortality [22]. Even though three recently published randomized, placebo-controlled, multicenter studies (LICORN, LEVO-CTS and CHEETAH [23–25]) demonstrated no significant difference between the levosimendan group and the control group for cardiac surgery, the post hoc subgroup analysis from LEVO-CTS (https://www.nejm.org/doi/ full/10.1056/NEJMoa1616218) suggested that levosimendan might be effective in patients undergoing only CABG procedure, but not patients undergoing valve replacement [26]. Based on these data, we speculated the effect of levosimendan on mortality might differ between surgeries.

Previous meta-analysis [18, 21, 27, 28] had evaluated the efficacy and safety of levosimendan in patients undergoing any cardiac surgery. However, to our knowledge, no meta-analysis has been done to investigate that in CABG procedure. Apart from the type of surgery, factors such as regimen of the control group, administration time, with/without a bolus, and the type of the CABG (on/off pump, isolated/combined with valve surgeries) could all influence the postoperative prognosis with the administration of levosimendan. Therefore, we performed this meta-analysis with a series of subgroup analyses according to the above-mentioned factors. We aimed to evaluate the efficacy and safety of prophylactic levosimendan in patients undergoing CABG by analyzing all relevant published RCTs.

Methods

This meta-analysis was conducted in accordance with the Cochrane methodology [29] and the preferred reporting items systematic reviews and meta-analysis (PRISMA) guidelines [30]. No ethics approval was required for this review. In addition, we had no funding or any conflict of interest.

Search strategy and selection criteria

An extensive background review of the literature was completed prior to the start of this meta-analysis. In April of 2018, two investigators conducted an online search without language restrictions in the following four databases: PubMed, Embase, Scopus, and Cochrane Library. The search strategy included a combination of the keywords and MeSH terms related to "coronary artery bypass graft" and "levosimendan". The search strings were adapted to the unique lexicons and the requirements of each database.

Two investigators independently went through the title and the abstract of each reference obtained from the searches, and then gathered and assessed the full texts of the relevant studies if they met the inclusion criteria according to the PICOS: (1) patients: adult patients undergoing CABG; (2) intervention: levosimendan; (3) comparison: any control; (4) outcome: clinical outcomes reported; and (5) study design: RCTs. We excluded the nonrandomized studies, pediatric studies, and other isolated cardiac surgeries without CABG (i.e., valve surgery only). Divergences between the investigators were resolved by a counselor.

Data extraction and outcome definitions

After identifying the eligible studies, two independent investigators extracted data to form a predefined extraction sheet. We distinguished the outcomes from efficacy outcomes to safety outcomes.

The efficacy outcomes included: the mortality at the longest follow-up, need for intra-aortic balloon pump (IABP), need for additional inotropic drugs, perioperative myocardial injury (MI, which was defined as any report on myocardial injury/myocardial infarction), renal dysfunction and need for renal replacement treatment.

The safety outcomes included: hypotension that needs vasoactive medication and postoperative atrial fibrillation (AF).

The length of ICU stay, the ventilation duration, and the length of hospital stay were also assessed. Disagreements in data extraction were resolved by consensus.

Statistical analysis

Most of the outcomes were dichotomous variables, for which the odds ratio (OR) with 95% confidence interval (CI) was calculated. The continuous variables were reported as standardized mean with standard deviation. And a $p < 0.05$ was considered statistically significant. Heterogeneity was estimated using Chi-squared test and I^2 (the percentage of total heterogeneity across trials that cannot be explained by chance alone). The fixed effect model was applied when $I^2 < 50\%$ and the p value for heterogeneity > 0.10, otherwise we employed the random effect model.

Publication bias was tested by funnel plots and the study quality was assessed according to the Cochrane Collaboration methods [29].

The primary analysis was applied to all included studies, after which we performed some subgroup analyses for all the outcomes according to: (1) the regimen of the control group (placebo-controlled or active-controlled); (2) the timing of administration (preoperative, intraoperative or postoperative); (3) levosimendan with or without bolus; (4) on-pump or off pump CABG; and (5) the isolated CABG or CABG combined with other cardiac procedures. Statistical analysis was conducted using RevMan, Version 5.3.

