Levosimendan and mortality after coronary revascularisation: a meta-analysis of randomised controlled trials

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Abstract

Introduction: Patients undergoing coronary revascularization often require inotropic support that has been associated with an increased risk for death and morbidity. The purpose of this study was to evaluate the effect of levosimendan versus control on survival after coronary revascularization.

Methods: A systemic review and meta-analysis of the literature was carried out on published randomized controlled clinical trials that investigated the efficacy of levosimendan compared to other therapy in patients having coronary revascularisation. The databases searched were Pubmed, EMBASE, the Cochrane Registry of Clinical Trials and the metaRegister of Controlled Trials. Studies that compared levosimendan to any other therapy for coronary revascularisation in adult humans and reported at least one outcome of interest were considered for inclusion. Both percutaneous coronary intervention and cardiac surgery were included. Data extraction was performed independently by two reviewers using predefined criteria. Relevant outcomes included mortality, cardiac index, cardiac enzymes, length of stay and post-procedural atrial fibrillation.

Results: The meta-analysis included 729 patients from 17 studies. Levosimendan was associated with a mortality reduction after coronary revascularization, (19/386 in the levosimendan group vs 39/343 in the control arm) odds ratio (OR) 0.40 (95% confidence interval (CI) 0.21 to 0.76, \( P \) for overall effect 0.005, \( P \) for heterogeneity = 0.33, \( I^2 = 12\)%) with a total of 729 patients. Levosimendan also had a favourable effect on cardiac index (standardised mean difference 1.63, 95% CI 1.43 to 1.83, \( P \) for overall effect < 0.00001), length of intensive care stay (random effects model, mean difference - 26.18 hours 95% CI 46.20 to 6.16, \( P \) for heterogeneity < 0.00001, \( I^2 = 95\)%, \( P \) for overall effect = 0.01), reductions in the rate of atrial fibrillation (OR 0.54, 95% CI 0.36 to 0.82, \( P \) for effect = 0.004, \( P \) for heterogeneity 0.84, \( I^2 = 0\)% for 465 patients) and troponin I levels group (mean difference -1.59, 95% CI 1.78 to 1.40, \( P \) for overall effect < 0.00001, \( P \) for heterogeneity < 0.00001, \( I^2 = 95\)%). Limitations of this analysis are discussed.

Conclusions: Levosimendan is associated with a significant improvement in mortality after coronary revascularization. There are also improvements in several secondary endpoints. A suitably powered randomised controlled trial is required to confirm these findings and to address the unresolved questions about the timing and dosing of levosimendan.

Introduction

Following coronary revascularisation, patients are still vulnerable to a low cardiac output state and tissue hypoperfusion. Some patients may require bridging therapy in order to realise the benefits of revascularisation. There is substantial geographic variation, but it is estimated that between 8 and 25% of patients undergoing coronary revascularisation require inotropic support for myocardial dysfunction [1-3]. This group of patients carry a substantial burden of morbidity and mortality [4]. Pharmacologic support is commonly limited to catecholamines and phosphodiesterase III inhibitors (PDEIs) with levosimendan gaining prominence [5]. There is a lack of suitably powered randomised controlled trials to guide the choice of inotrope in this group of patients.
patients. Both catecholamines and PDEIs are associated with increased post-operative myocardial oxygen consumption and arrhythmogenesis [6]. Additionally catecholamines have also been associated with impaired coronary vasodilatory reserve [7].

Levosimendan sensitises myofilaments to calcium by binding to the calcium saturated troponin C, increasing their load-independent contraction [8]. The pleiotropic effects of levosimendan include vasodilatation by opening ATP-sensitive potassium channels ($K_{ATP}$) in vascular smooth muscle as well as in mitochondrial $K_{ATP}$ channels.

Early clinical trials, though underpowered, have suggested that levosimendan would be useful in the setting of post coronary revascularisation myocardial dysfunction. More recently there have been several completed clinical trials in this group of patients. The principal objective of this study was to evaluate the association between levosimendan, compared with conventional therapy on mortality, in randomised control trials in patients having coronary revascularisation.

