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[Intervention Review]

Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

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ABSTRACT

Background

Cardiogenic shock (CS) and low cardiac output syndrome (LCOS) as complications of acute myocardial infarction (AMI), heart failure (HF) or cardiac surgery are life-threatening conditions. While there is a broad body of evidence for the treatment of people with acute coronary syndrome under stable haemodynamic conditions, the treatment strategies for people who become haemodynamically unstable or develop CS remain less clear. We have therefore summarised here the evidence on the treatment of people with CS or LCOS with different inotropic agents and vasodilative drugs. This is the first update of a Cochrane review originally published in 2014.

Objectives

To assess efficacy and safety of cardiac care with positive inotropic agents and vasodilator strategies in people with CS or LCOS due to AMI, HF or cardiac surgery.

Search methods

We searched CENTRAL, MEDLINE, Embase and CPCI-S Web of Science in June 2017. We also searched four registers of ongoing trials and scanned reference lists and contacted experts in the field to obtain further information. No language restrictions were applied.

Selection criteria

Randomised controlled trials in people with myocardial infarction, heart failure or cardiac surgery complicated by cardiogenic shock or LCOS.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We identified 13 eligible studies with 2001 participants (mean or median age range 58 to 73 years) and two ongoing studies. We categorised studies into eight comparisons, all against cardiac care and additional other active drugs or placebo. These comparisons investigated the efficacy of levosimendan versus dobutamine, enoximone or placebo, epinephrine versus norepinephrine-dobutamine, amrinone versus dobutamine, dopexamine versus dopamine, enoximone versus dopamine and nitric oxide versus placebo.

All trials were published in peer-reviewed journals, and analysis was done by the intention-to-treat (ITT) principle. Twelve of 13 trials were small with few included participants. Acknowledgement of funding by the pharmaceutical industry or missing conflict of interest statements emerged in five of 13 trials. In general, confidence in the results of analysed studies was reduced due to serious study limitations, very serious imprecision or indirectness. Domains of concern, which show a high risk of more than 50%, include performance bias (blinding of participants and personnel) and bias affecting the quality of evidence on adverse events.

Levosimendan may reduce short-term mortality compared to a therapy with dobutamine (RR 0.60, 95% CI 0.37 to 0.95; 6 studies; 1776 participants; low-quality evidence; NNT: 16 (patients with moderate risk), NNT: 5 (patients with CS)). This initial short-term survival benefit with levosimendan vs. dobutamine is not confirmed on long-term follow up. There is uncertainty (due to lack of statistical power) as to the effect of levosimendan compared to therapy with placebo (RR 0.48, 95% CI 0.12 to 1.94; 2 studies; 55 participants, very low-quality evidence) or enoximone (RR 0.50, 95% CI 0.22 to 1.14; 1 study; 32 participants, very low-quality evidence).

All comparisons comparing other positive inotropic, inodilative or vasodilative drugs presented uncertainty on their effect on short-term mortality with very low-quality evidence and based on only one RCT. These single studies compared epinephrine with norepinephrine-dobutamine (RR 1.25, 95% CI 0.41 to 3.77; 30 participants), amrinone with dobutamine (RR 0.33, 95% CI 0.04 to 2.85; 30 participants), dopexamine with dopamine (no in-hospital deaths from 70 participants), enoximone with dobutamine (two deaths from 40 participants) and nitric oxide with placebo (one death from three participants).

Authors' conclusions

Apart from low quality of evidence data suggesting a short-term mortality benefit of levosimendan compared with dobutamine, at present there are no robust and convincing data to support a distinct inotropic or vasodilator drug-based therapy as a superior solution to reduce mortality in haemodynamically unstable people with cardiogenic shock or LCOS.

Considering the limited evidence derived from the present data due to a generally high risk of bias and imprecision, it should be emphasised that there remains a great need for large, well-designed randomised trials on this topic to close the gap between daily practice in critical care medicine and the available evidence. It seems to be useful to apply the concept of 'early goal-directed therapy' in cardiogenic shock and LCOS with early haemodynamic stabilisation within predefined timelines. Future clinical trials should therefore investigate whether such a therapeutic concept would influence survival rates much more than looking for the 'best' drug for haemodynamic support.

PLAIN LANGUAGE SUMMARY

Inotropic and vasodilator strategies in people with cardiogenic shock or low cardiac output

Review question

We reviewed evidence of the treatment with different inotropic agents and vasodilative drugs for their effects on mortality in people with cardiogenic shock (CS) or low cardiac output syndrome (LCOS).

Background

CS and LCOS still remain life-threatening complications. Inotropic and vasoactive drugs are potent, but potentially harmful agents. Their benefits and harms are associated with mortality.

Study characteristics

This evidence is current to June 2017. We included 13 studies with 2001 participants with CS or LCOS as complications of myocardial infarction, heart failure or cardiac surgery, with follow-up periods between the length of the recovery period up to 12 months. Four studies were funded by a drug manufacturer.

Key results

We compared different approaches to standard therapies with possible addition of inotropic or vasoconstrictive drugs as levosimendan, dobutamine, enoximone, epinephrine. This review presents low-quality evidence that levosimendan compared to dobutamine reduces short-term mortality. The survival benefit with levosimendan vs. dobutamine is not confirmed on long-term follow up. Very low-quality evidence shows uncertainty around the effect of levosimendan compared to placebo or enoximone. Very low-quality evidence shows uncertainty on the comparison of epinephrine with norepinephrine-dobutamine, amrinone or enoximone with dobutamine, dopexamine with dopamine, and nitric oxide with placebo.

Quality of evidence

We have reduced confidence in the results of the studies that we analysed (low- or very low-quality evidence) due to serious study limitations, very serious imprecision or indirectness.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Levosimendan compared to dobutamine for cardiogenic shock or low cardiac output syndrome

Patient or population: people with cardiogenic shock or low cardiac output syndrome
Settings: hospital
Intervention: levosimendan
Comparison: dobutamine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with dobutamine	Risk with levosimendan				
All-cause, short-term mortality: range 15 days to 12 months	**Moderate**[1]		**RR 0.60** (0.37 to 0.95)	1776 (6 studies)	⊕⊕◯◯ **low**[3,4]	Studies included participants with LCOS or CS due to cardiac surgery, HF or AMI
	154 per 1000	**92 per 1000** (57 to 146)				
	High[2]					
	500 per 1000	**300 per 1000** (185 to 475)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMI: acute myocardial infarction; **CI:** confidence interval; **CS**: cardiogenic shock; **HF**: heart failure; **LCOS**: low cardiac output syndrome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from the median risk among the control group risk in included studies with participants with low cardiac output, low cardiac output or cardiogenic shock, or cardiogenic shock.

[2]Control group risk estimate comes from a large observational study, due to the small size of included studies in this population (Singh 2007).

[3]Downgraded one step due to study limitations because of lack of blinding of participants and physicians in four studies, high risk of bias due to loss to follow-up in one study, and baseline imbalances on prognostic relevance in one study.

[4]Downgraded one step for imprecision due to few events.

BACKGROUND

Worldwide, cardiovascular disease is one of the leading causes of morbidity, death, and loss of disability-adjusted life years (Gaziano 2010; Lozano 2012; Moran 2008; Murray 1996). In 2013 in the USA, the overall rate of death attributable to cardiovascular disease was 222.9 per 100,000 Americans (Mozaffarian 2016). The estimated direct and indirect annual costs for cardiovascular disease and stroke were USD 317 billion for 2011 to 2012 (Mozaffarian 2016). As the population ages, the economic impact of cardiovascular diseases on the nation's healthcare system will become even greater (CDC 2011). Data from the INTERHEART study showed that rates of cardiovascular disease have greatly increased in low-income and middle-income countries, with about 80% of the global burden of cardiovascular disease occurring in these countries (Yusuf 2004).

Cardiovascular diseases are the most common cause of cardiogenic shock (CS). AMI (acute myocardial infarction) is complicated by CS in approximately 5% to 10% of cases (Goldberg 1999; Hochman 1999). The incidence of CS remained unchanged between 2001 and 2014 in an analysis of five Italian registries (De Luca 2015). Among people with CS, the proportion of people with hypertension, renal dysfunction and previous primary percutaneous coronary intervention (PCI) has increased over time, whereas the proportion of people with previous heart failure (HF) has declined. PCI was established as a standard therapy for revascularisation in people with AMI complicated by CS. This has led to an increase of PCI from 19% to 60% over the years. In hospital, mortality decreased from 68% in 2001 to 38% in 2014. In 2014 more people presented with CS on admission and fewer developed CS during their stay in hospital (De Luca 2015; WHO 2014).

Therapeutic strategies in people with CS due to AMI rely predominantly on acute and effective revascularisation of the infarct-related artery and dependent myocardium (Hochman 1999; Hochman 2001; Hochman 2006). Subsequently, drugs like dopamine, dobutamine, norepinephrine or epinephrine are used to increase perfusion pressure and cardiac output (Dickstein 2008; O'Gara 2013; Steg 2012; Werdan 2012). Recently, new therapeutic strategies have been established, such as treatment with phosphodiesterase (PDE) inhibitors or calcium sensitisers (Reyentovich 2016).

Description of the condition

There is no absolute definition of a low cardiac output state. Haemodynamic criteria that are sometimes used include cardiac index less than 1.8 L/min/m^2, or less than 2.2 L/min/m^2 if inotropic drugs are administered, and a pulmonary capillary wedge pressure (PCWP) of at least 15 mmHg (Reyentovich 2016). However, the definitions in clinical trials vary (Reyentovich 2016). Clinically defined, the condition presents with hypotension (a systolic blood pressure of less than 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of 90 mmHg or more) and end-organ hypoperfusion (cool extremities, urine output of less than 30 mL per hour, altered mental status, or elevated serum lactate). There is a continuum from low cardiac output syndrome (LCOS) to CS. In CS the low system oxygen delivery going along with low cardiac output is complicated by multi-organ dysfunction. CS represents an acute, life-threatening medical condition, which needs immediate attention. Pathogenesis of CS is broad. Apart from CS following AMI as discussed above, it includes unstable angina, valvular heart diseases, etc., but also systemic illnesses that trigger cardiac dysfunction, for example, septic shock with severe cardiac depression. CS with low cardiac output is a complex syndrome that involves a cascade of acute left ventricular dysfunction, decreased cardiac output, hypotension, and tissue hypoperfusion (Hochman 2007).

Description of the intervention

Medical drug therapy can be characterised under different aspects:

- inotropic myocardial stimulation (positive inotropes that increase contractility) (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Fuhrmann 2008; Garci a-González 2006; Husebye 2013; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007);
- left ventricular unloading (vasodilators) (Baldassarre 2008; Rosseel 1997).

Medical drug therapy in CS is predominantly based on inotropic and vasoactive substances. They are administered for haemodynamic stabilisation through increased cardiac output and perfusion pressures by optimising systemic vascular resistance (SVR). In the early stages, increased SVR often requires vasodilatory drugs. The following stages are characterised by an escalating systemic inflammatory response syndrome so that only vasopressors, often in increasing dosages, can elevate the decreased SVR. Therapeutic approaches of anticoagulation and platelet inhibition may also be applied to modulate the systemic inflammatory response and improve the microcirculatory disturbances.

How the intervention might work

To stabilise people with CS or LCOS, drugs for positive inotropic support, vasopressors and sometimes vasodilators are commonly used. Drugs like dobutamine, dopexamine, enoximone, milrinone, amrinone, levosimendan and istaroxime are used to increase cardiac contractility and induce additional reduction of SVR for left ventricular unloading (How 2010; Leone 2004; Mattera 2008; McGhie 1992; Pietrangelo 2010; Rognoni 2011; Sehgal 2011). While there is some evidence that inotropes like levosimendan might be cost effective in treating elective, high-risk, cardiac-surgery patients (Severi 2011), there is no comparable evidence in CS. Since there is limited evidence for drug treatment strategies in CS, the beneficial effects on quality of life or cost become

much more important (Harjola 2010; HFMA 2010; Komamura 2008; Loisance 1991; Loisance 1993). A follow-up analysis of the SHOCK trial showed that, although one-year mortality after emergency revascularisation remained high (54%), most survivors had good functional status. The level of recovery for people with CS undergoing early revascularisation was similar to that of historical controls not in CS and undergoing elective revascularisation (Sleeper 2005). The use of classic inotropic agents activating the beta-receptor cyclic adenosine monophosphate (cAMP) pathway (that is dobutamine or milrinone) should be restricted to 'rescue' therapy in people with acute HF and signs of peripheral hypoperfusion (hypotension, renal dysfunction) refractory to volume replacement, diuretics and vasodilators. This approach is largely supported by observations from clinical trials suggesting that both short-term treatment of acute HF without an essential requirement for inotropic support as well as long-term inotropic therapy in people with severe chronic HF with classical inotropic agents can increase arrhythmias and mortality (Landmesser 2007). Overall, we assume that the potential benefits of inotropic support in CS provide an opportunity for haemodynamic improvement by enhanced myocardial performance. With increased dosages of inotropic support, these potential benefits have to be judged against the background of the increased myocardial oxygen consumption by the ischaemic myocardium. Without myocardial revascularisation, infarct-related CS inotropic support may show temporary beneficial haemodynamic effects superimposed on the background of expanding AMI. These disadvantages may be seen as general risks or side effects of undergoing inotropic support. At present there is only poor evidence for reduced risks of increased cellular damage or superiority in myocardial protection of the ischaemic myocardium for one of the investigated inotropic drugs (Landmesser 2007; Mentzer 2011; Triposkiadis 2009; Zheng 2009). Pure vasodilators like nitroglycerin or nitroprusside may only be used in certain subgroups of CS (Menon 2000) under conditions of guided haemodynamic monitoring to improve left ventricular performance by left ventricular unloading via vasodilation (Belskii 1987; Den Uil 2009; Hollenberg 2007).

The main strategies in the treatment of people with CS remain re-establishing adequate macro- and microcirculatory conditions for the stabilisation of the oxygen supply at the cellular level, and modulation of the systemic inflammatory response to avoid functional and morphological cellular damage, to prevent multi-organ dysfunction or failure (De Backer 2010; Hermansen 2011; Shpektor 2010). Once cellular damage has become irreversible every further therapeutic intervention, regardless of whether pharmacological- or device-related, has no significant impact on short- or long-term mortality (De Backer 2010; Hermansen 2011; Shpektor 2010).

Why it is important to do this review

While there is a broad body of evidence for the treatment of people with acute coronary syndromes (ACS) under stable haemodynamic conditions, there is only poor evidence, due to the low number of trials, for treatment strategies for people who become haemodynamically unstable or develop CS. These findings are correlated with limited or controversial treatment recommendations in the case of haemodynamic instability or shock (Buerke 2011). The German-Austrian S3 Guideline provides the first dedicated guidance for the treatment of infarct-related CS (Werdan 2012). These recommendations reveal the lack of evidence for all recommended therapeutic measures (De Waha 2012). In contrast to the established recommendation of intra-aortic balloon pump (IABP) support in infarct-related CS (strong recommendation on the basis of small studies), a recent, large randomised controlled trial showed that there is no survival benefit for people treated with IABP (Thiele 2012; Thiele 2013). Randomised clinical trials are difficult to perform and costly in people with CS or LCOS. However, as AMIs are frequent and CS is associated with high mortality, any mortality-reducing intervention is likely to have major public health implications and should be thoroughly tested.

Vasopressors are relevant to this review but were excluded, as they are the topic of another Cochrane Review on vasopressors in hypotensive shock (Gamper 2016).

Most of the existing randomised trials of people with CS have showed improved haemodynamics without effects on other relevant outcomes (Thiele 2009; Triumph 2007; Unverzagt 2011). Such improved haemodynamic status might not be a suitable surrogate marker for survival. Provided that quality of life is not compromised, all-cause mortality constitutes the ultimate proof of patient benefit.

OBJECTIVES

To assess efficacy and safety of cardiac care with positive inotropic agents and vasodilator strategies in people with CS or LCOS due to AMI, HF or cardiac surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) of parallel-group design that evaluated efficacy and safety within a follow-up including at least the in-hospital period (reports of mortality). We excluded cross-over trials due to the investigation of all-cause mortality as the primary outcome. Our focus was on the acute setting and, therefore, we excluded prevention trials and long-term studies (treatment lasting one month or more).

Abstracts or unpublished data were included only if sufficient information on study design, characteristics of participants, interventions and outcomes was available, or if the full information and final results were confirmed by contact with the first author.

Types of participants

Adult patients, aged 18 years and over, with acute LCOS (medium risk study population) or CS (high risk study population) with a follow-up period that included at least hospitalisation.

Types of interventions

- Experimental intervention: we summarised treatments with investigational single drugs or combinations (whatever the dosage or intensity and mode, frequency, timing and duration of delivery) in one intervention group per substance. Therapeutic regimens were 'investigational' if they had been recently introduced into clinical practice or were compared to accepted therapeutic strategies, no matter whether these drugs had been investigated in regard to therapeutic efficacy or superiority.
- Control intervention: treatments without specific experimental single drugs or corresponding combinations, or treatment options including other inotropic or vasodilative drugs. We summarised placebo or no treatment in one control group.

Types of outcome measures

Primary outcomes

- All-cause mortality (short term: in hospital or intensive care unit (ICU) up to four months; long term: 6 to 12 months)

Secondary outcomes

- Major adverse cardiac events (MACE), including in-hospital death, coronary artery bypass graft (CABG) surgery, stroke or transient ischaemic attack, AMI, and repeat PCI at the same site during the index hospital stay (Moscucci 2005) (in hospital or ICU)
- Length of hospital stay
- Quality of life (in hospital or ICU)
- Haemodynamics (cardiac index, mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP) (in hospital or ICU)
- Adverse events (in hospital or ICU)
- Costs (in hospital or ICU)

Search methods for identification of studies

We conducted searches in co-operation with Cochrane Heart to identify published and unpublished RCTs.

Electronic searches

We updated our searches in the following databases on 22 June 2017; Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5) in the Cochrane Library, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and MEDLINE (Ovid, 1946 to 22 June 2017), Embase Classic and Embase (Ovid, 1947 to 21 June 2017) and CPCI-S (Conference Proceedings Citation Index-Science) Web of Science (Thomson Reuters, 1990 to 22 June 2017).

We used a combination of subject headings and text strings relating to CS, LCOS, drug therapy and comparative therapy trials to construct the search strategy for the review (Appendix 1). We applied the Cochrane sensitivity-maximising RCT search filter to MEDLINE and adaptations of it to Embase and Web of Science (Lefebvre 2011). No language restrictions were imposed.

We also searched the following registers of ongoing and completed trials (Appendix 1).

- controlled-trials.com (28 July 2017)
- centerwatch.com (28 July 2017)
- clinicalTrials.gov (28 July 2017)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) apps.who.int/trialsearch (28 July 2017).

Searching other resources

We contacted members of Cochrane Heart, experts in the field, and manufacturers of the drugs (Carinoharm GmbH Germany, Fresenius Kabi Germany, Orion Corporation Finland, Sanofi Aventis Deutschland GmbH Germany, UCB Pharma GmbH Germany) for further information. In addition, we scanned reference lists from eligible trials and contacted the first authors to obtain further information on study design and to collect individual participant data.

