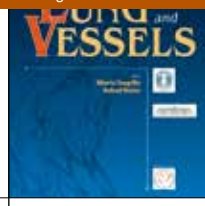

ORIGINAL ARTICLE

Heart, Lung and Vessels. 2015; 7(1): 35-46

Beneficial impact of levosimendan in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials

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Heart, Lung and Vessels. 2015; 7(1): 35-46

ABSTRACT

Introduction: The incidence of Acute Kidney Injury is nowadays high in critically ill patients. Its etiology is multifactorial and a primary role is played by low cardiac output syndrome. Everything targeted to normalize cardiac output should increase the renal perfusion and abolish the secondary vasoconstriction. Levosimendan is a calcium sensitizer drug with inotropic properties that improves cardiac output and seems to increase renal blood flow. The aim of this meta-analysis was to evaluate the role of levosimendan in critically ill patients with or at risk of Acute Kidney Injury.
Methods: We performed a meta-analysis of randomized controlled trials searching for trials that compared levosimendan with any comparator. The endpoints were the number of patients receiving Renal Replacement Therapy after randomization and the number of patients developing Acute Kidney Injury.
Results: Final analysis included 33 trials and 3,879 patients (2,024 levosimendan and 1,855 control). The overall analysis showed that the use of levosimendan was associated with a significant reduction in the risk of Renal Replacement Therapy (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, relative risk = 0.52 [0.32 to 0.86], p for effect = 0.01) and of Acute Kidney Injury (114 of 1,598 [7.1%] in the levosimendan group versus 143 of 1,529 [9.4%] in the control arm, relative risk = 0.79 [0.63 to 0.99], p for effect = 0.048).
Conclusions: This meta-analysis suggests that the use of levosimendan is associated with a significant reduction of Renal Replacement Therapy in critically ill patients.

Keywords: *levosimendan, acute kidney injury, critical care, renal replacement therapy.*

INTRODUCTION

Despite considerable progress in terms of diagnosis and treatment, the incidence of Acute Kidney Injury (AKI) remains high in critically ill patients. Interventions or medications that can alter the clinical course of AKI and change the outcome of critically ill patients are scarce (1).

The etiology of acute renal failure in critically ill patients is multifactorial and a primary role is played by low cardiac output

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syndrome and sepsis. The main determinants of renal perfusion are cardiac output, blood pressure and blood volume. The kidneys normally receive 20-25 % of the cardiac output, although their total weight is less than 1 % of total body weight. The decrease in cardiac output due to hypovolemia or cardiac dysfunction decreases renal perfusion with direct and indirect mechanisms. Indeed, in addition to the reduction in renal blood flow, activation of sympathetic nervous system, renin-angiotensin system and vasopressin secretion occur. Each intervention targeted to normalize cardiac output and systemic perfusion should be able to increase the renal perfusion and abolish the secondary vasoconstriction.

Levosimendan is a calcium sensitizer drug with inotropic properties (2). It also has vasodilating properties interacting with ATP-sensitive K^+channels of vascular smooth muscles cells. Levosimendan seems to reduce the release of pro-inflammatory cytokines and to prevent the cardiomyocyte apoptosis. Therefore, it improves cardiac output and seems to increase renal blood flow by its vasodilating effects. Levosimendan has already been associated with reduction of mortality in critically ill patients in a meta-analysis of randomized clinical trials, but its effects on renal function have never been systematically assessed (3).

The aim of this meta-analysis of randomized trials was to evaluate the role of levosimendan in critically ill patients with or at risk of AKI.

METHODS

We performed a systematic review and meta-analysis of randomized trials in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.

We searched for all randomized controlled trials that compared levosimendan with any pharmacological comparator or placebo in any clinical setting. Potentially eligible trials were identified by searching the Cochrane central register, Embase, Scopus and Medline using a combination of subject headings and text words to identify randomized controlled trials of levosimendan. The search was updated at January 2013. The full PubMed search strategy is available in the supplemental item S1. Searches were not restricted by language or publication status. To identify ongoing or unpublished trials, we searched the Clinical Trial Registry. We also examined the reference lists of eligible trials and reviews together with the abstracts of international congresses. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment and comparison of levosimendan vs. control. There were no restrictions on age, drug's dose or time of administration. Exclusion criteria were overlapping publications, abstracts published before 2010, oral administration of levosimendan, and lack of data on renal outcome. Two authors independently screened the search output to identify records of potentially eligible trials, the full texts of which were retrieved and assessed for inclusion.