**Materials and methods**

**Search strategy**

The primary search for randomised clinical trials (RCTs) was conducted using Pubmed, EMBASE and the Cochrane Registry of Clinical Trials. The search term used was ‘levosimendan’. The search was combined with filters to identify RCTs in the Pubmed and EMBASE database and is available as supplementary material (see Additional file 1 for details). We also searched the metaRegister of Controlled Trials using the term ‘levosimendan’ [9]. No language restriction was placed but the search was limited to adult human subjects. We used backward snowballing by reviewing the bibliographies of included RCTs and review articles to identify otherwise unreconised publications. The electronic database search included publications from 1966 and was finalised on 31 August 2010. The study did not require ethical approval.

**Study selection**

The authors reviewed all abstracts to identify potential RCTs in a standardised manner. The inclusion criteria were reports of RCTs that compared levosimendan to any other therapy for coronary revascularisation in adult humans and reported at least one outcome of interest. Relevant outcomes included mortality, haemodynamic parameters (for example, cardiac index), cardiac enzymes, length of stay and post-procedural atrial fibrillation. If the abstract suggested that the study could potentially meet the inclusion criteria, the full text article was then retrieved and reviewed. Disagreements between reviewers were resolved by consensus.

**Data abstraction and study characteristics**

All included studies were assessed for internal validity and risk of bias according to the Cochrane Collaboration methods. Each report was assessed for the adequacy of allocation concealment, blinding, performance of an intention to treat analysis and the extent of loss to follow-up.

Data included baseline patient characteristics including age and co-morbidity, baseline left ventricular ejection fraction, details of levosimendan dose and specifics of comparator therapy, type of coronary revascularisation, haemodynamic and clinical outcome data. When data was missing attempts were made to contact the authors.

**Data synthesis and analysis**

Agreement on inclusion of studies was assessed using the kappa statistic. Heterogeneity was measured using the Cochrane Q test and quantified with the $I^2$ statistic. An $I^2$ value of > 50% was considered at least moderate heterogeneity.

Data from individual studies were collected to allow calculation of odds ratio (OR). The primary analysis was conducted by means of the Peto fixed effects method when $I^2 < 25\%$ and with the random effects model when $I^2 > 25\%$. Weighted mean difference (WMD) and 95% CI were calculated for continuous variables (haemodynamics and troponin I). The potential for bias was assessed by visual inspection of funnel plots. Sensitivity analyses were conducted by comparing the fixed and random effects models as well as by evaluating the risk of mortality in studies with a low risk of bias only. The analysis was performed using statistical software SPSS 16 (SPSS Chicago, IL, USA) and Revman 5.0 (available from the Cochrane Collaboration Group). The study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [10,11].

**Results**

There were 680 reports identified by the search, 79 full text articles retrieved for in depth review. We identified 17 eligible studies involving 729 patients that were included in the final analysis. Figure 1 describes the flow and reasons for exclusion. Agreement on study inclusion was reached in 76 of the 79 cases (kappa = 0.92). The characteristics of the included studies are described in Table 1. An appraisal of study quality and risk of bias is presented in Table 2. Overall studies were of variable quality and many reports lacked relevant details to assess selection, performance or reporting bias. A risk of bias graph is included in the supplementary material (see Additional file 2 for details).
Analysis of the data showed that, compared with a control intervention, levosimendan was associated with a significant mortality reduction, (19/387 in the levosimendan group vs 39/342 in the control arm) OR 0.41 (95% CI 0.23 to 0.74, $P$ for overall effect 0.005, $P$ for heterogeneity = 0.33, $I^2$ = 12% with a total of 729 patients) (Figure 2). A subgroup analysis comparing the effect of levosimendan on mortality in elective versus
emergency coronary revascularisation was performed. The elective revascularisation showed a statistically significant mortality benefit compared with the emergency revascularisation group (OR 0.36, 95% CI 0.18 to 0.72, \( P < 0.00001 \)). A sub-group analysis was undertaken to explore the heterogeneity. Subgroups were defined by the comparator drug, that is, the placebo, dobutamine or phosphodiesterase inhibitors. The sub-group analysis did not show any difference in treatment effect (Figure 3).

Post revascularisation, troponin I levels were significantly higher in the control group compared with the levosimendan group (mean difference -1.59, 95% CI 1.78 to 1.40, \( P < 0.00001 \), for overall effect < 0.00001, \( I^2 = 95% \)) with 361 patients included (Figure 4).