Data collection and analysis

Selection of studies

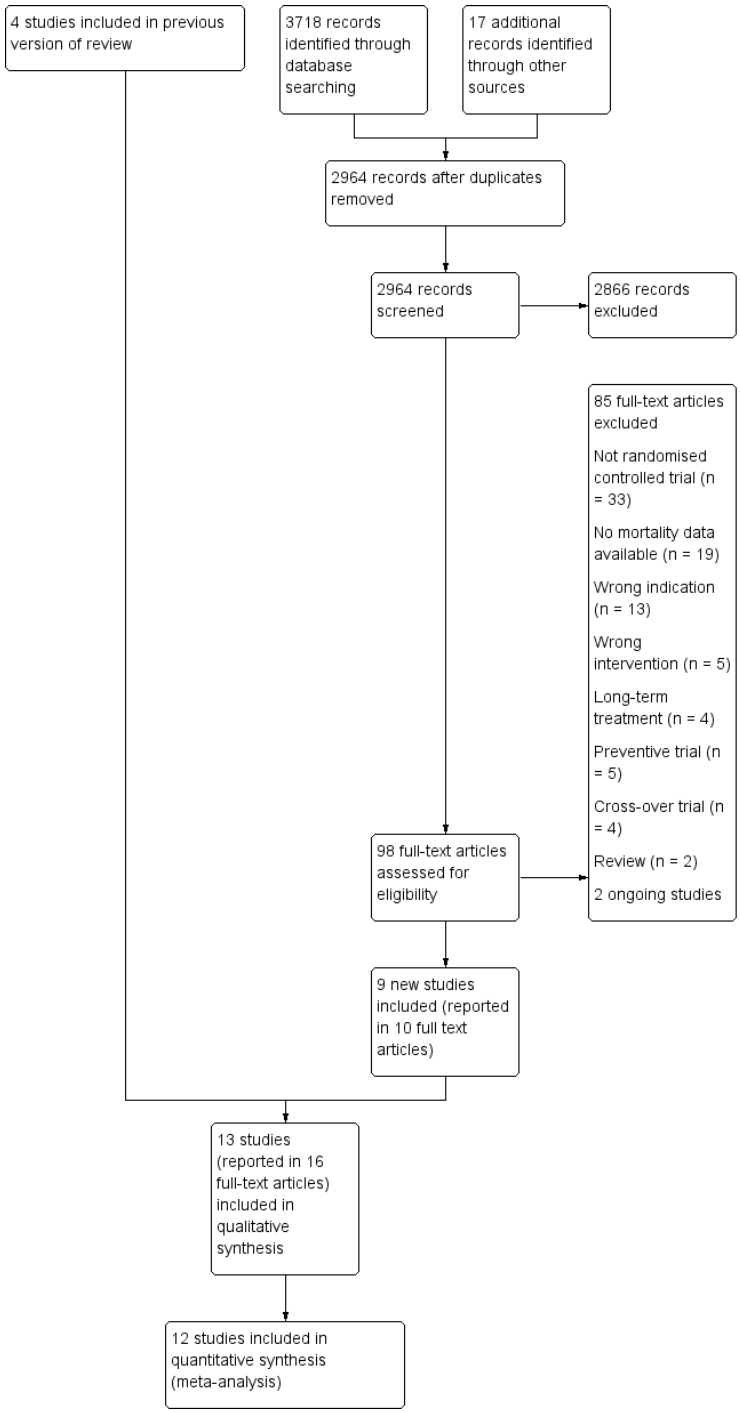
Two review authors (JS plus HS and EH plus SW) independently screened studies identified using the search strategy described above by title, keywords and abstract. We accessed the full articles for further assessment if the information given suggested that the study:

- included participants with AMI, HF or cardiac surgery complicated by CS or LCOS;

- compared
    - cardiac care with versus without inotropic therapies, or
    - cardiac care with versus without therapies having vasodilator properties;
- used designs with randomised allocation of participants; and
- included primary data.

We settled differences in opinion by consensus with a third review author (SU or SF). After the exclusion of non-relevant publications and duplicates, we assessed the full-text versions of the remaining papers against the inclusion and exclusion criteria, extracted data and entered them into standardised data extraction tables. We recorded the selection process in a PRISMA flow chart according to Moher 2009 (Figure 1).

Figure 1. Study flow diagram



Data extraction and management

Two review authors independently extracted the details of study population, interventions and outcomes (EH, HS). The data extraction tables included the following items.

- General information: title, authors, source, contact address, country, published or unpublished, language and year of publication, sponsoring of trial
- Trial characteristics including study design, timing and follow-up, and quality assessment as specified above
- Participants: inclusion and exclusion criteria, definition of indication, baseline characteristics, similarity of groups at baseline, number of people eligible/randomised/completing/analysed, reasons for withdrawals/loss to follow-up.
- Interventions: dosage, route and timing of drug therapy and comparison intervention
- Outcomes: participants per group, mortality at specific time points (in hospital or ICU, 28 or 30 days, 6 and 12 months), adverse effects (with definitions, methods for monitoring), MACE, haemodynamics (cardiac index, MAP, PCWP), length of hospital and ICU stay, quality of life, costs.

The two review authors who performed data extraction resolved any differences by consensus with a third review author (JS), referring back to the original article. As this review was planned as an individual participant data (IPD) meta-analysis, we contacted the first authors of all eligible trials (SU) and asked them to provide IPD and other missing information. We compared IPD provided by the trial authors with the extracted, published results and checked them for consistency.

Assessment of risk of bias in included studies

Two review authors (EH, HS) independently assessed the internal validity of eligible studies according to the Cochrane 'Risk of bias' tool (Higgins 2011a), resolving any disagreements by discussion until consensus was obtained. We described risk of bias and judged it as high, low or unclear in six specific domains:

- random sequence generation;
- allocation concealment;
- double blinding of participants, personnel and outcome assessment;
- incomplete outcome data addressed;
- selective reporting;
- other sources of bias (cross-over, baseline differences regarding the most important prognostic factors, conduct of the study affected by interim results, deviation from the study protocol, not reflecting clinical practice, inappropriate administration of an intervention, contra-active or similar pre-randomisation intervention).

We used the following items to assess the quality of evidence on adverse effects (AEs) (Higgins 2011a).

- Are definitions of reported AEs given?
- Were the methods that were used for monitoring AEs reported (e.g. use of prospective or routine monitoring; spontaneous reporting; participant checklist, questionnaire or diary; systematic survey of participants)?
- Were any participants excluded from the AE analysis?
- Does the report provide numerical data by intervention group?
- Which categories of AEs were reported by the investigators?

Measures of treatment effect

We presented effect measures for the primary endpoint (all-cause mortality) of the RCTs as risk ratios (RRs) with their 95% confidence intervals (CIs) and short-term (less than six months) follow-up periods.

We used RRs and 95% CIs to compare frequencies of MACE events. We calculated mean differences and 95% CIs as effect measures for haemodynamic measures. The data on haemodynamics (cardiac index, MAP, PCWP), length of hospital and ICU stay were reported differently for the included studies and are summarised in an additional table. No information on quality of life or costs was available from the eligible trials.

Unit of analysis issues

We randomised participants individually into treatment groups. The unit of analysis was the individual participant with one single measurement for each outcome.

Dealing with missing data

If data were not available in the trial report or data collection, we contacted the trial investigators to provide missing data.

Assessment of heterogeneity

This systematic review brings together diverse material, with studies differing in the participants, interventions and exposure times, therefore we did not expect a single-study effect and planned to apply a random-effects model. To quantify the extent of variability among the studies we planned to estimate the Q-test for heterogeneity in order to quantify heterogeneity as a proportion of variability with Thompson's I^2 statistic and to calculate the between-study variance τ^2 (Higgins 2002; Rücker 2008).

The following factors are possible sources of clinically relevant heterogeneity and we have summarised them in the table Characteristics of included studies.

- Different variations of standard therapies (other vasoactive drugs, revascularisation, IABP, mechanical ventilation, renal replacement therapy)
- Different variations of the experimental intervention (doses and scheduling)
- Different variations of control groups (treatment without investigated single drugs or combinations, treatment with placebo, or no treatment)
- Differences in outcome-relevant prognostic factors (age, gender, co-morbidities, cardiac index, ejection fraction, time from symptom onset to intervention)
- Different definition of the indication (CS versus LCOS)
- Quality of studies

Assessment of reporting biases

The use of funnel plots for the graphical detection of publication bias was not possible due to the small number of eligible trials.

Data synthesis

The analysis was based on the intention-to-treat (ITT) principle. We undertook meta-analyses on the basis of the random-effects model of comparable studies with reference to the expected clinical heterogeneity arising from differences in study characteristics and the associated assumption that the effects being estimated in the different studies were not identical, but followed some distribution.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for all-cause mortality with regard to sex, age, and cause of LCOS/CS. We conducted subgroup analyses for the comparison levosimendan versus control (Analysis 1.2, Analysis 1.4) but not for other treatment strategies due to lack of available data.

Sensitivity analysis

We performed the following sensitivity analyses.

- Only including studies with a low risk of bias (at least six of seven 'Risk of bias' domains need to be of low risk of bias).
- Comparing results of the random-effects model and the fixed-effect model.

'Summary of findings' table and GRADE assessment

We created 'Summary of findings' tables using GRADEpro GDT (GRADEpro GDT 2015) to summarise evidence and included our primary outcome (short-term, all-cause mortality) (Guyatt 2011a; Guyatt 2013). We estimated the assumed risk of death in the control group with standard cardiac care on the basis of estimated mortality risks from Singh 2007 for people with CS. We used the five GRADE considerations (study limitations, inconsistency, imprecision, indirectness and other considerations) to rate our overall confidence in effect estimates. We used methods and recommendations as described in GRADE to rate the quality of evidence (Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f) and justified all decisions to downgrade the quality of evidence using footnotes. We added comments to aid the reader's understanding of the review where necessary (Santesso 2016).

We used the median risk among control groups to describe the baseline risk for people with low cardiac output syndrome (moderate risk). In the case of one study with participants with low cardiac output syndrome, we used the control group risk from this study. Due to the small size of included studies of people with CS or mixed populations, we also used the control group risk from a well-designed observational study to describe the high baseline risk for people with CS (Singh 2007).

RESULTS

Description of studies

Results of the search

The previous version of this review included four studies. We updated the searches to identify any new potentially relevant references and identified a total of 2964 references after duplicates had been removed. In total, we thought 98 full-text papers were of relevance and assessed them against the inclusion and exclusion criteria. Of these, nine new studies (reported in 10 full-text papers) met our predefined inclusion criteria (see Characteristics of included studies). The remaining studies are listed in Characteristics of excluded studies. We recorded the process in a PRISMA flow chart (Figure 1).

Included studies

Thirteen randomised controlled trials met the inclusion criteria. Four of these investigated people with AMI complicated by CS or LCOS (Baldassarre 2008; Fuhrmann 2008; Garcı a-González 2006; Husebye 2013), four investigated people with acute HF complicated by CS or LCOS (Adamopoulos 2006; Follath(LIDO) 2002; Levy 2011; Mebazaa (SURVIVE) 2007), and five investigated people with cardiac surgery complicated by CS or LCOS (Alvarez 2006; Atallah 1990; Dupuis 1992; Levin 2008; Rosseel 1997).

The majority of published clinical trials examined levosimendan (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Fuhrmann 2008; Garcı a-González 2006; Husebye 2013; Levin

2008; Mebazaa (SURVIVE) 2007). There was only one trial investigating epinephrine (Levy 2011), one trial investigating dopexamine (Rosseel 1997), one trial investigating enoximone (Atallah 1990), one trial investigating amrinone (Dupuis 1992), and one trial investigating nitric oxide (Baldassarre 2008). Control group participants were treated with dobutamine (Adamopoulos 2006; Alvarez 2006; Atallah 1990; Dupuis 1992; Follath(LIDO) 2002; Garcı a-González 2006; Levin 2008; Mebazaa (SURVIVE) 2007), dopamine (Rosseel 1997), enoximone (Fuhrmann 2008), norepinephrine-dobutamine (Levy 2011), or placebo (Adamopoulos 2006; Baldassarre 2008; Husebye 2013).

Eight studies were conducted as single-centre trials in Spain (Alvarez 2006; Garcı a-González 2006), France (Atallah 1990; Levy 2011), Germany (Fuhrmann 2008), Greece (Adamopoulos 2006), Norway (Husebye 2013), and in Canada (Dupuis 1992). Four studies were conducted as multi-centre trials in Argentina (Levin 2008), the Netherlands plus Belgium (Rosseel 1997), Europe (Follath(LIDO) 2002), or Europe, Israel and Russia (Mebazaa (SURVIVE) 2007). One trial (Baldassarre 2008) was planned as a multi-centre trial in Europe and the USA; this trial was stopped early due to low enrolment rates.

Each study characteristic is presented briefly in the table Characteristics of included studies. We included Information from two secondary publications of one included trial (Garcı a-González 2006). A more comprehensive assessment of the included studies is given below.

Participants

Altogether, 1828 participants were enrolled in the trials on levosimendan; 905 were treated with levosimendan, and 923 served as controls and were treated with dobutamine (23 participants in Adamopoulos 2006, 20 participants in Alvarez 2006, 97 participants in Follath(LIDO) 2002, 11 participants in Garcı a-González 2006, 68 participants in Levin 2008, 660 participants in Mebazaa (SURVIVE) 2007), enoximone (16 participants in Fuhrmann 2008) or placebo (23 participants in Adamopoulos 2006, five participants in Husebye 2013). Husebye 2013 included 61 participants with AMI complicated by acute HF. The trial authors provided additional information and IPD on all participants with CS (n = 9). The trial on epinephrine (Levy 2011) included 30 participants, with 15 of them receiving norepinephrine-dobutamine as control. The trial on dopexamine (Rosseel 1997) included 70 participants with 35 of them receiving dopamine as control. The trial on amrinone (Dupuis 1992) included 30 participants with 15 of them receiving dobutamine as control. And the trial on enoximone (Atallah 1990) included 40 participants with 20 of them receiving dobutamine as controls. The trial on nitric oxide (Baldassarre 2008) included only three participants at two centres in the USA. These were two men and one woman, with a mean age of 69 years. Two of them received nitric oxide and one placebo. The trial authors provided no further information on their participants.

The mean or median age varied between 58 and 73 years. Husebye 2013 excluded participants under 20 years of age, Follath(LIDO) 2002 excluded participants under 21 years of age, and Rosseel 1997 excluded participants over 75 years of age. No age restriction was described in Adamopoulos 2006; Alvarez 2006; Atallah 1990; Dupuis 1992; Fuhrmann 2008; Garcı a-González 2006; Levin 2008; Levy 2011, and Mebazaa (SURVIVE) 2007. Between 44% (Alvarez 2006) and 90% (Dupuis 1992) of participants in the included trials were male. Time of randomisation varied between trials. Participants in Fuhrmann 2008 had to be included within two hours following PCI and 24 hours of CS, participants in Husebye 2013 needed a median time of three hours from start of AMI symptoms to PCI, participants in Alvarez 2006 had to be included within four hours post cardiac surgery, participants in Levin 2008 within six hours post cardiac surgery, and participants in Atallah 1990 within 24 hours post cardiac surgery. Information concerning time of randomisation was unavailable in Adamopoulos 2006; Dupuis 1992; Follath(LIDO) 2002; Garcı a-González 2006; Levy 2011; Mebazaa (SURVIVE) 2007, and Rosseel 1997.

Baseline MAP varied between 55 ± 9 mmHg and 54 ± 8 mmHg in Levy 2011's two treatment groups, and 85 ± 18 mmHg and 84 ± 14 mmHg in Atallah 1990's two treatment groups. Baseline cardiac index varied between 1.6 ± 0.4 L/min*m^2 in both treatment groups of Levy 2011, and 2.3 (interquartile range (IQR) 2.1 to 2.5) L/min*m^2 and 2.2 (IQR 1.7 to 2.4) L/min*m^2 in the two treatment groups of Fuhrmann 2008. Baseline PCWP varied between 12.6 ± 2.8 mmHg and 13.2 ± 2.4 mmHg in the two treatment groups of Rosseel 1997, and 27 ± 5 mmHg in Garcı a-González 2006. Information concerning baseline MAP, cardiac index or PCWP was unavailable in Mebazaa (SURVIVE) 2007 and Dupuis 1992 only displayed these data graphically.

Participants in all trials were treated at the time of randomisation with different vasoactive drugs including diuretics (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007), ACE inhibitors (Adamopoulos 2006; Follath(LIDO) 2002; Levy 2011; Mebazaa (SURVIVE) 2007), beta blockers (Adamopoulos 2006; Dupuis 1992; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007), nitrates (Dupuis 1992; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007), dopamine (Dupuis 1992; Mebazaa (SURVIVE) 2007), digitalis (Atallah 1990; Garcı a-González 2006), aldosterone antagonists (Adamopoulos 2006; Levy 2011; Mebazaa (SURVIVE) 2007), digoxin (Alvarez 2006; Follath(LIDO) 2002; Levin 2008), catecholamines (Fuhrmann 2008; Husebye 2013; Levin 2008), and calcium channel blockers (Dupuis 1992; Follath(LIDO) 2002).

According to the inclusion and exclusion criteria described, six studies included solely participants suffering from LCOS (Adamopoulos 2006; Alvarez 2006; Atallah 1990; Dupuis 1992; Levin 2008; Levy 2011), five studies included solely participants suffering from CS (Baldassarre 2008; Fuhrmann 2008;

García-González 2006; Husebye 2013; Rosseel 1997), and two studies included participants suffering from either LCOS or CS (Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007).

Interventions

Eight included trials investigated the efficacy and safety of the calcium-sensitiser levosimendan in combination with established therapeutic regimens. The comparisons were the following.

- Adamopoulos 2006: levosimendan 6 µg/kg over 10 minutes, followed by a constant rate of 0.1 µg/kg/minute for 24 hours compared with either placebo (5% dextrose) or 5 µg/kg/min dobutamine for 24 hours; the infusion rate of dobutamine was gradually doubled if an adequate haemodynamic response was not achieved after two hours.
- Alvarez 2006: levosimendan 12 µg/kg over 15 to 20 minutes, followed by a constant rate of 0.2 µg/kg/minute for 24 hours compared with 7.5 µg/kg/minute dobutamine for 24 hours.
- Follath(LIDO) 2002: levosimendan 24 µg/kg over 10 minutes, followed by a constant rate of 0.1 µg/kg/minute compared with 5 µg/kg/min dobutamine; the infusion rate of either levosimendan or dobutamine was doubled if an adequate haemodynamic response was not achieved after two hours.
- Fuhrmann 2008: levosimendan 12 µg/kg over 10 minutes, followed by a constant rate of 0.1 µg/kg/minute for 50 minutes and 0.2 µg/kg/minute for 23 hours compared with 0.5 µg/kg enoximone for 30 minutes followed by 2 to 10 µg/kg/minute continuously titrated to the best haemodynamic response.
- García-González 2006: levosimendan 24 µg/kg over 10 minutes followed by a constant rate of 0.1 µg/kg/minute for 24 hours compared with 5 µg/kg/min dobutamine for 24 hours; if an adequate haemodynamic response was not achieved after two hours, the infusion rate of dobutamine was doubled until the desired haemodynamic response was achieved.
- Husebye 2013: levosimendan at a constant rate of 0.2 µg/kg/minute for one hour followed by a constant rate of 0.1 µg/kg/min for 24 hours compared with placebo.
- Levin 2008: levosimendan 10 µg/kg over one hour followed by a constant rate of 0.1 µg/kg/minute for 24 hours compared with 5 µg/kg/minute dobutamine for 24 hours; the infusion rate of dobutamine was increased at 15-minute intervals to 7.5/10/12.5 µg/kg/minute if no adequate haemodynamic response was achieved.
- Mebazaa (SURVIVE) 2007: levosimendan 12 µg/kg over 10 minutes followed by a constant rate of 0.1 µg/kg/minute for 50 minutes followed by a constant rate of 0.2 µg/kg/minute for 23 hours (if tolerated) compared with 5 µg/kg/minute dobutamine for at least 24 hours; the infusion rate of dobutamine could be increased to a maximum rate of 40 µg/kg/minute if no adequate haemodynamic response was achieved.

One included trial investigated the efficacy and safety of epinephrine:

- Levy 2011: 0.1 µg/kg/minute epinephrine compared with 0.1 µg/kg/min norepinephrine-dobutamine; both treatment groups were titrated on MAP at 5-minute intervals to obtain a MAP of between 65 and 70 mmHg with a stable or increased cardiac index.

One included trial investigated the efficacy and safety of dopexamine:

- Rosseel 1997: 0.5/1.0/2.0 mg/kg/minute dopexamine for six hours compared with 1.5/3.0/6.0 mg/kg/min dopamine for six hours; both treatment groups were titrated in three steps at 15-minute intervals until a cardiac index greater than 2.5 L/min/m^2 was reached.

One included trial investigated the efficacy and safety of enoximone:

- Atallah 1990: 1 mg/kg enoximone over 10 minutes, followed by a mean dosage of 5 to 10 µg/kg/minute compared with a mean dosage of 5 to 10 µg/kg/min dobutamine.

One included trial investigated the efficacy and safety of amrinone:

- Dupuis 1992: 0.75 mg/kg amrinone, immediately followed by a constant rate of 10 µg/kg/minute for five minutes (if the treatment objectives were not achieved another 0.75 mg/kg were given) compared with 5 µg/kg/minute dobutamine for 5 to 10 minutes (if the treatment objectives were not achieved, stepwise increase to 15 µg/kg/minute).

One included trial planned to investigate the efficacy and safety of inhaled nitric oxide:

- Baldassarre 2008: 40 ppm or 80 ppm nitric oxide over eight hours followed by a constant rate of 40 ppm compared with placebo (40 ppm nitrogen gas) over eight hours.

