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Perioperative use of levosimendan in patients undergoing cardiac surgery: systematic review and meta-analysis

Uso perioperatorio de levosimendán en pacientes sometidos a cirugía cardiaca: revisión sistemática de la literatura y metaanálisis

Keywords: Meta-analysis, Mortality, Cardiac Output, Low, Acute Kidney Injury, Dialysis, Atrial fibrillation

Palabras clave: Metaanálisis, Mortalidad, Gasto Cardíaco Bajo, Lesión renal aguda, Diálisis, Fibrilación auricular

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Abstract

Introduction: Patients undergoing cardiac surgery frequently develop low cardiac output syndrome (LCOS). Multiple interventions including levosimendan have been used in the prevention and treatment of LCOS. Preliminary studies reported lower mortality respect to placebo or other inotropes, however, recently, 3 clinical trials found no benefit against this outcome.

Objective: Our objective was to evaluate the evidence of levosimendan on mortality and secondary outcomes in patients undergoing cardiac surgery, and to determine the sources of heterogeneity.

Methods: We conducted a systematic review and meta-analysis of the clinical trials that evaluated the efficacy of levosimendan in patients undergoing cardiac surgery. We obtained the odds ratio (OR) of mortality and other outcomes such as kidney injury with dialysis requirement and LCOS, using fixed and random effects models. The risk of bias was assessed and the sources of heterogeneity were explored.

Results: Of 47 studies identified, 14 studies were selected (n=2752). Regarding the mortality outcome and use of levosimendan, only a decrease was found in the studies of low quality (OR 0,30; CI 95%, 0,18 to 0,51). While high-quality studies, there was no protective effect (OR 0.99, 95% CI 0.70–1.40) with an $I^2=0\%$. The quality of the studies and ejection fraction were the main sources of heterogeneity.

Conclusion: In high-quality studies, the use of levosimendan in patients undergoing cardiovascular surgery has no effect on 30-day mortality. There was a protective effect on postoperative renal failure with dialysis.

Resumen

Introducción: los pacientes llevados a cirugía cardiaca tienen riesgo de desarrollar síndrome de bajo gasto cardiaco postoperatorio (SBGC). Estudios previos han encontrado una menor mortalidad con levosimendán respecto a placebo u otros inotrópicos; sin embargo, tres experimentos clínicos no encontraron beneficio frente a este desenlace.

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Objetivo: evaluar la evidencia del levosimendán sobre la mortalidad y los desenlaces secundarios en pacientes sometidos a cirugía cardiaca, y determinar las fuentes de heterogeneidad.

Métodos: mediante una revisión sistemática y metaanálisis de los experimentos clínicos que evaluaron la eficacia del levosimendán en los pacientes llevados a cirugía cardiaca, se evaluó la eficacia en la mortalidad y en otros desenlaces, como lesión renal y SBGC, utilizando los modelos de efectos fijos y aleatorios.

Resultados: De 47 estudios identificados, fueron seleccionados 14 ($n=2752$). Respecto al desenlace de mortalidad y el uso de levosimendán solo se encontró una disminución en los estudios de baja calidad (OR 0,30; IC 95%, 0,18–0,51), mientras que para los de alta calidad no hubo efecto protector (OR 0,99; IC 95%, 0,70–1,40) con un $I^2=0\%$. La calidad de los estudios y la fracción de eyección fueron las principales fuentes de heterogeneidad.

Conclusión: el uso del levosimendán en los pacientes llevados a cirugía cardiovascular no tiene efectos sobre la mortalidad a 30 días en los estudios de alta calidad. Hubo efecto protector sobre la falla renal postoperatoria con necesidad de diálisis.

Introduction

The number of patients undergoing heart surgery has increased worldwide. In Europe and the United States, about 1 million heart–lung bypass surgeries are performed each year.[1] Although less invasive procedures have been developed for the management of complex coronary artery disease and valvular heart disease, cardiovascular surgery remains central to treatment. Patients who undergo these interventions usually have comorbidities that increase the risk of perioperative adverse outcomes.[2] Between 1994 and 2009, mortality after cardiac surgery decreased from 2.4% to 1.5%, but was much higher in the subgroup of patients with low cardiac output syndrome (LCOS), reaching values ranging from 17% to 24%.[3] In turn, LCOS incidence has been reported between 3% and 14%; however, in the presence of preoperative ejection fraction <40%, this risk doubles when compared to those patients with preserved left ventricular ejection fraction (LVEF) (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.7–2.4).[3]

