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Prophylactic levosimendan in patients with low ejection fraction undergoing coronary artery bypass grafting: A pooled analysis of two multicentre randomised controlled trials

Abbreviated Title (Running Head): Levosimendan in CABG with or without valve surgery

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Conflicts of Interest: Several authors (BC, TC, JHA, RM, MH, and WT) have received honoraria (participation to advisory boards) or lecturing fees from Orion or Tenax Pharmaceuticals.

Contribution to authorship: BC and TC wrote the first draft of the manuscript. BC, TC and GC contributed to the design of the analysis and to the interpretation of the results. BC, TC, JHA, RHM, MH and WT contributed to the interpretation of the results. GC, BC, TC, AY and CAN contributed to the methodological approach and to the interpretation of the results. All the authors made significant revisions to the final manuscript and approved it.

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Keywords: coronary artery bypass surgery (CABG), valve replacement surgery, levosimendan, mortality

Abstract

Objectives: To assess the effect of preoperative levosimendan on mortality at Day-90 in patients with left ventricular ejection fraction (LVEF) \leq 40%, and to investigate a possible differential effect between patients undergoing isolated coronary artery bypass grafting (CABG) *versus* CABG combined with valve replacement surgery.

Design: Pooled analysis of two multicentre randomised controlled trials (RCT) investigating prophylactic levosimendan *versus* placebo prior to CABG surgery on mortality at Day-90 in patients with LVEF \leq 40%. A meta-analysis of all RCT investigating the same issue was also conducted.

Results: A cohort of 1084 patients (809 isolated CABG, and 275 combined surgery) resulted from the merging of LEVO-CTS and LICORN databases. Seventy-two patients were dead at day 90. The mortality at day 90 was not different between levosimendan and placebo (Hazard Ratio (HR): 0.73, 95% CI: 0.41–1.28, $p = 0.27$). However, there was a significant interaction between the type of surgery and the study drug ($p = 0.004$). We observed a decrease in mortality at day 90 in the isolated CABG subgroup (HR: 0.39, 95% CI: 0.19–0.82, $p = 0.013$), but not in the combined surgery subgroup (HR: 1.73, 95% CI: 0.77–3.92, $p = 0.19$). The meta-analysis of 6 RCT involving 1441 patients confirmed the differential effect on mortality at day 30 between the 2 subgroups.

Conclusions: Preoperative levosimendan did not reduce mortality in a mixed surgical population with LV dysfunction. However, the subgroup of patients undergoing isolated CABG had a reduction in mortality at day 90, whereas there was no significant effect in combined surgery patients. This finding requires confirmation with a specific prospective trial.

Introduction

The inotrope and vasodilator levosimendan has been proposed to treat and prevent low cardiac output syndrome (LCOS) and related adverse outcomes after cardiac surgery. Despite promising preliminary data, large randomised controlled trials (RCT) aiming to demonstrate the benefits of levosimendan failed to show superiority to placebo for both treatment [1] and prevention [2, 3] of postoperative LCOS. At odds with these results, recent meta-analyses suggested a reduced mortality with perioperative use of levosimendan in patients with altered left ventricular ejection fraction (LVEF) [4, 5]. However, the authors of these meta-analyses acknowledged that the heterogeneity of the studies and the high risk of bias were confounders potentially hampering the reliability of their findings. Heterogeneity among studies was related to several factors, *i.e.*, type of surgery (coronary artery bypass surgery [CABG], valve, or combined), on-pump or off-pump, levosimendan regimen (pre- or postoperative administration, with or without bolus, and dosing).

Recently, the results of a predefined subgroup analysis from one of the large prospective RCT showed a differential effect between levosimendan and placebo depending on the type of surgery: isolated CABG *versus* combined surgery (*i.e.*, valve plus CABG) or isolated valve surgery [6]. The authors observed a reduction in mortality at day 90 in patients who underwent isolated CABG but not in patients who underwent valve or combined surgery. In order to consolidate this exploratory finding and to investigate potential clues explaining such a difference, we conducted a pooled analysis of the two multicentre RCT (LEVO-CTS [3] and LICORN [2] that compared the prophylactic use of levosimendan *versus* placebo prior to cardiac surgery on mortality at day 90. We also investigated possible differential effects in pre-specified subgroups, *i.e.*, the interaction between treatment (levosimendan or placebo) and the type of surgery (isolated CABG or combined surgery),

preoperative beta-blocker treatment or not, and the severity of left ventricular dysfunction (LVEF < 30%, or 30% ≤ LVEF ≤ 40%).

