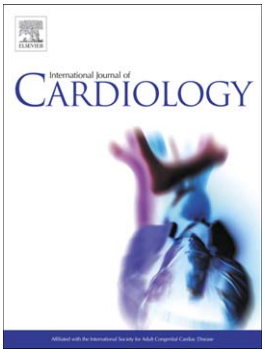

Levosimendan meta-analyses: Is there a pattern in the effect on mortality?

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Levosimendan meta-analyses: is there a pattern in the effect on mortality?

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Abstract

Background. Levosimendan is an inodilator developed for treatment of acute heart failure and other cardiac conditions where the use of an inodilator is considered appropriate. Levosimendan has been studied in different therapeutic settings including acutely decompensated chronic heart failure, advanced heart failure, right ventricular failure, cardiogenic shock, septic shock, and cardiac and non-cardiac surgery. This variety of data has been re-analysed in 25 meta-analyses from 15 different international research groups, based on different rationales to select the studies included.

Methods. We here review all previously published meta-analyses on levosimendan to determine any common denominators for its effects on patient mortality. In addition, we also perform a comparative meta-analysis of the six phase II and III randomized double-blind trials which were taken into consideration by the regulatory authorities for the purpose of introducing levosimendan into the market.

Results. Irrespective of clinical setting or comparator, all meta-analyses consistently show benefits for levosimendan, with lower relative risk (or odds ratio) for patient mortality. In 3/25 of the meta-analyses these beneficial trends did not reach statistical significance, while in 22/25 significance was reached. The relative risk is consistent overall, and very similar to that obtained in our own meta-analysis that considered only the 'regulatory' studies.

Conclusion. The existing meta-analyses, now based on a population of over 6,000 patients, provide the general message of significant benefits for levosimendan in terms of patient mortality. The weight of evidence is now clearly in favour of usefulness/efficacy of levosimendan, with data from multiple randomized trials and meta-analyses.

Key words: meta-analysis, mortality, heart failure, cardiac surgery, acute cardiac care, inodilator

Introduction

Levosimendan is a calcium sensitizer and ATP-dependent potassium channel opener [1] that was developed as an inodilating drug for use in the treatment of acute heart failure (AHF) or other cardiac situations where an inodilator is considered appropriate [2].

Over the last two decades, many studies have been conducted to determine the effects of levosimendan in different therapeutic settings [2], such as acutely decompensated chronic heart failure, advanced heart failure, right ventricular failure, and cardiogenic shock, and also in septic shock, and cardiac and non-cardiac surgery. In a search of PubMed on September 2015, 184 papers were found that describe the results of clinical trials of levosimendan in cardiology, cardiac surgery, and cardiac-anaesthesiology, and in the intensive care setting. In the latest 20 years levosimendan has been compared to several other drugs, such as dobutamine, milrinone, and enoximone, as well as alone or as an addition to best standard of care. The comparison to placebo has been obscured by the fact that studies allowed for other inotropes or vasoactive drugs to be used either as best standard of care or as rescue drugs in both arms. Among these studies, six are the Phase II and III randomized double-blind trials that were included in the regulatory proceedings for the registration of *i.v.* levosimendan in Europe and Latin America.

To date, this plethora of information has been re-analysed in 25 meta-analyses by 16 different international research groups. These analyses have been also different in terms of clinical settings in which levosimendan was considered, selection of comparators, endpoints measured, and statistical tools used. Each research group also used different rationales to select the studies to be included in their meta-analyses, with some being more strict, and other more comprehensive.

As the number of meta-analyses in the medical literature is overall growing [3], we decided to review all of the published meta-analyses on levosimendan to determine any common denominator that can shed light on the effects of this drug.

Methods

Two of the authors (PP, MK) independently searched PubMed for <'meta-analysis' AND 'levosimendan'> between Nov 1995 and Nov 2015, and obtained 37 hits. From this list, 12 reports were considered irrelevant because they were either pooled analyses, letters, editorials, comments, or reviews. The remaining 25 meta-analyses [4-28] were analysed systematically for their clinical setting, number of studied, endpoints, statistical tools, results, and finally, statistical significance of the conclusions. The identity and geographical locations of the research groups were also collected, to define multiple meta-analyses from the same groups.

We also performed an additional comparative meta-analysis on the effect of levosimendan on patient mortality through the selection of only the six Phase II and III randomized double-blind trials that were filed by the originator and taken into consideration by the regulatory authorities for the purpose of introducing levosimendan into the market [29-34]. The rationale of this study selection is based on the fact that only such studies are usually considered as fitting the approved settings for the use of a drug. The data on outcome extracted from those papers were analysed with RevMan 5.2 (freeware available from The Cochrane Collaboration) [35]. The pooled statistics were calculated using Cochran-Mantel-Haenszel tests, controlling for each study.

Results

The 25 meta-analyses considered in this review are listed in chronological order in Table 1. For each of these studies, this includes year of publication, name of the first author, country of origin of the research group (in a few cases there were multiple countries), clinical settings, number of studies included, comparator(s) used in the studies, main end-point, result of the meta-analysis on that main endpoint expressed as relative risk if not otherwise specified (also odds ratio, risk ratio, risk difference, and z-test value were in fact used), and finally, statistical significance of the main result.

The authorship of these 25 meta-analyses was divided among 16 research groups from eigth countries as: eigth analyses from Italy (from one research group)[6,7,9,12,18,20,21,25, 27], five from China (from five different research groups)[14,16,22,24, 28], three from the U.K. (from two research groups)[4,5,11], and one each from Brazil [8], Australia [10], Spain [13] U.S.A [15], and The Netherlands [19]. Finally, three meta-analyses were published by international research groups with authorship scattered across two or more countries [17,23,26].

