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Original Investigation

Levosimendan for Prevention of Acute Kidney Injury After Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

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Background: Levosimendan has been shown to confer direct renoprotection in renal endotoxemic and ischemia-reperfusion injury and could increase renal blood flow in patients with low-cardiac-output heart failure. Results from clinical trials of levosimendan on acute kidney injury (AKI) following cardiac surgery are controversial.

Study Design: A random-effect meta-analysis was conducted based on evidence from PubMed, EMBASE, and Cochrane Library.

Settings & Population: Adult patients undergoing cardiac surgery.

Selection Criteria for Studies: Randomized controlled trials comparing the renal effect of levosimendan versus placebo or other inotropic drugs during cardiac surgery.

Intervention: Perioperative levosimendan continuous infusion at a rate of 0.1 to 0.2 μg/kg/min following a loading dose (6-24 μg/kg) for 24 hours or only 1 loading dose (24 μg/kg) within 1 hour.

Outcomes: AKI, need for renal replacement therapy, mechanical ventilation duration, intensive care unit stay during hospitalization, and postoperative mortality (in-hospital or within 30 days).

Results: 13 trials with a total of 1,345 study patients were selected. Compared with controls, levosimendan reduced the incidence of postoperative AKI (40/460 vs 78/499; OR, 0.51; 95% CI, 0.34-0.76; $P = 0.001$; $I^2 = 0.0\%$), renal replacement therapy (22/492 vs 49/491; OR, 0.43; 95% CI, 0.25-0.76; $P = 0.002$; $I^2 = 0.0\%$), postoperative mortality (35/658 vs 94/657; OR, 0.41; 95% CI, 0.27-0.62; $P < 0.001$; $I^2 = 0.0\%$), mechanical ventilation duration (in days; n = 235; weighted mean difference, −0.34; 95% CI, −0.58 to −0.09; $P = 0.007$], and intensive care unit stay (in days; n = 500; weighted mean difference, −2.2; 95% CI, −4.21 to −0.13; $P = 0.04$).

Limitations: Different definitions for AKI among studies. Small sample size for some trials.

Conclusions: Perioperative administration of levosimendan in patients undergoing cardiac surgery may reduce complications. Future trials are needed to determine the dose effect of levosimendan in improving outcomes, especially in patients with decreased baseline kidney function.

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INDEX WORDS: Levosimendan; acute kidney injury (AKI); cardiac surgery; heart surgery; renal replacement therapy (RRT); postoperative mortality; calcium sensitizer; inotropic drug; renal blood flow; ischemia/reperfusion injury; renoprotection; meta-analysis.

Acute kidney injury (AKI) is a common complication after cardiac surgery, occurring in up to 45% of patients, and is associated with prolonged respiratory support and intensive care unit (ICU) stay,[1,2] as well as death.[3-6] The increase in mortality risk has been observed in patients undergoing cardiac surgery with even a minor elevation in creatinine levels from baseline[7,8] and is doubled in those requiring hemodialysis.[9] Moreover, along with the increasing population with high-risk status (such as advanced age, diabetes mellitus, severe heart dysfunction, and prolonged cardiopulmonary bypass time), AKI following cardiac surgery has become a challenging issue in clinical practice.[10,11]

Although this issue has been the focus of many studies, the results are mixed. Several isolated reports suggest that perioperative administration of *N*-acetylcysteine, fenoldopam, and sodium bicarbonate may prevent AKI,[11] but precise information about effectiveness remains elusive.[12-14] Hence, novel promising strategies need to be identified.

Levosimendan, a novel calcium sensitizer with inotropic and vasodilatory effects, has been found to increase renal blood flow accompanied by improved cardiac output in patients with low-output heart failure.[15,16] In addition, there is accumulating evidence

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that levosimendan could offer direct protective effects in renal endotoxemic[17] and ischemia-reperfusion[18,19] injury animal models. Whether perioperative levosimendan can reduce the risk for AKI in patients undergoing cardiac surgery remains unclear. Several single-center randomized controlled trials (RCTs) with relatively small sample sizes have addressed this question since 2006.[20-22] To our knowledge, there has been no systematic review that comprehensively focuses on the potential renal effect of levosimendan administration in adult patients undergoing cardiac surgery. Therefore, we conducted a meta-analysis to evaluate the effect of perioperative levosimendan (compared to placebo or other inotropic drug) on risk for AKI and renal replacement therapy (RRT) and mortality.