Excluded studies

We excluded 33 trials because they were not RCTs (Affonti 2013; Andriange 1971; Aronski 1978; Belskii 1987; Bussmann 1983; Caimmi 2011; Canella 1981; Clark 1983; De Monte 1986; Delle Karth 2003; Dhainaut 1990; Estanove 1988; Fowler 1980; Friedle 1992; Gray 1981; Hobbs 1998; Lanfear 2009; Lima 2010; Lopez 1997; Lvoff 1972; Nadjamabadi 1980; Orellano 1991; Russ 2009; Santman 1992; Shah 2014; Sterling 1984; Tacon 2012; Tritapepe 1999; Tritapepe 2009; Tzimas 2009; Verma 1992; Wright 1992; Zerkowski 1992). Information on mortality was missing in 19 studies (Carmona 2010; Duygu 2008; Feneck 2001; Galinier 1990; George 1989; Gunnicker 1995; Kikura 1997; Kikura 2002; Lancon 1990; MacGregor 1994; Meissner 1996; Nijhawan 1999; Patel 1993; Seino 1996; Slawsky 2000; Sunny 2016; Timewell 1990; Wimmer 1999; Zwölfer 1995). We excluded 13 trials due to wrong indication (Al-Shawaf 2006; Barisin 2004; Cotter 2003; Cuffe 2002; Erb 2014; Felker 2003; Landoni 2017; Levin 2012;

Lilleberg 1998; Mehta 2017; Meng 2016; O'Connor 1999; Packer 2013), and five trials due to wrong intervention (Avanzini 2002; Beller 1995; Genth-Zotz 2000; Ochiai 2014; Pouleur 1992). An additional four trials performed long-term treatment (Berger 2007; Jondeau 1994; Mavrogeni 2007; Stanek 1999). Five studies investigated the preventive use of inotropic agents or vasodilator strategies (Butterworth 1993; De Hert 2007; Hoffman 2003; Lechner 2012; Sharma 2014), and four trials used a cross-over design (Dominguez-Rodriguez 2007; Ferrario 1994; Loeb 1971; Richard 1983). Furthermore, we screened two reviews (Kaplan 1980; Perret 1978) for eligible trials. Reasons for exclusion are presented briefly in tabulated form (see Characteristics of excluded studies).

Ongoing studies

We identified two ongoing studies investigating sodium nitroprusside versus dobutamine (NCT02767024) and milrinone versus dobutamine (NCT03207165) for CS treatment. For details of the planned investigations in tabulated form please see Characteristics of ongoing studies.

Risk of bias in included studies

All trials were published in peer-reviewed journals. Trials acknowledging funding by the pharmaceutical industry were Dupuis 1992 (supported by a grant from Sanofi-Winthrop); Follath(LIDO) 2002 (supported by Quintiles/Innovex (study management), Ercopharma, and a grant from Orion Pharma, which was involved in the study design, planning/running of the statistical analyses, and preparation of the trial report); Husebye 2013 (received an unrestricted educational grant from Orion Pharma); and Mebazaa (SURVIVE) 2007 (supported by Orion Pharma and Abbott Laboratories). In Levy 2011 conflict of interest was not disclosed. No clinical report or final publication was published on the trial on nitric oxide but the results were confirmed by contact with the responsible investigator.

Included trials were small and the number of included participants ranged from three to 199, with the exception of Mebazaa (SURVIVE) 2007, who enrolled 1320 participants. In all trials analysis was done by ITT. Figure 2 and Figure 3 present a summary of all investigated sources of bias in the thirteen eligible studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

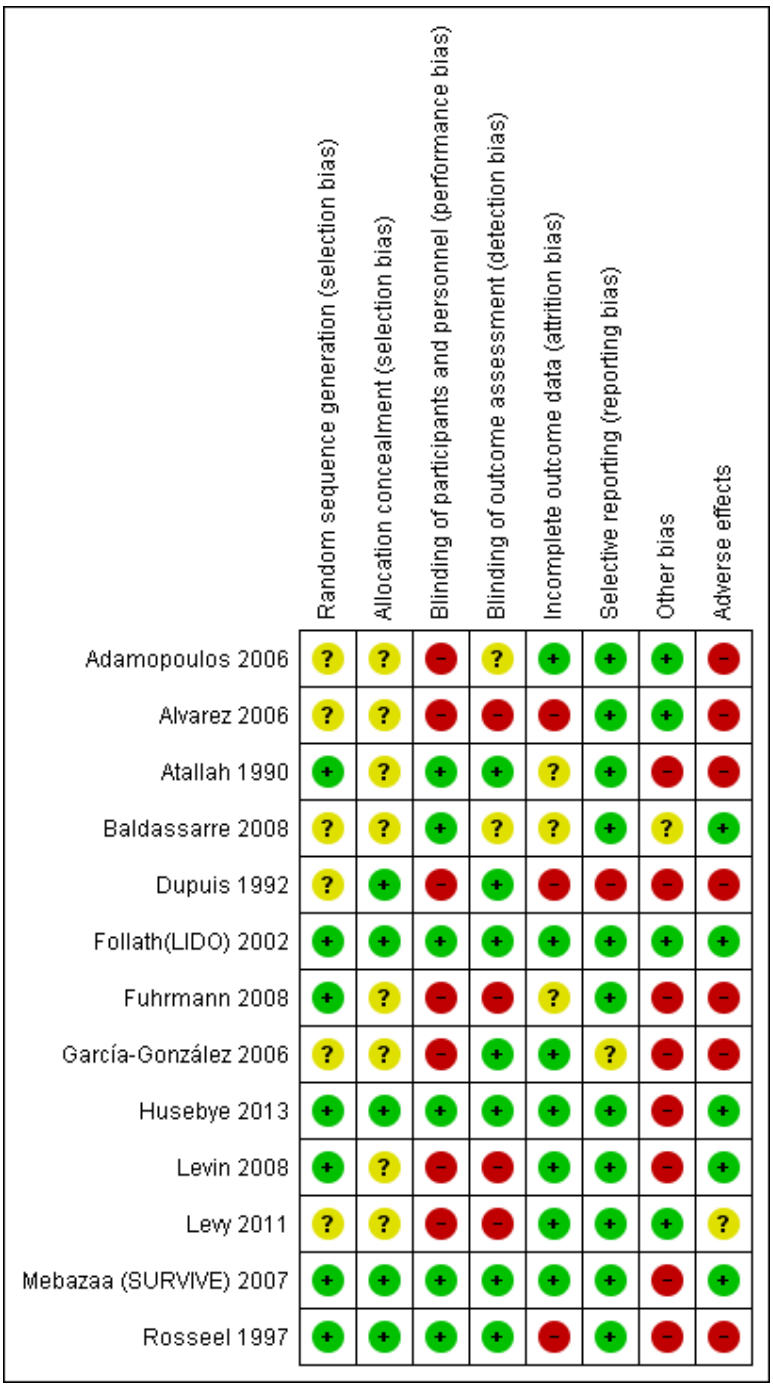
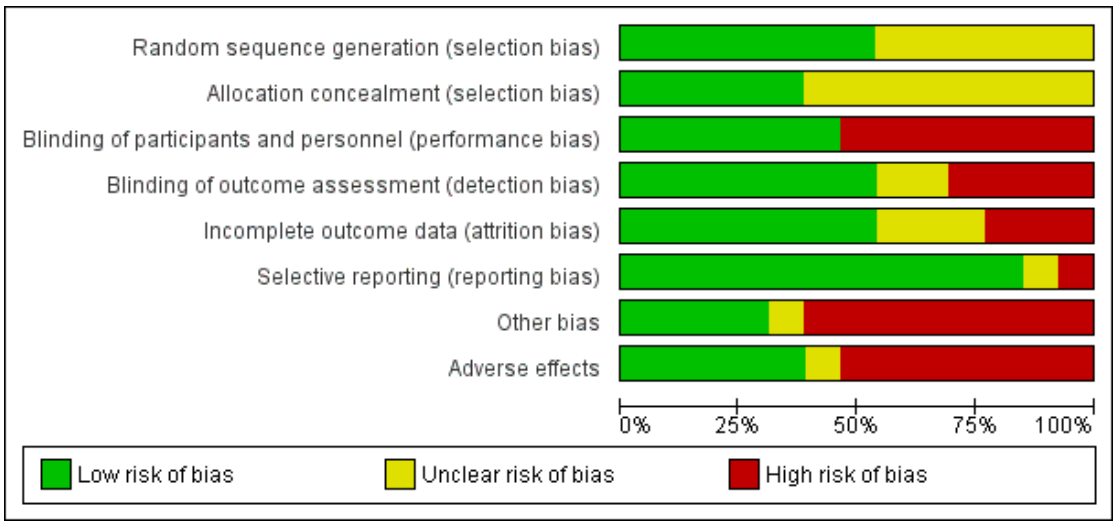


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Random sequence generation (selection bias)

The method of sequence generation was reported in eight trials (Atallah 1990; Dupuis 1992; Follath(LIDO) 2002; Fuhrmann 2008; Husebye 2013; Levin 2008; Mebazaa (SURVIVE) 2007; Rosseel 1997). Follath(LIDO) 2002; Fuhrmann 2008; Husebye 2013; Levin 2008; and Rosseel 1997 used blocked random tables by means of a computer random number generator with Husebye 2013 using an extra stratum for participants with CS. Atallah 1990 performed sequence generation by drawing of lots. Mebazaa (SURVIVE) 2007 randomised participants centrally, using an interactive, voice-response system, stratified by a biased coin algorithm with previous acute decompensated heart failure and country as factors. Dupuis 1992 randomised participants according to their ability to separate from cardiopulmonary bypass.

Allocation

Dupuis 1992; Follath(LIDO) 2002; Husebye 2013; Mebazaa (SURVIVE) 2007 and Rosseel 1997 described the method of allocation concealment. Allocation was performed by a blinded investigator according to a pre-determined list. No information was available from the other eight trials.

Blinding

Risk of bias due to performance or detection was low in Atallah 1990; Follath(LIDO) 2002; Husebye 2013; Mebazaa (SURVIVE) 2007, and Rosseel 1997. In Adamopoulos 2006; Alvarez 2006; Levin 2008, and Fuhrmann 2008 blinding was either not performed or not possible due to different timing of administration of the study drug. In Garca-González 2006 and Dupuis 1992 outcome assessment was blinded but not personnel/participants. Levy 2011 was described both as an open-label study and as a double-blind study but no further information was provided.

Incomplete outcome data

The included studies investigated all-cause mortality, haemodynamics, MACE and AEs. Eight studies (Atallah 1990; Follath(LIDO) 2002; Fuhrmann 2008; Garca-González 2006; Husebye 2013; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007) reported 30-day follow-up data on all-cause mortality distribution. Four trials (Follath(LIDO) 2002; Garca-González 2006; Husebye 2013; Mebazaa (SURVIVE) 2007) reported six-month follow-up data on all-cause mortality distribution. Nine trials with follow-up times ranging from 6 to 72 hours reported haemodynamic, post-interventional data (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Fuhrmann 2008; Garca-González 2006; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007; Rosseel 1997), but data concerning CI, MAP, and PCWP were

given solely in Adamopoulos 2006; Alvarez 2006; Fuhrmann 2008; García-González 2006; Levin 2008; Levy 2011; and Rosseel 1997. MACE events were reported during the study drug infusion, time in hospital, over 30 days or up to six months.

Five studies reported exclusion of participants (Alvarez 2006; Atallah 1990; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007; Rosseel 1997). Dupuis 1992 presented full data for solely 43% of enrolled participants. Fuhrmann 2008 reported haemodynamic changes in 36 participants but randomised only 32 participants.

Selective reporting

Adamopoulos 2006; Alvarez 2006; Atallah 1990; Follath(LIDO) 2002; Fuhrmann 2008; García-González 2006; Husebye 2013; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007, and Rosseel 1997 reported all primary outcomes pre-specified in the method section. Pre-specified secondary endpoints were missing in García-González 2006. Baldassarre 2008 had restricted reporting on mortality and adverse events. Dupuis 1992 gave only part of the outcomes for subgroups of treatment groups, called "Blocks".

Other potential sources of bias

None of the included trials reported any cross-over or deviation from the study protocol.

There were some potentially important baseline differences in prognostic factors such as sex, timetable or co-morbidities in Atallah 1990; Dupuis 1992; Fuhrmann 2008; García-González 2006; Husebye 2013, and Rosseel 1997. No information on baseline differences was available for the trial with a subgroup of participants with CS (Husebye 2013).

The conduct of two trials was affected by interim results. Fuhrmann 2008 was stopped after recruitment of 36% of the pre-planned sample size as a result of a planned interim analysis, due to a trend toward reduced mortality for levosimendan. In Mebazaa (SURVIVE) 2007 the originally targeted number of participants (n = 700) was increased to 1320 following a blinded review of mortality after 131 deaths to achieve the target number of 330 deaths.

Three trials reported inappropriate delivery, with interruptions of study drug administration. In Follath(LIDO) 2002 (203 participants enrolled) four participants (2.0%) did not receive the study drug at all (one in levosimendan group, three in dobutamine group), 16 participants (7.8%) were classified as permanent discontinuation before 24 hours owing to adverse events or insufficient clinical response (six in levosimendan group, 10 in dobutamine group), 11 participants (5.4%) were prone to a temporary interruption due to a dose-limiting event (five in levosimendan group, six in dobutamine group), and 14 participants (6.9%) received the study drug for less than 18 hours (six in levosimendan group, eight in dobutamine group). In Mebazaa (SURVIVE) 2007 (1220 participants receiving study drug) 71 participants (5.8%) discontinued the intervention due to adverse events (30 in levosimendan group, 41 in dobutamine group). In Husebye 2013 discontinuation was necessary in one participant (1.6%) from the levosimendan group due to atrial fibrillation and one participant (1.6%) from the placebo group due to hypotension, although these participants were in CS.

All clinical trials evaluating shock participants addressed the problem of pre-randomisation drug-treatment strategies. Most of the included trial participants were not randomised to the study drug at the index event (onset of LCOS/CS) and they were therefore pre-treated with different inotropic and vasoactive drugs, which could have influenced their microcirculation and thereby affected prognosis.

To the best of our knowledge no trial used a complex standardised study protocol for vasopressor down-titration for the assessment of the lowest necessary vasopressor dosage in each individual participant.

Although the title and inclusion criteria of the study conducted by García-González 2006 implied that the enrolled participants suffered from CS-complicating AMI, there remained major concerns regarding the eligibility of the included participants. This was because none of them developed multi-organ failure and the mortality rates appeared very low in comparison to commonly reported data.

Bias affecting the quality of evidence on adverse events

Reports on AEs were missing in two trials (Adamopoulos 2006; García-González 2006). Only Husebye 2013 and Levin 2008 gave definitions of the reported AEs. Information on monitoring of AEs was restricted to Follath(LIDO) 2002; Husebye 2013, and Mebazaa (SURVIVE) 2007. Follath(LIDO) 2002 collected AEs as spontaneous reports without breaking blinding. In Husebye 2013, study personnel blinded to treatment allocation throughout the study period of five days and at the six-week follow-up monitored AEs. Mebazaa (SURVIVE) 2007 collected AEs for 31 days following initial study drug administration and during all blinded drug re-administrations. With the exception of Dupuis 1992, who reported AEs solely for particular Blocks of participants (43%), no trial excluded participants from AE analysis.

Although we were aware of the methodological problems and restrictions, especially in regard to the definition of CS in the study of García-González 2006, we nevertheless decided to include all studies that randomised participants with AMI complicated by CS or LCOS, mainly because of the limited number of trials that were available. The 'Risk of bias' tables of the individual trials are given in Characteristics of included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Levosimendan compared to dobutamine for cardiogenic shock or low cardiac output syndrome; **Summary of findings 2**

Levosimendan compared to placebo for cardiogenic shock or low cardiac output syndrome; **Summary of findings 3** Levosimendan compared to enoximone for cardiogenic shock; **Summary of findings 4** Epinephrine compared to norepinephrine-dobutamine for low cardiac output syndrome; **Summary of findings 5** Amrinone compared to dobutamine for low cardiac output syndrome; **Summary of findings 6** Dopexamine compared to dopamine for cardiogenic shock or low cardiac output syndrome; **Summary of findings 7** Enoximone compared to dobutamine for low cardiac output syndrome; **Summary of findings 8** Nitric oxide compared to placebo for cardiogenic shock

1. Levosimendan versus dobutamine

Three small, single-centre trials with 109 participants (Adamopoulos 2006; Alvarez 2006; Garcı a-González 2006) as well as three multi-centre trials with 1667 participants (Follath(LIDO) 2002; Levin 2008; Mebazaa (SURVIVE) 2007) investigated levosimendan compared with dobutamine in people with AMI (Garcı a-González 2006), acute HF (Adamopoulos 2006; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007), or cardiac surgery (Alvarez 2006; Levin 2008) complicated by CS/LCOS with low-quality evidence.

All-cause mortality

Short-term

A lower all-cause mortality was reported, with 96 deaths out of 891 participants (10.7%) in the intervention arm with levosimendan compared with 131 deaths out of 885 participants (14.8%) in the control groups treated with dobutamine (RR 0.60, 95% CI 0.37 to 0.95; participants = 1776; studies = 6; low-quality evidence) with low heterogeneity between single studies (I^2 = 35%) (Summary of findings for the main comparison; Analysis 1.1). Out of 1000 people with CS, approximately 500 would be expected to die with standard cardiac care with dobutamine (Singh 2007) within a short-term follow-up period compared to 300 (95% CI 185 to 475) with levosimendan (Summary of findings for the main comparison; Analysis 1.1). In people at moderate risk, approximately 154 per 1000 would be expected to die with standard cardiac care with dobutamine compared to 92 (95% CI 57 to 146) with levosimendan (Summary of findings for the main comparison; Analysis 1.1).

Long-term

The protective effect of levosimendan was reduced in the long-term follow-up. Three trials with 1552 participants (Follath(LIDO) 2002; Garcı a-González 2006; Mebazaa (SURVIVE) 2007) reported 200 deaths out of 778 participants (25.7%) in the levosimendan group compared with 223 deaths out of 774 participants (28.8%) in the dobutamine group (RR 0.85, 95% CI 0.65 to 1.12) (Analysis 1.3).

Subgroup analyses

Treatment effects were higher in studies on participants with LCOS due to cardiac surgery (Alvarez 2006; Levin 2008; RR 0.38, 95% CI 0.17 to 0.87) compared to studies on participants with LCOS due to HF (Adamopoulos 2006; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007; RR 0.69, 95% CI 0.42 to 1.11) when investigating levosimendan compared to dobutamine. Only one study compared the effect depending on gender, age and history of congestive HF (Mebazaa (SURVIVE) 2007) (Analysis 1.2). They observed a worse efficacy in participants with no history of congestive HF (RR 1.54, 95% CI 0.82 to 2.87) compared to participants with a history of congestive HF (RR 0.76, 95% CI 0.55 to 1.04).

Sensitivity analyses

A sensitivity analysis showed no differences depending on the statistical model, but there is uncertainty on the result from two studies with blinding of personnel and participants (Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007; RR 0.70; 0.39 to 1.27) (Analysis 2.2). Results from three trials regarding long-term mortality over six months (RR 0.85, 0.65 to 1.12) (Analysis 1.3) were comparable. Sensitivity analysis on the basis of the fixed-effect model (RR 0.73, 95% CI 0.57 to 0.93) (Analysis 2.1) and on the basis of studies with low risk of bias (RR 0.70, 95% CI 0.39 to 1.27) (Analysis 2.2) stated the results from the main analysis.

Major adverse cardiac events (MACE)

Information on MACE was restricted to Garcı a-González 2006 and Levin 2008. Garcı a-González 2006 documented no re-infarction or cerebrovascular accident in either group during hospitalisation (Table 1). Levin 2008 reported perioperative infarction in one out of 69 participants (1.4%) of the levosimendan intervention arm but eight out of 68 participants (11.8%) of the dobutamine intervention arm, and stroke in two out of 69 participants (2.9%) of the levosimendan intervention arm but six out of 68 participants (8.8%) of the dobutamine intervention arm (Table 1).

Length of hospital stay

Information on length of hospital stay was restricted to Levin 2008, which reported a shorter median intensive care unit (ICU) time in the levosimendan intervention arm compared to the dobutamine intervention arm, with high imprecision (66 (IQR 58 to 74) hours compared to 158 (106 to 182) hours) (Table 2).

Quality of life

No results were available from the included studies.

Haemodynamics

Information on cardiac index was restricted to Adamopoulos 2006; Alvarez 2006; Garcı a-González 2006, and Levin 2008; information on pulmonary capillary wedge pressure (PCWP) was restricted to Adamopoulos 2006, and information on mean arterial pressure (MAP) was restricted to Alvarez 2006 and Levin 2008. In every case beneficial effects of levosimendan were reported compared to dobutamine (cardiac index: MD between 0.1 L/min/m^2; 95%CI 0.06 to 0.14 and 0.7 L/min/m^2; 95%CI 0.65 to 0.75; not pooled due to considerable heterogeneity (I^2 = 99%); PCWP: MD -4.0 mmHg; 95% CI -4.6 to -3.4; MAP: MD --2.2 mmHg; 95% CI -4.6 to -0.3) (Analysis 1.5; Analysis 1.6; Analysis 1.7; Table 3).

Adverse events (AEs)

AEs were reported by Alvarez 2006; Follath(LIDO) 2002; Garcı a-González 2006; Levin 2008, and (very detailed) Mebazaa (SURVIVE) 2007. In Garcı a-González 2006, no AEs occurred. Levin 2008 reported a better safety profile of levosimendan compared to dobutamine (Table 4). In contrast, Alvarez 2006; Follath(LIDO) 2002, and Mebazaa (SURVIVE) 2007 did not observed marked differences in the safety profile of the drugs compared (Table 4).

Costs

No results were available from the included studies.

