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Levosimendan Reduces Mortality and Low Cardiac Output Syndrome in Cardiac Surgery

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Abstract

Background There has been conflicting evidence concerning the effect of levosimendan on clinical outcomes in patients undergoing cardiac surgery. Therefore, we performed a systematic review and conducted this meta-analysis to provide evidence for/against the administration of levosimendan in cardiac surgery patients.

Methods We performed a meta-analysis from literature search in PubMed, EMBASE, and Cochrane Library. Only randomized controlled trials comparing the administration of levosimendan in cardiac surgery patients with a control group (other inotrope, standard therapy/placebo, or an intra-aortic balloon pump) were included. In addition, at least one clinical outcome had to be mentioned: mortality, myocardial infarction, low cardiac output syndrome (LCOS), acute kidney injury, renal replacement therapy, atrial fibrillation, prolonged inotropic support, length of intensive care unit, and hospital stay. The pooled treatment effects (odds ratio [OR], 95% confidence intervals [CI]) were assessed using a fixed or random effects model.

Results The literature search retrieved 27 randomized, controlled trials involving a total of 3,198 patients. Levosimendan led to a significant reduction in mortality (OR: 0.67; 95% CI: 0.49–0.91; $p = 0.0087$). Furthermore, the incidence of LCOS (OR: 0.56, 95% CI: 0.42–0.75; $p < 0.0001$), acute kidney injury (OR: 0.63; 95% CI: 0.46–0.86; $p = 0.0039$), and renal replacement therapy (OR: 0.70; 95% CI: 0.50–0.98; $p = 0.0332$) was significantly decreased in the levosimendan group.

Conclusion Our meta-analysis suggests beneficial effects for the prophylactic use of levosimendan in patients with severely impaired left ventricular function undergoing cardiac surgery. The administration of levosimendan was associated with a reduced mortality, less LCOS, and restored adequate organ perfusion reflected in less acute kidney injury.

Keywords
- cardiac
- coronary artery bypass graft surgery
- CABG
- heart failure

Introduction

Acute perioperative low cardiac output syndrome (LCOS) is a major complication affecting up to 20% of patients undergoing cardiac surgery.[1,2] It leads to end-organ dysfunction and is associated with a 10 to 17-fold increase in mortality rates.[3]

The therapeutic management of LCOS includes an early revascularization strategy and hemodynamic support with inotropic agents, vasopressors and circulatory assist devices,

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such as an intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation.[4,5] However, inotropic agents as dobutamine or epinephrine enhance myocardial contractility by increasing myocardial oxygen consumption. Therefore, they have been associated with increased morbidity and mortality.[4,6,7] The calcium sensitizer levosimendan binds calcium dependent to troponin, opens adenosine triphosphate-sensitive potassium channels, and provides positive inotropy with a neutral effect on oxygen consumption.[8,9]

A series of small randomized, controlled trials (RCTs) and meta-analyses conducted in the past suggested that levosimendan could help to prevent LCOS and even reduce mortality in patients undergoing cardiac surgery.[10–15] In contrast, the three larger recently published randomized, placebo-controlled trials (LEVO-CTS,[16] CHEETAH,[1] and LICORN[4] trial)[a] report no difference in primary end points in patients undergoing cardiac surgery treated with levosimendan compared with placebo.

Due to the conflicting evidence, we performed an updated systematic review and conducted this meta-analysis including data of LEVO-CTS, CHEETAH, and LICORN trial to reassess the effect of levosimendan on clinical outcomes in patients undergoing cardiac surgery.

Patients and Methods

Selection Criteria and Search Strategy

This systematic review was performed according to the guidelines for Quality of Reporting of Meta-analysis (PRISMA) (►**Supplemental Data S1**, available online only)[17] and as described elsewhere.[18]

RCTs published between 1998 and 2017 that compared a levosimendan treated group to a control therapy group in cardiac surgery patients were identified. Studies were included in the systematic review following a priori defined inclusion criteria: (1) cardiac surgery patients, (2) studies comparing levosimendan therapy versus control therapy, and (3) reported data on the incidence of at least one desired postoperative clinical end point including mortality, myocardial infarction (MI), LCOS, acute kidney injury (AKI), renal replacement therapy, atrial fibrillation, or prolonged inotropic support. Primary outcome was mortality, and secondary outcomes were LCOS, AKI, MI, renal replacement therapy, atrial fibrillation, and prolonged inotropic support. For sensitive analysis, we first included only RCT reporting on preemptive levosimendan therapy prior to cardiac surgery. In a second sensitive analysis, only RCT with preemptive levosimendan therapy and severely impaired left ventricular function (<35%) were included. Type of heart surgery or the use of cardiopulmonary bypass during cardiac surgery was not taken into account.

