Effects of levosimendan on mortality in patients undergoing cardiac surgery: A systematic review and meta-analysis

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Abstract
Purpose: We sought to determine the impact of levosimendan on mortality following cardiac surgery based on large-scale randomized controlled trials (RCTs).

Methods: We searched PubMed, Web of Science, Cochrane databases, and ClinicalTrials.gov for RCTs published up to December 2017, on levosimendan for patients undergoing cardiac surgery.

Results: A total of 25 RCTs enrolling 2960 patients met the inclusion criteria; data from 15 placebo-controlled randomized trials were included for meta-analysis. Pooled analysis showed that the all-cause mortality rate was 6.4% (71 of 1106) in the levosimendan group and 8.4% (93 of 1108) in the placebo group (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.55-1.04; P = 0.09). There were no significant differences between the two groups in the rates of myocardial infarction (OR: 0.91; 95% CI, 0.68-1.21; P = 0.52), serious adverse events (OR: 0.84; 95% CI, 0.66-1.07; P = 0.17), hypotension (OR: 1.69; 95% CI, 0.94-3.03; P = 0.08), and low cardiac output syndrome (OR: 0.47; 95% CI, 0.22-1.02; P = 0.05).

Conclusion: Levosimendan did not result in a reduction in mortality in adult cardiac surgery patients. Well designed, adequately powered, multicenter trials are necessary to determine the role of levosimendan in adult cardiac surgery.

KEYWORDS
cardiac surgery, levosimendan, meta-analysis, mortality

1 | INTRODUCTION

Low cardiac output syndrome is a major complication occurring in 3-14% of patients after cardiac surgery and is associated with a significant increase in mortality and morbidity.1-4

Low cardiac output syndrome is managed with positive inotropic agents, including beta-adrenergic agonists and phosphodiesterase inhibitors, and mechanical cardiac support. Unfortunately, these agents improve cardiac output at the expense of increased atrial and ventricular arrhythmias and myocardial oxygen demand, and may exacerbate existing myocardial ischemia.5 Meta-analyses and nonrandomized studies suggest that catecholamines and phosphodiesterase inhibitors may increase mortality.5,6 Levosimendan (Simdax, Orion, Espoo, Finland), a novel calcium sensitizer and an adenosine triphosphate-sensitive potassium-channel

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opener, has been shown to decrease mortality in small randomized controlled trials (RCTs) and meta-analyses, involving patients undergoing cardiac surgery. A Bayesian network analysis suggested that levosimendan might be the best inotrope for survival advantage among patients undergoing cardiac surgery. However, these meta-analyses were based on small clinical trials with varying drug dosages, administered at different times, to patients undergoing a variety of cardiac surgical procedures. Recently, two large-scale RCTs (LEVO-CTS and CHEETAH) did not find a survival benefit for levsimendan in cardiac surgery. We therefore performed a systematic review of all available randomized studies and a meta-analysis of placebo-controlled randomized trials to evaluate the effectiveness and safety of levsimendan in the treatment of patients undergoing cardiac surgery.

2 | METHODS

2.1 | Literature-search strategy

A systematic literature search was conducted in December 2017 without restrictions for geographical locations or languages. We searched the databases of Web of Science, PubMed, Cochrane Library, and ClinicalTrials.gov using the search terms levsimendan, simdax, heart surgery, and cardiac surgery. The reference lists of retrieved articles and relevant reviews were carefully screened for further studies.

2.2 | Inclusion and exclusion criteria

Studies were included if they met the following requirements: (1) trial included patients undergoing cardiac surgery; (2) patients were randomly assigned to receive levsimendan or controls. No restrictions on dose or time of administration were applied; (3) one or more of the outcomes mentioned below were reported. Duplicate publications, secondary reporting format, abstracts, nonadult studies, and non-randomized trials were excluded.

2.3 | Data extraction and outcomes of interest

Two authors (PL. Chen and XQ. Wu) independently extracted and summarized data from the identified studies into a standardized data extraction form, including study baseline characteristics (design, sample size, comparators, and follow-up), levsimendan infusion dose and duration, as well as primary outcomes and secondary outcomes. Any discrepancies were resolved by consensus. The primary outcomes evaluated were all-cause mortality (in-hospital or within 30 days), serious adverse events, and myocardial infarction. The secondary endpoints included hypotension and low cardiac output syndrome. We contacted corresponding authors for detailed outcomes if they were missing in the original papers. The quality evaluation of included trials was performed using the Cochrane risk of bias assessment tool.