METHODS

Search Strategy and Study Criteria

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[23] and approved by the Institutional Review Board in Fuwai Hospital. We did a systematic search (Item S1, available as online supplementary material) in PubMed (1966 to March 2015), EMBASE (1988 to March 2015), and Cochrane Library (1990 to March 2015) and scientific sessions (2011-2014) of the American Heart Association, American College of Cardiology, and European Society of Cardiology using the keywords "levosimendan," "cardiac surgery," "heart surgery," "kidney," and "renal." English-published RCTs concerning adult patients were included. Exclusion criteria were as follows: emergency surgery, intra-aortic balloon pump counterpulsation as the control, and studies without reporting of serum creatinine levels, AKI, or RRT as an end point.

Literature Review and Data Extraction

The literature review and data extraction were independently completed by 2 investigators (J.G. and D.C.). In the case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion to reach consensus. Quality assessment was completed using the Cochrane risk of bias tool: randomization, allocation concealment, blinding, withdrawals and dropouts, and intention-to-treat analysis. Data extraction included patient characteristics (age, proportion of males, proportion with diabetes, proportion with history of myocardial infarction, proportion with hypertension, baseline left ventricular ejection fraction, baseline creatinine levels, β-blocker use, and statin use), as well as levosimendan and controlled drug dosages.

Postoperative Outcomes

The primary end point was incidence of AKI (defined as a relative increase $>$ 50% or absolute increase $>$ 0.3 mg/dL in serum creatinine from baseline, serum creatinine level $>$ 1.5 mg/dL, or relative decrease in estimated glomerular filtration rate $>$ 25% from baseline within 7 days after cardiac surgery). Secondary outcomes included in-hospital RRT, all-cause mortality (in-hospital or within 30 days), postoperative serum creatinine levels, mechanical ventilation duration, and ICU length of stay.

Statistical Analysis

For dichotomous outcomes (reported with incidence), we calculated the odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes (reported as mean ± standard deviation, median and interquartile range, or median and range), we calculated mean differences for each study according to the statistical method of Hozo et al[24] and used weights (the inverse variance of the estimate) to pool the estimate (weighted mean difference) with 95% CI. Random-effects models were used to analyze the data in light of the heterogeneity in results and study clinical characteristics. Inverse variance weights using the DerSimonian-Laird method were applied to construct the pooled estimate of effect. Studies with no events in either treatment group were excluded from the pooled analysis. When only 1 group of the study contained no events, a fixed value (0.5) was added to each cell of the 2×2 table for the pooled analysis. $P < 0.05$ (2 sided) was considered to be statistically significant for hypothesis testing. All statistical analyses were performed in Stata (version 9.0; StataCorp LP).

RESULTS

Study Characteristics

After 1,024 abstracts were excluded from the initial search due to duplications, reviews, experimental designs, and irrelevant contents, 87 potential studies were selected for detailed evaluation. Thereafter, 74 studies were further excluded for the following reasons: noncardiac surgery (n= 37), pediatric patients (n = 6), intra-aortic balloon pump counterpulsation as control group (n = 2), emergency surgery (n = 1), nonrenal end points (n = 14), systematic reviews (n = 6), retrospective design (n = 3), and case reports (n = 5).

Thirteen trials[20-22,25-34] with a total of 1,345 patients ultimately met our criteria (Fig 1). Ten studies were for coronary artery bypass grafting (on-pump[20,22,25,26,28,31-34] or off-pump[29]), 2 were for combined cardiac surgery,[21,27] and 1 was for mitral valve replacement.[30] Nine trials[22,25-31,34] used placebo

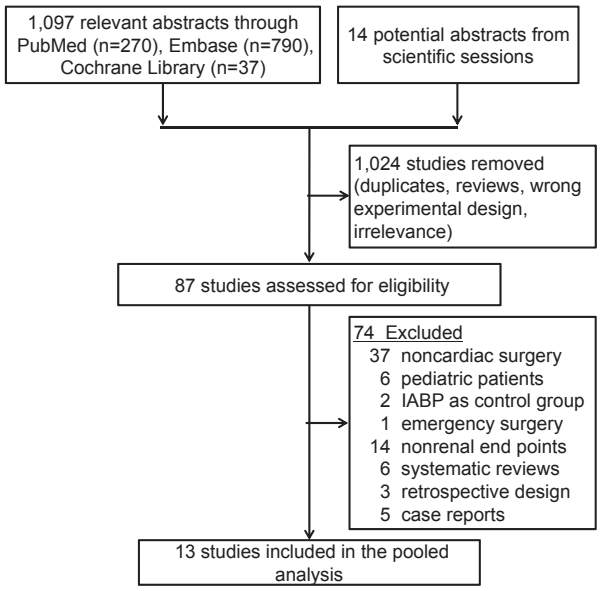

Figure 1. Search process for eligible studies. Abbreviation: IABP, intra-aortic balloon pump counterpulsation.