In further detail, five of these 25 meta-analyses considered all of the clinical trials on levosimendan [7, 12,14,19, 27], five focused on the effects of levosimendan in AHF [4,5,8,10, 24], four on the effects of repetitive infusions of levosimendan in advanced chronic heart failure (AdHF)[17,18,22,26], ten on the peri-operative uses of levosimendan in cardiac surgery [6,9,11,13,15,16,20,21,23,28] (two of them describing mainly the effects of the drug on the kidney [16,20]), and finally one on sepsis and septic shock [25].

Finally, we collected the data from the the six phase II and III randomized double-blind trials on levosimendsan [29-34] that were filed by the originator and taken into consideration by the regulatory authorities for the purpose of introducing levosimendan into the market. These trials included the dose-finding study by Slawsky et al. [29], the dose-escalation and

withdrawal study by Nieminen et al. [30], the LIDO study by Follath et al. (vs. dobutamine) [31], the RUSSLAN study by Moiseyev et al. (vs. placebo) [32], the SURVIVE study by Mebazaa et al. (vs. dobutamine) [33], and the REVIVE (I and II) study by Packer et al. (vs. placebo on top of standard of care) [34].

When we performed a comparative meta-analysis on the effects of levosimendan on patient mortality with the selection of only these six studies (Figure 1), we obtained a risk reduction of 0.82 (95% CI = 0.67; 1.01) which is in line with all of the meta-analyses included in the present review, although this was only showing a strong trend for a difference ($p = 0.054$).

Meta-analyses for levosimendan in all settings

Five meta-analyses considered all of the clinical trials on levosimendan in all settings [7, 12,14,19, 27]. One of them was performed by a research group in the Nederlands [19], one in China [14], and three by an Italian group [7, 12, 27]. All five describe an overall reduction of risk of 20% as it regards mortality, with a statistical significance reached in the Italian and Chinese analyses, but not in the work by the Dutch group.

In details, the analysis by Landoni et al. [7] was based on 3,350 patients from 27 randomised studies for different indications. Levosimendan was associated with significant reduction in patient mortality, as 17.6% (333/1,893) vs. 22.4% (326/1,457) in the levosimendan and control groups, respectively, for an odds ratio of 0.74 (95% confidence interval 0.62-0.89), at a significance of $p=0.001$. With levosimendan, myocardial infarction was seen significatly less often, and hypotension significantly more often.

In the more recent analysis by Landoni et al. [12], data from 5,480 patients in 45 studies were included. The overall mortality rate was 17,4% (507/2,915) in levosimendan-treated patients and 23.3% (598 /2,565) in the control group, for a risk ratio of 0.80 (95% CI, 0.72-

0.89; p <0.001). Reduction in mortality was confirmed in studies with placebo or dobutamine as a comparator and in studies performed in cardiac surgery or cardiology. Length of hospital stay was reduced in the levosimendan group (weighted mean difference –1.31; 95% CI, –1.95- –0.31; p = 0.007).

The analysis by Huang et al. [14] was performed with randomized studies to compare the efficacy of levosimendan and dobutamine. Data from a total of 3,052 patients from 22 trials were included. The use of levosimendan was associated with a significant reduction in mortality, as 19.6% (269/1,373) vs. 25.7% (328/1, 278), for a risk ratio of 0.81 (95% CI, 0.70–0.92; p =0.002). The benefit was found in the subgroups of cardiac surgery, ischemic heart failure, and concomitant β-blocker therapy.

Koster et al. [19] included data from 6,688 patients in 49 trials in their analysis. One trial was considered as having 'low risk' of bias and nine trials (representing 2,490 patients) as 'lower risk' of bias. The pooling of all trials that included heterogenous populations was considered inappropriate. When these authors pooled 30 trials that included critically ill patients who did not have cardiac surgery, a reduction in mortality was shown (risk ratio, 0.83; 95% CI, 0.59–0.97). However, when only the trials with lower risk of bias were considered, no significant difference was seen (risk ratio, 0.83; 95% CI, 0.48–1.55). Conversely, their conventional meta-analysis of the14 trials that included cardiac surgery patients showed significant reduction in mortality with levosimendan (risk ratio, 0.52; 95 % CI, 0.37–0.73), while the same analysis limited to the studies considered at lower risk of bias did not reach significance (risk ratio, 1.02; 95 % CI 0.48–2.16).

Finally, Belletti et al. [27] published an extensive meta-analysis of 177 randomized trials on the effect of inotropes and vasopressors on mortality. Among the subsetting analysed, the authors pooled 48 studies on levosimendan and showed a significant reduction of mortality (risk ratio, 0,80; 95 % CI 0.68–0.94; p=0.008).

Meta-analyses for levosimendan in acute heart failure

Five meta-analyses focused on the effects of levosimendan in AHF [4,5,8,10, 24]. One of them was performed by a Brazilian research group [8], one in the United Kingdom [10], and one in China [24]. Finally, two were performed over 10 years ago by a group in the United Kingdom and are cited here only for the sake of completeness. All five describe an overall reduction of risk as it regards mortality, with a statistical significance reached in the U.K. and Chinese analyses, but not in the work by the Brazilian group.