2. Levosimendan versus placebo

Two small, single-centre trials with 55 participants investigated levosimendan compared with placebo in context of people suffering from AMI (Husebye 2013) or acute HF (Adamopoulos 2006) complicated by LCOS/CS with very low-quality evidence.

All-cause mortality

Short-term

No benefit of levosimendan treatment was reported compared to placebo in the short-term follow-up (RR 0.48, 95% CI 0.12 to 1.94; participants = 55; studies = 2; very low-quality evidence) with very low heterogeneity between single studies (I^2 = 0%) (Adamopoulos 2006; Husebye 2013). Out of 1000 people, approximately 500 people with CS would be expected to die within a short-term follow-up period with standard cardiac care (Singh 2007) compared to 240 (95% CI 60 to 970) with levosimendan. In people with moderate risk, approximately 187 per 1000 people would be expected to die with standard cardiac care compared to 90 (95% CI 22 to 363) with levosimendan (Summary of findings 2; Analysis 1.1).

Long-term

No benefit of levosimendan treatment was reported compared to placebo in the long-term follow-up (RR 0.63, 95% CI 0.08 to 4.66) (Husebye 2013).

Subgroup analyses

Subgroup analysis revealed no difference in treatment effects in studies with participants with LCOS due to AMI (Husebye 2013; RR 0.40, 95% CI 0.02 to 7.82) compared to studies on participants with LCOS due to HF (Adamopoulos 2006; RR 0.50; 95% CI 0.10 to 2.47) when investigating levosimendan compared to placebo (Analysis 1.2).

Sensitivity analyses

Sensitivity analysis on the basis of the fixed-effect model (RR 0.47, 95% CI 0.12 to 1.93) stated the results from the main analysis (Analysis 2.1).

MACE

Information on MACE was restricted to Husebye 2013, which reported four of nine participants (44%) with CS to suffer from MACE (Table 1).

Length of hospital stay

No results were available from the included studies.

Quality of life

No results were available from the included studies.

Haemodynamics

Information on haemodynamics was restricted to Adamopoulos 2006, which reported beneficial effects of levosimendan compared to placebo for the cardiac index (MD 0.10 L/min/m^2, 95% CI 0.04 to 0.16) as well as PCWP (MD -4.0 mmHg; 95% CI -4.58 to -3.42) (Table 3). There were no data available for MAP.

Costs

No results were available from the included studies.

AEs

Information on AEs was restricted to Husebye 2013. From the nine participants with CS, two out of four participants (50%) with levosimendan compared to one out of five (20%) participants with placebo suffered from hypotension during drug infusion, with a decrease in MAP of > 10 mmHg. Furthermore, one out of four participants (25%) from the levosimendan intervention arm each suffered from either non-sustained ventricular tachycardia or atrial fibrillation compared to three out of five participants (60%) suffering from non-sustained ventricular tachycardia or no participant suffering from atrial fibrillation in the placebo group (Table 4).

3. Levosimendan versus enoximone

There was only one small, single-centre study with 32 participants investigating levosimendan compared with enoximone in people with AMI complicated by CS (Fuhrmann 2008) with very low-quality evidence.

All-cause mortality

Short-term

There were five deaths out of 16 participants (31.3%) in the intervention arm with levosimendan compared with ten deaths out of 16 participants (62.5%) in the control groups treated with enoximone, but RR indicated no survival benefit (RR 0.50, 0.22 to 1.14; participants = 32; studies = 1; very low-quality evidence). Out of 1000 people, approximately 625 would be expected to die with standard cardiac care with enoximone within a short-term follow-up period compared to 313 (95% CI 138 to 712) with levosimendan (Summary of findings 3; Analysis 1.1).

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were not possible on the basis of this one trial without reported subgroup analyses.

MACE

No results were available from the included study.

Length of hospital stay

A shorter median ICU time was reported in the levosimendan group compared to the enoximone, with high imprecision (10 (IQR 5 to 23) days compared to 13 (IQR 7 to 19) days) (Table 2).

Quality of life

No results were available from the included studies.

Haemodynamics

We found no differences in cardiac index between participants randomised to levosimendan or enoximone (median cardiac index 3.1 L/min/m^2 in both groups; IQR 2.5 to 3.5 on levosimendan versus 2.8 to 3.3 on enoximone). Only small differences were found in MAP between participants randomised to levosimendan and enoximone (median MAP 75 mmHg (IQR 58 to 79) on levosimendan versus 70 mmHg (IQR 63 to 83) on enoximone) (Table 3).

Costs

No results were available from the included study.

Adverse events (AEs)

Reported AEs included requiring mechanical ventilation, acute renal failure, need for continuous renal replacement therapy, new onset atrial fibrillation, ventricular tachycardia or fibrillation, pneumonia, urinary infections, and sepsis (Table 4). Levosimendan showed a slightly better safety profile compared to enoximone.

4. Epinephrine versus norepinephrine-dobutamine

There was only one small, single-centre study with 30 participants investigating epinephrine compared with norepinephrine-dobutamine in the context of acute HF complicated by LCOS (Levy 2011), with very low-quality evidence.

All-cause mortality

Short-term

No reported difference in short-term mortality with five deaths out of 15 participants (33.3%) in the intervention arm with epinephrine compared with four deaths out of 15 participants (26.7%) in the control groups treated with norepinephrine-dobutamine (RR 1.25; 95% CI 0.41 to 3.77; participants = 30; studies = 1; very low-quality evidence) . Out of 1000 people, approximately 267 per 1000 would be expected to die with standard cardiac care compared to 333 (95% CI 109 to 1000) with epinephrine (Summary of findings 4).

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were not possible on the basis of this one trial without reported subgroup analyses.

MACE

No results were available from the included study.

Length of hospital stay

No results were available from the included study.

Quality of life

No results were available from the included study.

Haemodynamics

The reported cardiac index and MAP showed no differences between participants randomised to either epinephrine or norepinephrine-dobutamine. (cardiac index: 2.9 ± 0.5 vs. 2.8 ± 0.4; MAP: 64 ± 9 vs. 65 ± 11) (Table 3). Concerning PCWP there were no data available from the included study.

Costs

No results were available from the included study.

Adverse events (AEs)

In the epinephrine group, two out of 15 (13.3%) participants suffered from supraventricular arrhythmia, and one out of 15 (6.7%) participants suffered from sustained ventricular tachycardia. No such AEs are reported for the participants treated with norepinephrine-dobutamine (Table 4).

5. Amrinone versus dobutamine

There was only one small, single-centre study with 30 participants investigating amrinone compared with dobutamine in the context of cardiac surgery complicated by LCOS (Dupuis 1992), with very low-quality evidence.

All-cause mortality

Short-term

Mortality within the recovery period was reported to be one out of 15 participants (6.7%) in the amrinone group, and three out of 15 participants (20%) in the dobutamine group (RR 0.33; 95% CI 0.04 to 2.85; participants = 30; studies = 1; very low-quality evidence) (Summary of findings 5). Out of 1000 people, approximately 200 per 1000 would be expected to die with dobutamine compared to 66 (95% CI 8 to 570) with amrinone (Summary of findings 5).

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were not possible on the basis of this one trial without reported subgroup analyses.

MACE

From the participants randomised to dobutamine, six out of 15 (40%) suffered from MACE (re-infarction within two hours) whereas no MACE were reported for participants randomised to amrinone (Table 1).

Length of hospital stay

No results were available from the included study.

Quality of life

No results were available from the included study.

Haemodynamics

No results were available from the included study.

Costs

No results were available from the included study.

Adverse events (AEs)

From the participants randomised to dobutamine four out of 15 (26.7%) suffered from cardiac ischaemia whereas no such events were reported for participants randomised to amrinone. There were no differences between treatment groups with regard to myocardial ischaemia (four out of 15 participants (26.7%) randomised to either amrinone or dobutamine) (Table 4).

6. Dopexamine versus dopamine

There was only one small, multi-centre study with 70 participants investigating dopexamine compared with dopamine in the context of cardiac surgery complicated by LCOS/CS (Rosseel 1997) (Summary of findings 6) with very low-quality evidence. No RR and resulting estimations on absolute risk reduction were possible.

All-cause mortality

Concerning in-hospital mortality no deaths were reported in either intervention arm. Subgroup and sensitivity analyses were not possible.

MACE

Perioperative infarctions were reported for three out of 35 participants (8.6%) in the dopexamine intervention arm, and two out of 35 (5.7%) participants in the dopamine intervention arm (Table 1).

Length of hospital stay

No results were available from the included study.

Quality of life

No results were available from the included study.

Haemodynamics

The reported cardiac index, PCWP, and MAP showed no significant differences between participants randomised to either dopexamine or dopamine after six hours of treatment (cardiac index: MD 0.30 L/min/m^2, 95% CI -0.01 to 0.61; PCWP: MD -1.5 mmHg, 95% CI -3.1 to 0.1; MAP: MD -1.9 mmHg, 95% CI -8.1 to 4.3) (Table 3).

Costs

No results were available from the included study.

Adverse events (AEs)

In the dopexamine group 19 out of 35 participants (54.3%) suffered from cardiac events, two out of 35 participants (5.7%) suffered from abnormal blood loss, and one out of 35 participants (2.9%) suffered from kidney failure. In the dopamine group, cardiac events occurred in 22 out of 35 participants (62.9%), and both abnormal blood loss and kidney failure occurred in one out of 35 participants (2.9%), but no major AEs occurred in either group (Table 4).

7. Enoximone versus dobutamine

There was only one small, single-centre trial with 40 participants investigating enoximone compared with dobutamine in the context of cardiac surgery complicated by LCOS/CS (Atallah 1990) (Summary of findings 7) with very low-quality evidence. No RR and resulting estimations on absolute risk reduction were possible.

All-cause mortality

Within one month, two deaths were reported, which were not specified between treatment groups. Subgroup and sensitivity analyses were not possible.

MACE

No results were available from the included study.

Length of hospital stay

A shorter stay in the ICU was reported in the enoximone group compared to the dobutamine group, with high imprecision in particular in the dobutamine intervention arm (92 ± 37 hours compared to 155 ± 129 hours) (Table 2).

Quality of life

No results were available from the included study.

Haemodynamics

No results were available from the included study.

Costs

No results were available from the included study.

Adverse events (AEs)

No results were available from the included study.

8. Nitric oxide versus placebo

There was only one small, single-centre trial investigating nitric oxide compared with placebo in people with AMI complicated by CS (Baldassarre 2008) (Summary of findings 8) with very low-quality evidence. The study authors reported three included participants.

All-cause mortality

The study authors claim that no participant with nitric oxide and one participant with placebo died (Table 2). Subgroup and sensitivity analyses were not possible.

MACE

The study authors claim AMIs for one out of two participants (50%) in the nitric-oxide intervention arm, and one out of one participants (100%) in the placebo intervention arm (Table 1). No RR and resulting estimations on absolute risk reduction were possible.

Length of hospital stay

No results were available from the included study.

Quality of life

No results were available from the included study.

Haemodynamics

No results were available from the included study.

Costs

No results were available from the included study.

Adverse events (AEs)

No results were available from the included study.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Levosimendan compared with placebo for cardiogenic shock or low cardiac output syndrome

Patient or population: adults with cardiogenic shock or low cardiac output syndrome
Settings: hospital
Intervention: levosimendan
Comparison: placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with placebo	Risk with levosimendan				
All-cause short-term mortality: range 4 to 6 months	**Moderate**[1]		**RR 0.48** (0.12 to 1.94)	55 (2)	⊕⊕◯◯ **very low**[3,4]	Studies included participants with LCOS or CS due to HF or AMI
	187 per 1000	**90 per 1000** (22 to 363)				
	High[2]					
	500 per 1000	**240 per 1000** (60 to 970)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMI: acute myocardial infarction; **CI:** confidence interval; **CS**: cardiogenic shock; **HF**: heart failure; **LCOS**: low cardiac output syndrome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from median risk among the control group risk in included studies with low cardiac output or cardiogenic shock.

[2]Control group risk estimate comes from a large observational study, due to the small size of included studies in this population (Singh 2007).

[3]Downgraded one step due to study limitation because of lack of blinding of participants and physicians, and missing information on randomisation in the larger study.

[4]Downgraded two steps for imprecision due to few events and the confidence interval crosses the line of no difference and includes possible benefit from both approaches.

Levosimendan compared with enoximone for cardiogenic shock

Patient or population: adults with cardiogenic shock
Settings: hospital
Intervention: levosimendan
Comparison: enoximone

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with enoximone	Risk with levosimendan				
All-cause short-term mortality: 30 days	625 per 1000[1]	**313 per 1000** (138 to 712)	**RR 0.50** (0.22 to 1.14)	32 (1)	⊕◯◯◯ **very low**[2,3]	Study included participants with CS due to AMI

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMI: acute myocardial infarction; **CI:** confidence interval; **CS**: cardiogenic shock; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from the control group risk in a small included study with low cardiac output or cardiogenic shock.
[2]Downgraded one step for imprecision because the confidence interval crosses the line of no difference and includes possible benefit from both approaches.
[3]Downgraded two steps due to study limitation with lack of blinding of participants and physicians, baseline differences and stopping for early benefit in one study.

Epinephrine compared with norepinephrine-dobutamine for low cardiac output syndrome

Patient or population: adults with low cardiac output syndrome
Setting: in-hospital
Intervention: epinephrine
Comparison: norepinephrine-dobutamine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with norepinephrine-dobutamine	Risk with epinephrine				
All-cause short-term mortality: 28 days	267 per 1000	**333 per 1000** (109 to 1000)	**RR 1.25** (0.41 to 3.77)	30 (1)	⊕◯◯◯ **very low**[1,2]	Study included participants with LCOS due to HF

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **LCOS**: low cardiac output syndrome; **HF**: heart failure; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two steps for imprecision due to few events, and the confidence interval crosses the line of no difference and includes possible benefit from both approaches.
[2]Downgraded one step due to study limitation, with lack of blinding of participants and physicians.

Amrinone compared with dobutamine for low cardiac output syndrome

Patient or population: adults with low cardiac output syndrome
Setting: hospital
Intervention: amrinone
Comparison: dobutamine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with dobutamine	Risk with amrinone				
All-cause short-term mortality: 30 days	200 per 1000[1]	**66 per 1000** (8 to 570)	**RR 0.33** (0.04 to 2.85)	30 (1)	⊕◯◯◯ **very low**[2,3]	Study included participants with LCOS following cardiac surgery

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **LCOS**: low cardiac output syndrome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from the control group risk in participants with low cardiac output and no cardiogenic shock in the included small study.
[2]Downgraded two steps for serious imprecision due to few events, and the confidence interval crosses the line of no difference and includes possible benefit from both approaches.
[3]Downgraded one step due to study limitation, with lack of blinding of participants and physicians.

Dopexamine compared with dopamine for cardiogenic shock or low cardiac output syndrome

Patient or population: adults with cardiogenic shock or low cardiac output syndrome
Setting: hospital
Intervention: dopexamine
Comparison: dopamine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with dopexamine	Risk with dopamine				
All-cause short-term mortality: time in hospital	500 per 1000[1]	Not estimable[2]	RR not estimable[2]	70 (1)	⊕◯◯◯ **very low**[3,4]	Study included participants with LCOS/CS following elective surgery for CABG

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CABG: coronary artery bypass graft surgery; **CI:** confidence interval; **CS**: cardiogenic shock; **LCOS**: low cardiac output syndrome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from a large observational study, due to the small size of included studies in this population (Singh 2007).
[2]No in-hospital deaths were observed in the study.
[3]Downgraded two steps for imprecision due to no observed events, and not estimable risk ratio and confidence interval, which results in possible benefit from both approaches.
[4]Downgraded one step due to indirectness. Due to the very low mortality and morbidity in the study population, we assume that inclusion of participants with low cardiac output syndrome was based on other definitions, as there were no hospital deaths or major adverse events in this study.

Enoximone compared with dobutamine for low cardiac output syndrome

Patient or population: adults with low cardiac output syndrome
Setting: hospital
Intervention: enoximone
Comparison: dobutamine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with dobutamine	Risk with enoximone				
All-cause short-term mortality: 1 month	500 per 1000[1]	Not estimable[2]	RR not estimable[2]	40 (1)	⊕◯◯◯ **very low**[3,4]	Study included participants with LCOS after mitral valve surgery

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **LCOS**: low cardiac output syndrome; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from a large observational study, due to the small size of included studies in this population (Singh 2007).
[2]No in-hospital deaths were observed in the study.
[3]Downgraded two steps for imprecision due to few events, and risk ratio and confidence interval were not estimable, which results in possible benefit from both approaches.
[4]Downgraded one step due to indirectness. Due to the very low mortality in the study population, we assume that inclusion of participants with low cardiac output syndrome was based on other definitions.

Nitric oxide compared with placebo for cardiogenic shock

Patient or population: adults with cardiogenic shock
Setting: in-hospital
Intervention: nitric oxide
Comparison: placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality	Comments
	Risk with nitric oxide	Risk with placebo				
All-cause short-term mortality: 1 month	500 per 1000[1]	Not estimable[2]	RR not estimable[2]	3 (1)	⊕◯◯◯ **very low**[3,4]	Study included participants with CS due to AMI

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMI: acute myocardial infarction; **CI:** confidence interval; **CS**: cardiogenic shock; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Control group risk estimate comes from a large observational study, due to the small size of included studies in this population (Singh 2007).
[2]One death out of one participant with placebo and no deaths in two participants with nitric oxide, risk ratio was not estimable due to the small number of participants.
[3]Downgraded two steps for imprecision because the risk ratio and confidence interval were not estimated due to few events and participants, which results in possible benefit from both approaches
[4]Downgraded one step due to study limitation, with early stop due to lack of enrolment.

DISCUSSION

Summary of main results

This systematic review includes thirteen RCTs that analysed 2001 participants in trials with greatly differing mortality rates of between 0% and 47%.

Drugs examined

Eight studies investigated levosimendan and compared its efficacy and safety with standard cardiac care and dobutamine, enoximone or placebo. One trial investigated epinephrine compared with norepinephrine and continued dobutamine, one trial investigated amrinone compared with dobutamine, one trial investigated dopexamine compared with dopamine, and one trial investigated enoximone compared with dobutamine. One small RCT on vasodilator strategies compared the effects of nitric oxide, a gas for inhalation, with placebo.

Endpoints

All studies reported mortality outcomes, while length of hospital and ICU stay were reported in three trials only (Atallah 1990; Levin 2008; Fuhrmann 2008). Haemodynamic parameters (as a surrogate marker for morbidity) were available in seven trials (Adamopoulos 2006; Alvarez 2006; Garci a-González 2006; Levin 2008; Fuhrmann 2008; Levy 2011; Rosseel 1997), and MACE/adverse events were reported in 11 studies (Alvarez 2006; Baldassarre 2008; Dupuis 1992; Follath(LIDO) 2002; Fuhrmann 2008; Garci a-González 2006; Husebye 2013; Levin 2008; Levy 2011; Mebazaa (SURVIVE) 2007; Rosseel 1997). No data were available for quality of life or costs in any of the trials.

As regards the development of multi-organ failure, it became obvious that the participants included in some of the trials (Atallah 1990; Garci a-González 2006; Rosseel 1997) must have been less severely compromised compared to the participants in the other eligible trials because none or only a few of these participants developed multi-organ failure. Organ failure determines the clinical course and outcome of CS patients much more than haemodynamics alone (Prondzinsky 2010).

Mortality

There was low-quality evidence from six trials that participants on levosimendan had lower short-term mortality rates compared to those on dobutamine. Very low-quality evidence shows uncertainty around the effect of levosimendan compared to placebo or enoximone. All studies investigating the comparison of epinephrine with norepinephrine-dobutamine, amrinone or enoximone with dobutamine, dopexamine with dopamine, and nitric oxide with placebo presented uncertainty on their effect on short-term mortality, with very low-quality evidence and based on only one single RCT.

Haemodynamics

Levosimendan showed beneficial effects in cardiac index, MAP, and PCWP in comparison to dobutamine (Adamopoulos 2006; Alvarez 2006; Garci a-González 2006; Levin 2008) and placebo (Adamopoulos 2006). No clinically relevant differences in cardiac index, MAP, and PCWP were reported for levosimendan compared with enoximone (Fuhrmann 2008), epinephrine compared with norepinephrine-dobutamine (Levy 2011) as well as dopexamine compared with dopamine (Rosseel 1997). No data were available regarding the comparisons of either amrinone or enoximone with dobutamine (Atallah 1990; Dupuis 1992), and of nitric oxide with placebo (Baldassarre 2008).

Length of hospital and ICU stay

Only three of the thirteen trials reported length of stay in ICU (Atallah 1990; Fuhrmann 2008; Levin 2008). Levin 2008 showed a shorter time in the ICU on levosimendan compared to dobutamine, Fuhrmann 2008 on levosimendan compared to enoximone, and Atallah 1990 on enoximone compared to dobutamine, but in all of these studies the results of comparison groups showed a high level of uncertainty.