The primary endpoint was the number of patients receiving Renal Replacement Therapy (RRT) after randomization; the secondary endpoint was the number of patients developing AKI (as per author definition). We also collected data on serum peak creatinine and glomerular filtration rate. We contacted trial authors to obtain any missing outcome data. We extracted data on setting, dose of levosimendan, type of comparator, outcome data and length of follow up. We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding, and completeness of outcome data. We rated the risk of bias as being low, unclear, or high according to established criteria (4).

Statistical analysis. For binary outcome we calculated the natural logarithm (ln) of risk ratios (RR) and its standard deviation. We pooled these using the inverse variance method and a fixed effect model in case of low statistical inconsistency (I-square≤25 %) or with random-effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency (I-square > 25 %). Weighted Mean Difference (WMD) and 95 % confidence intervals were computed for continuous variables using the same methods as just described (4). To assess heterogeneity in results of individual studies, we used Cochran's *Q* statistic and the I-square statistic (I-square > 25 % was considered as a threshold indicating significant heterogeneity). Publication bias was assessed by visually inspecting funnel plots of the primary outcome, by analytical appraisal based on the Begg adjusted-rank correlation test and on Egger's linear regression test (a two-sided p value of 0.10 or less was regarded as significant).

Subgroup analyses were carried out to examine whether the effect of levosimendan on RRT varied by setting or type of infusion. Sensitivity analyses were done to quantify the effect of levosimendan when restricted to trials with low risk of bias. We also investigated the influence of a single study on the overall risk estimate by sequentially removing study in order to test the robustness of the main results.
Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Data analysis was performed using STATA 11.0 Software (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of the included individual studies. Our search strategy identified 599 unique publications, the titles and abstracts of which were screened for inclusion. The full text of 97 articles was retrieved, of which 33 (5-37) met the inclusion criteria (*Figure 1*). Reasons for exclusion of the