2.4 | Data synthesis and analysis

Computations were conducted with Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). Odds ratio (OR) with 95% corresponding confidence interval (CI) was applied for dichotomous outcomes. Statistical heterogeneity in studies was measured with $I^2$ statistic and the chi-square test. A $P$-value < 0.10 or an $I^2 > 50\%$ indicated the presence of high heterogeneity. The fixed-effects models were applied if there was no significant heterogeneity. Otherwise, the random-effects model was considered. $P < 0.05$ is considered statistically significant for hypothesis testing.

3 | RESULTS

3.1 | Search results and study characteristics

The literature search retrieved 797 eligible studies. A 702 articles were excluded after initially screening titles or abstracts (Figure 1). The full papers of 95 remaining studies were further evaluated, and 25 articles were identified in this systematic review based on prespecified criteria. Table 1 summarizes the main characteristics of the 25 identified studies. A total of 15 trials compared levsimendan with placebo, 9 trials compared levsimendan with other inotropes, including epinephrine (1 trial), dobutamine (4 trials), and milrinone (3 trials), 2 other trials compared levosimendan with nitroglycerin or with the intra-aortic balloon pump. To minimize heterogeneity across the trials, quantitative synthesis was only performed for the 15 placebo-controlled randomized trials.

FIGURE 1  Flow diagram of studies included and excluded
| Study                  | Patients                                      | N₁  | N₂  | Control   | Bolus dose μg/kg | Continuous infusion dose μg/kg/min | Length of infusion | Follow-up          |
|-----------------------|-----------------------------------------------|-----|-----|-----------|-----------------|-----------------------------------|--------------------|-------------------|
| Al-Shawaf et al²⁹     | Elective CABG                                 | 14  | 16  | Milrinone | 12              | 0.1-0.2                           | 24 h               | End of hospitalization |
| Alvarez et al³⁰       | Heart surgery                                 | 25  | 25  | Dobutamine| 12              | 0.5                               | 24 h               | 15 days           |
| Anastasiadis et al¹⁵  | CABG                                          | 16  | 16  | Placebo  | -               | 0.1                               | 24 h               | 7 days            |
| Barisin et al¹⁶       | CABG                                          | 21  | 10  | Placebo  | 12-24           | -                                 | End of hospitalization |
| Baysal et al¹⁷        | MVR                                           | 64  | 64  | Placebo  | 6               | 0.1                               | 24 h               | 10 days           |
| De Hert et al⁴³       | CABG Valve                                    | 15  | 15  | Milrinone| -               | 0.1                               | 19 ± 4 h           | End of hospitalization |
| Erb et al²⁸           | Elective CABG ± mitral surgery                | 17  | 16  | Placebo  | -               | 0.1                               | -                  | 24 h              |
| Eriksson et al¹⁹      | CABG                                          | 30  | 30  | Placebo  | 12              | 0.2                               | 24 h               | 30 days           |
| Gandham et al²⁸       | MVR                                           | 30  | 30  | Dobutamine| -               | 0.1                               | -                  | 36 h              |
| Husedžinović et al⁰⁰ | CABG                                          | 12  | 13  | Placebo  | 12              | -                                 | -                  | End of hospitalization |
| Jarvela et al²¹       | Aortic valve surgery ± CABG                   | 12  | 12  | Placebo  | -               | 0.2                               | 24 h               | 18 mos            |
| Juul-Olsen et al²²    | AVR                                           | 10  | 10  | Placebo  | -               | 0.1                               | 8 h                | 6 mos             |
| Kandasamy et al⁴⁷     | CABG                                          | 40  | 40  | Dobutamine| -               | 0.1                               | 24 h               | End of hospitalization |
| Lahtinen et al²³      | CABG valve others                             | 103 | 104 | Placebo  | 24              | 0.2                               | 24 h               | End of hospitalization |
| Landoni et al²³       | CABG, MVR                                     | 248 | 258 | Placebo  | -               | 0.025-0.2                         | 48 h               | 6 mos             |
| Leppikangas et al²⁴   | AVR+ CABG                                     | 12  | 12  | Placebo  | 12              | 0.2                               | 24 h               | -                |
| Levin et al²¹         | Elective CABG                                 | 69  | 68  | Dobutamine| 10              | 0.1                               | 24 h               | End of hospitalization |
| Levin et al²⁵         | Elective CABG                                 | 127 | 125 | Placebo  | 10              | 0.1                               | 24 h               | 7 days            |
| Lomivorotov et al²²   | Elective CABG                                 | 60  | 30  | IABP     | 12              | 0.1                               | 24 h               | -                |
| Mehta et al²⁷         | CABG valve others                             | 428 | 421 | Placebo  | 0.2             | 0.1                               | 24 h               | 90 days           |
| Mishra et al²⁶        | valve surgery                                 | 20  | 20  | Milrinone| 10              | 0.1                               | 24 h               | End of hospitalization |
| Nijhawan et al²⁶      | Myocardial revascularization, valve replacement| 12  | 6   | Placebo  | 18/26           | 0.2-0.3                           | 6 h                | End of hospitalization |
| Sahu et al⁴⁹          | Elective CABG                                 | 25  | 22  | Nitroglycerine| 10              | 0.1                               | 24 h               | End of hospitalization |
| Salgado Filho et al⁰⁰ | CABG                                          | 42  | 39  | Epinephrine| -               | 0.2                               | -                  | -                |
| Tritapepe et al²⁷     | Elective CABG                                 | 53  | 53  | Placebo  | 24              | -                                 | -                  | 30 days           |