In details, Ribeiro et al. [8] included data from 19 studies in their analysis. In the comparison with placebo (7 trials, 1,652 patients), the RR for overall mortality was 0.87 (95% CI, 0.65-1.18) although this was not significant. In comparison with dobutamine (10 trials, 2,067 patients), the relative risk was 0.87 (95% CI, 0.75-1.02), which again was not significant. Three studies reported data on length of hospital stay. Levosimendan, when compared to placebo and dobutamine, showed decreases of 2.27 and 2.30 days, respectively ($p < 0.05$ for both).

Delaney et al. [10] included data from a total of 3,650 patients from 19 trials. These authors did not find a significant reduction in mortality with levosimendan compared with placebo, odds ratio = 0.83 (95% CI 0.62–1.10; p=0.20). The result was, however, significantly favourable against dobutamine, odds ratio = 0.75 (95% CI, 0.61–0.92; p=0.005). Levosimendan was associated with improvements in hemodynamic parameters when compared with both placebo and dobutamine.

Gong et al. [24] included data from 5,349 patients in 25 trials. In the total population, levosimendan significantly reduced mortality, as 17.1% vs. 20.8% (risk ratio, 0.84; 95% CI, 0.75-0.94). Compared with dobutamine, levosimendan was also associated with a significant reduction in mortality at the final follow up (risk ratio=0.86; 95% CI, 0.76-0.97; p=0.02).

Furthermore, compared with placebo, there was a significant reduction in long-term (> 6-months) mortality (risk ratio=0.34; 95% CI, 0.15- 0.76; p=0.009). Levosimendan was also associated with significant improvements in hemodynamic and echocardiographic-derived parameters, although it increased the risks of extrasystoles, hypotension, and headache or migraine. One advantage with this meta-analysis is that the effects of levosimendan on short-, mid- and long-term mortality are presented separately. However, these findings by Gong et al. [24] have to be interpreted with some caution, as it appears that they included the SURVIVE study data [33] twice in the analysis.

For the sake of completeness we cite two early meta-analyses by Cleland et al. [4,5], in which the few trials completed at that time were pooled (2004, 2006, respectively). These papers describe early meta-analyses on levosimendan, although their results are no longer directly relevant as they have been superceded by further meta-analyses.

Meta-analyses for intermittent use of levosimendan in advanced chronic heart failure

Four meta-analyses focused on the effects of repetitive infusions of levosimendan in advanced chronic heart failure [17,18,22,26]. One was perfomed by an Italian group [18], one by an European panel of experts [17], and one by a Chinese group [22]. Finally, one was a cooperation between an Italian and a Finnish group [26]. All four describe a statistically significant overall reduction of risk as it regards mortality.

In details, the meta-analyses produced by Nieminen et al. [17], Silvetti et al. [18], and Silvetti and Nieminen [26] are considering the studies in which the effects of intermittent or repetitive levosimendan treatment on AdHF patients were described . Of the 10 studies found in the literature, Nieminen et al. [17], and Silvetti et al. [18] selected groups of 7 studies each, which were not fully overlapping. Nieminen et al. [17] considered a total of 345 patients and showed that levosimendan was associated with a significant reduction in mortality (risk ratio,

0.47; 95% CI, 0.32–0.70; p = 0.0002). Silvetti et al. [18] also showed that levosimendan was associated with a significant reduction in mortality, here at the longest follow-up available, as 19 % (32/168) vs. 35% (46/133) in the control arm, with relative risk = 0.55 (95 % CI 0.37–0.84; p = 0.005). Both of these meta-analyses were, however, criticized for their selection of studies [36].

When new studies became available a corrected and updated meta-analysis was produced [18] in which a total of 438 adult patients on intermittent levosimendan treatment in a cardiological setting were included, with an average follow-up period of 8 ± 3.8 months. The use of levosimendan was associated with a significant reduction in mortality at the longest follow-up available, as 16 % (41/ 257) in the levosimendan group vs. 21.5% (39/ 181) in the control group (OR, 0.54; 95 % CI, 0.32–0.91; p for effect, 0.02; p for heterogeneity, 0.64; I2, 0 %).

The meta-analysis by Yi et al. [22] also consisted of studies with repeated levosimendan infusions. Here, levosimendan significantly reduced mortality, as 10.2 % (23/226) vs. 26.8 % (53/198) in the control arm (relative risk, 0.40; 95 % CI 0.26–0.63; p < 0.0001).

Meta-analyses for levosimendan in surgery

Ten meta-analyses focus on the effects on the peri-operative uses of levosimendan in cardiac surgery [6,9,11,13,15,16,20,21,23,28]. Four were performed by an Italian group [6, 9, 20, 21], one by a group in the U.K. [11], one in the U.S.A. [15], one in Spain [13], two in China [16, 28], and one was published as a cooperation of various interational research groups [23]. The eigth meta-analyses describing an effect on mortality [6,9,11,13,15,21,23,28] concur in a statistically significant overall reduction of risk. Also the two which describe renal effects [16,20] concur in a statistically significant overall reduction of risk.

In details, Zangrillo et al. [6] performed the first meta-analysis in the cardiac surgery field on a total of 139 patients from five studies. The endpoint was postoperative peak cardiac troponin release. Levosimendan was found to have significantly lower peak release than the comparators, with a weighted mean difference of 2.5 ng/dL (range, 1.14-3.86; p = 0.0003).

When Landoni et al. [9] updated the meta-analysis by Zangrillo et al [6], 440 patients from 10 studies were included . Levosimendan was associated with a significant reduction in postoperative mortality, as 4.7% (11/235) in the levosimendan group *versus* 12.7% (26/205) in the control arm (OR, 0.35; 95% CI, 0.18-0.71; p = 0.003).