The two investigators (CW and ACD) performed an electronic literature search in Medline, EMBASE, and The Cochrane Library using a predefined keywords list (►**Supplemental Data S2—search strategy**, available online only). All studies published in full-text or abstract forms were eligible for inclusion. Studies not including a control therapy group, animal studies, in-vitro studies, editorials, letters, review articles, or trials that failed to report the listed outcomes were excluded after initial abstract review. All potentially relevant studies were identified and full-text publications were retrieved for detailed evaluation (►**Fig. 1**). References of relevant reports and reviews were screened to identify other eligible studies. When more than one publication from the same patient cohort existed, then the study with the most complete dataset was included in the systematic review.

Data Extraction and Quality Assessment

All data with regard to authorship, year of publication, type of publication (abstract, full-text), study design, length of follow-up, patient population (sample size, age, gender, preoperative risk factors), length of intensive care unit (ICU) and hospital stay, and desired clinical end points were extracted. Methodological quality of the included studies was assessed by two independent investigators (CW and ME) using the Jadad Score (total score from 0 [poor] to 5 [excellent]) for RCT,[19] and the Downs and Black Checklist (total score from 0 [poor] to 29 [excellent]) for both RCT and observational trials, respectively.[20] Disagreements were resolved by consensus.

Statistics

Statistical analyses were performed using Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and StatsDirect (Version 2.7.8; StatsDirect Ltd., Cheshire, United Kingdom). I^2-statistics were performed to test for heterogeneity between included studies. A standard fixed effects model (Mantel–Haenszel method) was used in the absence of heterogeneity among studies. In the presence of heterogeneity ($I^2 > 50\%$), the DerSimonian and Laird random effects model was used. Pooled effect estimates of categorical data were calculated as a weighted average of the treatment effects and are given as odds ratio (OR) and its 95% confidence interval (95% CI) with an OR of < 1 favoring levosimendan over control. For continuous variables, the weighted mean difference (WMD) was calculated with values below zero favoring levosimendan over control. Outcomes that were reported only as medians with quartiles were not included for WMD calculation. Funnel plots were constructed to visually assess the presence of publication bias with the treatment effects, given as the OR on a logarithmic scale, were plotted against a measure of precision expressed as the standard error. Additionally,

[a] LEVO-CTS: Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass.
CHEETAH: Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial.
LICORN: Effect of Levosimendan on Low Cardiac Output Syndrome in Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass.