AVR, aortic valve replacement; C, control; CABG, coronary artery bypass grafting; IABP, intraaortic balloon pump; L, levosimendan; MVR, mitral valve surgery; N, number of participants in each group.
3.2 | Primary outcomes

3.2.1 | All-cause mortality

Eleven studies reported data on all-cause mortality and the data were suitable for meta-analysis (Figure 2).\textsuperscript{12,13,15,17,19,21,23,25,27} The pooled OR was 0.76 (95% CI: 0.55-1.04, \( P = 0.09 \)), indicating no superiority of levosimendan over placebo in terms of mortality. No substantial heterogeneity was observed amongst the studies (\( I^2 = 20\% , \ P = 0.26 \)).

3.2.2 | Myocardial infarction

Pooling the data from seven RCTs that assessed myocardial infarction in 2067 subjects demonstrated a non-significant difference between the levosimendan and placebo groups (10.2% and 11.0%; OR: 0.91; 95% CI, 0.68-1.21; \( P = 0.52 \)) (Figure 3).\textsuperscript{12,13,15,17,23,25,27}

3.2.3 | Serious adverse events

Four trials reported a serious adverse event rate for levosimendan and placebo. Pooling the data of the 1413 subjects in these four RCTs showed no significant difference between groups (OR: 0.84; 95% CI, 0.66-1.07; \( P = 0.17 \)) (Figure 4).\textsuperscript{12,13,15,18}

3.3 | Secondary outcomes

3.3.1 | Hypotension

Four trials reported hypotension data for the 1800 included patients. Pooling the data of these four studies demonstrated no significant difference between the levosimendan and placebo groups (OR: 1.69; 95% CI, 0.94-3.03; \( P = 0.08 \)) (Figure 5).\textsuperscript{12,13,23,25}

3.3.2 | Low cardiac output syndrome

Data on low cardiac output syndrome were reported by the LEVO-CTS trial and Levin et al.\textsuperscript{12,25} The low cardiac output syndrome rate for the levosimendan and placebo groups was 18.2% versus 25.7%, and 7.1% versus 20.8%, respectively. Pooled analysis demonstrated no significant difference between the levosimendan and placebo groups (OR: 0.47; 95% CI, 0.22-1.02; \( P = 0.05 \)) (Figure 6).

3.3.3 | Risk of bias assessment of included studies

The methodological quality was satisfactory across most studies, as summarized in Figure 7. All included studies adopted a randomized, prospective, and comparative design. There was low risk of bias for selective reporting of outcomes, or incomplete outcome data. Two
trials endured high risk of bias regarding random sequence generation.\textsuperscript{20,28} Four studies had high risk of masking bias.\textsuperscript{29–32}

**DISCUSSION**

This meta-analysis of 15 placebo-controlled randomized trials involving 2315 participants assessed the effectiveness and safety of levosimendan in patients who were undergoing cardiac surgery. Levosimendan did not provide significant survival benefit over placebo. There were also no significant difference in myocardial infarction, serious adverse events, or hypotension between the levosimendan and the placebo groups.