Results

Trial and patient characteristics

The details of the selection process are shown in Fig. 1. Since we aimed to investigate the prophylactic use of levosimendan, we excluded one study [31] exploring the therapeutic effect of levosimendan on the patients who already developed postoperative LCOS. A total of 21 studies including 1727 patients were included in this meta-analysis, among which 16 studies were single-center, four were two-center and one was multicenter. The baseline characteristics of the included studies are summarized in Supplement 2. 17 studies investigated levosimendan in isolated CABG except four in CABG combined with valve surgeries. Sixteen studies adopted on-pump CABG, while four used off pump CABG and one did not mention this. The cardiac status of the included patients varied from normal to severe. In the subgroup analysis of the regimen of levosimendan, eight studies administered the levosimendan with a bolus (most were 12 μg/kg of levosimendan during a 10-min interval before the anesthesia induction), while 13 studies did not. And the dose of the maintenance infusion varied among studies (from 0.03 μg/kg/min to 2.4 μg/kg/min), and half of them infused the levosimendan at 0.1 μg/kg/min for 24 h. Seven out of 21 studies started the administration preoperatively, 12 intraoperatively, 1 postoperatively and 1 did not mention the timing of administration. The time span of the maintenance infusion varied from 10 min to 24 h (24 h in 13 studies). Fourteen studies used placebo as the control, while the other seven studies used active control. The risk of bias of the included studies is displayed in Fig. 2. All the studies were at low/unclear risk of bias except for two studies [32, 33] with high risk of bias.

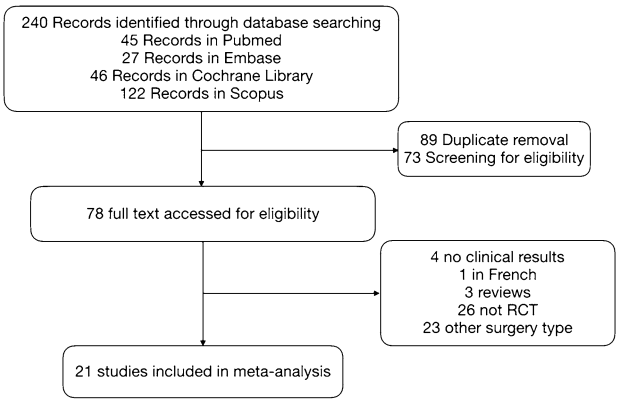


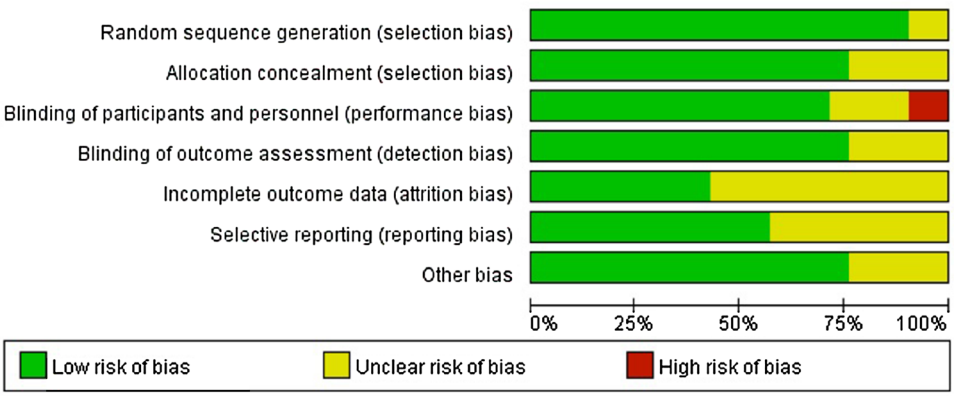
Fig. 1 Study flow sheet

Efficacy

Mortality

A total of 10 studies and 1062 patients were included in the analysis of mortality. Usage of levosimendan is associated with a lower mortality rate compared to the control group [OR 0.43, 95% CI (0.26, 0.71), $p = 0.001$, $I^2 = 0\%$, Fig. 3]. The subgroup analysis by the surgery type demonstrated that the survival benefit was mainly observed in isolated CABG subgroup [OR 0.27, 95% CI (0.12, 0.60), $p = 0.001$, $I^2 = 0\%$, Fig. S1.1.1) other than the CABG combined with valve surgery subgroup [OR 0.70, 95% CI (0.36, 1.39), $p = 0.31$, $I^2 = 0\%$; p for interaction = 0.07]. Further subgroup analyses showed that the mortality benefit was only observed in the following subgroups: the placebo-controlled subgroup [OR 0.45, 95% CI (0.27, 0.76), $p = 0.002$, $I^2 = 0\%$, Fig. S1.1.2), preoperative administration subgroup [OR 0.27, 95% CI (0.12, 0.59), $p = 0.001$, $I^2 = 0\%$, Fig. S1.1.3), bolus subgroup [OR 0.26, 95% CI (0.12, 0.61), $p = 0.002$, $I^2 = 0\%$, Fig. S1.1.4), and on-pump subgroup [OR 0.46, 95% CI (0.27, 0.76), $p = 0.003$, $I^2 = 0\%$, Fig. S1.1.5).