Methods

Ethical approval

All original studies operated under supervision of an appropriate human ethics committee. This study is exempt from ethics approval because the study collected data from previous clinical trials in which informed consent was already obtained.

Pooled analysis

The LEVO-CTS and LICORN trials had very similar designs and involved patients with LVEF ≤ 40% undergoing on-pump isolated CABG or CABG combined with valve surgery. The two studies were randomised, the comparator was placebo, and investigators have used comparable regimens of levosimendan. The risk of bias of these two studies evaluated using the Cochrane tool (ROB2) was minimal on all items [7]. We merged the databases of these two trials to conduct a pooled analysis on individual patient data.

Meta-analysis

To verify that our choice of focusing on two large homogeneous high quality RCT did not bias our findings, we also conducted a meta-analysis of all RCT that investigated prophylactic levosimendan against placebo in patients with LVEF ≤ 40% undergoing on-pump CABG. We did a systematic review conducted in accordance with the “Preferred Reporting Items for Systematic Review and Meta-analysis” (PRISMA) statement 2015 [8]. We excluded trials in

which levosimendan was administered postoperatively, those comparing levosimendan against active drugs, enrolling patients with preserved left ventricular function (LVEF > 40%) or undergoing off-pump CABG. We searched MEDLINE, EMBASE, and CENTRAL databases for eligible RCTs up to the 31st of December 2019, with no restriction on language or year of publication. The search algorithm is presented in detail in **eTable 1** (in the **Supplementary file**). Unpublished or ongoing trials were searched by screening registers (Clinicaltrials.gov, WHO ICTRP, and Clinical Study Data Request) and by contacting the company that produces levosimendan (Orion Corporation). The review protocol was prospectively registered with PROSPERO (#CRD42020163432).

Data collection and quality assessment

The literature search was conducted according to the PICO framework (**eTable 2**, in the **Supplementary file**) [9]. Three investigators (TC, BC, and BS) independently screened titles, abstracts, and full texts to assess eligibility of each report. Discrepancies were resolved by consensus between investigators. Duplicate references were excluded. As a first approach, we extracted summary estimates from the selected published reports or obtained them directly from the authors when unavailable in the publication. Two investigators independently assessed the risk of bias domains [7] and discrepancies were resolved by consensus.

Outcomes

The primary outcome of the pooled analysis was mortality at postoperative day 90. In three pre-specified subgroups: type of surgery (isolated CABG *versus* CABG combined with valve surgery), presence or absence of a preoperative beta-blocker treatment, and severity of LV dysfunction (LVEF < 30% *versus* 30% ≤ LVEF ≤ 40%), we investigated the interaction between the study drug (levosimendan or placebo) and the subgroup. Other secondary outcomes included: 1) the need for inotropic agents beyond 24 hours following the end of levosimendan/placebo infusion; 2) the need for a mechanical cardiac assist device at any time postoperatively, 3) the need for renal replacement therapy (RRT) during the ICU stay; 4) the ICU and hospital lengths of stay. The outcome of the meta-analysis of all selected studies was mortality at day 30, since further follow-up was not available.

Statistical Analysis

As a first step, we re-analysed the data from the two trials separately to ensure that we could replicate the results reported in the original publications. Any discrepancy was resolved directly with the original study data manager. From the LEVO-CTS cohort, 97 patients who underwent isolated valve surgery were removed. This did not affect randomisation as 49 patients were allocated to levosimendan while 48 received placebo. Baseline characteristics for these patients are available in the study from van Diepen et al. [6]. In addition, one patient from LEVO-CTS and two from LICORN who did not have surgery were also excluded from the analysis. For each outcome, the overall effect estimate of the treatment and the interaction between treatment effect and subgroup were assessed. A Cox model with proportional effect on the hazard function and a random treatment effect was used to determine the hazard ratio for mortality. The assumptions of the proportional hazard were checked using the Schoenfeld residuals. For binary endpoints, a mixed logistic