Once LCOS is in place, there are a number of therapeutic interventions, including the use of inotropic agents and mechanical circulatory assist devices; however, the results have not been encouraging. Support with different first-line inotropic drugs has been associated with increased morbidity and mortality.[4–6] In relation to mechanical circulatory support, the preoperative use of the intra-aortic balloon pump (IABP) was studied in 2 meta-analyses that showed a reduction in postoperative mortality, but with limitations in the individual design of the included clinical trials.[7,8] Left ventricular assist devices capable of providing higher flows than the IABP have also been studied. Impella 5.0 (©ABIOMED, Massachusetts, USA) was evaluated in patients with refractory cardiogenic shock of different etiologies[9] and in subjects with LCOS,[10] and thus was documented improvement of hemodynamic parameters and reduction in inotropic dose. One study compared the use of TandemHeart (©ABIOMED, Massachusetts, USA) with IABP in patients with cardiogenic shock of various causes, including LCOS, and found a greater impact on hemodynamic variables, but without affecting mortality.[11] Extracorporeal membrane oxygenation is an accepted rescue strategy, but survival is only from 16% to 41%.[12] Levosimendan is a drug that acts through the sensitization of calcium by troponin C, which produces a protective effect against ischemia and myocardial damage by the phenomenon of ischemia-reperfusion, thanks to its role on the mitochondrial K-channels, and its vasodilating action by promoting the opening of K-ATP-dependent channels in the smooth muscle cell membrane.[13,14] In cardiac surgery, it has been used before the intervention in patients with previous systolic dysfunction, or as part of the management when LCOS is established.[15] In 2013, Harrison et al[16] published a meta-analysis evaluating the role of levosimendan on mortality in patients undergoing cardiac surgery with or without left systolic dysfunction, understood as left ventricular ejection fraction (LVEF) < 40%, and documented a reduction in mortality in favor of levosimendan in the subgroup of patients with decreased LVEF. In contrast to these findings, 3 clinical trials[17–19] that did not demonstrate benefit over mortality have recently been published. The objective of this systematic review is to assess the impact of the use of levosimendan on mortality and other outcomes, such as the development of acute renal injury in patients undergoing cardiac surgery, as well as to assess possible sources of heterogeneity of studies.

Method

Selection of studies

A systematic review of the literature was conducted to identify controlled clinical experiments using levosimendan in patients undergoing cardiac surgery, without language restriction. The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration[20] were followed. To identify the studies, the following electronic databases were consulted until week 26, 2018: Medline, Medline In-Process & Other Non-Indexed Citations, Medline Daily Update, Embase, PsycINFO, and Lilacs. The manual search was complemented with the snowball strategy, Google Scholar and the search in gray literature through OpenGrey. The search included terms that identified patients with cardiovascular surgery, levosimendan transoperative treatment and that reported 30-day mortality and other intermediate outcomes such as acute renal failure and LCOS as outcomes (Annex 1).

Criteria for including studies in this review

- *Type of study:* controlled clinical experiments.
- *Population:* patients over 18 years of age undergoing cardiac surgery.
- *Intervention:* use of levosimendan versus standard therapy.
- *Primary outcome:* 30-day mortality.
- *Secondary outcomes:* acute postoperative renal injury in need of renal replacement therapy, and LCOS.
- *Adverse events:* postoperative atrial fibrillation (PAF).

Information extraction

Articles were independently selected by 2 reviewers (HO and CR) according to the above search criteria. Disagreements were resolved through consensus.

Statistical analysis

Study quality and risk of bias were assessed following the instructions of the Cochrane Collaboration to evaluate clinical trials.[21] OR values were determined for dichotomous variables, and for continuous variables standardized mean differences with their respective standard deviation values were obtained. Heterogeneity of studies was assessed using Cochran's Q and the I^2 considering the limitations of these 2 statisticians with a low power, a high heterogeneity with a low power was considered ($I^2>50\%$). For each of the summary measures, the 30-day mortality OR values were obtained using the Mantel and Hansen fixed-effects model and the DerSimonian–Laird statistic for the random-effects model; additionally, for the mortality outcome the quality of the studies was stratified, and low and high-quality studies were combined separately. All analyses were performed using the statistical package STATA version 14 (StataCorp, College Station, TX).

Results

General findings and evaluation of the quality of studies

By means of the search strategy 47 articles were identified. Of the studies, 13 were excluded after reviewing title and abstract. Of the 34 articles reviewed in full text, 20 were excluded as they did not meet the inclusion criteria. Fourteen studies were finally selected for analysis (Fig. 1).[17–19,22–32]

The characteristics of the studies are shown in Table 1. Regarding the ejection fraction (EF), it was considered low <40%, and preserved, >40%, as this is the most frequently used cutoff point in the included clinical trials, given that it is associated with a higher risk of LCOS.[3] Of the 14 included studies, 11 were conducted in patients with ESA < 40%, and 3, in subjects with ESA > 40%. In assessing study quality and risk of bias,[21] we found 4 studies of high quality, and 10 of low quality.

Mortality at 30 days

The effect of levosimendan on 30-day mortality was assessed in 14 studies (n=2752). The summary measure showed a significant reduction in the risk of mortality in the exposed group (OR 0.69, 95% CI 0.52–0.93, $I^2=24\%$); however, when this outcome was stratified according to study quality by assessing risk of low and high bias, protective effect was found only in low-quality studies for high risk of bias (OR 0.30, 95% CI 0.18–0.51), finding no statistically significant differences in high-quality studies with low risk of bias (OR 0.99, 95% CI 0.70–1.40). On the other hand, stratification reduced heterogeneity ($I^2=0\%$ in each subgroup) (Figs. 2 and 3A). When mortality was analyzed according to LVEF, a reduction in mortality risk was found among those exposed to levosimendan when LVEF was <40% (OR 0.53, 95% CI 0.36–0.78, $I^2=10.7\%$); however, when only high-quality studies were included no differences were found (OR 0.95, 95% CI 0.55–1.65). There was no benefit on mortality with the use of levosimendan in the group of subjects with preserved LVEF (Fig. 3B).