Fig. 2 Risk of bias graph



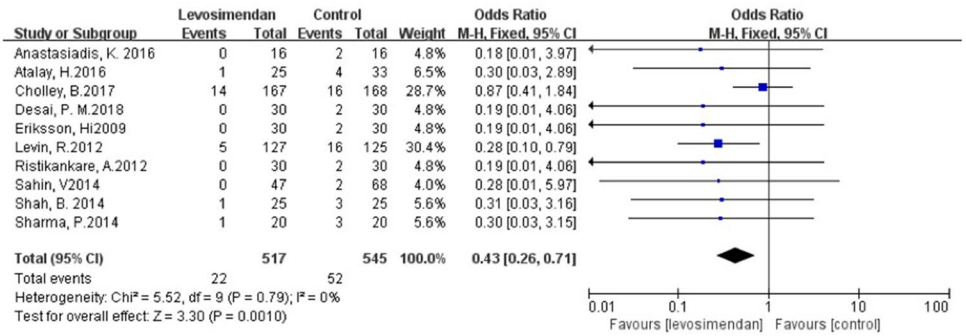


Fig. 3 Forest plot for mortality at the longest follow-up

Organ protective effect

Cardiac effect

Need for intra-aortic balloon pump (IABP) 11 studies including 1115 patients contributed to the analysis of the need for IABP. Less need for IABP was observed in levosimendan group [OR 0.39, 95% CI (0.19, 0.78), $p = 0.008$, $I^2 = 52\%$, Fig. S1.2.1). The subgroup analysis by the surgery type revealed that the need for IABP was significantly reduced in isolated CABG subgroup [OR 0.21, 95% CI (0.11, 0.38), $p < 0.00001$, $I^2 = 0\%$, Fig. S1.2.2] other than the CABG combined with valve surgery subgroup [OR 0.83, 95% CI (0.44, 1.55), $p = 0.55$, $I^2 = 11\%$, p for interaction = 0.002, Fig. S1.2.2). Other subgroup analyses by the control regimen (Fig. S1.2.3), the timing of administration (Fig. S1.2.4), with/without bolus (Fig. S1.2.5) and on/off pump (Fig. S1.2.6) were provided in the Supplement 1.

Need for additional inotropic drugs The need for additional inotropic drugs were reported by 11 studies (involving 1051 patients) and there was a significantly reduction in the levosimendan group [OR 0.35, 95% CI (0.18, 0.68), $p = 0.002$, $I^2 = 72\%$, Fig. S1.3.1). The subgroup analysis by the surgery type demonstrated that the need for additional inotropic drugs was significantly reduced in the isolated CABG subgroup [OR 0.31, 95% CI (0.15, 0.63), $p = 0.001$, $I^2 = 62\%$, Fig. S1.3.2). Another subgroup analysis by the timing of administration demonstrated that there was an inter-group difference between the preoperative administration subgroup [OR 0.07, 95% CI (0.04, 0.14), $p < 0.00001$, $I^2 = 0\%$) and the intraoperatively administration subgroup [OR 0.59, 95% CI (0.43, 0.81), $p = 0.001$, $I^2 = 0\%$, p for interaction < 0.00001, Fig. S1.3.3). The results of further subgroup analyses by the control regimen (Fig. S1.3.4), with/without bolus (Fig. S1.3.5) and on/off pump (Fig. S1.3.6) were provided in the Supplement 1.

Myocardial injury (MI) There were six studies including 521 patients included in the analysis of MI. The result showed that levosimendan significantly reduced the incidence of postoperative MI [OR 0.32, 95% CI (0.14, 0.72), $p = 0.006$, $I^2 = 0\%$, Fig. S1.4.1]. The subgroup analyses by the control regimen (Fig. S1.4.2), the timing of administration (Fig. S1.4.3) and with/without bolus (Fig. S1.4.4) were provided in the Supplement 1.

Renal effect

Renal dysfunction Six studies and 527 patients were included in the analysis of the incidence of renal dysfunction, and a lower incidence was observed in the levosimendan group [OR 0.45, 95% CI (0.27, 0.76), $p = 0.003$, $I^2 = 0\%$, Fig. S1.5.1). The subgroup analyses by the control regimen (Fig. S1.5.2), the timing of administration (Fig. S1.5.3), with/without bolus (Fig. S1.5.4) and on/off pump (Fig. S1.5.5) were provided in the Supplement 1.