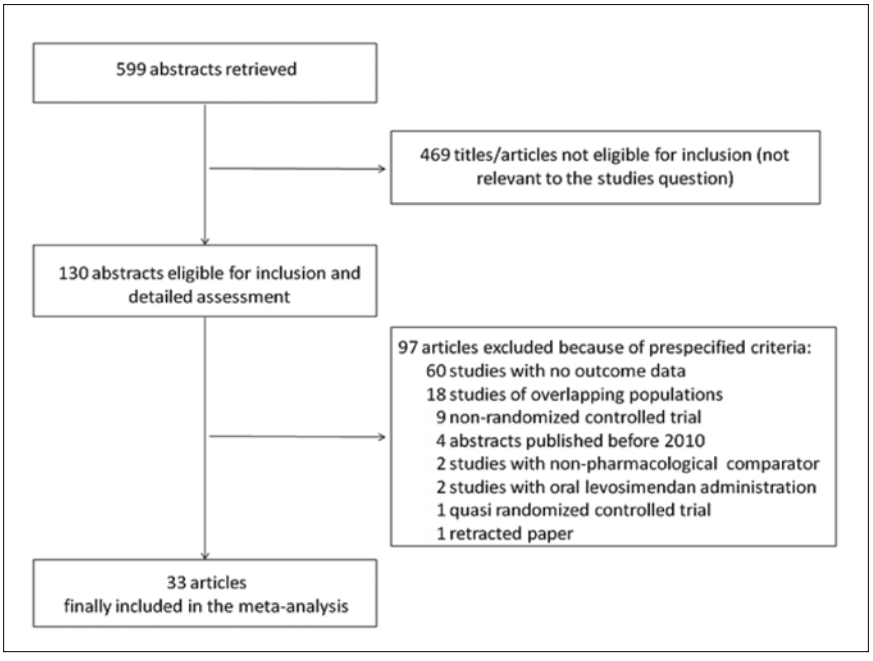

Figure 1 - *Flow diagram: selection process of included articles.*

Table 1 - *Description of the 33 studies included in the meta-analysis.*

Author	Year	Journal	Control	Setting	Setting details
Al-Shawaf E	2006	J Cardiothorac Vasc Anesth	Milrinone	Cardiac surgery	LCOS after CABG
Alvarez J	2005	Rev Esp Anestesiol Reanim	Dobutamine	Cardiac surgery	LCOS after cardiac surgery with CPB
Alvarez J	2006	Rev Esp Cardiol	Dobutamine	Cardiac surgery	LCOS after cardiac surgery with CPB
Barisin S	2004	J Cardiovasc Pharmacol	Placebo	Cardiac surgery	20 min before surgery OPCABG
Baysal A	2013	J Cardiothorac Vasc Anesth	Inotropes	Cardiac surgery	Cardiac surgery
Bonios MJ	2012	Int J Cardiol	Dobutamine	Cardiology	HF (end stage)
Bragadottir G	2013	Crit Care Med	Placebo	Cardiac surgery	Cardiac surgery
De Hert SG	2007	Anesth Analg	Milrinone	Cardiac surgery	Cardiac surgery with CPB
Flevari P	2006	Am J Cardiol	Placebo	Cardiology	HF (decompensated advanced)
Fuhrmann JT	2008	Crit Care Med	Enoximone	Cardiology	Patients with acute myocardial infarction and cardiogenic shock
Hou ZQ	2013	Cardiovasc Ther	Placebo	Cardiology	LVEF < 40 %
Iyisoy A	2010	Turk J Med Sci	Dobutamine	Cardiology	ADHF
Jarvela K	2008	J Cardiothorac Vasc Anesth	Placebo	Cardiac surgery	After induction in aortic valve surgery with severe aortic valve stenosis and LV hypertrophy
Kurt IH	2010	Heart Vessels	Standard of treatment	Cardiology	HF (NYHA class III-IV)
Lahtinen P	2011	Crit Care Med	Placebo	Cardiac surgery	Heart valve surgery
Leppikangas H	2008	Acta Anaesthesiol Scand	Placebo	Vascular surgery	Infrarenal abdominal aortic aneurysm
Levin R	2008	Rev Esp Cardiol	Dobutamine	Cardiac surgery	LCOS after CABG
Malfatto G	2012	J Cardiovasc Pharmacol	Furosemide	Cardiology	HF (chronic)
Mebazaa A	2007	JAMA	Dobutamine	Cardiology	ADHF
Moertl D	2005	Eur J Heart Fail	Pge1	Cardiology	HF (decompensated chronic)
Momeni M	2011	J Cardiothorac Vasc Anesth	Milrinone	Neonatal cardiac surgery	Cardiac surgery
Morelli A	2005	Intensive Care Med	Dobutamine	Sepsis	LV dysfunction post septic shock after 48 hours of conventional treatment
Morelli A	2010	Crit Care	Dobutamine	Septic shock	
Nijhawan N	1999	J Cardiovasc Pharmacol	Placebo	Cardiac surgery	ASA III-IV undergoing elective cardiac surgery
Packer M	2013	JACC Heart Fail	Placebo and standard HF treatment	Cardiology	Cardiology
Parissis JT	2006	Heart	Placebo	Cardiology	HF (NYHA III-IV and LVEF≤30 %)
Ricci Z	2012	Intensive Care Med	Standard inotropic management	Pediatric cardiac surgery	Cardiac surgery
Ristikankare A	2012	J Cardiothorac Vasc Anesth	Placebo	Cardiac surgery	Cardiothoracic surgery
Slawsky MT	2000	Circulation	Placebo	Cardiology	HF (NYHA class III-IV)
Tritapepe L	2009	Br J Anaesth	Placebo	Cardiac surgery	CABG
Yilmaz MB	2007	Cardiovasc Drugs Ther	Dobutamine	Cardiology	Worsening of HF
Yontar OC	2010	Arq Bras Cardiol	Dobutamine	Cardiology	HF (ischemic)
Zemljic G	2007	J Card Fail	Nothing	Cardiology	HF (advanced, waiting for heart transplantation)

LCOS = low cardiac output syndrome; CABG = coronary artery bypass grafting; OPCABG = off-pump coronary artery bypass grafting; CPB = cardiopulmonary bypass; HF = heart failure; ADHF = acute decompensated heart failure; NYHA = New York Heart Association; ASA = American Society of Anesthesiology Physical Classification System; LV = left ventricle; LVEF = left ventricular ejection fraction.

remaining articles are detailed in *Figure 1*. The list of the 97 major exclusions is available in the supplemental *Table S1*.