There was a significantly lower rate of post-revascularisation new-onset atrial fibrillation in the levosimendan group compared with the control group (OR 0.89, 95% CI 0.79 to 0.99, \( P = 0.02 \)). A sub-group analysis showed a significantly lower rate of atrial fibrillation in the levosimendan group compared with the control group (OR 0.39, 95% CI 0.27 to 0.57, \( P < 0.00001 \)) with 361 patients included (Figure 4).

### Table 1 Description of the studies included in the meta-analysis

| Source            | Year | Patients | Mean Age (years ± SD) | Setting                                                                 | Time of administration | Mean Baseline LVEF % ± SD | Control | Follow-up         |
|-------------------|------|----------|-----------------------|-------------------------------------------------------------------------|------------------------|---------------------------|---------|------------------|
| Al-Shawaf et al.  | 2006 | 30       | 60.5 ± 11             | Type 2 diabetes with LCOS after CABG                                   | Post intervention      | 29 ± 6                    | Levosimendan | Hospital stay    |
| et al.            |      |          |                       |                                                                         |                        |                           | Control |                  |
| et al.            | 2005 | 30       | 71.5 ± 5.2            | Elective CABG with LCOS                                                | Post intervention      | 35 ± 5                    | Levosimendan | Hospital stay    |
| et al.            | 2006 | 50       | 71.2 ± 7.2            | Elective CABG with LCOS                                                | Post intervention      | 35 ± 4                    | Levosimendan | Hospital stay    |
| et al.            | 2004 | 33       | 62.4 ± 7.1            | Elective OPCAB with good LV function                                   | Pre-intervention       | 62 ± 8                    | Levosimendan | Hospital stay    |
| De Hert et al.    | 2007 | 30       | 67 ± 11               | Elective CABG                                                          | Intraoperatively       | 24 ± 6                    | Levosimendan | Hospital stay    |
| et al.            | 2008 | 60       | 67.5 ± 9.5            | Elective CABG                                                          | Intraoperatively       | 22 ± 5                    | Levosimendan | Hospital stay    |
| et al.            | 2005 | 26       | 58.6 ± 8.7            | Acute MI undergoing PCI                                                | Post intervention      | 28 ± 3                    | Levosimendan | Hospital stay    |
| Samimi-Fard et al.| 2009 | 60       | 64 ± 10               | Elective CABG with LVEF<50%                                            | Intraoperatively       | 36 ± 8                    | Levosimendan | Hospital stay    |
| et al.            | 2008 | 32       | 68 ± 74               | Cardiogenic shock after acute MI                                       | Post intervention      | 22 ± 9                    | Levosimendan | Hospital stay    |
| et al.            | 2008 | 24       | 61 ± 5.4              | Elective OPCAB with normal LVEF                                        | Pre-intervention       | 56 ± 5                    | Levosimendan | Hospital stay    |
| Jarvela et al.    | 2008 | 24       | 69 ± 11               | Elective AVR and CABG                                                  | Intraoperatively       | 50 ± 4                    | Levosimendan | Hospital stay    |
| et al.            | 2008 | 137      | 62.4 ± 6.1            | LCOS after elective CABG                                               | Post intervention      | 37 ± 4                    | Levosimendan | Hospital stay    |
| et al.            | 1998 | 23       | 56.9 ± 7.9            | Elective low risk CABG                                                 | Post intervention      | 61 ± 9                    | Levosimendan | Hospital stay    |
| Sonntag et al.    | 2008 | 22       | 65 ± 12               | Acute MI with Cardiogenic shock after PCI                              | Post intervention      | 29 ± 2                    | Levosimendan | Hospital stay    |
| et al.            | 2004 | 24       | 60 ± 60               | PCI after acute MI                                                     | Post intervention      | 58 ± 3                    | Levosimendan | Hospital stay    |
| et al.            | 2006 | 24       | 66.5 ± 5.9            | Elective CABG                                                          | Pre-intervention       | 50 ± 7                    | Levosimendan | Hospital stay    |
| et al.            | 2009 | 106      | 66.5 ± 7.8            | Elective CABG                                                          | Pre-intervention       | 44 ± 10                   | Levosimendan | Hospital stay    |