The need for renal replacement therapy The need for renal replacement therapy was reported in five studies (involving 717 patients) and no significant difference was found between levosimendan and control groups [OR 0.96, 95% CI (0.53, 1.72), $p = 0.88$, $I^2 = 17\%$, Fig. S1.6].

Safety

Hypotension that needs vasoactive medication

Hypotension that needs vasoactive medication was analyzed in 13 studies (1114 patients). It was demonstrated that levosimendan was associated with a higher incidence of hypotension that demanded vasoactive medication compared to the control group [OR 2.26, 95% CI (1.05, 4.85), $p = 0.04$, $I^2 = 79\%$, Fig. S1.7.1]. The subgroup analyses by the control regimen (Fig. S1.7.2), the timing of administration (Fig. S1.7.3), with/without bolus (Fig. S1.7.4), on/off pump (Fig. S1.7.5) and the surgery type (Fig. S1.7.6) were provided in the Supplement 1.

Postoperative atrial fibrillation (AF)

Postoperative AF was analyzed in ten studies (1175 patients). It was demonstrated that levosimendan was associated with a lower incidence of AF compared to the control group [OR 0.50, 95% CI (0.26, 0.97), $p = 0.04$, $I^2 = 76\%$, Fig. 4]. The subgroup analysis by the surgery type revealed that a reduction of postoperative AF was only observed in isolated CABG subgroup [OR 0.35, 95% CI (0.17, 0.73), $p = 0.005$, $I^2 = 50\%$, Fig. S1.8.1) other than the CABG combined with valve surgery subgroup [OR 1.43, 95% CI (0.96, 2.13), $p = 0.08$, $I^2 = 0\%$; p for interaction = 0.0009, Fig. S1.8.1). The subgroup analyses by the control regimen (Fig. S1.8.2), the timing of administration (Fig. S1.8.3), with/without bolus (Fig. S1.8.4) and on/off pump (Fig. S1.8.5) were provided in the Supplement 1.

Other outcomes

The results for ventilation duration, length of ICU stay and hospital stay were provided in the Supplement 1 (Part 1).

Discussion

To the best of our knowledge, this was the first meta-analysis that evaluated and showed levosimendan as an effective and well-tolerated inotropic agent for patients undergoing CABG. The prophylactic use of levosimendan is associated with a lower mortality, better-preserved cardiac and renal function, lower incidence of postoperative AF, shorter postoperative ventilation duration and ICU stay, compared with either placebo or active control in CABG surgery. Moreover, subgroup analyses revealed that such kind of benefit was mainly observed in the isolated CABG, preoperative administration, with-bolus and on-pump CABG subgroups. No significant benefit in hospital stay was found in the levosimendan group.

While our study demonstrated the efficacy of prophylactic levosimendan in reducing mortality and AF in isolated CABG, previous meta-analysis concluded that prophylactic levosimendan was not effective in the broad-spectrum population undergoing any cardiac surgery. This discrepancy could be caused by the fact that types of surgery differed between our study and theirs. Moreover, clinical data [22, 24] have suggested that levosimendan might be effective in CABG, but not in valve surgery. The different effects of prophylactic levosimendan in CABG and valve surgeries can be explained as follows. Compared with CABG, valve surgeries are more traumatic and associated with increased risk of AF [34]. The patients undergoing CABG, a relatively low-risk patient population, can be satisfied by the levosimendan-induced coronary vasodilation and increased cardiac contractility. They are also capable of withstanding levosimendan-induced hypotension. Therefore, they might be the better candidates to be given prophylactic levosimendan. However, patients undergoing valve replacement might demand more than what benefit levosimendan can offer and might be unable to suffer from its side effects.

Although vasodilation caused by levosimendan is regarded as a side effect, which might lead to hypotension, it does provide organ protection against ischemia [13], which has been suggested by recently published studies [15, 18, 21, 35]. In our study, levosimendan lowered the incidence of MI, renal dysfunction and the need for renal replacement treatment.

When an inotrope is needed, the safety of the chosen agent should be an important selection criterion. Postoperative AF and hypotension are two major adverse effects in cardiac surgery patients receiving levosimendan and have been discussed a lot in the prior studies. Some experimental studies and meta-analyses declared an increased incidence of postoperative AF as well as hypotension associated with the use of levosimendan [21, 27]. Our meta-analysis found that levosimendan was associated with a lower incidence of postoperative AF, which is consistent with some other recent studies [18, 36]. The mechanism involved in the levosimendan effect of suppression of postoperative AF is not clear, but can be partly attributed to the antioxidant and anti-inflammatory properties of levosimendan [36]. Levosimendan was invariably associated