In their meta-analysis, Maharay et al. [11] included 729 patients from 17 studies. Levosimendan was associated with mortality reduction after coronary revascularization, as 4.9% (19/386) *versus* 11.4% (39/343) in the control arm (OR, 0.40; 95% CI, 0.21-0.76; p = 0.005). Levosimendan also significantly improved cardiac index, shortened intensive care unit stay, and reduced rate of atrial fibrillation and magnitude of postoperative troponin I release.

Hernandez et al. [13] included 654 patients from 13 studies in their analysis (published in Spanish). Levosimendan was associated with a significant reduction in postoperative mortality, as 5.2% (18/344) *versus* 12.6% (39/310) in the control arm (OR, 0.36; 95% CI, 0.20-0.64; p = 0.001).

Harrison et al. [15] included 1,155 patients from 14 studies in their analysis. Here, patients with a mean left ventricular ejection fraction (LVEF) <40% were defined as low-EF. The pooled data demonstrated reduction in mortality with levosimendan, as risk difference (RD) −4.2% (95% CI, −7.2%, −1.1%; p = 0.008). Subgroup analysis showed that this benefit was confined to the low-EF studies, as RD −7.0% (95% CI, −11.0%, −3.1%; p <0.001). No benefit was observed in the preserved-EF subgroup. Significant reductions were also seen in the need for dialysis, as RD −4.9% (95% CI, −8.2%, −1.6%; p = 0.003), for postoperative

atrial fibrillation, as RD –8.1% (95% CI, –13.3%, –3.0%; p = 0.002) and for myocardial injury, as RD –5.0% (95% CI, –8.3%, –1.7%; p = 0.003).

Niu et al. [16] included data from 529 patients in five trials to demonstrate that levosimendan is associated with a lower incidence of acute kidney injury (AKI). Indeed, only 9.5% (25/264) in the levosimendan group, compared to 19.2% (51/265) in the control group, developed AKI (OR, 0.44; 95% CI, 0.22-0.85; p = 0.02).

Similarly, Bove et al. [20] included 3,879 patients from 33 trials in a meta-analysis evaluating the effect of levosimendan on the need of renal replacement therapy. The incidence of renal replacement therapy was 3.5% (17/492) in the levosimendan group *versus* 8.7% (37/427) in the control group (RR, 0.52; 95% CI, 0.32-0.86; p = 0.01). AKI (as per author definition) was also examined, where levosimendan was associated with lower incidence of 7.1% (114/1598) *versus* 9.4% (143/1529) in the control group (RR, 0.79; 95% CI, 0.63-0.99; p = 0.048).

The objective of the study by Greco et al. [21] was to conduct a Bayesian network meta-analysis on the effects of inodilators on survival in adult cardiac surgery patients, and to compare and rank these drugs, as they had not been adequately compared in head-to-head trials. The following drugs were evaluated: dobutamine, enoximone, levosimendan, and milrinone. The data were based on 2,647 patients in 46 trials. Only the use of levosimendan was associated with decrease in mortality when compared with placebo (posterior mean of OR, 0.48; 95% CI, 0.28-0.80). The posterior distribution of the probability for each inodilator to be the best and the worst drug showed that levosimendan was the best agent for the improvement of patient survival after cardiac surgery (90.8%, as posterior distribution derived by Bayesian hierarchical model with Markov Chain Monte Carlo algorithm).

Lim et al. [23] considered a total of 965 patients in 14 studies. Here, levosimendan significantly reduced early patient mortality, although as for the Harrison analysis [15], the

favourable data were driven by the studies with low preoperative EF, as 4.2% (15/360) *versus* 9.5% (34/357) (OR, 0.41; 95% CI, 0.24-0.77; p = 0.004). In the levosimendan group, postoperative acute renal failure was less frequent, and intensive care unit stay was shorter.

Finally, Zhou et al. [28] published a meta-analysis of 13 trials with a total of 1,345 study patients, in which levosimendan was compared to control of the incidence of postoperative AKI, renal replacement therapy, duration of mechanical ventilation, intensive care unit stay, and post-operative moratlity. Levosimendan was statistically superior in all parameters. As it regards mortality, OR was as low as 0.41 (95% CI 0,27-0,62; p<0.002). Postoperative AKIU was also reduced, with OR=0.51 (95% CI 0,34-0,76, P= 0.001).

Meta-analyses for levosimendan in sepsis

In the meta-analysis by Zangrillo et al. [25], 246 patients were included from seven studies. Levosimendan was associated with significantly reduced patient mortality compared with standard inotropic therapy, as 47% (59/125) *versus* 61% (74/121) (risk ratio, 0.79; 95% CI, 0.63-0.98; p = 0.03). In the levosimendan group, blood lactate was significantly lower and cardiac index was significantly higher. No differences in mean arterial pressure and norepinephrine use were observed.

Other pooled analyses and meta-analyses

For the sake of completeness, we also cite here the study of Kivikko et al. [37], which is a pooled analysis (*i.e.*, not a meta-analysis) of six randomized levosimendan trials, with a total of 3,004 patients, of which 1,700 were treated with levosimendan and 226 with both levosimendan and sulfonylureas. Here, the authors concluded that concomitant use of sulfonylureas and levosimendan does not attenuate the hemodynamic or other effects of levosimendan. Among the data, there was a nonsignificant reduction in mortality in the

levosimendan arms (with and without concomitant sulfonylureas), as 9.9% (169/1700) *versus* 11.3% (147/1304) for the comparators.