model with a random treatment effect adjusted on the study was performed. For counting endpoints, as number of days in ICU and number of days in hospital, mixed negative binomial models with a random treatment effect adjusted on the study was performed. We also performed two predefined subgroups analyses according to preoperative LVEF ($< 30\%$, and $30 \leq \text{LVEF} \leq 40\%$) and to the existence of a preoperative beta-blocker treatment. Among the safety variables, we analysed the markers of myocardial damage collected by the investigators: troponin or creatine kinase-MB (CK-MB), according to local routine. Regarding markers of myocardial lesion, the data could not be pooled since investigators in France used troponin I, while CK-MB was measured preferentially in North America. Separate analyses were performed on the log-transformed values of the cardiac markers. A linear regression model was then performed including the treatment arm, the type of surgery and the interaction between these two last variables. For the meta-analysis, as hazard ratios were not available, odds ratios of death were estimated for each study and each subgroup. The F test was used to assess differences between subgroups in a random effect meta-regression estimated using restricted maximum likelihood. All statistical tests were two-tailed. We used the software R version 3.3.3 (R172 Foundation for Statistical Computing, Vienna, Austria) for all analyses.

Results

The results of the literature search and study selection process are outlined in the PRISMA flow chart (**Figure 1**). Two studies, LICORN and LEVO-CTS, were at low risk of bias for the five domains defined by the Cochrane tool, while four others presented some risk of bias (**eFigure 1**, in the **Supplementary file**) [2, 3, 10-13]. The main characteristics of the six

studies selected are presented in **Table 1**. The **eTable 3** (in the **Supplementary file**) provides the list of non-selected studies and the reason for exclusion.

The two low-risk studies represented a total of 1084 CABG patients from 83 sites in France, Canada and the United States, after the removal of 100 patients who did not undergo CABG (97 patients underwent isolated valve surgery, 3 patients did not have surgery at all). Five hundred forty-six (546) patients were randomly assigned to levosimendan and 538 to placebo. The LEVO-CTS patients represented 69% of the cohort and the LICORN patients 31%. Baseline characteristics of patients are summarised in **Table 2**. Patients in the two groups were well balanced with regard to baseline demographics, medical history, preoperative medication, and surgical characteristics. Baseline demographics for each surgical group (isolated CABG and combined surgery) are presented in the **eTable 4** and **eTable 5**, respectively (in the **Supplementary file**).

Primary outcome: A total of 72 patients (6.6%) were dead at day 90. The overall mortality was not different between patients receiving levosimendan or placebo (HR: 0.73, 95% CI: 0.41–1.28, $p = 0.27$). Vital status was missing in 5 patients that were lost to follow-up.

Secondary outcomes and subgroup analyses: There was a significant interaction between the type of surgery and the treatment ($p = 0.004$). The results of the analysis are presented in **Figure 2**. We observed a reduction in mortality with levosimendan in the isolated CABG group: 12 (3%) vs. 31 (7.7%); HR: 0.39, 95% CI: 0.19–0.82, $p = 0.013$), but not in those who underwent combined surgery: 18 (12.9%) vs. 11 (8.2%); HR: 1.73, 95% CI: 0.77–3.92). There was no significant interaction between the type of surgery and the treatment for any secondary outcome (**Figure 2**).

We did not observe significant interactions in the other predefined subgroups (LVEF < 30% *versus* 30% ≤ LVEF ≤ 40%, and in presence or absence of preoperative beta-blockers) for the primary outcome and secondary outcomes (**eFigure 2**, in the **Supplementary file**).

The durations of cardiopulmonary bypass and aortic cross-clamp were shorter in patients undergoing isolated CABG *versus* combined surgery (100 ± 43 min and 65 ± 36 min *versus* 153 ± 65 min and 115 ± 50 min, respectively, $p < 0.001$) (**eTable 4** and **eTable 5**, in the **Supplementary file**). There was no significant interaction between the type of surgery and the treatment for troponin or CK-MB.