Quality of life and costs

No data were available to address quality of life and costs in any of these trials.

Adverse events (AEs)

Levin 2008 reported a better safety profile of levosimendan compared to dobutamine, but this was not found in the studies of Alvarez 2006; Follath(LIDO) 2002, and Mebazaa (SURVIVE) 2007. Reporting on AEs in the comparison of levosimendan with enoximone or placebo, epinephrine with norepinephrine-dobutamine, amrinone or enoximone with dobutamine, dopexamine with dopamine, and nitric oxide with placebo presented uncertainty, and were based on only one single RCT.

Overall completeness and applicability of evidence

Data were too limited to justify clinical strategies on the basis of the derived evidence on the efficacy and safety of levosimendan or nitric oxide. This statement is strictly related to the limited evidence from RCTs. It is not a judgement concerning the potential benefits of the investigated drugs and does not rule out the possibility that larger RCTs might in future verify the expected beneficial effects.

Quality of the evidence

We identified a total of thirteen eligible studies with 2001 participants and included these studies in eight comparisons to current standard therapies. All these studies were published as full texts, four of them were funded by manufacturers of the drugs (Dupuis 1992; Follath(LIDO) 2002; Husebye 2013; Mebazaa (SURVIVE) 2007).

Effect estimates for our primary outcome, all-cause mortality are based on the results from one to six RCTs of small to moderate size (between three and 660 participants). This may raise the possibility of publication bias, but the number of studies was insufficient to meet rigorous criteria to create funnel plots. The mortality rates reported by Atallah 1990; Garca-González 2006 and Rosseel 1997 were surprisingly low and in marked contrast to the expected mortality rates of between 40% and 80%. The limited data available for haemodynamic parameters showed clinically relevant differences in cardiac index at baseline in the different studies. The heterogeneity in the baseline haemodynamic characteristics introduces relevant concerns regarding the definitions of CS and LCOS used in these trials. This could also be an explanation for the surprising differences in mortality rates.

We downgraded high-quality evidence of our eligible RCTs due to relevant study limitations, imprecision or indirectness. We downgraded the quality of the evidence for the following outcomes for study limitations (risk of bias) as recommended in Guyatt 2011b. We downgraded the quality of the evidence for study limitations with high risk of performance bias due to lack of blinding of participants and physicians, high risk of attrition bias due to loss to follow-up or selection bias due to baseline imbalances. We downgraded the quality of the evidence for imprecision if clinical action would differ if the lower or the upper boundary of the CI represented the truth (Guyatt 2011d). We strongly suspected indirection due to the assumption that participants were included in the studies on the basis of different definition of LCOS or CS due to very low mortality and downgraded the quality of the evidence (Guyatt 2011c).

Levosimendan reduces short-term mortality compared to a standard therapy with standard cardiac care with dobutamine (RR 0.60, 95% CI 0.37 to 0.95; low-quality evidence). Six studies with 1776 participants generated the evidence (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Garca-González 2006; Levin 2008; Mebazaa (SURVIVE) 2007). Two studies (Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007) were funded by the manufacturers of levosimendan. We judged the evidence to be low quality and downgraded the evidence by one step for serious study limitations with lack of blinding of participants and physicians in four studies (Adamopoulos 2006; Alvarez 2006; Garca-González 2006; Levin 2008), high risk of bias due to loss to follow-up and per-protocol analysis in one study (Alvarez 2006) and baseline differences in prognostic-relevant factors in one study (Garca-González 2006). We additionally downgraded the evidence by a second step due to imprecision due to few events (Summary of findings for the main comparison).

There is uncertainty surrounding the effect of levosimendan compared to therapy with standard cardiac care with placebo on short-term mortality (RR 0.48, 95% CI 0.12 to 1.94; very low-quality evidence). The very low-quality evidence was based on two studies (Adamopoulos 2006; Husebye 2013) with 55 participants and we downgraded it by two steps for very serious imprecision due to few events and because the cardiac index crosses the line of no difference, which includes possible benefit from both approaches, and by one additional step for study limitations with high risk of performance bias due to lack of blinding of participants and physicians and missing information on randomisation in Adamopoulos 2006 (Summary of findings 2). One of these studies was funded by the manufacturer of levosimendan.

There is uncertainty surrounding the effect of levosimendan compared to standard cardiac care with enoximone on short-term mortality (RR 0.50; 95% CI 0.22 to 1.14; very low-quality evidence). This evidence was based on one study (Fuhrmann 2008) with 32 participants and we downgraded it by one step for serious imprecision because the cardiac index crosses the line of no difference, which results in possible benefit from both approaches, and by two steps due to very serious study limitations with lack of blinding of participants and physicians, baseline differences in prognostic-relevant factors and being stopped early for benefit (Summary of findings 3).

There is uncertainty surrounding the effect of epinephrine compared with standard cardiac care with norepinephrine and continued dobutamine on short-term mortality (RR 1.25, 95% CI 0.41 to 3.77; very low-quality evidence). This evidence was based on one study (Levy 2011) with 30 participants and we downgraded it by two steps for very serious imprecision due to few events and because the CI crosses the line of no difference, which results in possible benefit from both approaches. We downgraded the evidence by one more step due to serious study limitation and resulting high risk of performance bias due to lack of blinding of participants and physicians (Summary of findings 4).

There is uncertainty surrounding the effect of amrinone compared to standard cardiac care with dobutamine on short-term mortality (RR 0.33, 95% CI 0.04 to 2.85; 1 study; 30 participants; very low-quality evidence). The evidence was based on one study, which was funded by the manufacturer of amrinone (Dupuis 1992). We downgraded the evidence by two steps for very serious imprecision due to few events and because the cardiac index crosses the line of no difference, which results in possible benefit from both approaches, and by one additional step due to serious study limitation and resulting high risk of performance bias due to lack of blinding of participants and physicians (Summary of findings 5).

There is uncertainty surrounding the effect of dopexamine compared to standard cardiac care with dopamine on short-term mortality. The eligible study (Rosseel 1997) reported no in-hospital deaths out of 70 participants with LCOS after elective surgery for coronary artery bypass graft surgery. We downgraded the evidence

to very low-quality; downgrading by two steps based on serious imprecision because the RR and cardiac index were not estimable, which results in possible benefit from both approaches, and by one step based on suspected indirectness due to the very low mortality in the study population. We assume that the decision to include participants was based on a different definition of LCOS (Summary of findings 6).

There is uncertainty surrounding the effect of enoximone compared to standard cardiac care with dobutamine on short-term mortality. The eligible study (Atallah 1990) reported two deaths out of 40 participants with LCOS after mitral valve surgery. We downgraded the evidence by two steps to very low-quality for serious imprecision because the RR and CI were not estimable which results in possible benefit from both approaches and by one additional step for indirectness due to the very low mortality in the study population. We assume that the decision to include participants was based on a different definition of LCOS (Summary of findings 7).

There is uncertainty surrounding the effect of nitric oxide compared to standard cardiac care with placebo. The eligible study (Baldassarre 2008) was stopped due to low recruitment after the inclusion of three participants. One participant in the placebo arm died, two participants in the nitric-oxide arm survived. We downgraded the evidence by two steps to very low-quality for serious imprecision due to few events and participants, and because the RR and CI were not estimable, which results in possible benefit from both approaches, and by one additional step due to study limitation, with the study being stopped early due to lack of enrolment (Summary of findings 8).

Potential biases in the review process

We contacted all authors of eligible trials with a request for IPD. Considering that the total number of eligible studies and included participants was relatively small, bias could have been introduced by the mere fact that IPD were not provided, especially in trials reporting favourable effects for the study drug.

As CS is a haemodynamically defined diagnostic term, it is of concern that haemodynamic parameters were not available for all participants. The result was that inclusion criteria and CS definitions relied on the diagnostic definitions being established and reported in the included studies. For this reason we cannot be sure that all reported data refer to people with CS, as commonly defined in the SHOCK trial. The clinical criteria were hypotension (a systolic blood pressure of less than 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of greater than 90 mmHg), end-organ hypoperfusion (cool extremities or a urine output of less than 30 mL per hour), and a heart rate of greater than 60 beats per minute. The haemodynamic criteria were a cardiac index of no more than 2.2 L/m^2/minute of body surface area and a PCWP of at least 15 mmHg (Hochman 1999).

All except one trial investigating levosimendan administered the drug by an initial bolus application. Bolus application of levosimendan might be associated with hypotensive side effects, so we cannot rule out the possibility that the beneficial effects of the drug might have been limited by the bolus application.

One limitation of this review might be the exclusion of all studies not reporting on all-cause mortality, which possibly lessens the informative value with regard to haemodynamics.

Agreements and disagreements with other studies or reviews

During the last decades several RCTs, cohort studies and systematic reviews have investigated levosimendan and included participants with CS or acute LCOS. These trials have recently been investigated and analysed in ten systematic reviews and meta-analyses (Delaney 2010; Harrison 2013; Huang 2013; Koster 2015; Landoni 2010a; Landoni 2010b; Landoni 2012; Maharaj 2011; Ribeiro 2010; Thackray 2002).

Delaney 2010 described the efficacy and safety of levosimendan for the treatment of acute severe HF. The systematic search was finalised in June 2007. The meta-analysis included 19 randomised trials with 3650 participants with acute severe HF. Six studies with a total of 1578 participants, including one trial included in this review (Adamopoulos 2006), compared levosimendan with placebo and reported a non-significant reduction in mortality for levosimendan (OR 0.83, 95% CI 0.62 to 1.10) with low-level heterogeneity between the results of the individual trials (I^2 = 25.7%). Eight studies with a total of 1979 participants, including four trials included in this review (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Mebazaa (SURVIVE) 2007), compared levosimendan to dobutamine and reported a significant reduction in mortality on levosimendan (OR 0.75, 95% CI 0.61 to 0.92) with low heterogeneity (I^2 = 44.6%).

Harrison 2013 performed a meta-analysis investigating the effects of levosimendan in cardiac surgery patients with and without preoperative systolic dysfunction. Timing of levosimendan treatment in included studies (14 RCTs with 1155 participants) varied from preoperative to intraoperative and postoperative. The search was finalised in May 2012 and included one study included in this review (Alvarez 2006). Pooled results demonstrated a significant reduction in the risk of death with levosimendan (-4.2%, 95% CI -7.2% to -1.1%) with low-level heterogeneity (I^2 = 28%), which was not significantly affected by the timing of levosimendan administration or the type of control (either placebo or dobutamine or milrinone or IABP). Subgroup analysis showed that the levosimendan-associated benefit was restricted to studies investigating participants with a lower ejection fraction (mean ejection fraction < 40%), than those in our included trial, Alvarez 2006.

Huang 2013 analysed the clinical efficacy of levosimendan versus dobutamine in any setting in critically ill patients. The search was finalised in February 2012 and included 22 RCTs with a to-

tal of 3052 participants, including five trials included in this review (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Levin 2008; Mebazaa (SURVIVE) 2007). Compared with dobutamine, levosimendan was found to be associated with a significant reduction in mortality (RR 0.81, 95% CI 0.70 to 0.92), with small heterogeneity between the results of individual studies (I^2 = 6%). Subgroup analysis indicated that the benefit from levosimendan could be found in the subpopulations of cardiac surgery, ischemics HF, and concomitant beta blocker therapy, but not in the subpopulations of hypotension or (supra-)ventricular arrhythmias. The studies by Alvarez 2006 and Levin 2008 were included in the cardiac surgery setting, the studies by Adamopoulos 2006; Follath(LIDO) 2002, and Mebazaa (SURVIVE) 2007 were included in the cardiology setting.

Koster 2015 assessed the benefits and harms of levosimendan for LCOS in any setting in critically ill patients. The electronic literature search strategy was last updated in February 2014 and included 49 trials with a total of 6688 participants including eight studies included in this review (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Fuhrmann 2008; Garc a-González 2006; Husebye 2013; Levin 2008; Mebazaa (SURVIVE) 2007). Pooled analysis of all studies including critically ill patients not having cardiac surgery comprising any type of control showed an association between levosimendan and mortality (RR 0.83, 95% CI 0.59 to 0.97). Likewise, pooled analysis of all trials including cardiac surgery patients comprising any type of control showed an association between levosimendan and mortality (RR 0.52, 95% CI 0.37 to 0.73). However, in a subgroup analysis with previously defined trials with lower risk of bias, no association of levosimendan and mortality could be shown for either critically ill patients not having cardiac surgery (RR 0.83, 95% CI 0.48 to 1.55) or cardiac surgery patients (RR 1.02, 95% CI 0.48 to 2.16).

Landoni 2010a studied whether levosimendan was associated with improved survival in people undergoing cardiac surgery. The search was updated in January 2009 and identified 10 RCTs with 440 participants, including two studies included in this review (Alvarez 2006; Levin 2008). Levosimendan was associated with a significant reduction in postoperative mortality in the levosimendan intervention arm compared to the control arm (either placebo or dobutamine or milrinone) with OR 0.35 (95% CI 0.18 to 0.71) with low heterogeneity (I^2 = 27.4%).

Landoni 2010b investigated the impact of levosimendan on mortality in any setting dealing with critically ill patients. The systematic search was updated in November 2008 and identified 27 RCTs that compared levosimendan versus control, with a total of 3350 participants, including five studies included in this review (Adamopoulos 2006; Alvarez 2006; Follath(LIDO) 2002; Levin 2008; Mebazaa (SURVIVE) 2007). Levosimendan was associated with a significant reduction in mortality (OR 0.74, 95% CI 0.62 to 0.89) with low heterogeneity between the results of individual studies (I^2 = 11.3%), and an increase in the number of hypotensive participants (OR 1.38; 95% CI 1.06 to 1.80) with low heterogeneity (I^2 = 37.7%).

Landoni 2012 devised an updated meta-analysis of all RCTs of levosimendan to reach a definite conclusion for this substance in the management of patients requiring inotropic drugs. The search was updated in November 2010 and identified 45 RCTs with 5480 participants. Levosimendan was associated with a significant reduction in mortality (RR 0.80, 95% CI 0.72 to 0.89) and low heterogeneity between study results (I^2 = 15.4%). This result was confirmed in studies with different control groups and in different settings. Five of our included studies (Adamopoulos 2006; Follath(LIDO) 2002; Fuhrmann 2008; Garc a-González 2006; Mebazaa (SURVIVE) 2007) were in the subgroup of trials performed in cardiology, where a similar reduction of mortality was confirmed (RR 0.75, 95% CI 0.63 to 0.91) with low heterogeneity (I^2 = 25.5%). Two of our studies (Alvarez 2006; Levin 2008) were in the subgroup of trials performed in cardiac surgery, where the reduction in mortality was confirmed as well (RR 0.52, 95% CI 0.35 to 0.76) with no heterogeneity between the results of individual studies (I^2 = 0%).

Maharaj 2011 evaluated the effect of levosimendan versus control on mortality after coronary revascularisation. This systematic review was based on a search period up to August 2010 and included 17 RCTs involving 729 participants. Levosimendan was associated with a mortality reduction after coronary revascularisation (OR 0.40, 95% CI 0.21 to 0.76) with small heterogeneity of study results (I^2 = 12%). Elective revascularisation showed a significant benefit (OR 0.36, 95% CI 0.18 to 0.72) compared with emergency revascularisation (OR 0.61, 95% CI 0.19 to 1.89). The elective revascularisation group included two of our included studies (Alvarez 2006; Levin 2008); the emergency revascularisation group included one of our included studies (Fuhrmann 2008).

Ribeiro 2010 analysed morbidity and mortality reduction associated with levosimendan in the treatment of acute decompensated HF. The search was set to an end date of July 2009 and included 19 RTCs with 3719 participants. A non-significant reduction in relative risk for overall death was found for both the comparison of levosimendan with placebo (seven trials including 1652 participants, including one trial included in this review (Adamopoulos 2006); RR 0.87, 95% CI 0.65 to 1.18) with small heterogeneity between the results of individual studies (I^2 = 12%), and the comparison of levosimendan with dobutamine (10 trials including 2067 participants, including three trials included in this review (Adamopoulos 2006; Alvarez 2006; Mebazaa (SURVIVE) 2007); RR 0.87, 95% CI 0.75 to 1.02) with no heterogeneity between the results of individual studies (I^2 = 0%).

Thackray 2002 systematically reviewed the use of intravenous inotropic drugs acting through the adrenergic pathway in people with heart failure. In total 21 RCTs involving 632 participants were included. Three studies comprising 75 participants, including one trial included in this review (Atallah 1990), compared dobutamine with enoximone. No differences on mortality were identified between dobutamine and alternative inotropic agents

(OR 1.37, 95 % CI 0.23 to 8.46).

In conclusion, while some of our included studies have been used in recently published reviews, our systematic review differs from previously published reviews for several major reasons.

- This review comprises participants with AMI, HF or cardiac surgery complicated by CS or LCOS.
- With the exception of Koster 2015 none of the other meta-analyses were based on a previously published protocol, as recommended in Shea 2009.
- Our literature search was upgraded in June 2017 and is more up-to-date.
- Finally, this review is not restricted to levosimendan but investigates other inotropic or vasodilative drugs including epinephrine, amrinone, dopexamine, enoximone, and nitric oxide.

This systematic review focusses on CS and LCOS in the acute setting. Outpatient trials, as discussed in Nieminen 2014 and Silvetti 2014, are not within the scope of this meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

At present there are no robust and convincing data to support a specific inotropic or vasodilator drug therapy as the best solution to reduce mortality in haemodynamically unstable patients with cardiac shock (CS)- or low cardiac output syndrome (LCOS)-complicating acute myocardial infarction (AMI), cardiac surgery or heart failure (HF).

In terms of haemodynamic improvements, levosimendan may be useful for haemodynamic stabilisation but there are still major concerns as to whether these haemodynamic improvements can be translated into mortality benefits, especially in haemodynamic constellations in which inotropic support has to be combined with vasopressors.

If there is a need for inotropic support, levosimendan may be considered for additional therapeutic escalation ('ultima ratio') because at present there are no relevant data describing increased risks with levosimendan in these patients, although there is not enough evidence to claim therapeutic superiority in providing inotropic support.

Implications for research

As reported above, there were essential differences in baseline parameters and co-interventions between the different trials. Therefore, better comparability of baseline conditions, especially with regard to haemodynamic parameters, vasopressor management (standardised protocols for down-titration), systemic inflammation and multi-organ failure, seems to be necessary. A further issue in the interest of comparability is the consideration of the temporary circulatory support strategies used (in particular the timing and the proper selection of circulatory support).

The interface or 'missing link' in critically ill patients that is necessary for an understanding of macro-circulatory haemodynamics, as represented by cardiac index and mean arterial pressure (MAP), systemic inflammatory response and multiple organ failure, might be the impairment of micro-circulatory haemodynamics in CS and LCOS. Without re-establishing appropriate micro-circulatory conditions improved macro-circulatory parameters like cardiac output, cardiac input and MAP will remain without substantial prognostic impact in CS as also LCOS because the consecutive multi-organ failure will determine the clinical course and prognosis.

As it has been hypothesised that the choice of the 'best available inotropic or vasoactive' drug might be less important than early initiation of reperfusion of the occluded coronary vessel to prevent the development of CS (Nativi-Nicolau 2014), it seems to be useful to apply the concept of 'early, goal-directed therapy', as known from sepsis therapy, in CS and LCOS with early haemodynamic stabilisation within predefined timelines. Future clinical trials should therefore investigate whether following an early, goal-directed therapeutic concept within defined timelines would influence survival rates much more than looking for the 'best' drug for haemodynamic support. Obviously the therapeutic differences with regard to increasing survival rates with the established inotropic and vasoactive drugs seem to be marginal. Therefore, therapeutic corridors for haemodynamic parameters and the corresponding timelines should be defined and validated in future trials. It may possibly be unimportant which pharmacological treatment strategy is used to achieve haemodynamic stabilisation and rather, following the early, goal-directed treatment concept in sepsis and septic shock (Rivers 2001), how rapidly these improvements can be established in CS and LCOS.