Levosimendan is a novel inotrope with an action mechanism differing from that of other catecholamines. Through stabilizing the binding of calcium to troponin C, levosimendan strengthens actin-myosin cross-bridging and improves contractile force. It also reduces peripheral vascular resistance by acting on ATP-sensitive potassium channels of vascular smooth muscle cells.\textsuperscript{33} Since it does not elevate intracellular concentrations of free calcium, levosimendan does not increase myocardial oxygen consumption. As levels of calcium fall in diastole, levosimendan does not impair myocardial relaxation which can occur with other catecholamines.\textsuperscript{34} Furthermore, OR-1896, known as the active metabolite of levosimendan, has a half-life for elimination of 80 h. Consequently, a 24-h infusion may offer hemodynamic support for approximately 1 week.\textsuperscript{35}

Previous small clinical trials and meta-analyses of RCTs showed that levosimendan was associated with higher rates of survival, a lower incidence of periprocedural myocardial infarction, and lower rates of inotrope use than placebo, dobutamine, or milrinone among patients undergoing cardiac surgery.\textsuperscript{8–10} These positive results were not confirmed in our present meta-analysis of placebo-controlled randomized trials. In addition, a survival benefit of levosimendan was also not seen in trials involving patients with severe sepsis or heart failure.\textsuperscript{36–38}

It was postulated that patients undergoing cardiac surgery who develop postoperative low cardiac output syndrome would benefit from levosimendan, due to the transient nature of postoperative depressed myocardial function.\textsuperscript{39,40} Myocardial stunning is believed to be the main risk factor for the development of perioperative heart failure, and the heart function usually recovers within approximately 24-48 h.\textsuperscript{39–41} Considering its unique mechanism of action (increase in cardiac function with a neutral effect on oxygen consumption), levosimendan seemed to be the ideal inotrope in cardiac surgery patients. However, in our present study, treatment with levosimendan did not show a significant reduction in mortality as compared with placebo, nor did it decrease the incidence of myocardial infarctions, hypotension, low cardiac output syndrome or other adverse events. Our results do not support the treatment with levosimendan in addition to standard care for perioperative cardiac dysfunction among patients undergoing cardiac surgery.

There may be several factors responsible for the different results of clinical trials with levosimendan in cardiac surgery.\textsuperscript{10,17,25,42,43} Several previous trials of levosimendan in cardiac surgery, such as the LEVO-CTS trial, involved patients with reduced ejection fraction at baseline.\textsuperscript{12} Other trials, however, including the CHEETAH trial focused on patients with ongoing myocardial dysfunction requiring inotropic support.\textsuperscript{13} The dose of levosimendan differed among most trials. It is proposed that higher bolus doses of levosimendan may be more effective.\textsuperscript{25,44,45} However, such regimens have been showed to be associated with a higher incidence of adverse events and less survival in other studies.\textsuperscript{9} Moreover, the timing of administration of levosimendan may be of great importance, and treatment with levosimendan that is started just before surgery may not be effective to avoid perioperative myocardial

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**FIGURE 4** Forest plot for the risk of serious adverse events

**FIGURE 5** Forest plot for the risk of hypotension
damage. Most trials enrolled patients who were undergoing coronary artery bypass grafting (CABG), mitral-valve surgery, or CABG plus mitral-valve surgery. It is possible that perioperative myocardial dysfunction may have multiple pathophysiological features in these populations which may effect the benefits of levosimendan.\textsuperscript{46} Furthermore, many of these patients may have multiorgan failure as a result of low cardiac output which required mechanical, and not inotropic support.

The following limitations of this study must be taken into account. First, all four trials assessed levosimendan as added to routine clinical care rather than comparing levosimendan with other inotropic agents. Second, this study was conducted based on summary statistics instead of individual patient level data. There may be some confounders (eg, cardiac surgical operation, ejection fraction at baseline, etc.) at the patient-level influencing the clinical effect of levosimendan, but that were not available. Third, the dose of levosimendan varied across trials.

In conclusion, this study indicates that despite its unique inotropic and cardioprotective properties, levosimendan did not result in a higher rate of survival nor did it positively affect other secondary outcomes as compared with placebo for patients undergoing cardiac surgery. Well-designed, multicenter, large-scale RCTs are required to determine the role of levosimendan in cardiac surgery.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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