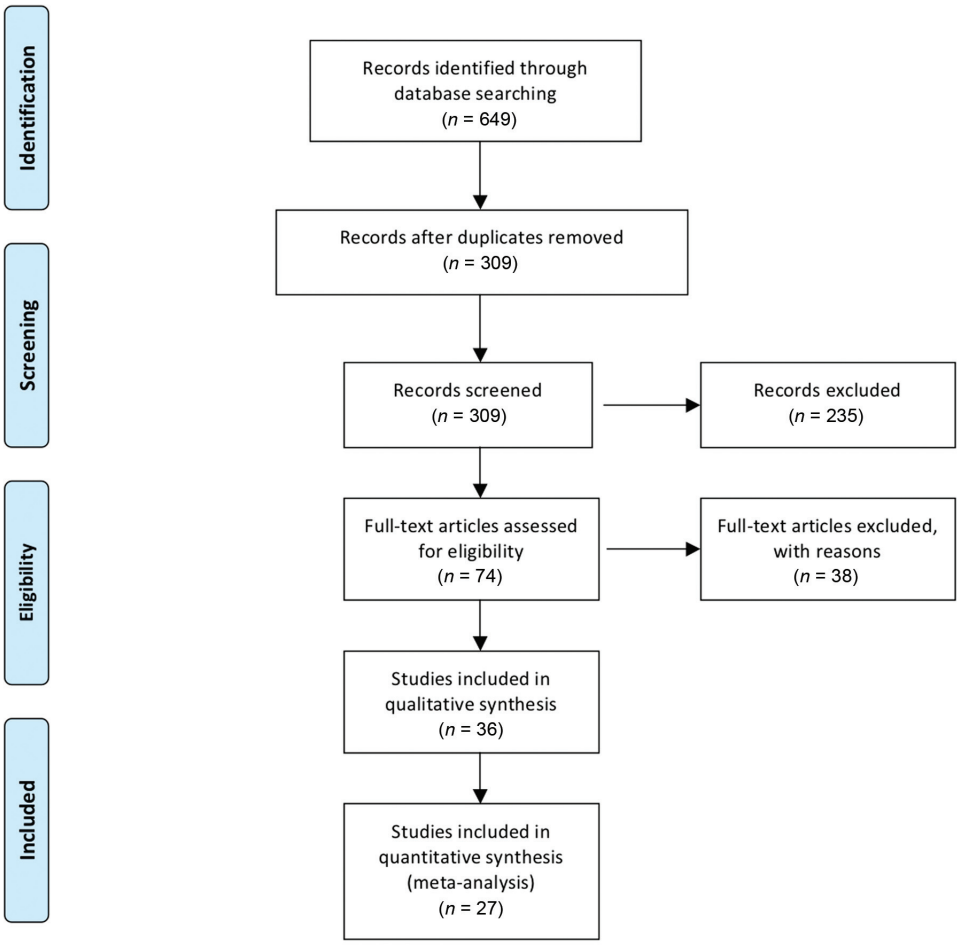

Fig. 1 PRISMA flow diagram.

Egger's weighted regression statistic was applied with a p-value < 0.05 indicating significant publication bias. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

After literature research in Medline, EMBASE, and the Cochrane Library 27 RCT fulfilled our inclusion criteria reporting on the administration of levosimendan compared with a control group in patients undergoing cardiac surgery. The control group was either treated with standard therapy/placebo ($n = 20$), other inotropes (milrinone [$n = 3$], dobutamine [$n = 2$], epinephrine [$n = 1$]), or an IABP ($n = 1$). The dose and timing of levosimendan differed in the included studies (►**Table 1**).

As the comparison of very inhomogeneous groups may lead to wrong conclusions or neglect effects for special patient groups, we performed subgroup analysis for RCTs reporting on a preemptive levosimendan administration. Pooled analysis of 14 trials comparing patients treated with levosimendan prior to surgery compared with a control group is depicted in ►**Table 2**.

As a further subgroup we included only five RCTs reporting on patients with a severely impaired left ventricular function <35% treated prophylactically with levosimendan compared with a control group (►**Table 3**; ►**Fig. 2**).

Mortality—In-hospital or 30-day mortality was reported in a total of 15 RCTs with an incidence of 7.1%. Levosimendan led to a significant reduction in mortality (OR: 0.67; 95% CI: 0.49–0.91; $p = 0.0087$). Pooled analysis of nine RCTs (1,645 patients) with preemptive levosimendan treatment revealed an absolute risk reduction of 3% (OR: 0.57; 95% CI: 0.37–0.87) (►**Table 2**). The number needed to treat for patients with impaired left ventricular ejection fraction is only 29 (►**Table 3**; ►**Fig. 2**). A fixed-effect model was applied in all three analyses since no heterogeneity was found among trials ($I^2 = 0\%$; $p =$ ns).

Myocardial infarction—A 10.1% incidence of MI, including non-Q wave infarction, for the entire patient population was reported without differences between levosimendan treated or control patients after 30 days. Heterogeneity was not observed among all trials ($I^2 = 21\%$) and pooled analysis using a fixed effects model showed no differences in subgroup analysis for preemptive levosimendan (OR: 0.93; 95% CI: 0.67–1.27; $p = 0.6929$; ►**Table 2**) or with preemptive levosimendan and impaired