Considering the limited evidence derived from the present data, due to a generally high risk of bias and imprecision due to few events, small number of participants and trials, it should be emphasised that there remains a great need for large, well-designed, randomised trials on this topic to investigate whether different drug regimens show significant mortality or safety benefits in people with CS or LCOS, independent of timelines and windows of opportunity, to close the gap between daily practice in critical care medicine and the available evidence.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adamopoulos 2006

Methods	Single-centre, 3-arm, parallel-group RCT (Greece) Follow-up: 4 months
Participants	n = 69 (enrolled) **Inclusion criteria:** known systolic LV dysfunction and symptoms of NYHA III/IV HF who had been admitted for acute decompensated HF **Exclusion criteria:** presence of acute or chronic infectious or inflammatory disease recent AMI (< 8 weeks), active ischaemia, hepatic or renal impairment (creatinine > 2.5 mg/dL) , use of immunosuppressive drugs, serious arrhythmias, supine systolic blood pressure < 85 mmHg **LCOS**: CIs $\leq$ 2.5 L/min/m^2 **Characteristics:** (levosimendan/dobutamine/placebo) (mean ± SEM) Age (years): 71 ± 1/67 ± 2/71 ± 2 Sex (male, %): 87/87/78 SBP (mmHg): 109 ± 3/106 ± 3/113 ± 4 DBP (mmHg): 67 ± 2/70 ± 1/71 ± 2 CI (L/min/m^2): 1.7 ± 0.04/1.7 ± 0.04/1.8 ± 0.1 PCWP (mmHg): 24 ± 1/23 ± 1/23 ± 1 LVEF (%): 24 ± 2/25 ± 1/27 ± 1 **Timetable:** treatment as 24-h infusion, observation at 0/24/48 h
Interventions	**Levosimendan** (n = 23): 6 µg/kg as a 10-min iv injection followed by a continuous infusion of 0.1 µg/kg/min for 24 h **Dobutamine** (n = 23): continuous infusion of 5 µg/kg/min for 24 h without a loading dose; if a symptomatic reduction was not achieved after 2 h the rate of dobutamine infusion was gradually doubled **Placebo** (n = 23): continuous infusion of 5% dextrose for 24 h **Concomitant medication**: diuretics (100%), ACE inhibitors (98%), beta blockers (61%), aldosterone antagonists (58%), amiodarone (46%)
Outcomes	**Primary:** disease progression, defined as death from any reason or rehospitalisation for decompensated HF **Secondary**: echocardiographic and haemodynamic measurements: LV stroke volume, EF, and end-systolic wall stress, central haemodynamic measurements (cardiac output and index, pulmonary wedge pressure, pulmonary and systemic vascular resistance), biochemical measurements: tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), soluble Fas (sFas), sFas ligand (sFasL), N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP)
Notes	Funding: no potential conflict of interests reported Contact: JT Parissis (phone: 30-210-6123720, fax: 30-210-5832326. email: jparissis@yahoo.com)
Risk of bias	

Adamopoulos 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (different administration of study drug)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	4-month all-cause mortality reported on all randomised participants
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	Low risk	Cross-over: no Baseline-differences: no Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: yes, at baseline participants were treated with ACE inhibitors, diuretics, beta blockers, aldosterone antagonists, amiodarone
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: no

Alvarez 2006

Methods	Single-centre, 2-arm, parallel-group RCT (Spain) Recruitment from May 2002-November 2004 Follow-up: > 15 days
Participants	n = 50 (randomised), n = 41 (enrolled) **Inclusion criteria:** LCOS within 4 hours after heart surgery involving extracorporeal circulation **Exclusion criteria:** need to reduce the dose or suspend the use of the agent due to

	secondary effects, need to continue treatment for longer than 24 h due to persistent signs of low cardiac output, need to use other inotropic or vasoactive agents concomitantly, absence of myocardial ischaemia/valve dysfunction/cardiac tamponade **LCOS:** CI < 2.2 L/min/m^2, PCWP > 15 mmHg despite adequate control of HR **Characteristics:** (levosimendan/dobutamine) (mean ± SD) Age (years) 71.15 ± 8.40/66.24 ± 5.18 Sex (male, %): 48/40 MAP (mmHg): 83.6 ± 6/81.4 ± 7 HR (bpm): 82.2 ± 12/84.6 ± 8 CI (L/min/m^2): 2.0 ± 0.2/2.1 ± 0.1 **Timetable:** onset of LCOS within 4 h after surgery Treatment as 24-h infusion, observation at 0/6/12/24/48 h
Interventions	**Levosimendan** (n = 21): loading dose of 12 μg/kg over 15-20 min followed by continuous infusion of 0.2 μg/kg/min for 24 h **Dobutamine** (n = 20): 7.5 μg/kg/min continuous infusion for 24 h **Concomitant medication**: support by fluid therapy or administration of digoxin, blood derivatives, and diuretics possible
Outcomes	**Primary**: haemodynamic effects **Secondary**: efficacy and safety, expressed as the number of participants showing a normalised CI **Safety:** number of dropouts because of continued LCOS or AE
Notes	Funding: no potential conflict of interests reported Contact: J Alvarez (julian.alvarez.escudero@sergas.es)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-Protocol-analysis after exclusion of 4 participants from levosimendan group (persistent hypotension) and 5 participants from dobutamine group (persistent signs of low cardiac output or hypotension), mor-

Alvarez 2006 (*Continued*)

		tality was not reported for these patients
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	Low risk	Cross-over: no Baseline-differences: no Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: support by digoxin and diuretics possible; no information concerning inotropic support at baseline
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

Atallah 1990

Methods	Single-centre, 2-arm, parallel-group RCT (France) Follow-up: 1 month
Participants	n = 40 (randomised), n = 37 (enrolled) **Inclusion criteria:** patients with LCOS after mitral valve surgery **Exclusion criteria:** pregnancy, renal insufficiency (creatine > 300 µmol/L), pre-existent adrenaline/noradrenaline treatment **LCOS:** CI < 2.2 L/min/m^2, PCWP > 15 mmHg **Characteristics:** (enoximone/dobutamine) (mean ± SD): Age (years): 58.44 ± 16.4/56.89 ± 23 Sex (male, %): 16/42 MAP (mmHg): 85 ± 18/84 ± 14 HR (bpm): 89 ± 10/89 ± 13 CI(L/min/m^2): 1.76 ± 0.27/1.71 ± 0.24 PCWP (mmHg): 18 ± 5/19 ± 5 **Timetable:** beginning of inotropic treatment (h): 14.94 ± 15.36/12.68 ± 19.47 Treatment time not defined, observation at 0/15/30/60/90 min and at 2/6/12/18/24 h
Interventions	**Enoximone** (n = 20), bolus of 1 mg/kg in 10 min followed by an infusion of 5-10 µg/kg/min (mean dosage in 61%: 7.7 ± 2.6 µg/kg/min; in 33% there was an augmentation of dosage, in 11% a reduction) **Dobutamine** (n = 20), 5-10 µg/kg/min (mean dosage in 63%: 8.4 ± 2.4 µg/kg/min; in 15% there was an augmentation of dosage, in 15% a reduction) **Concomitant medication**: digitalis (45%), antiarrhythmic medication (13%); pre-existent medication was continued such as other inotropic agents (adrenaline and nora-

	drenaline excluded)
Outcomes	**Primary:** appearance and duration of arrhythmias (supraventricular extrasystoles, atrial fibrillation and tachycardia, ventricular extrasystoles, special forms like doublets, polymorphs, salves, precox); HF **Secondary:** (not prespecified) mortality
Notes	Funding: no potential conflict of interests reported Contact: no corresponding author defined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants: no information provided Personnel: blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Interpretation of Holter ECG in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout of 3 participants due to errors of measurement at baseline
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: yes, differences in sex Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting prerandomisation intervention: inotropic support by digitalis, antiarrhythmic medication, dopamine and other inotropic drugs was possible but participants treated with adrenaline or noradrenaline monoamine were excluded

Atallah 1990 (*Continued*)

Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

Baldassarre 2008

Methods	Multi-centre, 3-arm, parallel-group RCT (US and Europe) Follow-up: 30 days
Participants	n = 75 (planned sample size), n = 3 (enrolled) **Inclusion criteria:** patients with AMI complicated by CS despite therapy (vasopressor or mechanical support, coronary revascularisation in case of unsuccessful right ventricular reperfusion) **Exclusion criteria:** PCWP $\geq$ 25 mmHg or mechanical complications of AMI requiring surgical correction, severe LV systolic dysfunction, unprotected left main coronary stenosis (> 50%), pulmonary infiltrates on chest X-ray consistent with pulmonary oedema, evidence of shock-related end-organ damage, disseminated intravascular coagulation or clinical evidence of diffuse brain injury, previous history of severe pericardial, congenital, or valvular heart disease, refractory haemodynamically significant arrhythmia, pneumonia, adult respiratory distress syndrome, or sepsis, prior history of pulmonary disease requiring chronic oxygen therapy **CS:** invasive haemodynamic evidence of haemodynamically-significant RV dysfunction, ratio of RA/PCW pressure $\geq$ 0.75, CI < 2.5 L/min/m^2, systolic systemic arterial blood pressure $\leq$ 90 mmHg or requiring vasopressor or mechanical support to maintain systolic pressure > 90 mmHg **Characteristics:** age (years, mean): 69 sex (male, %): 66
Interventions	**Inhaled nitric oxide** (n = 2): 40 or 80 ppm for 8 h followed by 40 ppm **Placebo** (n = 1): equivalent volume of 40 or 80 ppm nitrogen for 8 h Gases were given via facemask or mechanical ventilation. Nitric oxide should be given until the participant is free of IABP and/or external pacing and all vasoconstrictor medications except dopamine at a dose $\leq$ 2.5 µg/kg/min and be weaned off in 15-20-minute intervals, total treatment time up to 14 days
Outcomes	**Primary:** in-hospital or 30 day all-cause mortality (whichever occurs first) **Secondary:** 1 year all-cause mortality, echocardiographic assessment of right and left ventricular function (hospital discharge/30 days/1 year after initial hospitalisation), time on vasoconstrictor or inotropic medications, duration of IABP support (if applicable) , time in intensive care unit, duration or need for mechanical ventilation, change in CI by dose, change in RV function and size by dose, change in pulmonary vascular resistance by dose, change in any right-to-left intracardiac shunt flow, as assessed by contrast echocardiography, neurohormonal assessment of prognosis with BNP, NT-pro BNP **Safety:** mortality, adverse events, methaemoglobinaemia and elevated nitrogen dioxide concentrations requiring dose reduction

Baldassarre 2008 (*Continued*)

Notes	The trial was stopped due to lack of enrolment. Funding: no potential conflict of interests reported Contact: James Baldassarre (james.baldassarre@ikaria.com) Registration: NCT 00782652

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of a blinded version of the nitric oxide delivery system
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Low risk	No study report written, information available on mortality and adverse events
Other bias	Unclear risk	No information provided
Adverse effects	Low risk	All adverse events were reported

Dupuis 1992

Methods	Single-centre, 2-arm, parallel-group RCT (Canada) Follow-up: 32 days
Participants	n = 30 (enrolled) **Inclusion criteria:** patients developing perioperative low cardiac output following elective CABG **Exclusion criteria:** valvular or combined procedures (valve + CABG), significant renal or hepatic dysfunction, thrombocytopenia (< 100,000 platelets/mm^3) before randomisation, serious cardiac arrhythmia requiring treatment, prior use of inotropic therapy (with the exception of calcium chloride), IABP **LCOS**: inability to separate from CPB without inotropic support or CI < 2.4 L/min/m^2 after CPB regardless of blood pressure in the presence of PCWP ≥ 12 mmHg, haemoglobin > 8.0 g/dL, with normal electrolytes and ionised plasma calcium levels

Dupuis 1992 (*Continued*)

	Characteristics: (amrinone/dobutamine) Age (years, mean ± SD): 59 ± 7/60 ± 9 Sex (male, %) 90/100 Prior AMI (%): 93/100 Previous coronary artery surgery (%): 13/33 **Timetable:** treatment as 5-10 min infusion, observation at 0/15/30/45/60/75/90/105/120 min
Interventions	**Amrinone** (n = 15): initial bolus of 0.75 mg/kg followed by a maintenance infusion of 10 µg/kg/min for 5 min; if the treatment objectives (separation from CPB, CI ≥ 2.4 L/min/m^2 with MAP of 70-100 mmHg) were not achieved within 5 min another 0.75 mg/kg was given **Dobutamine** (n = 15): bolus of 5 µg/kg/min increased stepwise to 15 µg/kg/min within 5-10 min; if the treatment objectives (separation from CPB, CI ≥ 2.4 L/min/m^2 with MAP of 70-100 mmHg) were not achieved within 5-10 min any inotropic support was given **Intervention before baseline**: all cardiac medications were continued until surgery: beta blockers (20%), calcium channel blockers (20%), nitrates (23%) **Concomitant medications:** dopamine, epinephrine, norepinephrine, vasodilators as judged necessary
Outcomes	**Primary**: separation from CPB, CI ≥ 2.4 L/min/m^2 with a MAP of 70-100 mmHg, haemodynamic and metabolic parameters **Secondary**: (not specified) mortality **Safety**: myocardial ischaemia, arrhythmias, perioperative AMI, cross-clamp time
Notes	Funding: supported by a grant from Sanofi-Winthrop, Markham, Ontario, Canada, L3R6H3 Contact: HJ Nathan (Room H460A, Heart Institute Research Center, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario, Canada, K1Y4E9)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Firstly stratified to 2 blocks according to their ability to separate from CPB, then the participants were randomised to the treatment groups
Allocation concealment (selection bias)	Low risk	Anaesthesiologists and surgeons treating and including the participant were blinded until allocation of inotropic drugs
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no information provided Personnel: anaesthesiologists/surgeons were only blinded until after the decision of treatment, clinicians not blinded

Dupuis 1992 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiologists blinded to the identity of the participants and their clinical outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Haemodynamic data compared only for 'Block 2' (18 participants) because baseline values of 'Block 1' (12 participants) could not be obtained; incomplete results in tables that were meant to show the result for 'Block 2' but listed only the data for 13 participants (missing data for a total of 17 participants)
Selective reporting (reporting bias)	High risk	Listing of results very unordered with jumps between the comparison of 'blocks' and treatment groups; data reference not always clear
Other bias	High risk	Cross-over: no Baseline differences: yes, differences in sex Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting prerandomisation intervention: yes, all cardiac medications were continued until surgery; in dobutamine group any inotropic support was possible
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: yes, AEs listed only for 13 participants of 'Block 2' Numerical data by intervention: yes

Follath(LIDO) 2002

Methods	Multi-centre, 2-arm, parallel-group RCT (Austria, Denmark, Finland, France, Germany, Hungary, Italy, Switzerland, the Netherlands, Sweden, UK) Recruitment from January 1997-November 1998 Follow-up: 180 days
Participants	n = 203 (randomised), n = 199 (enrolled) **Inclusion criteria:** deterioration of severe chronic HF despite optimum oral therapy with vasodilators and diuretics including those awaiting cardiac transplantation, severe

	HF after cardiac surgery, acute HF related to a cardiac or non-cardiac disorder of recent onset **Exclusion criteria:** age < 21 years, childbearing potential, HF due to restrictive or hypertrophic cardiomyopathy or to uncorrected stenotic valvular disease, chest pain at the time of randomisation, sustained ventricular tachycardia or ventricular fibrillation within the previous 2 weeks, atrioventricular block of second or third degree, HR > 120 bpm at rest; SBP < 85 mmHg, severe renal failure (serum creatinine > 450 mol/L), hepatic failure, cardiac tamponade, adult respiratory distress syndrome, septic shock **LCOS/CS:** LVEF < 0.35 within 1 month of study enrolment, CI < 2.5 L/min/m^2, mean PCWP > 15 mmHg **Characteristics:** (levosimendan/dobutamine) (mean ± SD) Age (years): 58 ± 11/60 ± 11 Sex (male,%): 88/85 SBP (mmHg): 112 ± 18/117 ± 19 DBP (mmHg): 69 ± 12/71 ± 12 HR (bpm): 82 ± 15/81 ± 16 PCWP (mmHg): 25 ± 8/24 ± 7 CI (L/min/m^2): 1.94 ± 0.36/1.91 ± 0.44 **Timetable:** treatment as 24-h infusion, observation at 0/15 min and at 1/2/2.5/4/8/23.5/24/30 h
Interventions	**Levosimendan** (n = 102): loading dose of 24 µg/kg over 10 min followed by a continuous infusion of 0.1 µg/kg/min for 24 h **Dobutamine** (n = 97): continuous infusion of 5 µg/kg/min without a loading dose for 24 h If an adequate response (defined as an increase in CI of at least 30%) was not achieved after 2 h, the rate of infusion of the study-assigned drug was doubled **Concomitant medication**: the timing of other cardiovascular drugs (diuretics (93%) , ACE inhibitors (89%), digoxin (76%), nitrates (41%), beta blockers (38 %), class III antiarrhythmic agents (15%), calcium channel blockers (4%)) was standardised to minimise any effect on haemodynamic measurements. These drugs had to be given at least 6 h before baseline measurements, between 4 h and 18 h of the study period, or after the end of the study drug infusion. In general, the dose of these concomitant medications was held constant, unless urgent modifications were required on clinical or haemodynamic grounds. The protocol prohibited iv adrenergic agonists within 30 min before baseline haemodynamic measurements, iv vasodilators within 2 h, iv milrinone or enoximone within 12 h, and iv amrinone within 2 days
Outcomes	**Primary:** proportion of participants with haemodynamic improvement (≥ 30% increase in cardiac output and ≥ 25% (at least 4 mmHg) decrease in PCWP) at 24 h **Secondary:** changes from baseline in haemodynamic variables other than cardiac output and PCWP (e.g. CI, stroke volume, diastolic pulmonary-artery pressure, mean right atrial pressure, SBP, DBP, HR, total peripheral resistance) at 24 h; changes from baseline to 24 h in symptoms of HF on a four-grade scale, proportion of participants needing iv rescue therapy with positive inotropic drugs/vasodilators/diuretics during the infusion of study drug, number of days alive/out of hospital/not receiving iv drugs during the first month, time to development of worsening HF or death **Safety:** reports of adverse reactions, laboratory safety tests (blood and urine), all-cause mortality at 31 days and 180 days after randomisation

Notes	Funding: supported by a grant from Orion Pharma, Espoo, Finland. The sponsor was involved in the study design, planning and running of the statistical analyses, and preparation of the trial report. The study was managed and data obtained by Quintiles/Innovex (Biodesign, Freiburg, Germany), Orion Pharma (Espoo, Finland), and Ercopharma (Kvistgaard, Denmark) Contact: F Follath (dimffo@usz.unizh.ch)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated code created by Orion Pharma for each centre, block-randomisation
Allocation concealment (selection bias)	Low risk	Treatment allocation and size of randomisation blocks were concealed from the investigators, sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each participant received 2 simultaneous infusions (active and placebo) to blind participants and physicians
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study, all but 4 envelopes were returned unopened after the end of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Report of excluded participants: (levosimendan/dobutamine) Incomplete/interrupted intervention: 11/14, no study drug received: 1/3, Serious adverse event: 6/10 but mortality was reported for all randomised participants
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	Low risk	Cross-over: no Baseline differences: no Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: yes, 4 participants did not receive the study drug at all (1 in levosimendan group, 3 in dobutamine group), 16 participants were classified as permanent discontinuation before 24 h owing to adverse

Follath(LIDO) 2002 (*Continued*)

		events or insufficient clinical response (6 in levosimendan group, 10 in dobutamine group), 11 participants were prone to a temporary interruption due to a dose-limiting event (5 in levosimendan group, 6 in dobutamine group), and 14 participants received the study drug for < 18 h (6 in levosimendan group, 8 in dobutamine group) Contra-active or similar supporting prerandomisation intervention: inotropic support was possible but standardised with regard to time to minimise any effect on haemodynamic measurements
Adverse effects	Low risk	Definitions of AEs given: no Monitoring of AEs: yes, spontaneous reports of adverse events and all-cause mortality at 31 days without breaking blinding, analysis of 180-day mortality retrospectively after the code had been broken Participants excluded from AE analysis: no Numerical data by intervention: yes

Fuhrmann 2008

Methods	Single-centre, 2-arm, parallel-group RCT (Germany) Recruitment from April 2003-July 2005 Follow-up: 30 days
Participants	n = 32 (enrolled) **Inclusion criteria:** patients with AMI complicated by refractory CS despite recommended current therapy (immediate revascularisation, IABP support, optimal fluid status, and inotropes) within 2 h after PCI **Exclusion criteria:** hypotension related to any mechanical complications of AMI, severe stenotic valvular disease, sustained ventricular tachycardia, major bleeding, severe hepatic failure, severe systemic illness or sepsis syndrome, duration of CS > 24 h before arrival **CS:** deteriorating hypotension manifested by unaugmented SBP < 90 mmHg or requirement of inotropic amines and vasopressors to maintain unaugmented SBP > 90 mmHg, CI < 2.5 L/min/m^2, PCOP > 18 mmHg, and clinical signs of peripheral hypoperfusion (cold skin, mental confusion, or oliguria) **Characteristics** (levosimendan/enoximone) (median with IQR): Age (years): 68 (60-70/62-73) Sex (male, %): 69/56 Diabetes (%): 44/31 Hypertension (%): 87/81 Smoker (%): 50/50 Prior AMI/vascular intervention (%): 25/22 Lowest SBP (mmHg): 83 (72-91)/76 (69-88)