Secondary links

There were 10 studies reporting the outcome of acute postoperative renal injury requiring renal replacement therapy. Although individually none found a protective effect in favor of levosimendan, the summary measure obtained showed a significant reduction in the risk of requiring dialysis (OR 0.69, 95% CI 0.49–0.96, $I^2=0\%$) (Fig. 4A). There were 12 studies reporting the outcome of PAF, with no significant differences found between groups (OR 0.97, 95% CI 0.82–1.15, $I^2=63\%$) (Fig. 4B). Postoperative LCOS development was reported in 5 studies. A lower risk was found in those exposed to levosimendan (OR 0.46, 95% CI 0.35–0.60), but heterogeneity between studies was high ($I^2=75.5\%$) (Annex 2).

Publication bias

The evaluation of publication bias was made using the funnel plot and Egger's correlation test; the null hypothesis with a value of $P=0.14$ was not rejected, so it follows that there is no significant asymmetry in the studies with less precision (Fig. 5).

Discussion

In the present meta-analysis, the use of levosimendan in patients undergoing cardiac surgery showed decreased risk of mortality at 30 days in low-quality studies, without finding significant differences in high-quality studies. In the subgroup of patients with LVEF < 40%, mortality was lower among those exposed to levosimendan; however, the result was not consistent when only high-quality

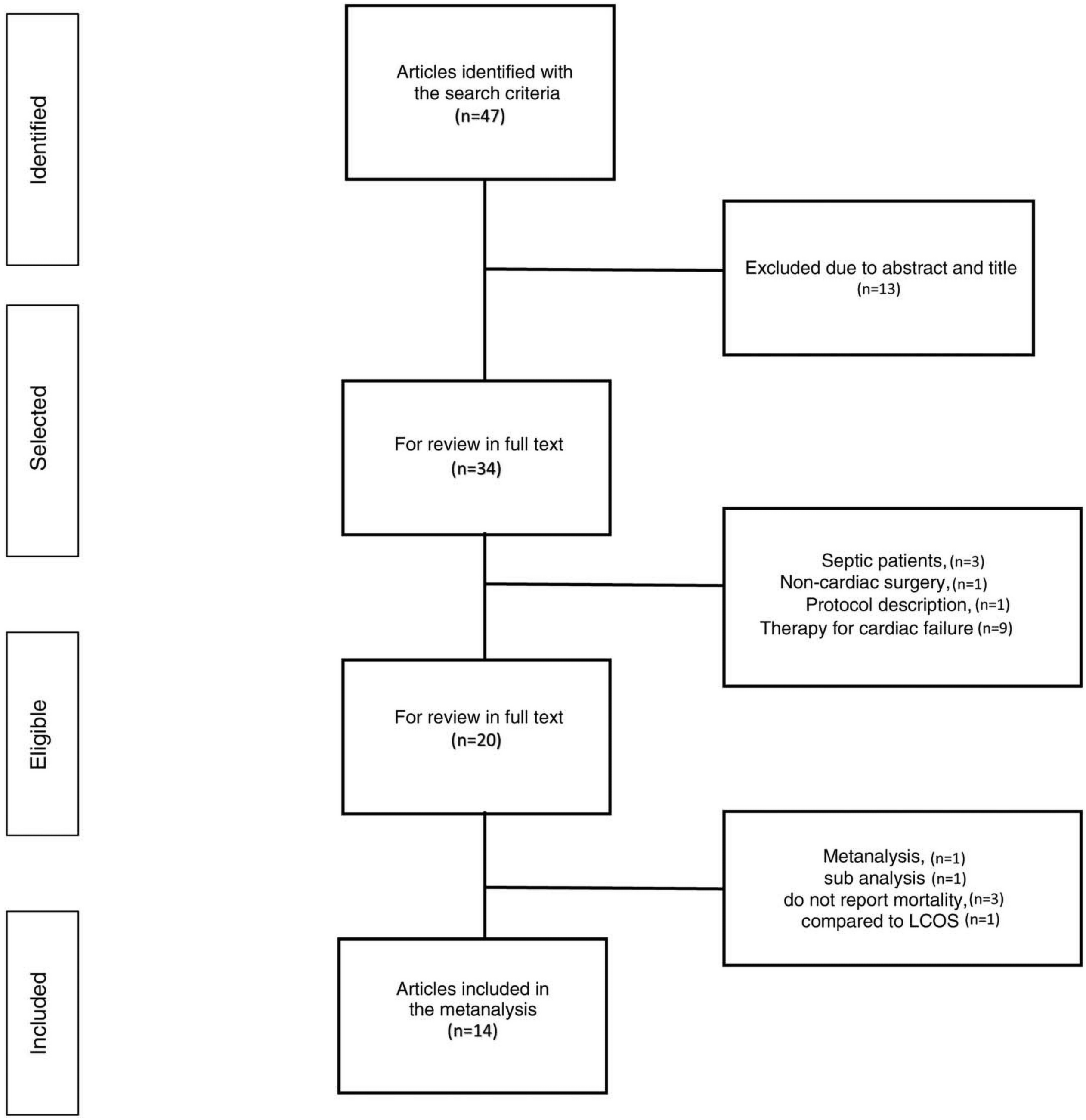

Figure 1. Identification and selection flowchart of studies that met the inclusion criteria.
Source: Authors.

studies were analyzed. In the evaluation of secondary outcomes, significant differences were found in favor of levosimendan in the reduction of the risk of acute postoperative renal injury requiring dialysis, and in the development of LCOS. There was no difference in the implementation of PAF with the use of levosimendan compared to the control group.