Again for the sake of completeness we cite also a meta-analysis by Qiao et al. [38], published very recently, in which levosimendan was found to be associated with a reduction in postoperative mortality of high-risk surgical patients with multi organ dysfunction syndrome (4.7% in the levosimendan group vs 12.7% in the control; odds ratio of 0.35 [0.18-0.71], p for effect 0.003; 440 patients included).

Discussion

The general trend of the meta-analyses we have evaluated here was to include only published data from randomized double-blind studies. In some cases, data published as abstracts were considered. All meta-analyses that we scrutinized here duly evaluated the internal validity and risk of bias of the trials that they included, according to the Cochrane Collaboration methods [39], with divergences resolved by consensus between the authors responsible for the selection. Publication bias is commonly assessed by visually inspecting funnel plots, or by analytical appraisal based on the Begg adjusted-rank correlation test [40] and Egger's linear regression test [41]. In several cases, sensitivity analyses were performed by sequentially removing each study and re-analyzing the remaining dataset (producing a new analysis for each study removed), and by analysis of data from studies with moderate and low risk of biasSome exceptions were justified on a case-to-case basis.

Koster et al [19] criticized the other meta-analyses because the bias levels of the studies is generally acknowledged *a posteriori* but not used *a priori* as a parameter for the selection of the publications to be included.

It can be noted that nearly all of the meta-analyses included sub-analyses of smaller sets of studies to address specific questions, in terms of settings, comparators, end-points, adverse

events, and others. As an example, the meta-analysis of Landoni et al. [12] considered 45 clinical trials, but included also sub-analyses for the cardiology and cardiac surgery settings, for dobutamine or placebo as comparators, and for use of a bolus dose of levosimendan or not. In terms of the comparators, many meta-analyses considered these separately, in terms of the studies in which levosimendan was compared to an active drug (*e.g.* dobutamine, milrinone, enoximone), and the studies where the comparator was placebo. In this regard, it must also be noted that due to the severity of the patient status, in the majority of cases active treatment and placebo were given on top of the best standard of care, or 'rescue' inotropic therapy was allowed (mainly inotropes or vasopressors). Thus the definition of 'placebo' as the control can vary from study to study, and from meta-analysis to meta-analysis.

Our meta-analysis on the effect of levosimendan on patient mortality incorporated only the six phase II and III randomized double-blind trials which were included in the regulatory registration proceedings for levosimendan. It is worth noting that the RR obtained was very similar to those provided by all of the other meta-analyses considered in this review, albeit for only borderline significance.

As it regards meta-analyses focused on the use od levosimendan in peri-operative settings, it has to be mentioned that there may be substantial differences in the pathophysiology of myocardial dysfunction (*e.g.* LV vs. RV, or ischemia vs. load) in different type of surgical procedure (*e.g.* all cardiac surgeries, just valve procedures, just CABG, etc.). Many of the meta-analyses described in this text do consider separately the studies on low EF patients from the high EF ones (e.g. the meta-analysis by Harrison et al. [15]).

At the moment, several studies on levosimendan are still ongoing. In the cardiosurgical field, data from the LICORN, LEVO-CTS and LEVO-HSR studies (for a total of >1,500 patients) are expected in 2016-17 [42]. In the cardiac field, data from the LION-HEART,

LAICA, and ELEVATE studies (for a total of >250 patients) are also expected in 2016 [17]. In addition, the LeoPARDS study (516 patients) will shed some light on the effects of levosimendan in sepsis [43]. All in all, several studies that include a total of over 2,250 patients are ongoing, and thus new or updated meta-analyses will probably be performed which could strengthen the evidence of survival benefits by levosimendan.

Conclusions

We have reviewed 25 meta-analyses on levosimendan, by 16 different research groups, and found that these have consistently showed benefits for levosimendan, with lower relative risk (or odds ratio) in the key endpoint of patient mortality. In 3/25 of these meta-analyses these beneficial signs did not reach statistical significance, while in 22/25, significance was demonstrated. The RR overall is relatively consistent, and very similar to that obtained in our meta-analysis that considered only the regulatory studies. All in all, the existing meta-analyses have been based on a population of over 6,000 patients, and the general trend is towards significant benefits. It thus appears that the weight of evidence is in favour of the usefulness/efficacy of levosimendan, with data from multiple randomized trials and meta-analyses.

Levosimendan can thus be differentiated from other hemodynamically active drugs used in the same settings [44]. An overall worse prognosis in the mid-term to long-term has indeed been associated with the use of dobutamine and PDE inhibitors in two focused meta-analyses by Tacon et al. [45] and Nony et al. [46], respectively. These authors concluded that dobutamine and PDE inhibitors do not provide any benefits in terms of patient survival. It appears thus wrong to consider ‘inotropes’ or ‘inodilators’ as a unique family of drugs with the same pattern of efficacy and safety.

Author contributions

PP and MK independently performed the preliminary searches for relevant publications. All of the authors contributed substantially to discussions of the existing literature, and reviewed the manuscript before submission.

Declaration of interest

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Figure legend

Figure 1. Effect of levosimendan on survival. Meta-analysis of the results of the phase II and III clinical trials considered in the regulatory process. These trials included the dose-finding study by Slawsky et al. [29], the dose-escalation and withdrawal study by Nieminen et al. [30], the LIDO study by Follath et al. [31], the RUSSLAN study by Moiseyev et al. [32], the SURVIVE study by Mebazaa et al. [33], and the REVIVE (I and II) study by Packer et al. [34]. #Pooled statistics was calculated using the Cochran-Mante-Haenszel test, controlling for the study.