Table 1. Summarized Study Design of Included Randomized Trials

Study	Country	Surgery	Levosimendan Dose	Control	Timing and Duration of Intervention or Control	No. of Patients[a]	Clinical End Points	AKI Definition	Follow-up
Al-Shawaf[20] (2006)	KW	On-pump CABG	12 μg/kg, 0.1-0.2 μg/kg/min	Milrinone, 50 μg/kg, 0.3-0.5 μg/kg/min	<12 h postsurgery; for 24 h	14 vs 16	AKI, RRT, MV duration, ICU stay, mortality	NA	In hospital
De Hert[21] (2007)	BE	Combined	0.1 μg/kg/min	Milrinone, 0.5 μg/kg/min	At cross-clamp release; for 20 h	15 vs 15	Scr, MV duration, ICU stay, mortality	NA	30 d
Levin[32] (2008)	US	On-pump CABG	10 μg/kg, 0.1 μg/kg/min	Dobutamine, 5-12.5 μg/kg/min	<6 h postsurgery; for 24 h	69 vs 68	AKI, RRT, ICU stay, mortality	↑Scr > 50%	30 d
Tritapepe[22] (2009)	GB	On-pump CABG	24 μg/kg	Placebo	Pre-CPB; for 10 min	52 vs 50	AKI, MV duration, ICU stay, mortality	Scr > 1.5 mg/dL	30 d
Levin[33] (2009)	US	On-pump CABG	10 μg/kg, 0.1 μg/kg/min	Dobutamine, 5-12.5 μg/kg/min	Postsurgery; for 24 h	126 vs 127	RRT, mortality	NA	In hospital
Lahtinen[27] (2011)	FI	Combined	24 μg/kg, 0.2 μg/kg/min	Placebo	Pre-CPB; for 24 h	99 vs 101	AKI, mortality	↑Scr > 50%, or Scr >2× ULN, or RRT	30 d
Levin[28] (2012)	US	On-pump CABG	10 μg/kg, 0.1 μg/kg/min	Placebo	Postsurgery; for 24 h	127 vs 125	AKI, RRT, mortality	↑Scr > 50%	30 d
Ristikankare[31] (2012)	FI	On-pump CABG	12 μg/kg, 0.2 μg/kg/min	Placebo	Pre-CPB; for 24 h	30 vs 30	Scr, AKI, RRT, Mortaltiy	>50% ↓eGFR	In hospital
Bragadottir[26] (2013)	SE	On-pump CABG	12 μg/kg, 0.1 μg/kg/min	Placebo	Postsurgery; for 1 h	15 vs 15	Scr	NA	In hospital
Sharma[25] (2014)	IN	On-pump CABG	200 μg/kg over 24 h	Placebo	Preoperative; for 24 h	20 vs 20	AKI, RRT, MV duration, ICU stay, mortality	↑Scr > 50%	30 d
Shah[29] (2014)	IN	Off-pump CABG	200 μg/kg over 24 h	Placebo	Preoperative; for 24 h	25 vs 25	AKI, RRT, mortality	↑Scr > 50%	30 d
Baysal[30] (2014)	TR	Mitral valve replacement	6 μg/kg, 0.1 μg/kg/min	Placebo	At cross-clamp release; for 24 h	64 vs 64	Scr, AKI, RRT, ICU stay, mortality	↑Scr > 50% mg/dL or 50%	30 d
Erb[34] (2014)	DE	CABG ± valve surgery	0.1 μg/kg/min	Placebo	Pre-CPB; for >20 h	17 vs 16	RRT, MV duration, ICU stay, mortality	NA	30 d

Note: Conversion factor for Scr in mg/dL to μmol/L, ×88.4.