The 33 included trials randomized 3,879 patients (2,024 to levosimendan and 1,855 to control). Clinical heterogeneity was mostly due to setting, dose and control treatment (*Tables 1* and *2*). In details, 15 studies used levosimendan in a cardiological setting (decompensated heart failure, NYHA III-IV), 15 in cardiac surgery (two of these in pediatric patients), two studies were conducted in septic patients and one in vascular surgery patients. Twenty-

Table 2 - *Description of levosimendan administration in the 33 studies included in the meta-analysis.*

Author	Year	Levosimendan bolus (ug/kg)	Levosimendan continuous infusion (ug/kg/min)	Lenght of levosimendan infusion (hours)
Al-Shawaf E	2006	12	0.1-0.2	24
Alvarez J	2005	12	0.2	24
Alvarez J	2006	12	0.2	24
Barisin S	2004	12 or 24		
Baysal A	2013	6	0.1	24
Bonios MJ	2012		0.3	6 hours for 6 months
Bragadottir G	2013	12	0.1	
De Hert SG	2007		0.1	19 + 4
Flevari P	2006		0.1	24
Fuhrmann JT	2008	12	0.1 for 50 min then 0.2	50 min- other 23 hours
Hou ZQ	2013	12	0.05 or 0.1 or 0.2	24
Iyisoy A	2010	12	0.1	24
Jarvela K	2008		0.2	24
Kurt IH	2010	12	0.1	24
Lahtinen P	2011	24	0.2	24
Leppikangas H	2008	24	0.2	24
Levin R	2008	10	0.1	24
Malfatto G	2012		0.1-0.4	24
Mebazaa A	2007	12	0.2	24
Moertl D	2005	12	0.1	24
Momeni M	2011		0.05	48
Morelli A	2005		0.2	24
Morelli A	2010		0.2	24
Nijhawan N	1999	18 or 26	0.2 or 0.3	6
Packer M	2013	12 (6 if under treatment with other inotropic or vasodilating drugs)	0.1 (0.2 if tolerated 0.1-0.05 if not tolerated)	24
Parissis JT	2006	6	0.1-0.4	24
Ricci Z	2012		0.1	72
Ristikankare A	2012	12	0.2	24
Slawsky MT	2000	6	0.1-0.4	4-6
Tritapepe L	2009	24		
Yilmaz MB	2007		0.1-0.2	24
Yontar OC	2010	0.3-0.6	0.1-0.2	24
Zemljic G	2007	12	0.1	24

three authors administered a loading dose and thirty-one used a continuous infusion (twenty-one of them following bolus). Dose varied between 0.3 and 0.6 mcg/kg as intravenous bolus and between 0.05 and 0.4 mcg/kg/min as a continuous infusion. Thirteen studies (39% of all) used placebo as control while ten (30% of all) used dobutamine and 31% other comparators. Study quality appraisal indicated that studies were of variable quality (supplemental *Table S2*) with 13 (39%) of them having low risk of bias.

Quantitative data synthesis. Overall analysis on principal endpoint (*Figure 2*) showed that the use of levosimendan was associated with a significant reduction in the risk of RRT (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, RR = 0.52, 95% confidence interval (CI) 0.32 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included). Visual inspection of funnel plots did not identify a skewed or asymmetrical shape (*Figure 3*) and quantitative evaluation did not suggest a presence of publication bias, as measured by the Begg test (p = 0.3) and Egger test (p = 0.9). All but one studies reporting RRT data administered levosimendan as bolus and the reduction in the need for RRT was confirmed in these 12 studies (17 of 480 [3.5%] in the levosimendan group versus 37 of 415 [8.9%] in the control arm,