LCOS is a frequent complication in the cardiac surgery setting, with an incidence of 3% to 14%.[3] The most commonly used definition includes cardiac index <2.0 L/min/m^2, systolic pressure <90 mm Hg and signs of hypoperfusion in the absence of hypovolemia.[33] When preoperative left ventricular ejection fraction (LVEF) is <40%, the risk of LCOS increases 2 times (OR 2.0, 95% CI 1.7–2.4), and more than 3 times, in the case of LVEF < 20% (OR 3.5, 95% CI 2.7–4.6).[3] Once LCOS is established, the risk of postoperative complications and mortality is higher,[33] so pharmacological and nonpharmacological interventions have been implemented, which have not shown significant improvement.[4–6,12]

Since its introduction in the management of patients with heart failure, and subsequently, as part of cardiovascular

Table 1. Characteristics of studies including 30-day mortality outcomes, postoperative acute renal injury with need for dialysis, and postoperative atrial fibrillation.

Reference	N	Country	Outcome	OR (95% CI)	LVEF	Quality
Al-Shawaf et al[26]	30	Kuwait	Mortality ARL and dialysis PAF	1.15 (0.07–20.3) 0.36 (0.01–9.47) 0.75 (0.18–3.17)	Low	Low
De Hert et al[27]	30	Belgium	Mortality PAF	0.12 (0.01–2.45) 0.76 (0.18–3.24)	Low	Low
Levin et al[28]	137	Argentina	Mortality ARL and dialysis PAF	0.29 (0.10–0.78) 0.22 (0.05–1.10) 0.42 (0.20–0.89)	Low	Low
Tritapepe et al[30]	102	Italy	Mortality PAF	0 1.20 (0.47–3.09)	Preserved	Low
Eriksson et al[29]	60	Finland	Mortality	0.19 (0.01–4.06)	Low	Low
Lahtinen et al[31]	200	Finland	Mortality PAF	1.02 (0.41–2.58) 1.31 (0.71–2.44)	Preserved	High
Levin et al[32]	252	USA	Mortality ARL and dialysis PAF	0.28 (0.10–0.79) 0.35 (0.09–1.37) 0.35 (0.19–0.66)	Low	Low
Erb et al[23]	33	Germany	Mortality ARL and dialysis	0.27 (0.03–2.92) 0.47 (0.09–2.42)	Low	Low
Shah et al[25]	50	India	Mortality ARL and dialysis PAF	0.31 (0.03–3.16) 1.00 (0.22–4.54) 0.13 (0.03–0.68)	Low	Low
Sharma et al[24]	40	India	Mortality ARL and dialysis PAF	0.30 (0.03–3.15) 0.63 (0.09–4.24) 0.75 (0.17–3.33)	Low	Low
Baysal et al[22]	128	Turkey	Mortality ARL and dialysis PAF	0.36 (0.11–1.22) 0.56 (0.19–1.64) 0.62 (0.23–1.63)	Low	Low
Landoni et al[18]	506	Multicentric Italy	Mortality ARL and dialysis PAF	1.01 (0.60–1.70) 0.73 (0.42–1.28) 0.82 (0.51–1.33)	Preserved	High
Mehta et al[17]	849	Multicentric USA	Mortality ARL and dialysis PAF	0.77 (0.39–1.53) 0.54 (0.24–1.24) 1.25 (0.94–1.65)	Low	High
Cholley et al[19]	335	Multicentric France	Mortality ARL and dialysis PAF	1.37 (0.56–3.34) 1.56 (0.68–3.58) 1.45 (0.94–2.24)	Low	High

Quality: to allocate the quality of the studies in high and low we considered the classification of risk of low and high bias, respectively. ARL = acute renal lesion, CI = confidence interval, LVEF = left ventricular ejection fraction, OR = odds ratio, PAF = postoperative atrial fibrillation.
[a]In the study of Tritape et al there were no events.
Source: Authors.