Abbreviations: ↑, increase in; ↓, decrease in; AKI, acute kidney injury; BE, Belgium; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; DE, Germany; eGFR, estimated glomerular filtration rate; FI, Finland; GB, United Kingdom; ICU, intensive care unit; IN, India; KW, Kuwait; MV, mechanical ventilation; NA, not available; RRT, renal replacement therapy; Scr, serum creatinine level; SE, Sweden; TR, Turkey; US, United States; ULN, upper limit of normal.

[a]Levosimendan versus control.

as control, whereas 2[20,21] used milrinone and 2[32,33] used dobutamine as "control." Levosimendan was continuously infused at a rate of approximately 0.1 to 0.2 μg/kg/min for 24 hours after a loading dose (6-24 μg/kg) in 8 studies,[20,26-28,30-33] or without a loading dose in 4,[21,25,29,34] and only loaded once (24 μg/kg) without continuous infusion in 1 study.[22] For postoperative outcomes, AKI incidence was reported in 9 trials[20,22,25,27-32]; need for RRT, in 9[20,25,28-34]; mortality, in 12[20-22,25,27-34]; serum creatinine level, in 4[21,26,30,31]; mechanical ventilation duration, in 5[20-22,25,34]; and ICU stay, in 7.[20-22,25,30,32,34] Study design and patient characteristics are summarized in Tables 1 and 2. The quality assessment is listed in Table 3.

Effect of Levosimendan on Incidence of AKI, RRT, and Mortality

The outcome of AKI was reported in 959 study participants, and the overall incidence was 12.3% (levosimendan group, 40/460; control group, 78/499). The postoperative incidence of AKI was significantly reduced by levosimendan (9 studies; OR, 0.51; 95% CI, 0.34-0.76; $P = 0.001$; $I^2 = 0.0\%$; Fig 2). Sensitivity analysis excluding each included study 1 at a time revealed that the individual studies were consistent with the direction and size of the overall AKI-reducing effect of levosimendan (P for all < 0.02).

The outcome of RRT was reported in 983 study participants, and the overall incidence was 7.2% (levosimendan group, 22/492; control group, 49/491). A lowered risk for postoperative RRT was observed in the levosimendan group (9 studies; OR, 0.43; 95% CI, 0.25-0.76; $P = 0.002$; $I^2 = 0.0\%$; Fig 3). Sensitivity analysis excluding each included study 1 at a time revealed that the individual studies were consistent with the direction and size of the overall RRT-reducing effect of levosimendan (P for all ≤ 0.01).

The outcome of mortality was reported in 1,322 study participants, and the overall incidence was 9.5% (levosimendan group, 38/661; control group, 88/661). Perioperative levosimendan significantly reduced the risk for mortality (12 studies; OR, 0.41; 95% CI, 0.27-0.62; $P < 0.001$; $I^2 = 0.0\%$; Fig 4). Sensitivity analysis excluding each included study 1 at a time revealed that the individual studies were consistent with the direction and size of the overall RRT-reducing effect (P for all < 0.001).

Effect of Levosimendan on Postoperative Serum Creatinine Level, Mechanical Ventilation Duration, and ICU Stay

Postoperative serum creatinine levels were reported in only 4 studies, and no statistically significant reduction by levosimendan was found (weighted mean difference, −0.07; 95% CI, −2.16 to 0.08;

Table 2. Summarized Patient Characteristics of Included Randomized Trials

Study	Age, y	Male Sex	DM	HTN	Prior MI	LVEF	CPB Duration, min	Anesthetic	Baseline Scr, mg/dL	β-Blocker	Statins
Al-Shawaf[20] (2006)	59.2	93.3%	100.0%	NA	NA	30.0%	131.0	Sevoflurane	NA	NA	NA
De Hert[21] (2007)	68.0	66.7%	NA	NA	NA	25.5%	131.5	Sevoflurane	1.16	56.7%	NA
Levin[32] (2008)	62.1	61.3%	29.2%	51.8%	17.5%	37.4%	81.7	Sevoflurane	NA	77.4%	54.0%
Tritapepe[22] (2009)	65.2	80.4%	0.0%	NA	NA	42.8%	84.5	Propofol	NA	81.4%	78.4%
Levin[33] (2009)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lahtinen[27] (2011)	69.0	70.0%	NA	NA	18.5%	>30% in 98%	181.0	NA	1.03	78.5%	65.5%
Levin[28] (2012)	63.3	74.6%	30.6%	NA	NA	18.1%	111.4	Sevoflurane	NA	84.5%	20.2%
Ristikankare[31] (2012)	64.0	90.0%	38.3%	66.7%	NA	36.0%	120.5	NA	0.82	93.3%	85.0%
Bragadottir[26] (2013)	67.4	93.0%	NA	70.0%	NA	57.0%	67.2	Sevoflurane	0.92	86.7%	NA
Sharma[25] (2014)	54.3	77.5%	27.5%	52.5%	12.5%	23.1%	128.9	Sevoflurane	0.97	12.5%	15.0%
Shah[29] (2014)	60.6	62.0%	58.0%	76.0%	30.0%	22.5%	NA	Sevoflurane	1.20	14.0%	12.0%
Baysal[30] (2014)	57.6	47.7%	0.0%	NA	0.0%	36.3%	74.0	Sevoflurane	1.05	55.5%	NA
Erb[34] (2014)	66.5	84.8%	45.4%	NA	0.0%	22.2%	101	Sevoflurane	NA	90.9%	69.7%