Table 1 Characteristics of included studies

Author	Year	Sample size Levo/Control	Control therapy	Operation	Inclusion LVEF	Timing of levosimendan infusion	Bolus	Levosimendan maintenance infusion
Anastasiadis et al[3]	2016	16/16	**Standard/ placebo**	CABG ± MVR	–	Pre-op (24h before surgery)	–	0.1 μg/kg/min
Baysal et al[30]	2014	64/64		MVR	<45%	Post-CPB	6 μg/kg	0.1 μg/kg/min
Bragadottir et al[32]	2013	15/15		Cardiac surgery with CPB	–	Post-op	12 μg/kg	0.1 μg/kg/min
Cholley et al[4]	2017	167/168		CABG or CABG combined	<40%	Pre-op (after induction of anesthesia)	–	0.1 μg/kg/min
Erb et al[33]	2014	17/16		CABG ± valve surgery	<30%	Pre-op (after induction of anesthesia)	–	0.1 μg/kg/min
Eriksson et al[11]	2009	30/30		CABG	<50%	Pre-op (after induction of anesthesia)	12 μg/kg	0.2 μg/kg/min
Husedzinović et al[27]	2005	12/12		OPCAB	>50%	Pre-op (after induction of anesthesia)	12 μg/kg	–
Järvelä et al[34]	2008	12/12		AVR ± CABG	–	Pre-op (after induction of anesthesia)	–	0.2 μg/kg/min
Jörgensen et al[28]	2008	12/11		AVR ± CABG	>50%	Post-op	12 μg/kg	0.1–0.2 μg/kg/min
Juhl-Olsen et al[35]	2015	10/10		AVR	>45%	Pre-op (4h before surgery)	–	0.1 μg/kg/min
Kodalli et al[36]	2013	15/15		OPCAB	>45%	Pre-op (after induction of anesthesia)	–	0.1 μg/kg/min
Lahtinen et al[37]	2011	99/101		Valve surgery ± CABG	–	Pre-op (after induction of anesthesia)	24 μg/kg	0.2 μg/kg/min
Landoni et al[1]	2017	248/258		Cardiac surgery	–	Peri-op	–	0.025–0.2 μg/kg/min
Leppikangas et al[23]	2011	12/12		AVR + CABG	<50%	Pre-op (day before surgery)	12 μg/kg	0.2 μg/kg/min
Levin et al[13]	2012	127/125		Cardiac surgery with CPB	<25%	Pre-op (24h before surgery)	10 μg/kg	0.1 μg/kg/min
Lilleberg et al[38]	1998	8/8		CABG	>30%	Post-op	24 μg/kg	–
Mehta et al[16]	2017	428/421		Cardiac surgery with CPB	<35%	Pre-op (30min)		0.1 μg/kg/min
Shah et al[39]	2014	25/25		OPCAB	<30%	Pre-op (24h before surgery)	–	200 μg over 24h
Sharma et al[40]	2014	20/20		CABG with MVR	<30%	Pre-op (24h before surgery)	–	200 μg over 24h
Tritape et al[12]	2009	52/50		CABG		Peri-op	24 μg/kg	–
Al-Shawaf et al[41]	2006	14/16	**Milrinone**	CABG ± MVR	<35%	Post-CPB	12 μg/kg	0.1–0.2 μg/kg/min
De Hert et al[10]	2007	15/15		Cardiac surgery with CPB	<35%	Post-CPB	–	0.1 μg/kg/min
Mishra et al[42]	2016	20/20		AVR or MVR with PAH	<50%	Post-op	10 μg/kg	0.1 μg/kg/min
Gandham et a[43]	2013	30/30	**Dobutamine**	MVR	–	Post-CPB	–	0.1 μg/kg/min
Kandasamy et al[44]	2017	40/40		OPCAB	–	Pre-op (after induction of anesthesia)	–	0.1 μg/kg/min
Salgado Filho et al[45]	2015	36/37	**Epinephrine**	CABG	>35%	Peri-op	–	0.2 μg/kg/min
Lomivorotov et al[46]	2012	30/30	**IABP**	CABG with CPB	<35%	Pre-op (after induction of anesthesia)	12 μg/kg	0.1 μg/kg/min

Abbreviations: AVR, aortic valve replacement; CABG; coronary artery bypass grafting, CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MVR, aortic valve replacement; OPCAB, off-pump coronary artery bypass; PAH, pulmonary arterial hypertension.