The meta-analysis on aggregate data of the six selected trials involved 1441 patients (1104 isolated CABG and 337 combined surgery) and confirmed the interaction between the type of surgery and the study drug on mortality at day 30. There was a reduction in mortality with levosimendan in the isolated CABG group (OR: 0.39, 95% CI: 0.22–0.71, $p = 0.002$), but not in the combined group (OR: 1.25, 95% CI: 0.51–3.09, $p = 0.586$) (**Figure 3**).

Discussion

The main finding of this analysis is that we observed no reduction in mortality at day 90 in the mixed population of cardiac surgical patients with reduced LVEF. However, the subgroup of patients who underwent isolated CABG and received levosimendan had a significant reduction in mortality, while we observed a non-significant increase in mortality in patients undergoing CABG combined with valve surgery. This differential effect in the two subgroups might explain, in part, the lack of benefit in the mixed surgical population.

The two large multicentre RCT (LICORN and LEVO-CTS) represented a total of 1084 patients and had very similar designs and endpoints [2, 3]. Both included primarily CABG patients with or without associated valve surgery, and a few patients (8% of the initial cohorts) undergoing other types of cardiac surgical repairs (n = 97) or who were not operated on for any reason (n = 3) were removed from the study population. All patients had preoperative LVEF equal to or less than 40% and received the study drug at the time of anaesthesia induction. As a minor difference, patients from the LEVO-CTS trial received 0.2 µg/kg/min levosimendan infusion for one hour and, then, 0.1 µg/kg/min for 23 hours, while the LICORN patients received 0.1 µg/kg/min for 24 hours. Both studies had a primary composite endpoint reflecting postoperative low cardiac output syndrome. Very similar data were used for both primary and secondary outcomes and were prospectively collected in the two studies. Therefore, our merged population was highly homogenous. In addition, the two trials were of high methodological quality according to the Cochrane risk of bias assessment tool.

A recently published post-hoc subgroup analysis of the LEVO-CTS study revealed a possible reduction in mortality at day 90 of the isolated CABG population receiving levosimendan [6]. By combining the LEVO-CTS and LICORN databases, we were able to analyse a cohort of 1084 patients to verify this observation with a much greater power, and try to determine possible explanatory factors. Our results confirmed that isolated CABG patients may have reduced mortality at day 90 when receiving levosimendan: there was a 4.7% absolute reduction in the risk of death. This indicates that one death can potentially be avoided for every 21 treated patients. The present finding is reinforced by the result of the meta-analysis on aggregate data performed on the six studies selected after our systematic review, which confirmed a reduction in mortality at day 30 in the isolated CABG group.

The mortality of our merged population (6.6%) was comparable between the North American and the French cohorts and was in the expected range based on the disease severity of the patients involved. The reasons for the benefit in patients undergoing isolated CABG remain largely speculative. The most obvious difference between our two groups is that the combined surgery patients had longer cardiopulmonary bypass and aortic cross-clamp durations. This prolonged ischaemia may have blunted the protective effect provided by levosimendan for shorter procedures. Levosimendan might reduce the ischaemic insult by two mechanisms. First, the drug has the ability to improve coronary blood flow as demonstrated both in experimental models [14] and in patients [15], thereby improving oxygen delivery to the ischaemic myocardium. Investigators using intraoperative ultrasound transit time technology were able to show that levosimendan infusion (0.1 µg/kg/min) initiated at the time of anaesthesia induction resulted in improved graft blood flow in patients 30 minutes after termination of cardiopulmonary bypass compared to placebo, regardless of the type of graft (arterial or venous, simple or sequential) [15]. In addition, levosimendan could also limit myocardial ischaemic damage via the activation of sarcolemmal [16] and mitochondrial K_{ATP} channels [17], which are involved with myocardial ischaemic preconditioning. Opening of the K_{ATP} channels is advocated to protect cardiac myocytes against ischaemic injuries, limit myocardial stunning, and provide protection against ischemia by energy sparing [18-20]. K_{ATP} channel opening also inhibits opening of the mitochondrial permeability transition pore, which is responsible for ischaemic cell death after ischaemia-reperfusion [21]. However, possible reduction in myocardial ischaemic damage could not be confirmed in the present cohort, as we could not observe any interaction between study drug and type of procedure for troponin or CK-MB. Clinically, the reduction in myocardial injury in patients receiving levosimendan has been confirmed in a

limited number of trials. Three studies reported that CABG patients receiving a bolus (followed or not by infusion) of levosimendan at the time of anaesthesia induction had lower postoperative troponin plasma levels than patients assigned to placebo [22-24]. Different markers of myocardial injury were used in LEVO-CTS and LICORN, which prevented the possibility to pool the data and limited the power of this analysis.