Note: Values are given as means unless otherwise specified. Conversion factor for Scr in mg/dL to μmol/L, ×88.4.

Abbreviations: CPB, cardiopulmonary bypass; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; Scr, serum creatinine.

Table 3. Summarized Quality Assessment of Included Randomized Trials

Study	Randomization Method	Allocation Concealment	Blinding	Withdrawals and Dropouts Described	Intention-to-Treat Analysis
Al-Shawaf[20] (2006)	Unclear	Sealed envelopes	Single	Yes	Unclear
De Hert[21] (2007)	Computer-generated randomization	Sealed envelopes	Single	Unclear	Unclear
Levin[32] (2008)	Computer-generated randomization	Unclear	Single	Yes	Unclear
Tritapepe[22] (2009)	Computer-generated randomization	Unclear	Double	Yes	Unclear
Levin[33] (2009)	Unclear	Unclear	Unclear	Unclear	Unclear
Lahtinen[27] (2011)	Randomly assigned by a pharmacist	Unclear	Double	Yes	Yes
Levin[28] (2012)	Unclear	Unclear	Unclear	Unclear	Unclear
Ristikankare[31] (2012)	Unclear	Unclear	Double	Unclear	Unclear
Bragadottir[26] (2013)	Unclear	Sealed envelopes	Unclear	Yes	Unclear
Sharma[25] (2014)	Simple digital method of randomization	Unclear	Double	Unclear	Unclear
Shah[29] (2014)	Simple digital method of randomization	Unclear	Double	Unclear	Unclear
Baysal[30] (2014)	Sequential number of randomization	Seal envelopes	Double	Yes	Unclear
Erb[34] (2014)	Computer-generated randomization	Unclear	Double	Yes	Unclear

$P = 0.4$; $I^2 = 67.5\%$). Levosimendan significantly shortened mechanical ventilation duration by 0.34 day (5 studies; 95% CI, −0.58 to −0.09; $P = 0.007$; $I^2 = 90.4\%$). There was also a significant difference in length of ICU stay, which was shorter by 2.2 days (7 studies; 95% CI, −4.21 to −0.13; $P = 0.04$; $I^2 = 97.9\%$; Table 4).

DISCUSSION

In this meta-analysis of 13 RCTs involving 1,345 adult patients undergoing cardiac surgery, we found that perioperative administration of levosimendan reduced the risk for clinical events including AKI, RRT, and death. Levosimendan was also found to shorten mechanical ventilation duration and ICU stay.

Postoperative AKI is a common complication, affecting about 7% to 45% of adult cardiac patients undergoing surgery when defined as a 50% increase in serum creatinine level from baseline.[1,5,35] Small increases in postoperative serum creatinine levels after cardiac surgery have been reported to be associated with increased duration of mechanical ventilation,[36] greater ICU length of stay,[37] and risk for short-term mortality.[3,37,38] In our current analysis, positive renoprotective effects were shown in 2 studies. However, there were also controversial or negative studies pertaining to the effect of levosimendan. Our analysis combining all these positive and negative studies showed that the incidence of AKI was similar to that reported by Niu et al,[39] in which 529 patients from 5 RCTs were analyzed with higher heterogeneity ($I^2 = 30\%$). In addition, we also found that levosimendan could reduce mechanical ventilation duration and length of ICU stay following adult cardiac surgery.