Table 2 Analyzed clinical outcomes among RCTs comparing prophylactic levosimendan therapy to control group prior to cardiac surgery ($n = 14$)

Dichotomous	Sample size (*n*)	Prevalence % (*n*)	Levosimendan % (*n*)	Control % (*n*)	OR (95% CI)	X^2-test (*p*-value)
Mortality	1,645	5.6% (92)	4.1% (34)	7.1% (58)	0.57 (0.37–0.87)[a]	0.0117
Myocardial infarction	1,371	12.9% (177)	12.5% (86)	13.3% (91)	0.93 (0.67–1.27)[b]	0.6929
Low cardiac output	1,191	19.8% (236)	15.3% (92)	24.4% (144)	0.56 (0.42–0.75)[c]	0.0001
Acute kidney injury	334	11.7% (39)	7.1% (12)	16.3% (27)	0.40 (0.20–0.82)[d]	0.0153
Renal replacement therapy	1,559	5.3% (82)	4.6% (36)	5.9% (46)	0.76 (0.48–1.19)[e]	0.2825
Atrial fibrillation	1,243	32.9% (409)	32.6% (204)	33.2% (205)	0.80 (0.34–1.84)[f]	0.8581
Prolonged inotropic support	1,208	58.2% (703)	54.2% (329)	62.2% (374)	0.71 (0.57–0.90)[g]	0.0056
Continuous	Sample size (*n*)	WMD		95% CI		*Overall effect* (*p*-value)
ICU stay (days)	72	–2.21		–6.18 to 1.75		0.2741[h]
LH (days)	346	–3.97		–4.69 to –3.25		<0.0001[i]

Abbreviations: CI, confidence interval; ICU, intensive care unit; LH, length of hospital; OR, odds ratio with values less than 1 favoring levosimendan; RCT, randomized controlled trial; WMD, weighted mean difference with [-] favoring levosimendan.
In hospital/30-day follow-up.
[a]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0085$.
[b]Heterogeneity: $I^2 = 30\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.6384$.
[c]Heterogeneity: $I^2 = 16\%$ fixed effects (Mantel–Haenszel): overall effect $p < 0.0001$.
[d]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0096$.
[e]Heterogeneity: $I^2 = 4\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.2318$.
[f]Heterogeneity: $I^2 = 78\%$ random effects (DerSimonian–Laird): overall effect $p = 0.5914$.
[g]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0043$.
[h]Heterogeneity: $I^2 = 96\%$ random effects (DerSimonian–Laird): overall effect $p = 0.2741$.
[i]Heterogeneity: $I^2 = 43\%$ fixed effects (Mantel–Haenszel): overall effect $p < 0.0001$.
Summary of pooled effect estimates of all included trials reporting data of clinical outcomes comparing prophylactic levosimendan therapy prior to cardiac surgery to a control therapy in. Effect estimates were calculated in the presence ($I^2 > 50\%$) or absence of heterogeneity among trials by either using the random effects (DerSimonian–Laird) or fixed effects method (Mantel–Haenszel) as indicated.

left ventricular function (OR: 0.60; 95% CI: 0.15–2.41; $p = 0.7795$; ►**Table 3**; ►**Fig. 2**).

Low cardiac output—Collective incidence of LCOS was 21.8%. With regard to LCOS preemptive levosimendan treatment is associated with a 9.1% absolute risk reduction resulting in a number needed to treat of 11. Similar results were found after pooled analysis of RCTs reporting preemptive levosimendan therapy for patients with impaired LV function (OR: 0.56; 95% CI: 0.42–0.75; $p = 0.0001$). A fixed-effect model was applied in all analyses since no heterogeneity was found among trials.

Acute kidney injury—Furthermore, levosimendan significantly decreased the incidence of postoperative AKI from 29.6% for the control group to 21.3% (OR: 0.63; 95% CI: 0.46–0.86; $p = 0.0039$). Subgroup analyses of patients with preemptive levosimendan administration (►**Table 2**) and impaired LV function (►**Table 3**) showed similar effects favoring levosimendan over standard regime.

Renal replacement therapy—Renal replacement therapy was less common in the patients treated with levosimendan. (OR: 0.70; 95% CI: 0.50–0.98; $p = 0.0332$). Subgroup analysis for prophylactic levosimendan therapy in all patients (►**Table 2**) or with impaired LV function (►**Table 3**) revealed similar results. A fixed-effect model was applied since no heterogeneity was found among trials ($I^2 = 0\%$).

Length of stay—Compared with control, fixed effects analysis ($I^2 = 43\%$) showed that levosimendan reduced length of hospital stay (WMD: 3.97 days; 95% CI: –4.69 to –3.25; ►**Table 3**) in patients with impaired LV function treated prior to surgery. This analysis included only 346 patients from five RCTs.