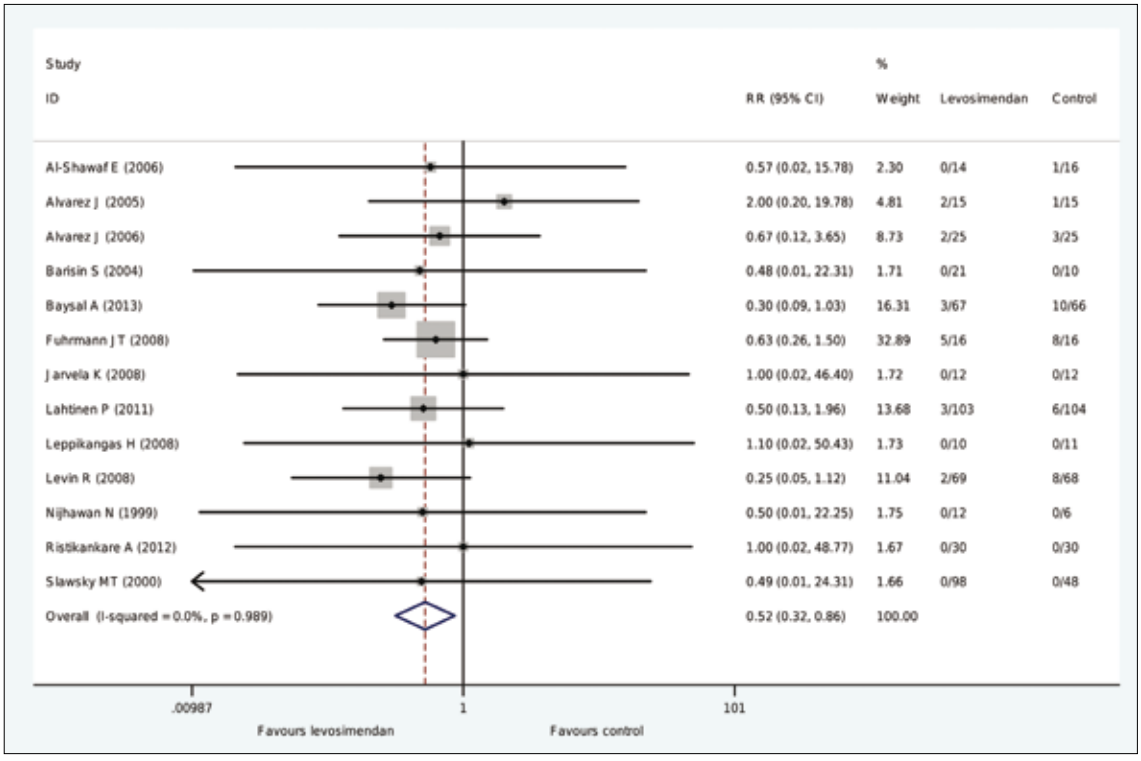

Figure 2 - *Forest plot for the risk of Renal Replacement Therapy. The use of levosimendan was associated with a significant reduction in the risk of RRT (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, RR = 0.52, 95% CI 0.32 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included).*
RR = risk ratio; CI = confidence interval.