In patients undergoing combined surgery, the 95% confidence interval is compatible, both, with increased injury and some benefit. The difference with what was observed in isolated CABG patients might be explained by the fact that patients with valve dysfunction on top of ischaemic heart disease may have different underlying cardiomyopathies. Those with aortic stenosis have hypertrophic remodelling as a result of chronic pressure overload leading to fibrosis and increased myocyte apoptosis [25]. Patients with mitral regurgitation have multiple associated conditions involving not only the LV, but also the left atrium and the right ventricle as a consequence of post-capillary pulmonary hypertension resulting from left atrial congestion. Histopathologically, mitral regurgitation results in excess oxidative stress leading to myofibrillar degeneration, even in the absence of associated ischaemia [26]. However, aortic stenosis and mitral regurgitation are two very different situations involving a more complex underlying myocardial disease than pure ischaemic cardiomyopathy and may be less accessible to the protective effect of levosimendan. It was clear from the LEVO-CTS study that the patients who only underwent valve surgery were those who benefitted less from levosimendan [3].

This pooled analysis also confirmed the lack of interaction between the study drug and the type of surgery on any of the secondary outcomes (prolonged need for catecholamines, need for renal replacement therapy or mechanical assist device, ICU and

hospital length of stays). None of the other predefined subgroups (very low ejection fraction < 30%, or patients receiving beta-blockers) were found to have a differential reduction in the mortality at day 90 for patients who received levosimendan.

Limitations: Although highly significant, the reduction in mortality at day 90 in isolated CABG patients should still be regarded as exploratory since mortality was not the primary endpoint of the LICORN and LEVO-CTS studies, and because it results from subgroup analysis. We choose to pool the results of only two trials with the highest level of methodological quality in order to avoid the risk associated with heterogeneity, which hampered the robustness of the conclusions of previous meta-analyses. However, a meta-analysis on aggregate data including all selected studies, regardless of their risk of bias, did not change our overall findings. Confirmation of this result will require a new specifically designed randomised controlled trial.

Conclusions: The present findings obtained a large homogeneous cohort of patients with LVEF \leq 40% suggest that patients undergoing isolated CABG and receiving prophylactic levosimendan may have a reduction in mortality at day 90. This effect was unlikely in patients undergoing CABG combined with valve surgery. This differential effect between the two subgroups might explain the overall lack of benefit of prophylactic levosimendan on mortality in the mixed cohort.