References

1. Papp Z, Édes I, Fruhwald S, De Hert SG, Salmenperä M, Leppikangas H, Mebazaa A, Landoni G, Grossini E, Caimmi P, Morelli A, Guarracino F, Schwinger RH, Meyer S, Algotsson L, Wikström BG, Jörgensen K, Filippatos G, Parissis JT, González MJ, Parkhomenko A, Yilmaz MB, Kivikko M, Pollesello P, Follath F. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol. 2012;159(2):82-7.
2. Nieminen MS, Fruhwald S, Heunks LM, Suominen PK, Gordon AC, Kivikko M, Pollesello P. Levosimendan: current data, clinical use and future development. Heart Lung Vessel. 2013;5(4):227-45.
3. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. Heart Lung Vessel. 2013;5(4):219-25.
4. Cleland JG, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, Coletta AP. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail. 2004;6(4):501-8.
5. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail. 2006;8(1):105-10.
6. Zangrillo A, Biondi-Zoccai G, Mizzi A, Bruno G, Bignami E, Gerli C, De Santis V, Tritapepe L, Landoni G. Levosimendan reduces cardiac troponin release after cardiac surgery: a meta-analysis of randomized controlled studies. J Cardiothorac Vasc Anesth. 2009;23(4):474-8.

7. Landoni G, Mizzi A, Biondi-Zoccai G, Bignami E, Prati P, Ajello V, Marino G, Guarracino F, Zangrillo A. Levosimendan reduces mortality in critically ill patients. A meta-analysis of randomized controlled studies. Minerva Anestesiol. 2010;76(4):276-86.
8. Ribeiro RA, Rohde LE, Polanczyk CA. [Levosimendan in acute decompensated heart failure: systematic review and meta-analysis]. Arq Bras Cardiol. 2010;95(2):230-7.
9. Landoni G, Mizzi A, Biondi-Zoccai G, Bruno G, Bignami E, Corno L, Zambon M, Gerli C, Zangrillo A. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2010;24(1):51-7.
10. Delaney A, Bradford C, McCaffrey J, Bagshaw SM, Lee R. Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. Int J Cardiol. 2010;138(3):281-9.
11. Maharaj R, Metaxa V. Levosimendan and mortality after coronary revascularisation: a meta-analysis of randomised controlled trials. Crit Care. 2011;15(3):R140.
12. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634-46.
13. Hernández A, Miranda A, Parada A. [Levosimendan reduces mortality in cardiac surgery: a systematic review and meta-analysis]. Rev Esp Anestesiol Reanim. 2012;59(1):6-11.
14. Huang X, Lei S, Zhu MF, Jiang RL, Huang LQ, Xia GL, Zhi YH. Levosimendan versus dobutamine in critically ill patients: a meta-analysis of randomized controlled trials. J Zhejiang Univ Sci B. 2013;14(5):400-15
15. Harrison RW, Hasselblad V, Mehta RH, Levin R, Harrington RA, Alexander JH. Effect of Levosimendan on Survival and Adverse Events After Cardiac Surgery: A Meta-analysis. J Cardiothorac Vasc Anesth. 2013;27(6):1224-32

16. Niu ZZ, Wu SM, Sun WY, Hou WM, Chi YF. Perioperative levosimendan therapy is associated with a lower incidence of acute kidney injury after cardiac surgery: a meta-analysis. J Cardiovasc Pharmacol. 2014;63(2):107-12

17. Nieminen MS, Altenberger J, Ben-Gal T, Böhmer A, Comin-Colet J, Dickstein K, Edes I, Fedele F, Fonseca C, García-González MJ, Giannakoulas G, Iakobishvili Z, Jääskeläinen P, Karavidas A, Kettner J, Kivikko M, Lund LH, Matskeplishvili ST, Metra M, Morandi F, Oliva F, Parkhomenko A, Parissis J, Pollesello P, Pölzl G, Schwinger RH, Segovia J, Seidel M, Vrtovec B, Wikström G. Repetitive use of levosimendan for treatment of chronic advanced heart failure: clinical evidence, practical considerations, and perspectives: an expert panel consensus. Int J Cardiol. 2014;174(2):360-7.

18. Silvetti S, Greco T, Di Prima AL, Mucchetti M, de Lurdes CM, Pasin L, Scandroglio M, Landoni G, Zangrillo A. Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials. Clin Res Cardiol. 2014;103(7):505-13.

19. Koster G, Wetterslev J, Gluud C, Zijlstra JG, Scheeren TW, van der Horst IC, Keus F. Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2015;41(2):203-21.

20. 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 Vessel. 2015;7(1):35-46.

21. Greco T, Calabrò MG, Covello RD, Greco M, Pasin L, Morelli A, Landoni G, Zangrillo A. A Bayesian network meta-analysis on the effect of inodilatory agents on mortality. Br J Anaesth. 2015;114(5):746-56.

22. Yi GY, Li JX, Zhang J, Niu LL, Zhang CY. Repetitive infusion of levosimendan in patients with chronic heart failure: a meta-analysis. Med Sci Monit. 2015;21:895-901.

23. Lim JY, Deo SV, Rababa'h A, Altarabsheh SE, Cho YH, Hang D, McGraw M, Avery EG, Markowitz AH, Park SJ. Levosimendan Reduces Mortality in Adults with Left Ventricular Dysfunction Undergoing Cardiac Surgery: A Systematic Review and Meta-analysis. J Card Surg. 2015;30(7):547-54.