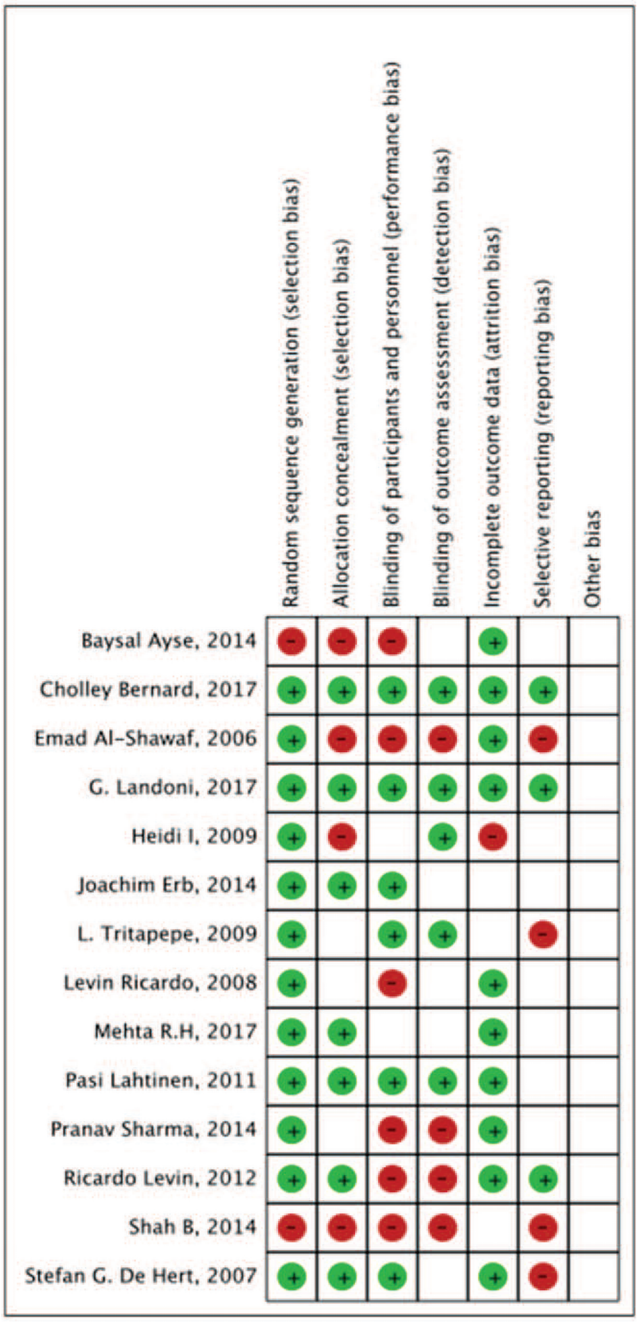

Figure 2. Evaluation of the risk of bias of the studies included in the meta-analysis. ***Notes:*** **In red: high risk; in green: low risk; and in white: not clear.**
Source: Authors.

surgery therapy, levosimendan has shown isolated benefits in mortality and some secondary outcomes; in part, thanks to a myocardial protective effect based on ischemic preconditioning.[13] The results of these initial studies were summarized in several meta-analyses that reported decreased mortality in favor of levosimendan in patients undergoing cardiac surgery; the benefit was greater in those with EF < 40%.[16,34,35] One of the limitations described in these publications was the poor quality of the included clinical trials. Consequently, 3 clinical experiments with adequate quality were recently published. Elbadawi et al carried out a meta-analysis that included 2 of the studies already cited.[17,19] There they evaluated the prophylactic administration of levosimendan in patients who went to heart surgery, without finding significant differences in mortality at 30 days. This finding was independent of EF.[36] Some authors suggest that such data should be interpreted carefully, since in the larger sample size studies, levosimendan was administered after anesthetic induction, leaving little time for cardiac preconditioning.[15,37] In 2017, Sanfilippo et al[38] published another meta-analysis in which they assessed the impact of levosimendan in patients with decreased EF or LCOS, and thus documented less mortality only within the subgroup with FE < 35%. The 3 recently published clinical trials were included in our meta-analysis. When the data were analyzed together, a decrease in mortality at 30 days was found (OR 0.69, 95% CI 0.52–0.93, $I^2 = 24\%$), but when stratifying for quality no significant differences were established within the high-quality studies (OR 0.99, 95% CI 0.70–1.40, $I^2 = 0\%$), and this highlights the lack of impact of levosimendan on mortality. Stratification controlled heterogeneity, and we concluded that differences in study quality were a source of heterogeneity. This is a strength of the present meta-analysis, since the finding of overestimation of results in low-quality studies has already been reported in other clinical scenarios, while high-quality studies usually have more conservative outcomes.[39]

Within the secondary outcomes, there was less risk of acute postoperative renal injury in need of dialysis among patients exposed to levosimendan. Several studies have reported benefit in renal outcomes[36,38] and in acute renal failure in need of dialysis.[40] Different mechanisms have been proposed to explain this benefit, such as increased cardiac output, leading to improved renal perfusion,[41] and action on dependent ATP potassium channels, which produce vasodilation of the afferent renal arteriole, increasing glomerular pressure and glomerular filtration rate.[42] It will be necessary to assess which specific group of patients could benefit most from this protective effect. Favorable hemodynamic effects in favor of levosimendan over other inotropic drugs have been described; in particular, greater increase in cardiac index and decrease in systemic and pulmonary vascular resistance.[43,44] Given these considerations, it has been suggested that the incidence of LCOS decreases.[38] Our findings show that, while there was a reduction in the risk of LCOS, heterogeneity between studies was very high ($I^2 = 75.5\%$).

This study has several limitations. The use of levosimendan bolus at baseline, as well as the maintenance dose and timing of administration, was not the same in all studies. In addition, the control group comparator included placebo or another inotropic agent. In addition,