	MAP (mmHg): 72 (63-80)/67 (60-77) HR (bpm): 109 (100-120)/101 (84-110) CI (L/min/m^2): 2.3 (2.1-2.5)/ 2.2 (1.7-2.4) PCWP (mmHg): 22 (18-24)/20 (17-31) LVEF (%): 22 (18-31)/27 (20-34) SVRI (dyne.s/cm^5/m^2): 2139 (1866-2447)/1960 (1711-2345) **Timetable:** onset time of CS (h, median with IQR): 6.0 (4.0-8.0)/7.0 (3.0-12.0) Treatment as 24-h infusion, observation at 0/2/12/24/48 h
Interventions	**Levosimendan** (n = 16): front-loading dose of 12 μg/kg over 10 min followed by 0.1 μg/kg/min for 50 min + 0.2 μg/kg/min infusion over the next 23 h **Enoximone** (n = 16): fractional bolus administration of 0.5 μg/kg over 30 min followed by 2-10 μg/kg/min continuously titrated to the best haemodynamic response **Concomitant medication**: dobutamine (100%), norepinephrine (87%), catecholamines were selected according to the European Society of Cardiology guidelines on the diagnosis and treatment of acute HF first published in 2005 (Nieminen 2006)
Outcomes	**Primary:** 30-day all-cause mortality **Secondary:** changes in invasively measured haemodynamic variables (arterial blood pressure, pulmonary artery pressure, mixed venous oxygen saturation, CI, LVSWI, cardiac power index) during the first 48 h
Notes	Funding: no potential conflict of interests reported Contact: Joerg Fuhrmann (joerg.fuhrmann@lycos.de) Study discontinuations as a result of a planned interim analysis based on a clear trend toward reduced mortality for levosimendan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Permutated block randomisation, sequence of random numbers from a computerised random-number generator
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (different administration of study drug)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30-day all-cause mortality reported on all randomised participants; changes in haemodynamics, haemodynamic support, fluid administration, diure-

Fuhrmann 2008 (*Continued*)

		sis and laboratory markers were reported for 36 participants (only 32 participants enrolled)
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: yes, comorbidities (diabetes mellitus 44% versus 31%, prior AMI 19 versus 31%) Influence of interim results on the conduct of the study: yes, study was stopped as a result of a planned interim analysis after recruiting 32 of the pre-planned sample size (n = 88) for ethical reasons based on a clear trend toward reduced mortality for levosimendan Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: yes, at baseline participants were treated with dobutamine and norepinephrine
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

Garcı a-González 2006

Methods	Single-centre, 2-arm, parallel-group RCT (Spain) Recruitment from January 2003-December 2004 Follow-up: 12 months
Participants	n = 22 (enrolled) **Inclusion criteria:** patients with STEMI complicated by CS secondary to severe LV systolic dysfunction after primary PCI **Exclusion criteria:** RV AMI, cardiac tamponade, HR ≥120 bpm, sustained ventricular tachycardia or ventricular fibrillation within the 2 previous weeks, ventricular septal rupture, haemodynamically severe mitral regurgitation or other valvular or congenital heart diseases, antecedents of HF, AMI, cerebral stroke or other major hospitalisation within 3 months, use of inotropic, calcium antagonist or antiarrhythmic drugs except digoxin (within the previous 7 days), second- or third-degree atrioventricular block, adult respiratory distress syndrome or severe pulmonary disease, septic shock, body mass index ≥ 32 kg/m^2, end-stage renal failure, liver cirrhosis and clinically overt thyrotoxicosis **CS:** according to Alexander 2001

	Characteristics: (levosimendan/dobutamine) (mean ± SD)**:** Age (years): 65 ± 12/63 ± 11 Sex (male, %): 86/75 Diabetes (%): 23/30 Hypertension (%): 31/35 Smokers (%): 50/45 MAP (mmHg): 75 ± 8/77 ± 9 HR (bpm): 85 ± 16/86 ± 12 CI (L/min/m^2): 1.7 ± 0.4/1.8 ± 0.3 PCWP (mmHg): 25 ± 4/28 ± 6 SVR (dyne.s/cm^5): 1725 ± 450/1690 ± 350 **Timetable:** symptoms onset to first balloon inflation (min, mean with standard deviation): 305 ± 68 Start of the procedure to opening of vessels (min, mean with standard deviation): 28 ± 12 Treatment as 24 h infusion, observation at 0/1/4/8/12/24/30 h
Interventions	**Levosimendan** (n = 11): front-loading dose of 24 μg/kg over 10 min followed by a constant rate of 0.1 μg/kg/min for 24 h **Dobutamine** (n = 11): 5 μg/kg for 24 h; if an adequate haemodynamic response was not achieved after 2 h the infusion rate was doubled until the desired response Infusions were interrupted if the participant had a major cardiovascular event or serious adverse reaction **Interventions before baseline**: successful resuscitation (100%), PCI (100%), stents (89%) **Co-interventions:** IABP (5%) **Concomitant medication**: furosemide, sodium nitroprusside, nitroglycerine, digitalis
Outcomes	**Primary:** ≥ 30% increase in cardiac power after 24 h of therapy **Secondary:** cardiac death (Samimi-Fard 2008)
Notes	Funding: no potential conflict of interests reported Contact: Miguel Bethencourt Muñ oz (phone +34 922679030, fax: +34 922 362716), Martin J Garcı a-González (mjgg181262@hotmail.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Garc a-González 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Haemodynamic measurements were made by two research team members who were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1-year all-cause mortality reported on all randomised participants
Selective reporting (reporting bias)	Unclear risk	Pre-specified primary outcome given, no pre-specified secondary endpoints
Other bias	High risk	Cross-over: no Baseline differences: yes, timetable time from onset of symptoms to first balloon inflation 330 ± 60 versus 280 ± 75 min Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no contra-active or similar supporting pre-randomisation intervention: inotropic support by furosemide, sodium nitroprusside, nitroglycerine, and digitalis was possible but participants treated with inotropic, calcium antagonist or antiarrhythmic drugs (except digoxin) within the previous 7 days were excluded
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: no

Husebye 2013

Methods	Single-centre, 2-arm, parallel-group RCT (Norway) Follow-up: 6 months
Participants	n = 61 (enrolled; subgroup of n = 9 with CS) **Inclusion criteria:** patients with acute PCI-treated AMI complicated with decompensated HF and open infarct artery; includes a prospectively defined subgroup of patients in CS **Exclusion criteria:** age ≤ 20 years, HR > 120 bpm, septic shock, acute respiratory distress syndrome, creatinine > 450 μmol/L, severe hepatic failure, significant mechanical outflow obstruction, anaemia (haemoglobin < 8 g/dL), allergy against study medication or one of its components, pregnancy **CS**: SBP < 90 mmHg after 60 min of adequate volume therapy or SBP between 90 and 100 mmHg in spite of inotropic support by catecholamine infusion and signs of organ

	hypoperfusion (oliguria, cold and clammy extremities) or reduced consciousness **Characteristics:** (all haemoglobin with AMI, levosimendan/placebo) (median with IQR) Age (years): 66 (56-74)/62 (56-74) Sex (male, %): 60/81 Diabetes (%): 17/3 Hypertension (%): 33/36 Smoker (%): 41/33 Prior AMI (%): 23/13 Congestive HF (%): 0/3 SBP (mmHg): 102 (93-114)/107 (93-115) DBP (mmHg): 67 (59-72)/66 (58-70) MAP (mmHg): 78 (72-85)/80 (73-84) LVEF (%): 43 (38-49)/40 (33-47) **Timetable:** start of symptoms to PCI (h, median with IQR): 3 (2-8)/3 (2-6) PCI to study infusion (h, median with IQR):24 (14-33)/2 (14-26) Treatment as 25-h infusion, observation at 0/7/13/19/25/48/72/96/120 h
Interventions	**Levosimendan** (n = 30, subgroup of 4 with CS): 0.2 μg/kg/min for 1 h followed by 0.1 μg/kg/min for 24 h **Placebo** (n = 31, subgroup of 5 with CS) Procedure in case of hypotension: volume therapy according to the clinicians' decision, reduction of the infusion rate to 0.05 μg/kg/min if SBP dropped below 80 mmHg or MAP dropped > 10 mmHg in participants with IABP, if a further drop in blood pressure occurred, an infusion of norepinephrine was started and eventually the study drug infusion was aborted **Interventions before baseline**: PCI (100%), IABP (28%) **Concomitant medication**: all participants received standard medical therapy according to national and international guidelines. The use of iv inotropic drugs was restricted to participants with CS, except norepinephrine in the setting of hypotension
Outcomes	**Primary**: change in wall motion index **Secondary**: changes in NT-pro BNP, wall motion score index, clinical score, use of inotropic or vasopressor drugs in participants without CS, infarct size, time to MACE including death, non-fatal AMI or revascularisation of the infarct-related artery), rehospitalisation for HF pre-specified **Safety:** hypotension, sinus tachycardia, atrial fibrillation, ventricular arrhythmia, ischaemic episodes
Notes	Funding: Centre for Heart Failure Research, University of Oslo, South-Eastern Norway Regional Health Authority, the Scientific Council at Oslo University Hospital Ulleval, and the Department of Cardiology, Oslo University Hospital Ullevål received an unrestricted educational grant from Orion Pharma (manufacturer of levosimendan) Contact: Trygve Husebye (phone: +47 40452621, fax: +47 22119181, email: trhuse@online.no or trygve.husebye@ous-hf.no) Registration: NCT00324766, EUCTR2004-002732-25-NO
Risk of bias	

Husebye 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence, participants with CS were stratified by block randomisation
Allocation concealment (selection bias)	Low risk	Code was kept in safe at the Oslo University hospital pharmacy, study medication (levosimendan or placebo) was prepared matching size, colour of solution and packaging by the hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants: no information provided Personnel: blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment by investigating doctors, nurses, and study personnel throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All-cause mortality and safety results reported on all randomised participants
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: yes, in sex and co-morbidities (dyslipidaemia 10 versus 32% (levosimendan versus placebo)) Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: yes, interruption of study drug administration in 2 (3.2%) participants without CS (3.3% levosimendan because of atrial fibrillation, 3.2% placebo because of hypotension) contra-active or similar supporting pre-randomisation intervention: yes, inotropic support by catecholamine infusion was possible
Adverse effects	Low risk	Definitions of AEs given: yes Monitoring of AEs: yes, recording from baseline to day 5 and at 6 weeks' follow-up by the blinded study personnel Participants excluded from AE analysis: no

Husebye 2013 (*Continued*)

		Numerical data by intervention: yes

Levin 2008

Methods	Multi-centre, 2-arm, parallel-group RCT (Argentina) Recruitment from December 2003-December 2006 Follow-up: 30 days
Participants	n = 137 (enrolled) **Inclusion criteria:** men and women developing LCOS after coronary surgery with extracorporeal circulation (ECC) **Exclusion criteria:** patients with pre-operative kidney failure (glomerular filtration rate < 59 mL/min), emergency surgery, valvular or combined techniques, surgery without ECC, low use of pre-operative balloon counterpulsation or inotropic drugs, uncorrected temperature anomalies, hypovolaemia, bradycardia, cardiac tamponade, post-operative ischemias **LCOS:** CI < 2.2 L/min/m^2, PCWP $\geq$ 16 mmHg, mixed venous saturation < 60 %, **Charactersitics:** (levosimendan/dobutamine) (mean ± SD) Age: (years): 62.4 /61.7 Sex: (male,%): 62.3/60.3 Diabetes (%): 30.4/27.9 Hypertension (%): 52.2/51.5 Prior AMI (%): 17.4/17.6 Angioplasty (%): 23.2/20.6 MAP (mmHg): 85.6 ± 6/84.7 ± 4 CI(L/min/m^2): 2 ± 0.2/2 ± 0.1 **Timetable:** onset time of LCOS within 6 h after surgery (diagnosis was made in all cases within 3 h of the intervention) Treatment as 24-h infusion, observation at 0/6/12/48 h
Interventions	**Levosimendan** (n = 69): bolus dose of 10 µg/kg for 1 h followed by a 24 h infusion of 0.1 µg/kg/min **Dobutamine** (n = 68): 24 h infusion of 5 µg/kg/min (if no favourable haemodynamic response was observed, dose was increased in 15-min intervals to 7.5/10/12.5 µg/kg/min) **Cocomitant medication:** in cases of persistent low cardiac output further inotropic drugs were added to the treatment regime: second-line = milrinone at a dose of 0.375 µg/kg/min/third-line = adrenaline at a dose of 1-10 µg/min, aspirin (96%), beta blockers (77%), nitrites (62%), statins (54%), ACE inhibitors (52%), calcium antagonists (31%) , diuretics (20%), clopidogrel (12%), amiodarone (9%), digoxin (9%), anticoagulants (9%)
Outcomes	**Primary**: haemodynamic parameters (CI, PCWP, MAP, HR, mixed venous saturation) **Secondary**: post-operative complications/morbidity (perioperative infarction, vasoplegia, kidney failure, prolonged ventilatory assistance, stroke, SIRS, sepsis, pneumopathy, adult respiratory distress, hospital mortality)

Levin 2008 (*Continued*)

Notes	Funding: no potential conflict of interests reported Contact: R. Levin (rllevin@gmail.com or Ricardo.levin@vanderbilt.edu)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	30-day all-cause mortality reported on all randomised participants
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: no Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: yes, inotropic support by milrinone, adrenaline, beta blockers, nitrites, statins, ACE inhibitors, calcium antagonists possible
Adverse effects	Low risk	Definitions of AEs given: yes Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

Levy 2011

Methods	Single-centre, 2-arm, parallel-group RCT (France) Recruitment for 26 months Follow-up: 28 days
Participants	n = 85 (enrolled), n = 30 (randomised) **Inclusion criteria**: acute or chronic HF, EF ≥ 30%, CI ≥ 2.2 L/min/m^2, absence of hypovolaemia, SBP > 90 mmHg or MAP > 60 mmHg, or a drop in MAP of 30 mmHg despite dopamine up to 20 g/kg/min, lactate level ≥ 2 mmol/L **Exclusion criteria**: signs of acute cardiac ischaemia or 2 negative troponin measurements at 6-h intervals in case of left bundle branch block, CS secondary to acute ischaemic events such as AMI, acute and sustained atrial and ventricular arrhythmias, septic shock, poisoning, and pulmonary embolism, pure right ventricular failure, immediate indication of a ventricular assist device **LCOS:** evidence of tissue hypoperfusion (cold and/or clammy skin, liver dysfunction, or impaired mentation) induced by HF after adequate correction of preload and major arrhythmia **Characteristics:** (epinephrine/norepinephrine-dobutamine) (mean ± SD) Age (years): 66 ± 12/64 ± 10 Sex (male, %): 67/73 MAP (mmHg): 55 ± 9/54 ± 8 HR (bpm): 121 ± 19/125 ± 15 CI (L/min/m^2): 1.6 ± 0.4/1.6 ± 0.4 **Timetable:** treatment time not defined, observation at 0/6/12/24 h
Interventions	**Epinephrine** (n = 15): initiated at 0.1 μg/kg/min and titrated on MAP at 5-min intervals to obtain a MAP of 65-70 mmHg with a stable or increased CI **Norepinephrine-dobutamine** (n = 15): norepinephrine initiated at 0.1μg/kg/min and titrated on MAP at 5-min intervals to obtain a MAP of 65-70 mmHg with a stable or increased CI, dobutamine was used at a dose ranging from 2-20 µg/kg/min **Co-interventions**: invasive mechanical ventilation (83%), noninvasive mechanical ventilation (17%) **Concomitant medication**: diuretics (100%), ACE inhibitors (83%), aldosterone antagonists (7%)
Outcomes	**Primary:** haemodynamic parameters (MAP, CI, HR, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, oxygen delivery index, oxygen consumption index), metabolic parameters (lactate, pyruvate), tonometric measurements (PCO_2) **Secondary:** (not specified) mortality
Notes	Funding: potential conflict of interests not disclosed Contact: B. Levy (b.levy@chu-nancy.fr)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided

Levy 2011 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study, no blinding of patients and physicians
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study, no blinding of patients and physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	28-days all-cause mortality reported on all randomised participants
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	Low risk	Cross-over: no Baseline differences: no Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: yes, at baseline participants were treated with ACE inhibitors and aldosterone antagonists
Adverse effects	Unclear risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

Mebazaa (SURVIVE) 2007

Methods	Multi-centre, 2-arm, parallel-group RCT (Austria, Finland, France, Germany, Israel, Latvia, Poland, Russia, and the UK) Recruitment from March 2003-December 2004 Follow-up: 180 days
Participants	n = 1327 (enrolled), n = 1320 (randomised) **Inclusion criteria:** EF $\leq$ 30% within the previous 12 months, required iv inotropic support as evidenced by an insufficient response to iv diuretics and/or vasodilators, at least 1 of the following at screening: dyspnea at rest or mechanical ventilation for HF/oliguria not as a result of hypovolaemia/PCWP $\geq$ 18 mmHg and/or CI $\leq$ 2.2 L/min/m^2 **Exclusion criteria:** severe ventricular outflow obstruction, SBP persistently < 85 mmHg or HR persistently at 130/min or higher, iv inotrope use during the index hospitalisation (except dopamine $\leq$ 2µg/kg/min or digitalis), history of torsade de pointes, serum

	creatinine level > 5.1 mg/dL (450 µmol/L) or dialysis **LCOS/CS:** requirement of inotropic support (EF ≤ 30%, PCWP ≥18 mmHg and/or CI ≤ 2.2 L/min/m^2) **Characteristics:** (levosimendan/dobutamine) (mean ± SD) Age (years): 67 ± 12/66 ± 12 Sex (male,%): 74/70 Diabetes (%): 31/34 Hypertension (%): 61/65 Prior AMI (%): 68/69 SBP (mmHg): 116 ± 18/116 ± 19 DBP (mmHg): 70 ± 12/70 ± 12 HR (bpm): 84 ± 17/83 ± 17 **Timetable:** treatment as 24-h infusion, observation at 24 h + 31/180 days
Interventions	**Levosimendan** (n = 660): loading dose of 12 µg/kg over 10 min followed by a constant infusion of 0.1 µg/kg/min for 50 min; the rate was increased to 0.2 µg/kg/min for additional 23 h as tolerated **Dobutamine** (n = 660): infusion of 5 µg/kg/min for at least 24 h (maintained as long as clinically appropriate and as tapered according to each participant's clinical status); infusion rate could be increased at the discretion of the investigator to a maximum rate of 40 µg/kg/min If participants required additional inotropic support during the study period, the intention was to maintain the blind by re-administering their originally assigned study drug and dosing regimen. However, this was not mandated so failure to do so was not considered a protocol violation. If re-administration occurred within 7 days of initial infusion, levosimendan was administered without a loading dose and at 0.1 µg/kg/min **Concomitant medication**: diuretics (79%), ACE inhibitors (69%), aldosterone antagonists (53%), beta blockers (51%), nitrates (37%), dopamine (7%)
Outcomes	**Primary:** all-cause mortality during the 180 days following randomisation **Secondary:** all-cause mortality during 31 days, change in BNP level from baseline to 24 h, number of days alive and out of hospital during the 180 days, change in participant-assessed dyspnea at 24 h, participant-assessed global assessment at 24 h, cardiovascular mortality through 180 days **Safety:** AEs were collected for 31 days following initial study drug administration and during all blinded drug re-administrations
Notes	Funding: Abbott and Orion Pharma funded the SURVIVE trail and data analysis activities; Dr Mebazaa reported being a consultant for Abbott, Orion Pharma, Protein Design Biopharma, and Sigma-Tau and receiving honoraria from Abbott, Guidant, and Edwards Life Sciences. Dr Nieminen reported being a consultant for Abbott, Orion Pharma, Scios, Medtronic, and Pfizer. Dr Cohen-Solal reported being a consultant for and receiving honoraria from Abbott, Orion Pharma, Protein Design Biopharma, AstraZeneca, Amgen, Takeda, and Menarini. Dr Kleber reported receiving research grants from Orion Pharma and being a consultant for Abbott and Orion Pharma. Dr Pocock reported being a consultant for Abbott, Orion Pharma, and Scios. Dr Packer reported being a consultant for Abbott and Orion Pharma. Drs Thakkar and Padley are Abbott employees. Drs Põder and Kivikko are Orion PHarma employees Contact: A. Mebazaa (alexandre.mebazaa@lrb.aphp.fr)

	Registration: NCT00348504	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised centrally, using an interactive voice-response system. Randomisation was stratified using a biased coin algorithm with previous ADHF and country as factors
Allocation concealment (selection bias)	Low risk	Vials containing the study drug were assigned a number, randomly permuted blocks
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To blind treatment differences additional placebo was given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Report of excluded participants: (levosimendan/dobutamine) Lost to follow-up: 3/8 Discontinued intervention: 30/41 Major cardiovascular events: 10/15 Serious AE: 9/9 Event judged by investigator to warrant withdrawal: 9/14 Other: 2/3
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: no Influence of interim results on the conduct of the study: yes, the originally targeted number of participants was 700 but was increased to 1320 following a blinded review of mortality after 131 deaths to achieve the target number of 330 deaths Deviation from study protocol: no Inappropriate administration of an intervention: yes, 71 participants (5.8%) discontinued intervention due to adverse events (30 in levosimendan group, 41 in