Publication Bias and Sensitivity Analysis

Assessment of publication bias using visual examination of funnel plots revealed a symmetrical distribution around the OR (►**Supplemental Data S3** and **S4—funnel plots**, available online only). Egger's weighted regression statistics indicated the absence of significant publication bias in RCTs with preemptive levosimendan administration for all end points including mortality ($p = 0.3601$), MI ($p = 0.3097$), LCOS ($p = 0.3391$), AKI ($p = 0.4646$), renal replacement therapy ($p = 0.6255$), and length of hospital stay ($p = 0.1244$).

For all included studies significant publication bias were seen for mortality ($p = 0.031$) and MI ($p = 0.0084$) (►**Supplemental Data S3** and **S4—funnel plots**, available online only).

Table 3 Analyzed clinical outcomes among RCTs comparing prophylactic levosimendan therapy prior to cardiac surgery in high-risk patients with an ejection fraction less than 35% ($n = 5$)

Dichotomous	Sample size (*n*)	Prevalence % (*n*)	Levosimendan % (*n*)	Control % (*n*)	OR (95% CI)	X^2-test (*p*-value)
Mortality	1,224	5.5% (67)	3.7% (23)	7.2% (44)	0.49 (0.29–0.83)[a]	0.0098
Myocardial infarction	1,141	12.4% (141)	12.0% (69)	12.7% (72)	0.60 (0.15–2.41)[b]	0.7795
Low cardiac output	1,191	19.8% (236)	15.3% (92)	24.4% (144)	0.56 (0.42–0.75)[c]	0.0001
Acute kidney injury	302	11.9% (36)	7.9% (12)	16.0% (24)	0.44 (0.21–0.93)[d]	0.0460
Renal replacement therapy	1,224	4.7% (57)	3.4% (21)	5.9% (36)	0.54 (0.31–0.95)[e]	0.0497
Atrial fibrillation	1,191	32.0% (381)	31.2% (187)	32.8% (194)	0.52 (0.19–1.40)[f]	0.5812
Prolonged inotropic support[1]	849	58.8% (499)	54.9% (235)	62.7% (264)	0.72 (0.55–0.95)[g]	0.0056
Continuous	Sample size (*n*)	WMD		95% CI		*Overall effect* (*p*-value)
ICU stay (days)	72	–2.21		–6.18 to 1.75		0.27[h]
LH (days)	346	–3.97		–4.69 to –3.25		<0.0001[i]

Abbreviations: CI, confidence interval; ICU, intensive care unit; LH, length of hospital; OR, odds ratio with values less than 1 favoring levosimendan; RCT, randomized controlled trial; WMD, weighted mean difference with [-] favoring levosimendan.
In hospital/30 day follow-up.
[a]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0067$.
[b]Heterogeneity: $I^2 = 53\%$ random effects (DerSimonian–Laird): overall effect $p = 0.4667$.
[c]Heterogeneity: $I^2 = 16\%$ fixed effects (Mantel–Haenszel): overall effect $p < 0.0001$.
[d]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0307$.
[e]Heterogeneity: $I^2 = 0\%$ fixed effects (Mantel–Haenszel): overall effect $p = 0.0328$.
[f]Heterogeneity: $I^2 = 84\%$ random effects (DerSimonian–Laird): overall effect $p = 0.1958$.
[g]Heterogeneity: I^2 random effects (DerSimonian–Laird): overall effect $p = 0.0211$.
[h]Heterogeneity: $I^2 = 96\%$ random effects (DerSimonian–Laird): overall effect $p = 0.2741$.
[i]Heterogeneity: $I^2 = 43\%$ fixed effects (Mantel–Haenszel): overall effect $p < 0.0001$.
1 Indicating a subgroup of only 1 included study.
Summary of pooled effect estimates of all included trials reporting data of clinical outcomes comparing prophylactic levosimendan therapy prior to cardiac surgery in high-risk patients with a severely impaired left ventricular function (<30%) to a control therapy. Effect estimates were calculated in the presence ($I^2 > 50\%$) or absence of heterogeneity among trials by either using the random effects (DerSimonian–Laird) or fixed effects method (Mantel–Haenszel) as indicated.