CABG, coronary artery bypass graft; LCOS, low cardiac output state; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPCAB, off pump coronary artery bypass graft; PCI, primary coronary intervention.
treated group (OR 0.54, 95% CI 0.36 to 0.82, $P$ for effect = 0.004, $P$ for heterogeneity 0.84, $I^2 = 0\%$ for 465 patients (Figure 5). There was also a significant difference in the length of intensive care stay in favour of levosimendan compared with control (random effects model, mean difference -26.18 hours 95% CI 46.20 to 6.16, $P$ for heterogeneity < 0.00001, $I^2 = 95\%$, $P$ for overall effect $P$ = 0.01) (Figure 6). The likelihood of small study bias robustness was evaluated by inspection of the funnel plot (Figure 7). Inspection of the funnel plot found no major evidence of such bias and added to the validity and robustness of the study. A sensitivity analysis that only included those studies with a low risk of bias (Table 1) found an OR of 0.25 (95% CI 0.09 to 0.68). A further sensitivity analysis to establish differential effects based on the comparator was performed. The largest effect size was observed in the levosimendan versus phosphodiesterase group (OR 0.23 (95% CI 0.08 to .65)). The levosimendan versus dobutamine group showed a strong trend in favour of levosimendan but was not statistically significant (OR 0.54 95% CI 0.25 to 1.17)). The levosimendan versus placebo group suggested a positive effect in favour of levosimendan but did not achieve statistical significance (OR 0.66 (95% CI 0.11 to 4.08)) (Table 3).

Table 2 Risk of bias assessment of included studies

| Source                  | Adequate sequence generation | Allocation concealment | Blinding | Incomplete outcome data addressed | Free of selective reporting | Free of other Bias | Concurrent therapies similar | Overall risk of bias |
|-------------------------|------------------------------|------------------------|----------|-----------------------------------|-----------------------------|-------------------|-----------------------------|---------------------|
| Al-Shawaf et al. [35]   | Unclear                      | Yes (sealed envelopes) | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Alvarez et al. [36]     | unclear                      | Unclear                | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Alvarez et al. [37]     | unclear                      | Unclear                | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Barisin et al. [38]     | Yes (computer generated)     | Yes                    | Yes (patients, doctors, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| De Hert et al. [39]     | Yes (computer generated)     | Yes (sealed envelopes) | Yes (adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| De Hert et al. [40]     | Yes (computer generated)     | Yes (sealed envelopes) | Yes (adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| De Luca et al. [41]     | Unclear                      | Unclear                | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Eriksson et al. [42]    | Yes (permuted books)         | Yes                    | Yes (patients, doctors) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| Fuhrmann et al. [33]    | Yes (computer generated)     | Yes                    | Yes (patients doctors) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| Husedzinvic et al. [43] | Yes (casting lots)           | Yes                    | Yes (patients, doctors) | Unclear                   | Yes                         | Yes                | Yes                         | Moderate            |
| Jarvela et al. [44]     | Yes (computer generated)     | Yes (sealed envelopes) | Yes (patients, doctors, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| Levin et al. [45]       | Yes (computer generated)     | Unclear                | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Lilleberg et al. [46]   | Unclear                      | Unclear                | Yes (patients, doctors, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Moderate            |
| Samimi-Fard et al. [47] | Unclear                      | Unclear                | No       | Unclear                           | Yes                         | Yes                | Yes                         | Moderate            |
| Sonntag et al. [48]     | Unclear                      | Yes                    | Yes (patients, doctors, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Moderate            |
| Tritapepe et al. [49]   | Yes (computer generated)     | Unclear                | Yes (Patients, physicians, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
| Tritapepe et al. [1]    | Yes (computer generated)     | Unclear                | Yes (patients, physicians, adjudicators) | Unclear                   | Yes                         | Yes                | Yes                         | Low                 |
Figure 2 Forest plot for risk of mortality with subgroups elective and emergency revascularisation.

Figure 3 Forest plot for cardiac index with sub-groups dobutamine, placebo and phosphodiesterase inhibitors.
Cardiogenic shock (CS) is a devastating complication of ST-segment myocardial infarction (STEMI) and occurs in 5 to 8% of these patients [12]. Thirty-day survival of STEMI patients in cardiogenic shock is between 40% and 60% [12,13]. Despite favourable trends in the last 30 years, survival to 6 years remains poor and may be as low as 30% [14-16]. This is comparable to many forms of cancer. Therapeutic options for haemodynamic support after coronary revascularisation are limited to pharmacologic or mechanical interventions. Pharmacologic choices are vasopressors and inotropic drugs. Inotropic agents are essential to address the contractile dysfunction that occurs by providing short-term haemodynamic improvement. However, this happens at a cost of increased oxygen demand, arrhythmogenesis and potential myocardial injury at a time when the myocardium is most vulnerable. Data on comparison between inotropes are scant and recent reports have highlighted the challenge in selecting the best pharmacologic option [17-19]. Compared with norepinephrine, the use of dopamine in patients with cardiogenic shock has been associated with an increased rate of death [17].