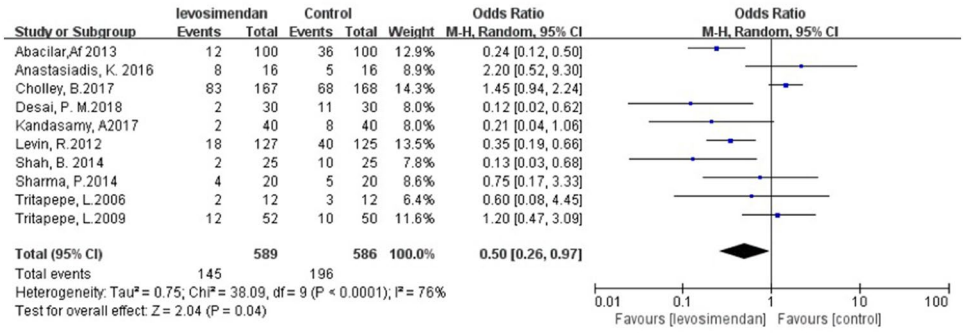


Fig. 4 Forest plot for postoperative atrial fibrillation (AF)

with a higher incidence of hypotension due to peripheral vasodilation. But as a trade-off, patients will benefit from coronary vasodilation with an anti-ischemic effect and increased myocardial contractility [37, 38]. As our data showed prophylactic levosimendan is effective in reducing mortality in CABG, we do believe that the therapeutic effect plays a more important role than levosimendan-induced hypotension. Also, all the hypotension cases in the included studies were easily controlled with phenylephrine or norepinephrine, and no severe hypotension occurred in any of the studies.

Levosimendan contributed to the decline in postoperative ventilation duration and ICU stay. It is somewhat surprising that no benefit in hospital stay was noted in the levosimendan group. This result may be explained by the fact that levosimendan was associated with a higher incidence of hypotension, and theoretically in-hospital hypotension raised clinician's concern and led to longer hospital stay. However, probably due to the advantages of prophylactic levosimendan, the disadvantage got neutralized. Furthermore, in subgroup analysis stratified by the timing of administration, preoperative administration of levosimendan significantly reduced the hospital stay.

In addition, we also found that preoperative levosimendan was effective in reducing mortality, while intraoperative administration was not. A possible explanation for this might be that the specific pharmacokinetics and pharmacodynamics of levosimendan promise steady inotropic features about 3–6 h after the infusion started [39–41]. In some studies like CHEETAH [25], levosimendan was administered postoperatively, and failed to show efficacy. Inconsistence of the timing of levosimendan administration confused clinicians and justified our subgroup analysis by the timing of administration.

Administration of a bolus was found to exert a less beneficial effect in previous studies. However, our subgroup analyses revealed that only in the with-bolus subgroup, levosimendan was associated with a lower mortality rate, less need for IABP, and the lower incidence of renal dysfunction.

Several limitations of this study must be taken into account. First, the heterogeneity in assessment of some outcomes was intermediate or high, however, not in the primary outcome. Nevertheless, we performed as many subgroup analyses as we could for each outcome to investigate sources of heterogeneity. In addition, we conducted the sensitivity analysis by excluding studies with high risk of bias. Excluding those studies did not alter the main results. Second, the regimen (with or without a bolus) of levosimendan still varied among studies due to heterogeneous practice patterns. The recent recommendation was a 0.1 μg/kg/min infusion for 24 h without a bolus [42], which was applied in half of the included studies. At last, follow-up time of mortality, definition of hypotension and postoperative AF as well as the threshold of the blood pressure that needs vasoactive medication were inconsistent among included studies.

Notwithstanding, this is the first systematic review and meta-analysis that evaluated prophylactic use of levosimendan in CABG and it has several strengths: (1) we focused on a specific cohort of patient undergoing CABG surgery, instead of a broad spectrum of cardiac surgeries. (2) We performed a rigorous screening of the literature, and analyzed all major outcomes available to evaluate both the efficacy and safety of levosimendan. (3) Subgroup analyses based on different regimens and the timing of administration were conducted. In addition, we found that levosimendan is significantly superior to the control in the isolated CABG, preoperative administration, with-bolus and on-pump subgroups.

Future studies on the current topic are, therefore, recommended to determine the best regimen of levosimendan and best candidates to receive levosimendan, and to report mortality rate, postoperative AF, and hypotension in a more standardized format.

Conclusions

In this systematic review and meta-analysis evaluating efficacy and safety of levosimendan in CABG surgery, we found that levosimendan is effective, well tolerated for patients undergoing isolated CABG surgery, especially administrated preoperatively, with a bolus and during on-pump CABG. However, more high-quality and well-designed prospective studies are needed to confirm or disprove our findings in future.

Compliance with ethical standards

Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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