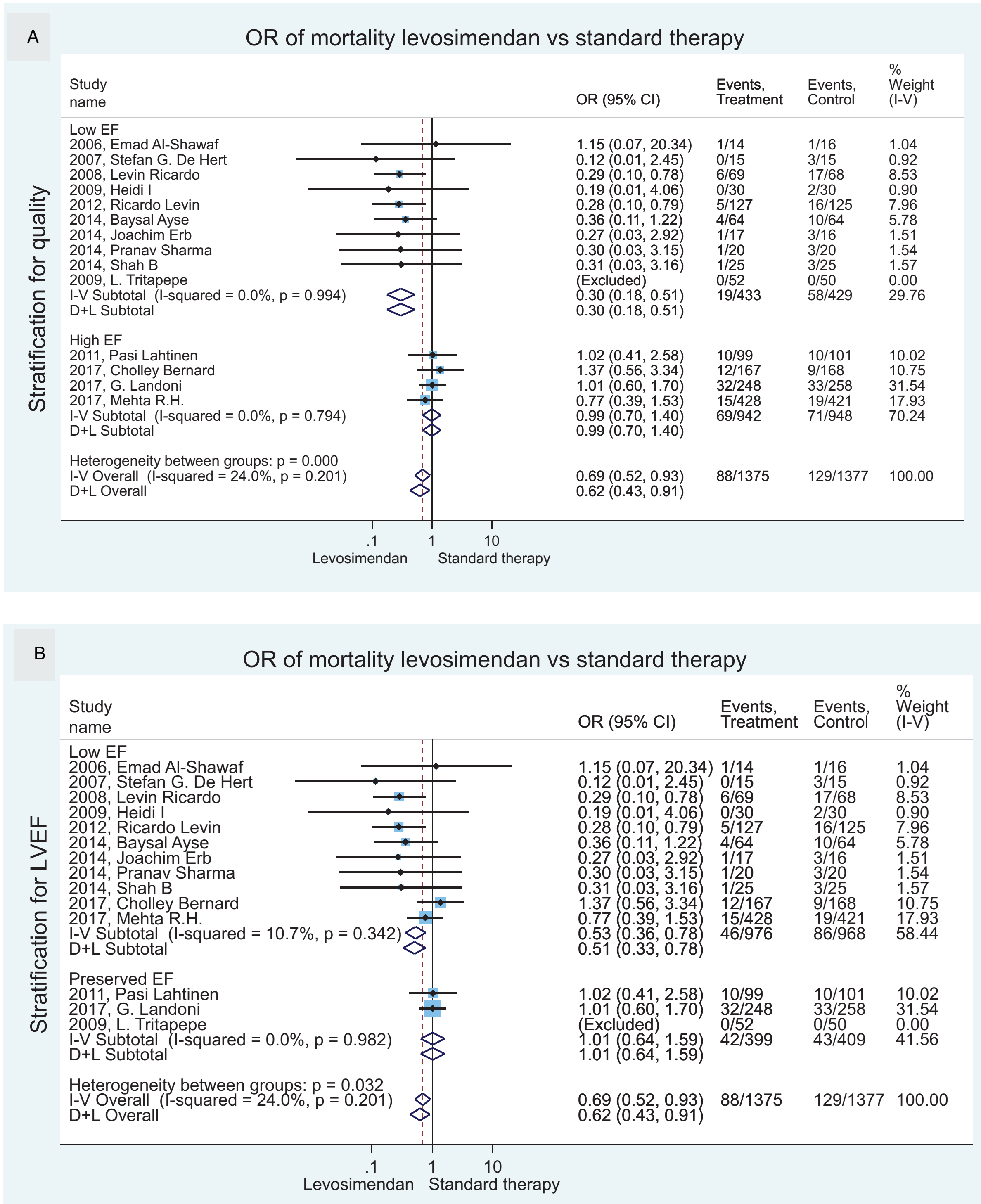

Figure 3. Effect of levosimendan treatment versus standard therapy on 30-day mortality in patients undergoing cardiac surgery. (A) Stratification according to the quality of the studies. (B) Stratification according to the pre-surgical left ventricular ejection fraction (LVEF): low: <40%; high: >40%. EF = ejection fraction.
Source: Authors.

most studies adjust outcomes according to the EF, without considering adjustment for other variables such as patient severity, based on prognostic models (EuroSCORE II and STS) or the type of surgery to which they were subject, either revascularization or valvular surgery; in the latter it is necessary to define the type of valvular disease, since adaptive ventricular changes can determine different responses to the drug under study.