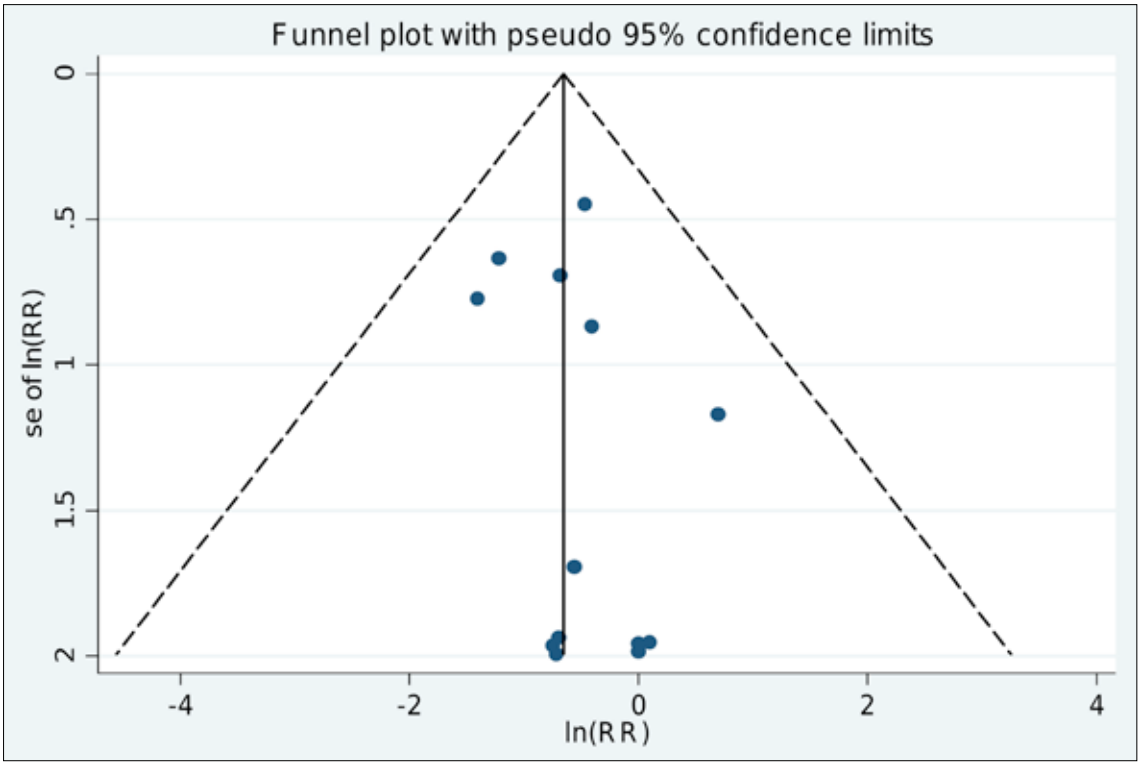

Figure 3 - *Funnel plot for the risk of Renal Replacement Therapy. RR = risk ratio; se = standard error.*

RR = 0.52, 95% CI 0.31 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%). All but two studies reporting RRT data administered levosimendan in the perioperative period and the reduction in the need for RRT was confirmed in these 11 studies (12 of 378 [3.2%] in the levosimendan group versus 29 of 363 [8%] in the control arm, RR = 0.48, 95% CI 0.26 to 0.89, p for effect = 0.02, p for heterogeneity = 0.9, I-square = 0%).

The analysis on secondary endpoints showed that the use of levosimendan was associated with a significant reduction in AKI risk (114 of 1,598 [7.1%] in the levosimendan group versus 143 of 1,529 [9.4%] in the control arm, RR = 0.79, 95% CI 0.63 to 0.99, p for effect = 0.048, p for heterogeneity = 0.8, I-square = 0%, with 19 studies included). This result was confirmed in the perioperative setting (39 of 411[9.5%] in the levosimendan arm versus 69 of 396 [17%] in the control arm, RR = 0.60, 95% CI 0.42 to 0.86, p for effect = 0.005, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included).

Glomerular filtration rate was better after randomization in patients receiving levosimendan (WMD = 8.08, 95% CI 3.35 to 12.80, p for effect = 0.001) in the 8 studies reporting it while no difference was found in peak serum creatinine values (WMD = -0.02, 95% CI -0.11 to 0.07, p for effect = 0.7) in the 15 studies reporting it.

Sensitivity analyses considering only data from studies with low risk of bias confirmed a trend towards reduction in the risk of RRT (3 of 238 [1.3%] in the levosi-