24. Gong B, Li Z, Yat Wong PC. Levosimendan Treatment for Heart Failure: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth. 2015 Mar 26. pii: S1053-0770(15)00186-X. doi: 10.1053/j.jvca.2015.03.023. [Epub ahead of print]

25. Zangrillo A, Putzu A, Monaco F, Oriani A, Frau G, De Luca M, Di Tomasso N, Bignami E, Lomivorotov V, Likhvantsev V, Landoni G. Levosimendan reduces mortality in patients with severe sepsis and septic shock: A meta-analysis of randomized trials. J Crit Care. 2015 May 29. pii: S0883-9441(15)00319-6. doi: 10.1016/j.jcrc.2015.05.017. [Epub ahead of print]

26. Silvetti S., Nieminen MS. Repeated or intermittent levosimendan treatment in advanced heart failure: an updated meta-analysis. Int J Cardiol. 2016;202:138–143.

27. Belletti A, Castro ML, Silvetti S, Greco T, Biondi-Zoccai G, Pasin L, Zangrillo A, Landoni G. The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. Br J Anaesth. 2015;115(5):656-75.

28. Zhou C, Gong J, Chen D, Wang W, Liu M, Liu B. Levosimendan for Prevention of Acute Kidney Injury After Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials. Am J Kidney Dis. 2015 Oct 27. doi: 10.1053/j.ajkd.2015.09.015

29. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute

hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation. 2000;102(18):2222-7

30. Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V, Nyquist O, Remme WJ. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol. 2000;36(6):1903-12.

31. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002;360(9328):196-202.

32. Moiseyev VS, Põder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI; RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 2002 Sep;23(18):1422-32.

33. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Põder P, Kivikko M; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007 May 2;297(17):1883-91.

34. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013 Apr;1(2):103-11

35. Review manager (RevMan) [computer program] version 5.0. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration; 2008 [Available at: http://ims.cochrane.org/revman . Accessed 10 September, 2015].

36. De Luca L. Inotropic agents in advanced heart failure: repetita iuvant? Int J Cardiol. 2014;176(1):6-7

37. Kivikko M, Nieminen MS, Pollesello P, Pohjanjousi P, Colucci WS, Teerlink JR, Mebazaa A. The clinical effects of levosimendan are not attenuated by sulfonylureas. Scand Cardiovasc J. 2012;46(6):330-8.

38. Qiao L, Xu C, Li X, Li F, Liu W. Heart calcium sensitizer on morbidity and mortality of high-risk surgical patients with MODS: systematic review and meta-analysis. Int J Clin Exp Med 2015;8(10):17712-17720.

39. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0, updated March 2011. http://www.cochranehandbook.org (4 January 2011)

40. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088-1101

41. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634

42. Toller W, Heringlake M, Guarracino F, Algotsson L, Alvarez J, Argyriadou H, Ben-Gal T, Černý V, Cholley B, Eremenko A, Guerrero-Orriach JL, Järvelä K, Karanovic N, Kivikko M, Lahtinen P, Lomivorotov V, Mehta RH, Mušič Š, Pollesello P, Rex S, Riha H, Rudiger A, Salmenperä M, Szudi L, Tritapepe L, Wyncoll D, Öwall A. Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion. Int J Cardiol. 2015;184:323-36.

43. Orme RM, Perkins GD, McAuley DF, Liu KD, Mason AJ, Morelli A, Singer M, Ashby D, Gordon AC. An efficacy and mechanism evaluation study of Levosimendan for the

Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS): protocol for a randomized controlled trial. Trials. 2014;15:199.

44. Pollesello P, Papp Z, Papp JGy. Calcium sensitizers:What have we learned over the last 25 years? Int J Cardiol 2016;203:543-8

45. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med 2012;38:359–67

46. Nony P, Boissel JP, Lievre M, Leizorovicz A, Haugh MC, Fareh S, de Breyne B. Evaluation of the effect of phosphodiestherase inhibitors on mortality in chronic heart failure patients. A meta-analysis. Eur J Clin Pharmacol 1994;46:191–6.