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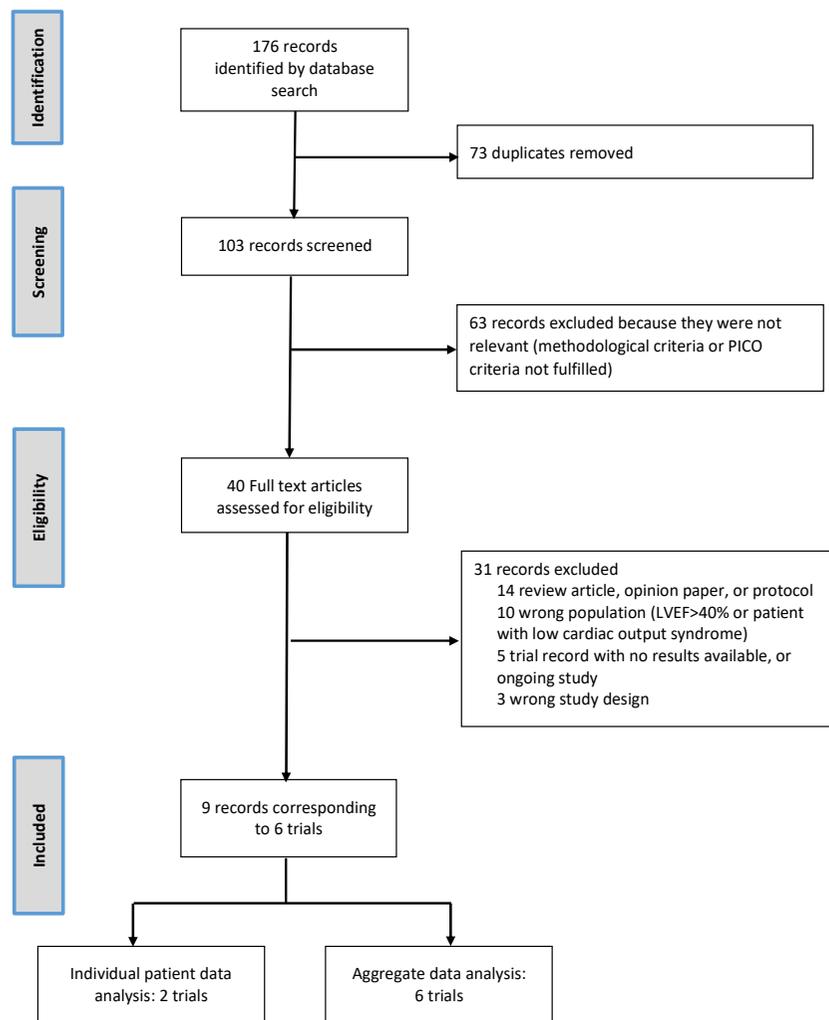
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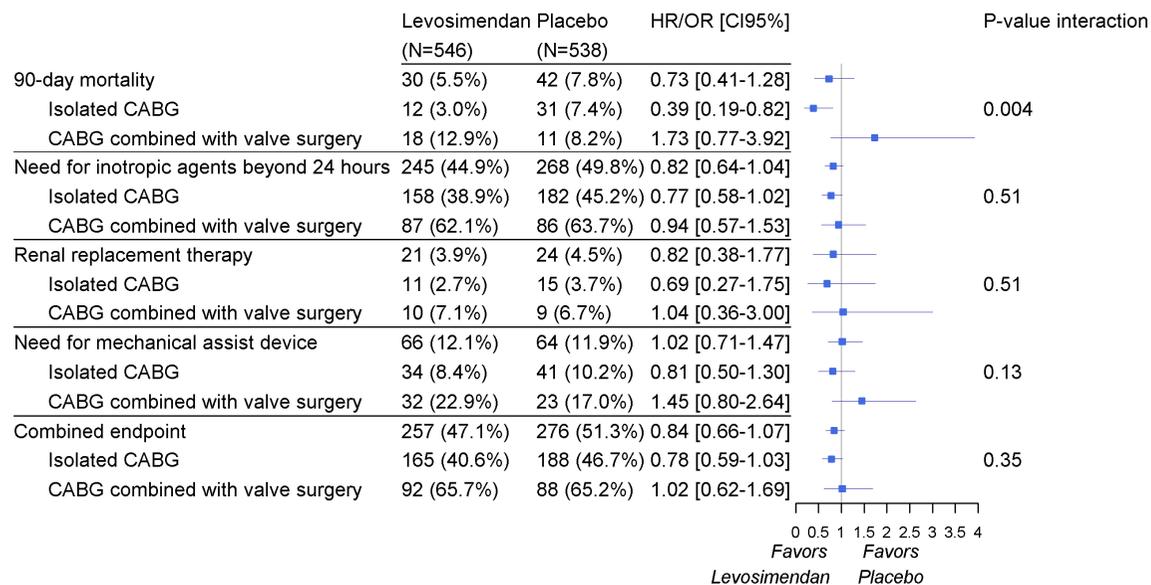
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Figure 1: Flow diagram for study selection