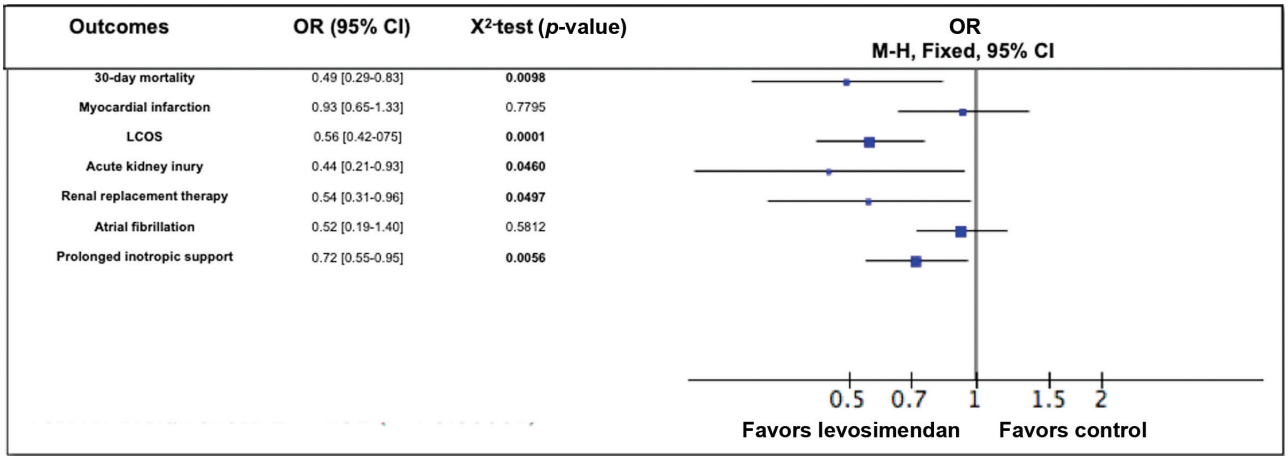

Fig. 2 Forest plot for randomized controlled trials comparing levosimendan with standard therapy in patients with severely impaired left ventricular ejection fraction. CI, confidence interval; LCOS, low cardiac output syndrome; OR, odds ratio.

Discussion

A perioperative LCOS in patients undergoing cardiac surgery is a life-threatening complication. With LCOS, the mortality rate can rise up to 17%.[8] The preoperative LV function has been recognized as the main risk factor for the development of an LCOS.[8] A series of small randomized trials and meta-analyses have compared the perioperative administration of

levosimendan with inotropes or placebo in patients undergoing cardiac surgery. Tritapepe et al conducted a randomized, double-blind, placebo-controlled trial and showed a significantly reduced tracheal intubation time, length of ICU stay, and patients requiring inotropic support for > 12 hours.[12] In addition, patients treated with levosimendan had a higher cardiac index.[12] Levin et al randomized patients with severely reduced left ventricular ejection fraction (LVEF) < 25% to either receive levosimendan or a placebo 24 hours before coronary artery bypass graft (CABG) surgery.[13] Patients pretreated with levosimendan exhibited lower mortality, a decreased risk for developing LCOS and reduced requirement for inotropes and IABP.[13] However, none of the trials were individually powered to show a survival benefit. Previous meta-analyses suggested a reduction in mortality, specifically in patients with severely reduced LVEF < 30%.[14]

In contrast to the preceding smaller trials, the three recent RCTs comparing the administration of levosimendan with a placebo in patients undergoing cardiac surgery did not find a difference in the primary end points between groups.[1,4,16]

Despite inclusion of the three recent trials (LICORN, LEVO-CTS, and CHEETAH),[1,4,16] our meta-analysis of RCTs suggests beneficial effects for the use of levosimendan in patients undergoing cardiac surgery. The administration of levosimendan was associated with a reduced mortality, less LCOS, and restored adequate organ perfusion reflected in less AKI. Statistical relevance remained intact when evaluating RCTs specifically addressing preemptive levosimendan use and patients with impaired LV function < 35%—subgroups that may preferentially benefit from levosimendan therapy.