As hard clinical end points, both the requirement for RRT and death should be of particular interest to clinicians in evaluating therapies directed against

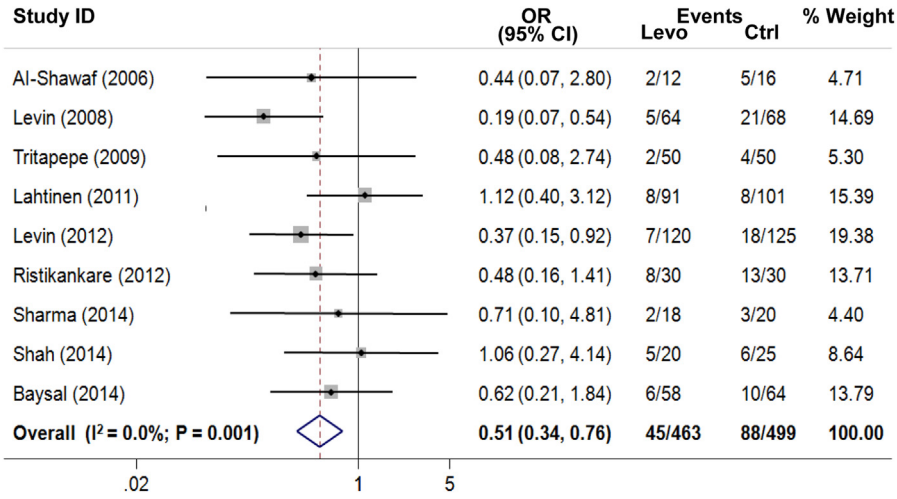

Figure 2. Levosimendan (Levo) reduced the incidence of acute kidney injury (odds ratio [OR], 0.51; $P = 0.001$]. Weights are from random-effects analysis. Abbreviations: CI, confidence interval; Ctrl, control.

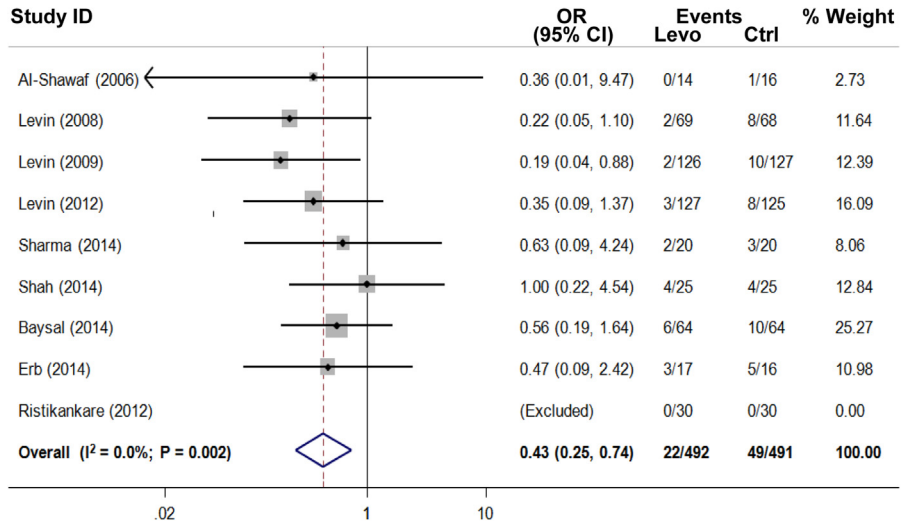

Figure 3. Levosimendan (Levo) reduced the need for renal replacement therapy (odds ratio [OR], 0.43; $P = 0.002$). Weights are from random-effects analysis. Abbreviations: CI, confidence interval; Ctrl, control.

cardiac surgery–related AKI.[40] The risk for death associated with AKI is proportional to its severity, with the highest rate among patients requiring hemodialysis following cardiac surgery.[5,41,42] In our investigation, the incidences of RRT and mortality were 7.2% and 9.5%, respectively, among the overall 1,345 study participants; some of these participants had normal preoperative serum creatinine levels. The high prevalence of these outcomes may be due to low baseline left ventricular function (mean left ventricular ejection fraction < 40% in 87.5% patients).[42] Nevertheless, our analysis found that levosimendan can decrease the risk for either hemodialysis therapy or death compared with control (placebo, milrinone, or dobutamine).