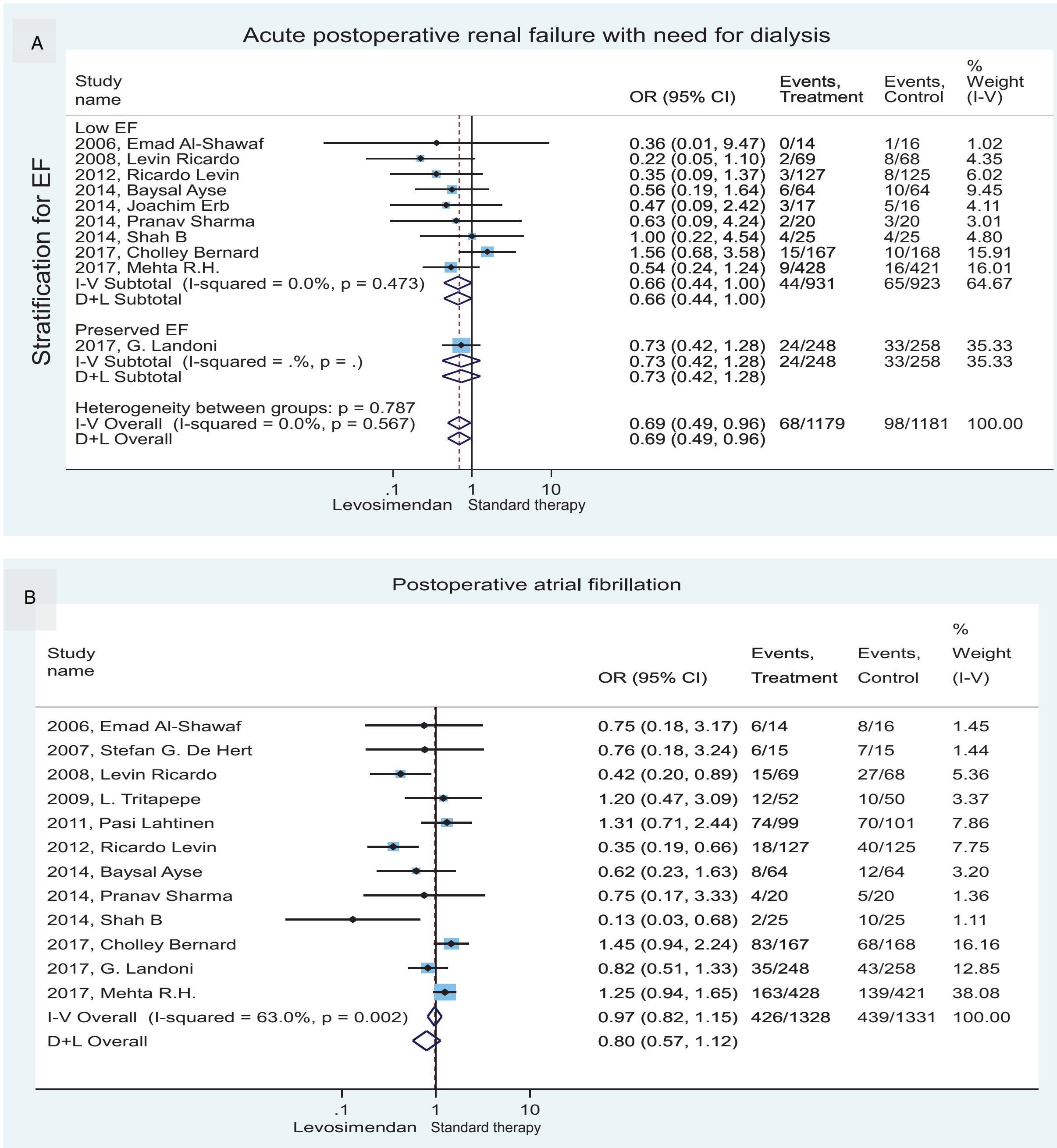

Figure 4. Effect on secondary outcomes of levosimendan versus standard therapy. (A) Acute postoperative renal failure with need for dialysis. (B) Postoperative atrial fibrillation. EF = ejection fraction.
Source: Authors.

Conclusion

In this meta-analysis, the use of levosimendan in patients undergoing cardiac surgery showed lower mortality at 30 days compared to controls; however, when high-quality studies were analyzed there were no significant differences. A decrease in the outcome of postoperative renal injury requiring dialysis was found in patients receiving levosimendan.

Ethical responsibilities

Protection of people and animals. The authors state that no human or animal experiments were conducted for this research.

Financing

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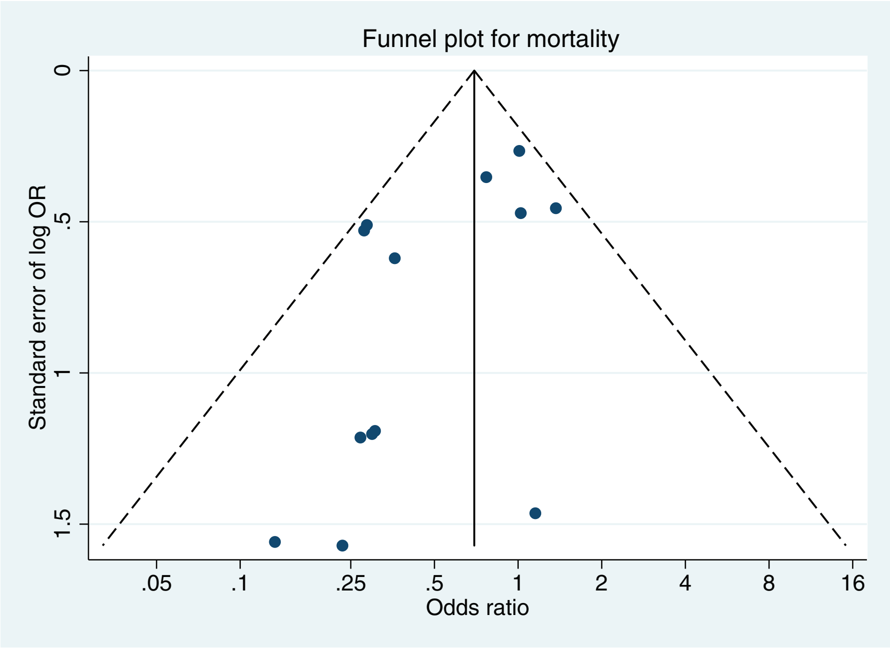