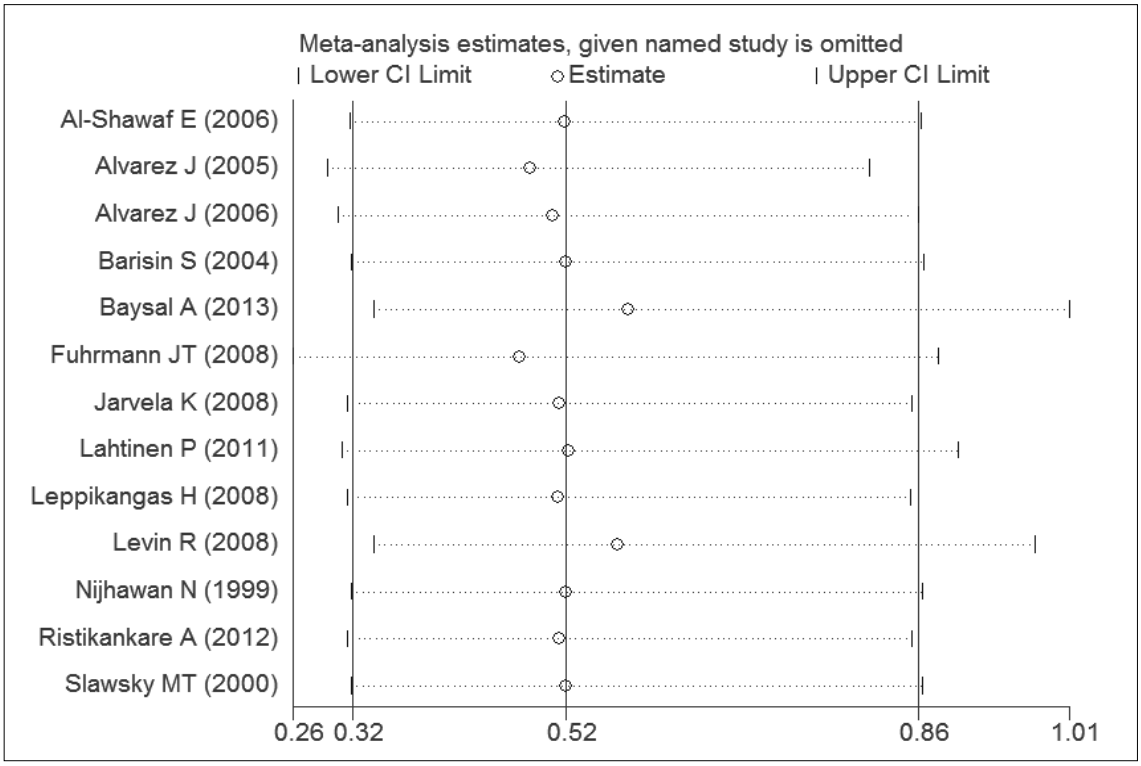

Figure 4 - *Analysis of the influence of levosimendan versus any control on the overall risk of Renal Replacement Therapy. This figure shows the influence of individual studies on the summary Risk Ratio. The middle vertical axis indicates the overall RR and the two vertical axes represent the 95 % CI.*
RR = risk ratio; CI = confidence interval.

mendan group versus 10 of 177 [5.6 %] in the control arm, RR = 0.41, 95 % CI 0.15 to 1.12, p for effect = 0.08, p for heterogeneity = 0.9, I-square = 0 %, with 6 studies included). When removing each single study from the meta-analysis to determine the influence of individual data sets to the pooled RRs, the corresponding pooled RRs were not altered (*Figure 4*) with the exception of the study of Baysal (9) (p = 0.054 when it was removed).

DISCUSSION

We performed a comprehensive and updated review of randomized controlled trials to investigate the role of levosimendan in the prevention and treatment of AKI in critically ill patients. The most important result of this study is the reduction in the need for RRT in levosimendan-treated critically ill patients.

In critically ill patients sepsis, major surgery (especially cardiac surgery) and acute decompensated heart failure are the most common triggers of AKI. The mainstay of prevention and treatment of AKI is the treatment of the cause of acute renal failure and withdrawal of nephrotoxic agents. If there are pre-renal or post-renal factors to be corrected, they must be identified. The optimization of hemodynamic conditions

should be the main goal of care and intravascular volume must be monitored and maintained in the normal range. In addition to the optimization of hemodynamic status and suspension of nephrotoxic agents no other pharmacological intervention has been shown to be effective in the prevention and treatment of AKI and a recent web based survey suggested that the15 interventions that might improve clinically relevant endpoints in critically ill patients with or at risk for AKI are supported by low levels of evidence.

Levosimendan [the (-) enantiomer of 4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenylhydrazonopropanedinitrile] is a new calcium enhancer with calcium-sensitizing activity. The mechanism of action that makes the levosimendan effective in preventing and treating kidney damage may be related to its beneficial action on the normalization of hemodynamic conditions.

The main mechanism of action of this drug is an increase in affinity of troponin C for calcium and therefore the stabilization of the conformation of troponin C. This mechanism of action translates into inotropic effect without determining increase intracellular cAMP or the intracellular calcium concentration at the doses used in clinical practice. This mechanism leads to acceleration of actin-myosin cross-bridge formation rate and deceleration of the dissociation rate. The binding becomes considerably weaker during diastole, when the intracellular calcium concentration is low, and this has a beneficial effect on the relaxation of myocardial muscle cells, resulting in improvement of diastolic function. The positive inotropic effect is obtained without impairing ventricular relaxation or increasing myocardial oxygen demand.