A recent meta-analysis evaluated the use of levosimendan in a variety of patient populations that included post-cardiac surgery, post-vascular surgery, sepsis, decompensated heart failure and post percutaneous coronary intervention (PCI) patients [20]. The proposed mechanisms of myocardial dysfunction in sepsis, after non-cardiac surgery and in the context of cardiogenic shock, are all quite disparate [21,22]. This implies that vasoactive drugs may perform differently, depending on the prevailing mechanism of shock making the interpretation of a pooled analysis of such a heterogeneous group of patients difficult. For this reason we limited this meta-analysis to patients having coronary revascularisation.

Overall, this study shows a mortality benefit when levosimendan was used in patients having coronary revascularisation. The effect was significant in the elective revascularisation group. The subset of patients undergoing emergency revascularisation was under-represented and the mortality benefit in this group was not statistically significant. This latter analysis is probably underpowered. Additionally, levosimendan was associated with favourable outcomes in several clinically
important endpoints. The rate of post-revascularisation atrial fibrillation was reduced. Atrial fibrillation after coronary revascularisation is associated with a prolonged hospital stay, increased morbidity and long-term mortality [23]. The analysis also found levosimendan to be associated with a reduction in peri-procedural cardiac troponin I levels. Elevations in cardiac troponin I levels are a valuable marker of myocardial damage after coronary revascularisation and have been associated with a significantly higher rate of in-hospital and long-term mortality [24-27]. The haemodynamic response to levosimendan was also favourable. It is likely that the improvement of haemodynamic profile observed with levosimendan can be sustained for a longer period of time compared to dobutamine or milrinone [28]. This is because levosimendan has a poorly protein-bound active metabolite and may exert clinical effects for up to a week [29], at a much lower energy expenditure than conventional inotropes.

The sub-group analysis comparing levosimendan to the placebo, dobutamine and phosphodiesterase inhibitors all showed a favourable trend towards levosimendan with only the latter group showing statistical significance. This observation could be interpreted as potential harm from exposure to phosphodiesterase inhibitors.

Levosimendan reduced the ICU length of stay by a mean of 26.18 hours (95% CI 46.20 to 6.16). The estimated mean cost of critical care is US$3,518/day in the United States and about £1,647/day in the United Kingdom [30,31]. Levosimendan is considerably more expensive than conventional treatment and this probably warrants further pharmaco-economic evaluation.

The findings of this meta-analysis must be viewed in the context of other randomised studies and systematic reviews comparing other vasoactive agents [17,29,32]. Thackray et al. systematically reviewed the use of inotropes in cardiac failure [32]. The drugs included were beta agonists, dobutamine, dopexamine and phosphodiesterase inhibitors. Compared with the placebo, these drugs were found to be associated with a non-significant trend for increased rate of death (OR 1.5, 95% CI 0.51 to 3.92).

Our study has several limitations. Several studies were of sub-optimal quality. Eight of the 17 studies included did not have clear allocation concealment. This has the potential to exaggerate treatment effects. Only five studies explicitly stated that the analysis was done by an intention to treat principle. The study by Fuhrmann had a small number of events (i.e. all cause mortality at 30 days) and was stopped early for patient benefit [33]. This study may potentially represent an exaggerated effect size in favour of levosimendan [34]. The sensitivity analysis considering the effect of levosimendan on mortality across comparator drugs showed a more pronounced effect compared with the phosphodiesterase group. Comparing levosimendan to placebo is probably of little value when suitable alternatives exist. These studies recruited low risk patients with a low event rate. Lower event rates require larger sample sizes and it is unsurprising that no statistically significant mortality difference was demonstrated.

Publication bias may account for some of the effects observed. Selective reporting of smaller studies, usually of lower methodological quality will tend to exaggerate treatment effects. The funnel plot was symmetrical, suggesting a low probability of publication bias. Not all
465 patients were included in the analysis of atrial fibrillation. A suitably powered RCT is required with improvement in haemodynamics and reduction in cardiac biomarkers, length of ICU stay and rate of associated with a significant reduction in mortality. This meta-analysis suggests that the use of levosimendan in patients undergoing coronary revascularisation is crucial to restoring haemodynamics and tissue perfusion though the ideal inotrope in this group of patients is controversial. Levosimendan has a potential role in reducing the mortality and morbidity associated with coronary revascularisation.