Figure 5. Funnel plot for 30-day mortality.
Source: Authors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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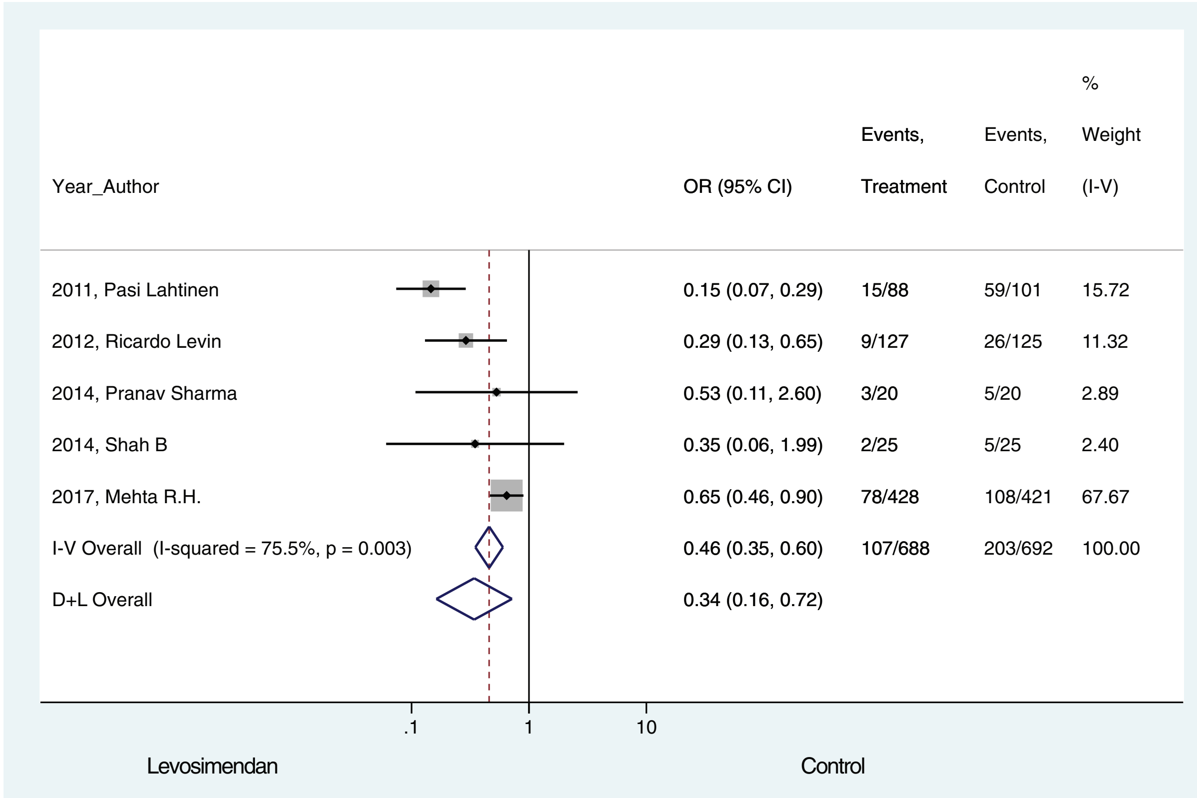
Annex 1. Study search strategy

((((((((((low[All Fields] AND left[All Fields] AND ("stroke volume"[MeSH Terms] OR ("stroke"[All Fields] AND "volume"[All Fields]) OR "stroke volume"[All Fields] OR ("ventricular"[All Fields] AND "ejection"[All Fields] AND "fractions"[All Fields]) OR "ventricular ejection fractions"[All Fields])) OR (high-risk[All Fields] AND ("thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) OR "cardiac surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields])))) OR ("coronary artery bypass"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "bypass"[All Fields]) OR "coronary artery bypass"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "bypass"[All Fields] AND "grafting"[All Fields]) OR "coronary artery bypass grafting"[All Fields])) OR ("coronary artery bypass"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "bypass"[All Fields]) OR "coronary artery bypass"[All Fields])) OR ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])) OR ("cardiopulmonary bypass"[MeSH Terms] OR ("cardiopulmonary"[All Fields] AND "bypass"[All Fields]) OR "cardiopulmonary bypass"[All Fields])) OR (bypass[All Fields] AND ("transplants"[MeSH Terms] OR "transplants"[All Fields] OR "graft"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]))) OR (low[All Fields] AND ejection[All Fields] AND fraction [All Fields])) AND ((((("standard of care"[MeSH Terms] OR ("standard"[All Fields] AND "care"[All Fields]) OR "standard of care"[All Fields] OR ("standard"[All Fields] AND "therapy"[All Fields]) OR "standard therapy"[All Fields]) OR (standard[All Fields] AND deviation[All Fields])) OR ("norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields])) OR ("dobutamine"[MeSH Terms] OR "dobutamine"[All Fields])) OR ("milrinone"[MeSH Terms] OR "milrinone"[All Fields]))) AND (((((((("length of stay"[MeSH Terms] OR ("length"[All Fields] AND "stay"[All Fields]) OR "length of stay"[All Fields]) AND ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR "icu"[All Fields])) OR ("length of stay"[MeSH Terms] OR ("length"[All Fields] AND "stay"[All Fields]) OR "length of stay"[All Fields])) OR ("haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields])) OR ("renal replacement therapy"[MeSH Terms] OR ("renal"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "renal replacement therapy"[All Fields])) OR ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) OR (("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("cardiac output, low"[MeSH Terms] OR ("cardiac"[All Fields] AND "output"[All Fields] AND "low"[All Fields]) OR "low cardiac output"[All Fields] OR ("low"[All Fields] AND "cardiac"[All Fields] AND "output"[All Fields])))) OR (Low[All Fields] AND ("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("cardiac output"[MeSH Terms] OR ("cardiac"[All Fields] AND "output"[All Fields]) OR "cardiac output"[All Fields])))) AND ("simendan"[Supplementary Concept] OR "simendan"[All Fields] OR "levosimendan"[All Fields]) AND Clinical Trial [ptyp]

Source: Authors.

Annex 2. Effect of levosimendan treatment versus standard therapy on LCOS development



LCOS=low cardiac output syndrome.
Source: Authors.