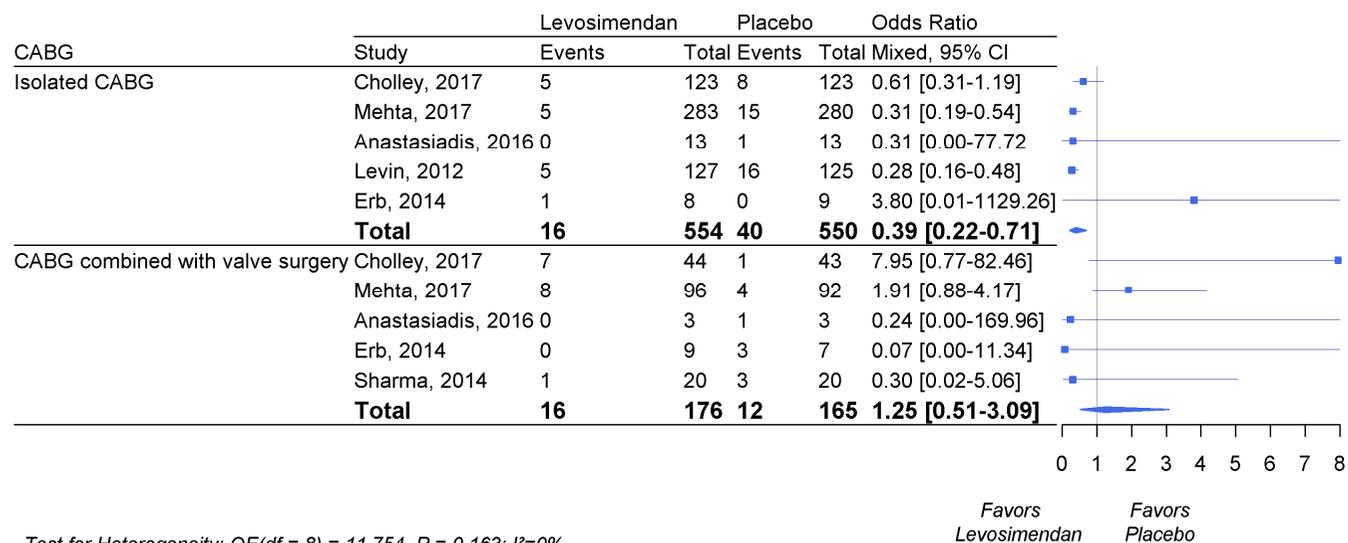
LVEF: left ventricular ejection fraction; PICO: Population, Intervention, Comparator, Outcome; RCT: randomised controlled trial

Figure 2: Forest plot for primary and secondary outcomes



CABG: coronary artery bypass grafting; HR: hazard ratio (for mortality); OR: odds ratio (for all other criteria). Isolated CABG receiving levosimendan: n = 406, or placebo: n = 403. Combined surgery receiving levosimendan: n = 140, or placebo: n = 135

Figure 3: Mortality at day 30 according to the type of surgery (Aggregate data of all the studies selected)



Test for Heterogeneity: $QE(df = 8) = 11.754, P = 0.163; I^2 = 0\%$
 Test for interaction: $QM(df = 1) = 4.453, P = 0.03$

CABG: coronary artery bypass grafting

Table 1: Main Characteristics of the Included Trials

	Levin (2012) ¹⁰	Sharma (2014) ¹¹	Erb (2014) ¹²	Anastasiadis (2016) ¹³	Mehta (2017) ³	Cholley (2017) ²
Registration	NA	NA	EudraCT2007-004674-49	NCT01318460	NCT02025621	NCT02184819
Number of centres	2	1	1	1	70	13
Number of patients	252	40	33	32	849*	335 †
Region	Argentina	India	Germany	Greece	USA & Canada	France
Mortality follow-up	Day 30	Day 30	Day 30	Day 30	Day 90	Day 180
Isolated CABG (Alive/dead at day 30)	252 (231/21)	0 (0/0)	17 (16/1)	26 (25/1)	563 (543/20)	246 (233/13)
combined CABG + valve (alive/dead at day 30)	0 (0/0)	40 (36/4)	16 (13/3)	6 (5/1)	188 (176/12)	87 (79/8)
Timing of levosimendan infusion	Preoperative (?)	Preoperative (24 h)	Anaesthesia induction	Preoperative (24 h)	Anaesthesia induction	Anaesthesia induction
Bolus	10 µg/kg over 60'	Yes (dose not specified)	No	No	0.2 µg/kg/min for 60 min	No
Continuous infusion	0.1 µg/kg/min during 23 h	Total dose 200 µg/kg over 24 h	0.1 µg/kg/min during 12 h	0.1 µg/kg/min during 24h	0.1 µg/kg/min during 23h	0.1 µg/kg/min during 24h
Primary endpoint	LCOS and mortality	Haemodynamic endpoint	Change in postoperative SOFA score	Change in SVI between pre-op and postop day 7	Composite endpoint: Death at day 30, RRT at day 30, MI at day 5, MAD at day 5	Composite endpoint: Need for catecholamine beyond 48 h, need for RRT, need for MAD
Funding	NA	None	None	Orion Pharma	Tenax Therapeutics	French Ministry of Health Orion Pharma provided study drugs free of charge