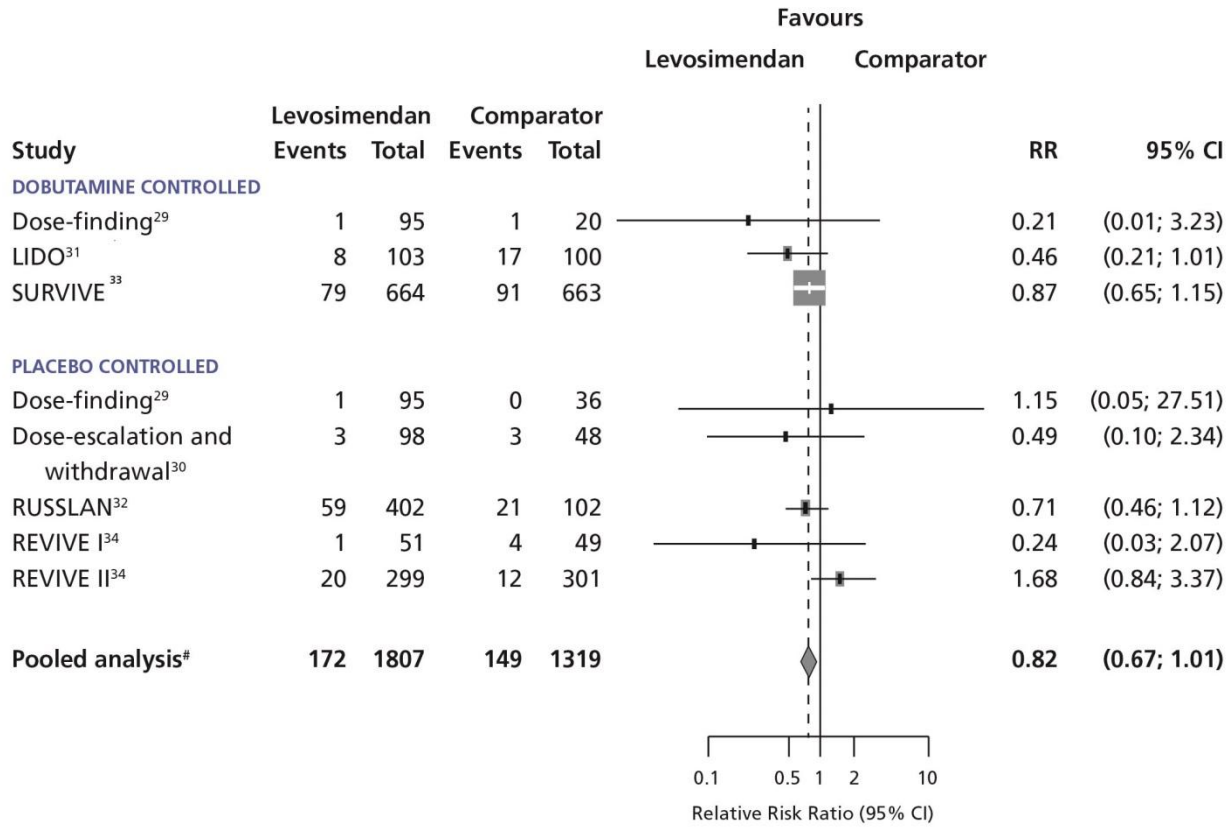
Table 1. Meta-analyses of levosimendan clinical studies.

Year	References	Country /ies	Clinical settings	N. of studies	Main endpoint	Relative risk/ Odds Ratio*	significant
2004	Cleland [4]		AHF	2[a]	mortality	OR=0.55	**yes**
2006	Cleland [5]		AHF	4[b]	mortality	OR=0.75	**no**
2009	Zangrillo [6]		card.surgery	5[c]	troponin release	Z=3,6	**yes**
2010	Landoni [7]		all	27[c]	mortality	OR=0,74	**yes**
	Ribeiro [8]		AHF	19[c]	mortality	RR=0,87	**no**
	Landoni [9]		card.surgery	10	mortality	OR=0,35	**yes**
	Delaney [10]		AHF	8[a]	mortality	OR=0,75	**yes**
2011	Maharaj [11]		card.surgery	17[c]	mortality	OR=0,40	**yes**
2012	Landoni [12]		all	45[c]	mortality	RR=0,80	**yes**
	Hernandez [13]		card.surgery	13[c]	mortality	OR=0,36	**yes**
	Huang [14]		all	22[a]	mortality	RR=0,81	**yes**
2013	Harrison [15]		card.surgery	14[c]	mortality	RD= –4,2%	**yes**
	Niu [16]		AKI/surg.	5[c]	AKI	OR=0,4	**yes**
2014	Nieminen [17]		rep./AdHF	7[c]	mortality	RR=0,47	**yes**
	Silvetti [18]		rep./AdHF	7[c]	mortality	RR=0,55	**yes**
2015	Koster [19]		all	49[c]	mortality	RR=0,69	**no**[e]
	Bove [20]		ARF	33[c]	renal re-placement	RR=0,52	**yes**
	Greco [21]		card.surgery	46[d]	mortality	OR=0,80	**yes**
	Yi [22]		rep./AdHF	8[c]	mortality	RR=0,40	**yes**
	Lim [23]		card.surgery	14[c]	mortality	OR=0,48	**yes**
	Gong [24]		AHF	25[c]	mortality	RR=0,84	**yes**
	Zangrillo [25]		sepsis	7[c]	mortality	RR=0,79	**yes**
	Silvetti [26]		rep./AdHF	7[c]	mortality	RR=0,54	**yes**
	Belletti [27]		all	48[c,f]	mortality	RR=0,80	**yes**
	Zhou [28]		card.surgery	13[c]	AKI and mortality	RR=0,41[g]	**yes**

Only the main analysis of each study are shown for clarity. AHF=acute heart failure; AKI=acute kidney injury; AdHF=advanced heart failure; ARF=acute renal failure; rep. = repetitive/

intermittent use; *if not otherwise specified (OR=odds ratio; RR=relative risk/risk ratio; RD=risk difference; Z=z-test value); the trend is shown as an arrow (green= statistically significant; yellow = non significant); [a]compared to dobutamine; [b]compared to placebo; [c]compared to all controls; [d]Bayesian network meta-analysis; [e]when only the predefined 'low bias' study were considered in the meta-analysis; [f]subsetting of randomized studies on levosimendan out of the 177 studies considered in the whole meta-analysis; [g]for mortality.

Figure 1



Highlights

- We systematically review all published meta-analyses on levosimendan, in any clinical setting.
- We perform our own meta-analysis by selecting only the six regulatory Phase III studies.
- The risk reduction is overall consistent, and similar to that obtained in our meta-analysis.
- The weight of evidence is in favour of the usefulness/efficacy of levosimendan.
- Levosimendan can be differentiated from other hemodynamic drugs used in the same settings.