### Key messages
- Acute cardiovascular dysfunction after coronary revascularisation occurs in about 8% to 25% of patients.
- The short-term use of inotropes is crucial to restoring haemodynamics and tissue perfusion though the ideal inotrope in this group of patents is controversial.
- Levosimendan has a potential role in reducing the mortality and morbidity associated with coronary revascularisation.

### Additional material

**Additional file 1: Search strategy for PUBMED**

**Additional file 2: Risk of Bias Table** (Figure 1).

### Competing interests

The authors declare that they have no competing interests.

### References

1. Tritapepe L, De Santis V, Vitale D, Guaraccino F, Pellegrini F, Pietropaoli P, Singer M. Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery. **Br J Anaesth** 2009, 102:198-204.

2. Lee CH, van Dornburg RT, Hoye A, Lemos PA, Tanabe K, Smits PC, van der Giessen WJ, de Feyter P, Semuys PW. Predictors of survival after contemporary percutaneous coronary revascularization for acute myocardial infarction in the real world. **J Invasive Cardiol** 2004, 16:627-631.

3. Holmes DR Jr, Califf RM, Van de Werf F, Berger PB, Bates ER, Simoons ML, White HD, Thompson TD, Topol EJ. Difference in countries’ use of resources and clinical outcome for patients with cardiogenic shock after myocardial infarction: results from the GUSTO trial. **Lancet** 1997, 349:75-78.

4. Pae WE Jr, Miller CA, Matthews Y, Pierce WS. Ventricular assist devices for postcardiotomy cardiogenic shock. A combined registry experience. **J Thorac Cardiovasc Surg** 1992, 104:541-552, discussion 552-543.

5. Mebazaa A, Pratsi AA, Rudiger A, Toller W, Longrois D, Ricksten SE, Bobek I, De Hert S, Wiesethaler G, Schimer U, von Segesser LK, Sander M, Poldermans D, Ranucci M, Karpati PC, Wouters P, Seegerer M, Schmid ER, Wieder W, Follath F. Clinical review: practical recommendations on the management of perioperative heart failure in cardiac surgery. **Crit Care** 14:201.

6. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. **J Cardiothorac Vasc Anesth** 2001, 15:306-315.

7. Fowler NR, Alderman BL, Oosterling SN, Derby G, Daughters GT, Stinson EB, Ingels NB, Mitchell RS, Miller DC. Dobutamine and dopamine after cardiac surgery: greater augmentation of myocardial blood flow with dobutamine. **Circulation** 1984, 70:103-111.

8. Pagel PS. Levosimendan in cardiac surgery: a unique drug for the treatment of perioperative left ventricular dysfunction or just another inodilator searching for a clinical application? **Anesth Analg** 2007, 104:759-761.

9. MetaRegister of Controlled Clinical Trials. [http://www.controlled-trials.com/mRCT](http://www.controlled-trials.com/mRCT).

10. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **BMJ** 2009, 339:b2535.

11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. **BMJ (Clin Res Educ)** 2009, 339:b2700.

12. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. **Circulation** 2008, 117:686-697.

13. Dauerman HL, Goldberg RJ, White K, Gore JM, Sadiq I, Gurfinkel E, Budaj A, Lopez de Sa E, Lopez-Sendon J. Global Registry of Acute Coronary Events. **G RACE Investigators.** Revascularization, stenting, and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. **Am J Cardiol** 2003, 90:838-842.

14. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward P, Col J, White HD. Early revascularization and long-term survival in cardiogenic shock. **Critical Care** 2011, 15:R140.
shock complicating acute myocardial infarction. JAMA 2006, 295:2511-2515.
15. Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, Califf RM, Holmes DR Jr: Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock: insights from the GUSTO-I trial. J Am Coll Cardiol 2007, 50:1752-1758.
16. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J: Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiac shock in patients with acute myocardial infarction: a population-based perspective. Circulation 2009, 119:1211-1218.
17. De Backer D, Biston P, Devriendt J, Madic C, Chochoadad D, Aldecoa C, Brasseur A, Defrance P, Gottigies N, Vincent JL: Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010, 362:779-789.
18. Pantoni JT, Rafoul-Stengruij P, Stanisna V, Piasogniakopoulos P, Melaza A: Inotropes in cardiac patients: update 2011. Curr Opin Crit Care 2010, 16:432-441.
19. Mebazaa A, Pitsis AA, Rudiger A, Toller W, Longrois D, Ricksten SE, Bobek I, Parissis JT, Rafouli-Stergiou P, Stasinos V, Psarogiannakopoulos P, Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, Califf RM, Mebazaa A: Acute myocardial infarction. Crit Care Med 2006, 34:284-287.
20. De Luca L, Piroietti P, Celotto A, Bucciarelli-Ducci C, Benedetti G, Di Roma A, Gardiner J, Fedele F: Levosimendan improves hemodynamics and coronary flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction and left ventricular dysfunction. Am Heart J 2005, 150:563-568.
21. Van Geene Y, van Swieten HA, Noyez L: Inotropes in cardiac surgery patients with poor left ventricular function. Anesth Analg 2007, 104:766-773.
22. De Hert SG, Lorsomrade S, Cromheecke S, Van der Linden PJ: The effects of levosimendan in cardiac surgery patients with poor left ventricular function. Anesth Analg 2007, 104:766-773.
23. Al-Sahaf E, Ayed A, Viscoli C, Radomir B, Dehrab N, Tarazi R: Levosimendan or milrinone in the type 2 diabetic patient with low ejection fraction undergoing elective coronary artery surgery. J Cardiothorac Vasc Anesth 2006, 20:533-537.
24. Alvarez J, Taboada M, Rodriguez J, Caruseo V, Bouzada M, Campana O, Bascuas B, Perez-Paz J, Ginesta V: Hemodynamic effects of levosimendan following surgical coronary artery bypass. Rev Esp Anestesiol Reanim 2005, 52:389-394.
25. Alvarez J, Bouzada M, Fernandez AL, Caruseo V, Taboada M, Rodriguez J, Ginesta V, Rubio J, Garcia-Bengochea JB, Gonzalez-Juanatey JR: [Hemodynamic effects of levosimendan compared with dobutamine in patients with low cardiac output after surgical coronary artery bypass. Rev Esp Cardiol 2006, 59:338-345.
26. Barini S, Husezinzovic I, Soncik Z, Bradic N, Barini A, Tonkovic D: Levosimendan in off-pump coronary artery bypass: a four-times masked controlled study. J Cardiovas Pharmacol 2004, 44:703-708.
27. De Hert SG, Lorsomrade S, Cromheecke S, Van der Linden PJ: The effects of levosimendan in cardiac surgery patients with poor left ventricular function. Anesth Analg 2007, 104:766-773.
28. De Luca L, Piroietti P, Celotto A, Bucciarelli-Ducci C, Benedetti G, Di Roma A, Gardiner J, Fedele F: Levosimendan improves hemodynamics and coronary flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction and left ventricular dysfunction. Am Heart J 2005, 150:563-568.
29. Sikorski HJ, Jolonen JR, Heikkilinen LO, Kivikko M, Laine M, Leino KA, Kuitunen AHT, Kuttula KT, Perakylä TK, Sarapohja TA, Suurjaranta-Ylinen KT, Valtonen M, Salmenpera MT: Levosimendan facilitates weaning from cardiopulmonary bypass in patients undergoing coronary artery bypass grafting with impaired left ventricular function. Ann Thorac Surg 2009, 87:448-454.
30. Husezinzovic I, Barini S, Bradic N, Barini A, Soncik Z, Milanovic R: Levosimendan as a new strategy during off-pump coronary artery bypass grafting: double-blind randomized placebo-controlled trial. Croat Med J 2006, 47:956-960.
31. Samimi-Fard S, Garcia-Gonzalez MJ, Dominguez-Rodriguez A, Abreu-Gonzalez P: Effects of levosimendan versus dobutamine on long-term survival of patients with cardiac shock after primary coronary angioplasty. Int J Cardiol 2008, 127:284-287.
32. Sonntag S, Sundberg J, Lehtonen LA, Reiber FX: The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. J Am Coll Cardiol 2004, 43:2177-2182.
33. Triapepe L, De Santis V, Vitale D, Akkila J, Heikkilä K, Kuitunen AHT, Mattila S, Salmenpera M: The effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J 1998, 19:660-666.