In 8 of 13 included trials, a wide range (6-24 μg/kg) was used for the levosimendan loading dose. To date, the optimal loading dose of levosimendan to improve kidney function after cardiac surgery is unclear. The loading dose of levosimendan may result in excessive hypotension[43] and negate its clinical benefits[44]; however, this potential adverse effect may be minimized by reducing dosing (<12 μg/kg), slowing delivery (>10 minutes),[22] and limiting its administration during cardiopulmonary bypass.[45] Moreover, the loading dose may evoke a preconditioning-like organ protection[45] and improvement in the heart's diastolic function.[46] We could not analyze the potential influence of loading dose of levosimendan on postoperative renal events because of the lack of

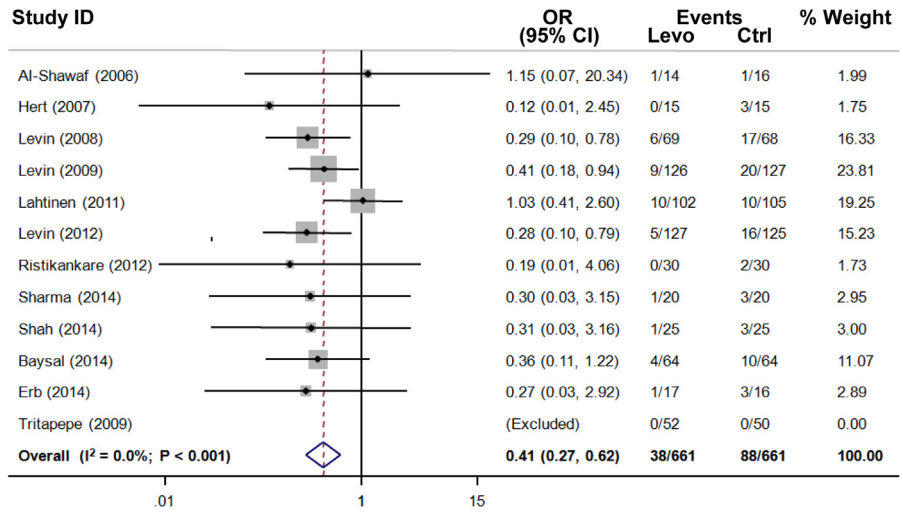

Figure 4. Levosimendan (Levo) reduced the risk for death (odds ratio [OR], 0.41; $P < 0.001$). Weights are from random-effects analysis. Abbreviations: CI, confidence interval; Ctrl, control.

Table 4. Pooled Analysis of Secondary End Points

Measurements	WMD (95% CI)	I^2	*P*
Scr, mg/dL	−0.07 (−2.16 to 0.08)	67.5%	0.4
MV duration, d	−0.34 (−0.58 to −0.09)	90.4%	0.007
ICU stay, d	−2.20 (−4.21 to −0.13)	97.9%	0.04

Note: Conversion factor for Scr in mg/dL to μmol/L, ×88.4.

Abbreviations: CI, confidence interval; ICU, intensive care unit; MV, mechanical ventilation; Scr, serum creatinine; WMD, weighted mean difference.

individual patient data. Future large-scale and well-designed randomized studies should explore the optimal loading dose of levosimendan to maximize its renal protective effect without adversely affecting early and late mortality.

Our analysis has several limitations. First, we were unable to access individual patient data. Therefore, the potential influences of comorbid conditions (age,[47] diabetes,[48] and baseline left ventricular ejection fraction[49]), cardiovascular medications (such as volatile anesthetics[50] and statins[51]), and other parameters (hemodynamic instability, cardiopulmonary bypass duration, use of starch volume expanders, and transfusions) may be underestimated. Second, the definitions for AKI are to some extent different in the included trials. Third, sample size in each study is relatively small. Fourth, our exclusion of non–English language publications could result in publication bias. Fifth, because some studies did not report certain outcomes, we cannot rule out the possibility of outcome reporting bias that arises when the studies that report an outcome systematically differ from those that do not. Last, long-term mortality remains inconclusive because of insufficient data.

In summary, available evidence from the present meta-analysis suggests that perioperative administration of levosimendan to patients undergoing cardiac surgery reduces the incidence of AKI, RRT, death, mechanical ventilation duration, and length of ICU stay. Future trials are needed to determine the dose effect of levosimendan in improving renal outcomes, especially in patients with decreased kidney function at baseline.

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Contributions: Study design: CZ; data acquisition: JG, DC; data analysis/interpretation: CZ; supervision or mentorship: WW, ML, BL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CZ takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Item S1: Search strategies.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.09.015) is available at www.ajkd.org

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