Levosimendan also has ancillary actions that may be responsible for the beneficial actions on renal function. Levosimendan indeed activates the opening of the ATP-sensitive sarcolemma K^+ channels of smooth muscle cells and myocytes determining their hyperpolarization with consequent vasodilatation, which may contribute to augmentation of renal perfusion and depression of central venous pressure. Central venous pressure is an independent predictor of glomerular filtration rate in patients with congestive heart failure (38). An important mechanism of action of levosimendan on renal function may be linked to its ownership of venodilation, which reduces the renal congestion and increases renal perfusion pressure. Administration of levosimendan also entails a reduction of circulating proinflammatory cytokines. This effect can be considered secondary to the inotropic and vasodilator properties of the drug, but may also result from the extracardiac downregulation of the synthesis of cytokines through transcription factors (39). In addition, the administration of this drug induces significant reduction of soluble mediators of apoptosis, such as Fas and Fas ligand (40, 41). Still, levosimendan improves endothelial function through downregulation of soluble cell adhesion molecules such as ICAM-1 and VCAM1 and regulates the mediators implicated in oxidative and nitrosative stress. Recent studies show that it can preserve organ function in acute and septic shock-induced myocardial depression via cooling down the oxidative burst of circulating cells (42, 43). Studies in animal models have yielded conflicting results regarding the effect of levosimendan on renal function. In fact, while in models of septic shock seem to outweigh the beneficial effects on hemodynamics, in animal models of ischemia reperfusion seems to prevail an effect of organ protection (44-49).

Bragadottir et al. (11) carried out a randomized, placebo-controlled clinical trial over the effects of levosimendan on the renal blood flow, the GFR, the renal oxygen

consumption and the renal oxygen supply/demand, in cardiac surgical setting. The main result of this paper is that levosimendan induces renal vasodilation, preferentially of pre-glomerular resistance vessels, increasing both renal blood flow and glomerular filtration rate, without impairing renal oxygen demand/supply relationship as demonstrated by the lack of effect on renal oxygen extraction. The careful analysis of the literature has identified 33 studies that evaluated the effect of levosimendan on renal function performed on critically ill patients in four different settings: cardiology (16 studies), cardiac surgery (15 studies), vascular surgery (1 study) and sepsis (2 studies). Although in most of them the impact of levosimendan on renal function was not the pre-planned primary outcome and most of them are individually statistically underpowered, many of them suggested a trend of benefit on renal function, and the pooled data analysis of 4,082 patients included in the meta-analysis suggests a beneficial effect of levosimendan on renal function including glomerular filtration rate, AKI as per author definition and RRT with sensitivity analyses confirming the validity of our findings.

The findings of our manuscript could be compared to those of three other papers. In a previous meta-analysis Landoni et al. highlighted the beneficial effects of levosimendan in critically ill patients (3). However, the authors did not investigate the renal outcomes and the search was updated at November 2010. A more recent meta-analysis (50) suggested for the first time a beneficial effect of levosimendan on AKI, but the study was limited to the cardiac surgery setting and to 529 patients. A recent consensus report (51) suggested a beneficial effect of levosimendan on renal outcomes but it was a systematic review of the literature without a meta-analytic approach.

The main limitation of the present meta-analysis is that several included RCTs were of suboptimal quality. Furthermore, traditional limitations of meta-analyses due to variations in the treatment regimens, in populations or major subgroups within trials, and in the conduct of the trials apply to this study. On top of that, great variability of clinical setting and a relative small number of studies analyzed for primary end point (RRT) should be acknowledged.

CONCLUSION

This meta-analysis shows that the use of levosimendan is associated with a significant reduction in incidence of RRT in critically ill patients. Since meta-analyses are hypothesis generating, large multicenter, randomized, placebo-control clinical trials designed to assess the role of levosimendan in the treatment of acute renal failure in critically ill patients are warranted.

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Cite this article as: Bove T, Matteazzi A, Belletti A, Paternoster G, Saleh O, Taddeo D, Dossi R, Greco T, Bradic N, Husedzinovic I, Nigro Neto C, Lomivorotov VV, Calabrò MG. Beneficial impact of levosimendan in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Heart, Lung and Vessels. 2015; 7(1): 35-46.

Source of Support: Nil. **Disclosures:** Dr. V. Lomivorotov has received modest speaker honoraria from Orion Pharma.