Although the three recent RCTs showed no benefit for levosimendan use, we consider that levosimendan might be effective in selected patients undergoing cardiac surgery. Some differences in patient selection, timing, and dosage of levosimendan might partially explain the discrepancy between the recent three RCTs and the results of our meta-analysis. Patients in LEVO-CTS and LICORN trial received levosimendan or a placebo preoperatively.[4,16] In the CHEETAH trial, levosimendan was administered after manifestation of a LCOS.[1] A steady-state concentration of levosimendan can be achieved within 4 to 8 hours after the start of continuous infusion without a loading dose.[21] Peak concentrations of levosimendan metabolites have been observed after 48 to 96 hours.[21–23] Eris et al showed that prophylactic preoperative initiation of levosimendan especially 12 hours before operation is associated with better improvement on cardiac functions as well as with lower mortality and complication rates, lower use of additional inotropic and vasopressor drugs, less need for IABP support, and shorter length of stay in the ICU.[24] Hence, pharmacokinetic evidences suggest that levosimendan should be used as a prophylactic agent preoperatively to achieve beneficial effects and the fully effectiveness during the operation and in the early postoperative phase. Contrarily, an administration during the operation might limit the potential protective effects of levosimendan. In addition, in the CHEETAH trial the dosage of levosimendan (0.066 ± 0.031 µg/kg/min) was only half of the recommended dosage in the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.[25] That leads to the presumption that an early or higher dosage of levosimendan might have been more effective with regard to the study protocol of the CHEETAH trial.

The authors of the LEVO-CTS trial conclude that prophylactic administration of levosimendan did not result in a lower rate of the short-term composite end point of death, renal-replacement therapy, perioperative MI, or use of a mechanical assist device compared with placebo.[16] However, although the primary end point could not be reached, patients with levosimendan had a significantly reduced incidence of LCOS and secondary inotropic use.[16] Both might influence the long-term outcome of the patients positively. In addition, the post hoc analysis of the subgroup of patients undergoing isolated CABG showed a significantly reduced 90-day mortality.[26]

Levosimendan might have a different effect in patients with LV dysfunction due to ischemic heart disease than due to pressure or volume overload. Therefore, the inclusion of patients undergoing nonischemic heart disease surgery might be a limitation of many of the included primary studies. Not only the kind of heart disease but also the underlying LVEF was inhomogenous in the included studies. Patients with an impaired LVEF might react and benefit differently on levosimendan administration. There has been evidence that especially patients with reduced LVEF benefited more than patients with preserved LVEF.[3,14,15] However, several primary studies including the CHEETAH trial report on patients with a preserved LVEF.[1,27,28]

Besides, Guarracino et al stated that the LICORN trial was underpowered to definitely exclude a meaningful beneficial effect of levosimendan on the primary composite outcome. The study was powered according to an expectation of an absolute risk reduction of 15%. The point estimate actually recorded was 7% and favored levosimendan, but the 95% CI included a reduction of 17% (range: –17 to 3%).

However, although the recent RCTs could not show a benefit with regard to mortality in patients receiving levosimendan, several trials did demonstrate a significantly reduced incidence of LCOS, secondary use of inotropes, or AKI. AKI is a common complication following cardiac surgery and is associated with increased morbidity and mortality.[29] There has been evidence that levosimendan might improve renal function through its effects on systemic hemodynamics (increase in cardiac output), preglomerular vasodilation, anti-inflammatory, and antiapoptotic effects leading to an improved immediate postoperative renal function and reduced need for renal replacement therapy.[29–31] This is in line with our findings, showing a significantly decreased incidence of postoperative AKI in patients receiving levosimendan.

Our meta-analysis has several limitations that need to be considered for the interpretation of the results. First, most of the included studies were underpowered due to a small sample size. Second, there was a lack of clear definition of high-risk patients in the primary studies. Third, the primary studies were inhomogenous with regard to the kind of

operation, dose, and timing of the levosimendan administration. Finally, for some analyzed outcomes, the number of patients was very small.

However, our meta-analysis suggests beneficial effects for the prophylactic use of levosimendan in patients with a severely impaired LV function undergoing cardiac surgery. The administration of levosimendan was associated with a reduced mortality, less LCOS, and restored adequate organ perfusion reflected in less AKI. However, an adequately powered prospective RCT in a defined high-risk cardiac surgery collective is required.

Conflict of Interest

None.

Acknowledgments

All authors made substantial contributions to the manuscript: CW, ACD, and TW conceived and supervised the meta-analysis, performed statistical analysis, interpreted data, and wrote the manuscript. ME, KE, ID, JM, and JM made substantial contributions to data acquisition and participated in revising the manuscript. AS, YHC, NM, and OJL made substantial contributions to the analysis and interpretation of data and provided important intellectual content. All authors read and approved the complete manuscript.

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