* includes 97 isolated valve surgery and 1 patient who did not have surgery. † includes 2 patients who did not have surgery. Abbreviations: CABG, Coronary artery bypass grafting; LCOS, Low Cardiac Output Syndrome; MAD, mechanical assist device; MI, Myocardial infarction; NA, not available; SOFA, Sequential Organ Failure Assessment; SVI, Stroke Volume Index. RRT, renal replacement therapy.

Table 2: Baseline Characteristics of Patients

Covariate	Whole sample (n = 1084)	Levosimendan (n = 546)	Placebo (n = 538)	P-value
Female sex	174 (16.1)	84 (15.4)	90 (16.7)	0.55
Age, years	66 ± 10	66 ± 10	65 ± 10	0.06
BMI, kg/m²	28.2 ± 5.4	28.0 ± 5.2	28.5 ± 5.5	0.14
LVEF				
[30%-40%]	582 (53.7)	294 (53.8)	288 (53.5)	0.98
< 30%	502 (46.3)	252 (46.2)	250 (46.5)	
Creatinine clearance, mL/min	92 ± 59	92 ± 76	92 ± 34	0.86
< 50	133 (12.5)	75 (14.0)	58 (11.0)	0.29
50 to 85	446 (41.9)	228 (42.6)	218 (41.3)	
> 85	485 (45.6)	233 (43.5)	252 (47.7)	
Medical history				
Peripheral vascular disease	205 (19.1)	97 (17.8)	108 (20.1)	0.37
Previous cardiac surgery	75 (6.9)	38 (7.0%)	37 (6.9)	0.95
Chronic lung disease	230 (21.7)	106 (19.8)	124 (23.6)	0.14
Endocarditis active	1 (0.1)	1 (0.2)	0 (0.0)	1
Resting angina	453 (44.7)	232 (45.2)	221 (44.1)	0.72
Hypertension	831 (77.1)	424 (78.4)	407 (75.9)	0.34
Diabetes mellitus	523 (48.3)	259 (47.5)	264 (49.1)	0.61
Preoperative atrial fibrillation	260 (24.1)	134 (24.6)	126 (23.5)	0.67
NYHA Score				
I	72 (8.0)	37 (8.3)	35 (7.8)	0.19

<i>II</i>	371 (41.4)	199 (44.6)	172 (38.1)	
<i>III</i>	380 (42.4)	174 (39.0)	206 (45.7)	
<i>IV</i>	74 (8.2)	36 (8.1)	38 (8.4)	
Preoperative medication				
<i>Beta-blocker</i>	852 (80.8)	420 (79.6)	432 (82.0)	0.32
<i>Statin</i>	794 (94.6)	403 (95.9)	391 (93.3)	0.09
<i>Antiplatelet therapy</i>	848 (80.4)	424 (80.3)	424 (80.4)	0.95
Preoperative Inotropes	3 (0.9)	1 (0.6)	2 (1.2)	0.62
Surgical procedures				
<i>Isolated CABG</i>	809 (74.6)	406 (74.4)	403 (74.9)	0.84
<i>CABG combined with valve surgery</i>	275 (25.4)	140 (25.6)	135 (25.1)	
<i>Duration of CPB, min</i>	113 ± 55	113 ± 57	114 ± 53	0.77
<i>Duration of aortic cross clamp, min</i>	78 ± 45	78 ± 47	78 ± 44	0.94

Abbreviations: BMI, body-mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; NYHA, New York heart association.
Data are n (%) for categorical variables and mean (SD) for continuous outcomes