Mebazaa (SURVIVE) 2007 (*Continued*)

		dobutamine group) Contra-active or similar supporting pre-randomisation intervention: yes, at baseline participants were treated with ACE inhibitors, aldosterone antagonists, beta blockers, nitrates, dopamine
Adverse effects	Low risk	Definitions of AEs given: no Monitoring of AEs: yes, AEs were collected for 31 days following initial study drug administration and during all blinded drug re-administrations Participants excluded from AE analysis: no Numerical data by intervention: yes

Rosseel 1997

Methods	Multi-centre, 2-arm, parallel-group RCT (Netherlands, Belgium) Recruitment for 18 months Follow-up: time in hospital
Participants	n = 70 (enrolled, included into safety analysis), n = 63 (included into efficacy analysis) **Inclusion criteria**: men/women developing CS after elective surgery for CABG **Exclusion criteria:** patients > 75 years, pregnant, treated with monoamine oxidase inhibitors or catecholamines or balloon pump or beta blockers, pre-operative renal dysfunction (serum creatinine > 200 µmol/L), liver dysfunction (γ-glutamyltransferase > 20% above normal), pheochromocytoma, CI < 1.5 L/min/m^2 or mixed venous oxygen saturation < 40%, AMI (developing Q wave and CK-MB), HR > 110 bpm, significant ventricular/supraventricular tachyarrhythmias, tamponade, abnormal blood loss, paced heart rhythm, rectal temperature < 33°C **CS**: CI < 2.2 L/min/m^2 in the absence of hypovolaemia (CVP ≥ 8 mmHg, PCWP ≥ 12 mmHg, diastolic pulmonary artery pressure ≥ 12 mmHg) **Characteristics:** (dopexamine/dopamine) (mean ± SD) Age (years, range): 66.4 (46-78)/65.9 (48 - 80) Sex: (male, %): 55/66 Hypertension (%): 45/46 Prior AMI (%): 65/56 SBP (mmHg): 114 ± 18.8/114 ± 19.6 DBP (mmHg): 61.9 ± 11.4/61.7 ± 10.7 MAP (mmHg): 80.6 ± 13.8/80.2 ± 12.7 HR (bpm): 69.1 ± 11.8/71.4 ± 14.2 PCWP (mmHg): 12.6 ± 2.8/13.2 ± 2.4 CI (L/min/m^2): 1.9 ± 0.2/1.9 ± 0.2 **Timetable:** treatment as 6-h infusion, observation at 0/1/2/3/4/5/6 h
Interventions	**Dopexamine** (n = 35, 31 included into efficacy analysis): titrated in 3 steps each at 15-min intervals at 0.5/1.0/2.0 mg/kg/min until CI was > 2.5 L/min/m^2; continuous infusion at effective dose level for 6 h **Dopamine** (n = 35, 32 included into efficacy analysis): titrated in 3 steps each at 15-min

	intervals at 1.5/3.0/6.0 mg/kg/min until CI was > 2.5 L/min/m^2; continuous infusion at effective dose level for 6 h **Concomitant medication**: vasodilators (76%), negative inotropes (16%), inodilators (10%), positive inotropes (3%), blood products (67%), crystalloids (9%), colloid (54%)
Outcomes	**Primary**: clinical efficacy (stable CI > 2.5 L/min/m^2, stable urine production of ≥ 0.5 mL/kg/h and stable blood pressure for 2 consecutive measurements with an interval of 1 h) **Secondary**: time required to reach clinical efficacy, difference in rectal and peripheral temperatures between start of treatment and the time clinical efficacy was reached, need for co-medication during treatment, change in haemodynamic parameters during treatment **Safety**: dysrhythmias, perioperative AMI, time to excubation, duration of stay in ICU, other unusual events/complications
Notes	Funding: no potential conflict of interests reported Contact: PMJ Rosseel (fax: +31 (76) 5602233)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list with balanced blocks of 4 within each centre
Allocation concealment (selection bias)	Low risk	Drugs were supplied by the hospital pharmacist as a blinded, prepared infusion according to the randomisation list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation list with the participant study number and the matching study medication was not revealed to the investigator or anyone else involved to maintain the blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation list with the participant study number and the matching study medication was not revealed to the investigator or anyone else involved to maintain the blind
Incomplete outcome data (attrition bias) All outcomes	High risk	One centre did not use CI as an entry criteria but used mixed venous oxygen saturation instead, data from particular participants were excluded from the efficacy analysis, but included in the safety analysis; 1 participant randomised to dopamine was excluded because he had a pacemaker; 2 participants > 75 years were included al-

		though falling outside the age restriction; 4 participants were not included in the analysis due to an inadequate effect during titration; 1 participant was withdrawn due to technical failure of equipment; 1 participant > 75 years was withdrawn after the titration phase
Selective reporting (reporting bias)	Low risk	Pre-planned endpoints were reported
Other bias	High risk	Cross-over: no Baseline differences: yes, differences in sex, LV function and number of grafts Influence of interim results on the conduct of the study: no Deviation from study protocol: no Inappropriate administration of an intervention: no Contra-active or similar supporting pre-randomisation intervention: inotropic support by vasodilators, negative inotropes, inodilators, and positive inotropes was possible but participants treated with monoamine oxidase inhibitors or catecholamines or beta blockers were excluded
Adverse effects	High risk	Definitions of AEs given: no Monitoring of AEs: not reported Participants excluded from AE analysis: no Numerical data by intervention: yes

ADHF: acute decompensated heart failure; AEs: adverse events; AMI: acute myocardial infarction; BNP: B-type natriuretic peptide; bpm: beats per minute; CABG: coronary artery bypass grafting; CI: cardiac index; CK-MB: creatine kinase MB isoenzyme; CPB: cardio-pulmonary bypass; CVP: central venous pressure; DBP: diastolic blood pressure; ECG: electrocardiogram; EF: ejection fraction; HF: heart failure; HR: heart rate; IABP: intra-aortic balloon pump; ICU: intensive care unit; iv: intravenous; LCOS: low cardiac output syndrome; LV: left ventricular; LVEF: left ventricular ejection fraction; LVSWI: left ventricular stroke work index; MACE: major adverse cardiac events; MAP: mean arterial pressure; NYHA: New York Heart Association; NT-pro BNP: N-terminal-pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention; PCOP: pulmonary capillary occlusion pressure; PCWP: pulmonary capillary wedge pressure; RA/PCW: right-arterial pulmonary wedge pressure; RCT: randomised controlled trial; RV: right ventricular; SBP: systolic blood pressure; SIRS: systemic inflammatory response syndrome; STEMI: ST-segment elevation myocardial infarction; SVR: systemic vascular resistance; SVRI: systemic vascular resistance index

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Affonti 2013	Not RCT
Al-Shawaf 2006	Wrong indication
Andriange 1971	Not RCT
Aronski 1978	Not RCT
Avanzini 2002	Wrong intervention (ACE-inhibitor)
Barisin 2004	Wrong indication
Beller 1995	Wrong intervention (ACE-inhibitor)
Belskii 1987	Not RCT
Berger 2007	Long-term treatment
Bussmann 1983	Not RCT
Butterworth 1993	Preventive
Caimmi 2011	Not RCT
Canella 1981	Not RCT
Carmona 2010	No mortality
Clark 1983	Not RCT
Cotter 2003	Wrong indication
Cuffe 2002	Wrong indication
De Hert 2007	Preventive
De Monte 1986	Not RCT
Delle Karth 2003	Not RCT
Dhainaut 1990	Not RCT
Dominguez-Rodriguez 2007	Cross-over trial
Duygu 2008	No mortality

(*Continued*)

Erb 2014	Wrong indication
Estanove 1988	Not RCT
Felker 2003	Wrong indication
Feneck 2001	No mortality
Ferrario 1994	Cross-over trial
Fowler 1980	Not RCT
Friedle 1992	Not RCT
Galinier 1990	No mortality
Genth-Zotz 2000	Wrong intervention (ß-blocker)
George 1989	No mortality
Gray 1981	Not RCT
Gunnicker 1995	No mortality
Hobbs 1998	Not RCT
Hoffman 2003	Preventive
Jondeau 1994	Long-term treatment
Kaplan 1980	Review
Kieler-Jensen 1995	Cross-over trial
Kikura 1997	No mortality
Kikura 2002	No mortality
Kones 1972	Not RCT
Lancon 1990	No mortality
Landoni 2017	Wrong indication
Lanfear 2009	Not RCT
Lechner 2012	Preventive

(*Continued*)

Levin 2012	Wrong indication
Lilleberg 1998	Wrong indication
Lima 2010	Not RCT
Loeb 1971	Cross-over trial
Lopez 1997	Not RCT
Lvoff 1972	Not RCT
MacGregor 1994	No mortality
Mavrogeni 2007	Long-term treatment
Mehta 2017	Wrong indication
Meissner 1996	No mortality
Meng 2016	Wrong indication
Nadjamabadi 1980	Not RCT
Nijhawan 1999	No mortality
O'Connor 1999	Wrong indication
Ochiai 2014	Wrong intervention (Sartan)
Orellano 1991	Not RCT
Packer 2013	Wrong indication
Patel 1993	No mortality
Perret 1978	Review
Pouleur 1992	Wrong intervention (ACE Inhibitor)
Richard 1983	Cross-over trial
Russ 2009	Not RCT
Santman 1992	Not RCT
Seino 1996	No mortality

(*Continued*)

Shah 2014	Not RCT
Sharma 2014	Preventive
Slawsky 2000	No mortality
Stanek 1999	Long-term treatment
Sterling 1984	Not RCT
Sunny 2016	No mortality
Tacon 2012	Not RCT
Timewell 1990	No mortality
Tritapepe 1999	Not RCT
Tritapepe 2009	Not RCT
Tzimas 2009	Not RCT
Verma 1992	Not RCT
Wimmer 1999	No mortality
Wright 1992	Not RCT
Zerkowski 1992	Not RCT
Zwölfer 1995	No mortality

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02767024

Trial name or title	Intravenous vasodilator vs. inotropic therapy in patients with HF reduced ejection fraction and acute decompensation with low cardiac output (PRIORITY-ADHF Study)
Methods	Single-centre, 2-arm, cross-over, open-label RCT in the USA Follow-up: 30 days

NCT02767024 (*Continued*)

Participants	n = 148 **Inclusion criteria**: history of HF-reduced EF (NYHA class IV) and known LV EF ≤ 40% within the last 6 months, hospitalised or presented to the emergency department for acute decompensated HF with the anticipated requirement if iv therapy (including iv diuretics), persistent dyspnea or orthopnoea or oedema at screening and at the time or randomisation, pulmonary congestion on chest radiograph, NT-proBNP ≥ 2000 pg/mL (for participants ≥ 75 years old or with current atrial fibrillation NT-proBNP ≥ 3000 pg/mL), clinically suspicious of low cardiac output state (narrow pulse pressure, cold extremities, mental obtundation, declining renal function, and/or low serum sodium), SBP measured ≥ 90 but < 120 mmHg at the start and the end of the screening without use of an iv vasopressor therapy, cardiac index ≤ 2.2 L/min/m^2, PCWP ≥ 20 mmHg, able to be randomised within the first 24 h from presentation at hospital including the emergency department **Exclusion criteria:** acute coronary syndrome currently or within 30 days prior to enrolment, significant and uncorrected LV outflow track obstruction, severe mitral stenosis, severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated, documented restrictive amyloid myocardiopathy or acute myocarditis or hypertrophic obstructive or restrictive or constrictive cardiomyopathy, complex congenital heart disease, significant arrhythmias (sustained ventricular tachycardia, atrial fibrillation or atrial flutter with sustained HR > 130 bpm), bradycardia with sustained ventricular rate < 45 bpm, temperature > 38.5° C, sepsis or active infection requiring iv anti-microbial treatment, history of malignancy or any terminal illness (other than HF) with a current life expectancy < 1 year, major surgery or major neurologic event including cerebrovascular events within 30 days prior to enrolment, need for mechanical circulatory support (intra-aortic balloon pump, ECMO or any ventricular assist device), need for mechanical ventilatory support (endotracheal intubation or mechanical ventilation), chronic HF, inotropic-dependent patients, current (within 2 h prior to screening) treatment with any iv vasoactive therapies, severe renal impairment, acute kidney injury, Child C cirrhosis or history of cirrhosis with evidence of portal hypertension such as varices, acute liver failure (AST and/or ALT > 3 times above the upper limit of normal), solid organ transplant recipient or planned/anticipated organ transplant within 1 year, hematocrit < 25%, history of blood transfusion within 14 days prior to screening, active life-threatening gastrointestinal bleeding, pregnant or nursing (lactating) women, history of hypersensitive to dobutamine or sodium nitroprusside, inability to follow instructions or comply with follow-up procedures, drug or alcohol use, psychiatric or behavioural or cognitive disorder **Characteristics:** both genders, ≥ 18 years
Interventions	**Sodium nitroprusside** (start at 25 μg/min and increased by 25 μg every 5 min to maximal dose of 400 μg/min) versus **Dobutamine** (start at 2.5 μg/kg/min and increased to doses of 5, 7.5 or maximal dose 10 μg/kg/min) Continuous iv furosemide infusion dose will be maintained by protocol. In the sodium nitroprusside arm PCWP and SBP will be measured every 5 min. If PCWP > 16 mmHg while maintaining SBP ≥ 90 mmHg, the investigator will proceed to titrate dose with the goal to achieve the target of PCWP ≤ 16 mmHg and cardiac index > 2.2 L/min/m^2, or maximal infusion dose has been reached, whichever comes earliest. In the dobutamine arm every 30 min, the investigator will collect pulmonary artery blood samples for pulmonary artery sat measurement to calculate cardiac output and cardiac index by Fick. If cardiac index ≤ 2.2 L/min/m^2, the investigator will proceed to titrate dose until cardiac index > 2.2 L/min/m^2 or maximal infusion dose has been reached, whichever comes earliest
Outcomes	**Primary:** arrhythmia incidence, serum troponin T release, hypotension incidence (time frame 72 h) **Secondary**: ≥ 2 point improvement in the 5-point Likert dyspnea scale, ≥ 30% improvement in the 100-point global patient assessment scale, assessment of difference in restrictive filling pattern by echocardiogram (time frame 72 h), reduction in the Cardiac Care Unit length of stay, reduction in the hospitalisation length of stay (time frame 30 days)

NCT02767024 (*Continued*)

Starting date	May 2016
Contact information	Cesar Y Guerrero-Miranda, M.D. (ivguerrerom@gmail.com), Snehal Patel, M.D. (SNEPATEL@montefiore.org)
Notes	Plan to share data is undecided

NCT03207165

Trial name or title	Milrinone versus dobutamine in critically ill patients
Methods	Single-centre, 2-arm RCT in Canada Follow-up: 12 weeks following admission
Participants	n = 192 **Inclusion criteria:** LCOS (SBP < 90 mmHg) plus end organ dysfunction), clinical evidence of systemic/pulmonary congestion despite use of vasodilators and/or diuretics, acute coronary syndrome complicated by CS (systolic blood pressure < 90 mmHg, cardiac index < 1.8 L/min/m^2 without support or < 2.2 L/min/m^2 with support, left ventricular end-diastolic pressure > 18 mmHg), augmentation of cardiac output when patient already on maximal vasopressor therapy, medical team's decision that patient needs inotropic therapy **Exclusion criteria:** unwillingness or inability to provide informed consent, pregnancy, out-of-hospital cardiac arrest, healthcare team preference for use of specific inotrope (milrinone or dobutamine **Characteristics:** both gender , ≥ 18 years
Interventions	**Milrinone** (initiated at 0.125 µg/kg/min (stage 1) titrated according to a blinded protocol from stage 2 to 5 (0.250, 0.375, 0.5, > 0.5 µg/kg/min) versus **Dobutamine** (initiated at 2.5 µg/kg/min (stage 1) titrated according to a blinded protocol from stage 2 to 5 (5.0, 7.5, 10, > 10 µg/kg/min)
Outcomes	**Primary:** all-cause in-hospital death, non-fatal myocardial infarction, transient ischemics attack or cerebrovascular accident, stay in coronary care unit ≥ 7 days, acute kidney injury requiring renal replacement therapy, need for advanced mechanical support (time frame: through duration of hospitalisation, up to 12 weeks following admission) **Secondary:** time on inotropes/non-invasive or invasive mechanical ventilation, change in cardiac index/PCWP/pulmonary vascular resistance/systemic vascular resistance, presence of acute kidney injury, serum lactate, arrhythmia requiring medical team intervention (time frame: through duration of hospitalisation, up to 12 weeks following admission) **Other:** sustained SBP hypotension, need for intravenous or oral-anti-arrhythmic therapy, atrial/ventricular arrhythmias, need for up-titration or addition of new vasopressor therapy (time frame: through duration of hospitalisation in coronary care unit, up to 12 weeks following admission)
Starting date	June 2017
Contact information	Benjamin M Hibbert, M.D., PhD (bhibbert@ottawaheart.ca), Rebecca T Mathew, M.D. (rmathew@ottawaheart.ca)
Notes	Plan to share data is undecided

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; EF: ejection fraction; HF: heart failure; iv: intravenous; LCOS: low cardiac output syndrome; LV: left ventricular; NYHA: New York Heart Association; NT-pro BNP: N-terminal-pro-B-type natriuretic peptide; PCWP: pulmonary capillary wedge pressure; RCT: randomised controlled trial; SBP: systolic blood pressure

DATA AND ANALYSES

Comparison 1. Levosimendan versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause short-term mortality	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Levosimendan versus dobutamine	6	1776	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.37, 0.95]
1.2 Levosimendan versus placebo	2	55	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.12, 1.94]
1.3 Levosimendan versus enoximone	1	32	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.22, 1.14]
2 All-cause short-term mortality: subgroup analysis	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Levosimendan versus dobutamine: males	1	956	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.27]
2.2 Levosimendan versus dobutamine: females	1	371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.32]
2.3 Levosimendan versus dobutamine: age < 65 years	1	501	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.81]
2.4 Levosimendan versus dobutamine: age ≥ 65 years	1	826	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.10]
2.5 Levosimendan versus dobutamine: LCOS due to HF	3	1576	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.42, 1.11]
2.6 Levosimendan versus dobutamine: LCOS due to cardiac surgery	2	178	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.17, 0.87]
2.7 Levosimendan versus placebo: LCOS due to HF	1	46	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.47]
2.8 Levosimendan versus placebo: CS due to AMI	1	9	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.02, 7.82]
2.9 Levosimendan versus dobutamine: LCOS with no history of CHF	1	156	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.82, 2.87]
2.10 Levosimendan versus dobutamine: LCOS with history of CHF	1	1171	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.04]
3 All-cause long-term mortality	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Levosimendan versus dobutamine	3	1552	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.12]
3.2 Levosimendane versus dobutamine	1	22	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.37, 24.58]
3.3 Levosimendan versus placebo	1	9	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.08, 4.66]
4 All-cause long-term mortality:subgroup analysis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

4.1 Levosimendan versus dobutamine: males	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Levosimendan versus dobutamine: females	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Levosimendan versus dobutamine: age < 65 years	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Levosimendan versus dobutamine: age ≥ 65 years	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Cardiac index	6		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Levosimendan versus dobutamine	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Levosimendan versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Epinephrine versus norepinephrine-dobutamine	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Dopexamine versus dopamine	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Pulmonary capillary wedge pressure	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Levosimendan versus dobutamine	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Levosimendan versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Dopexamine versus dopamine	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Mean arterial pressure	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Levosimendan versus dobutamine	2	178	Mean Difference (IV, Random, 95% CI)	-2.15 [-4.61, 0.31]
7.2 Epinephrine versus norepinephrine-dobutamine	1	30	Mean Difference (IV, Random, 95% CI)	-1.0 [-8.19, 6.19]
7.3 Dopexamine versus dopamine	1	59	Mean Difference (IV, Random, 95% CI)	-1.90 [-8.10, 4.30]

Comparison 2. Levosimendan versus control: sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause short-term mortality: fixed-effect model	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Levosimendan versus dobutamine	6	1776	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.93]
1.2 Levosimendan versus placebo	2	55	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.12, 1.93]
2 All-cause short-term mortality: low risk of bias	2	1530	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.39, 1.27]

Analysis 1.1. Comparison 1 Levosimendan versus control, Outcome 1 All-cause short-term mortality.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 1 All-cause short-term mortality

Study or subgroup	Levosimendan n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Levosimendan versus dobutamine					
Adamopoulos 2006	2/23	5/23		8.0 %	0.40 [0.09, 1.86]
Alvarez 2006	1/21	1/20		2.8 %	0.95 [0.06, 14.22]
Follath(LIDO) 2002	8/103	17/100		21.7 %	0.46 [0.21, 1.01]
Garcı a-Gonz lez 2006	0/11	0/11			Not estimable
Levin 2008	6/69	17/68		19.3 %	0.35 [0.15, 0.83]
Mebazaa (SURVIVE) 2007	79/664	91/663		48.2 %	0.87 [0.65, 1.15]
Subtotal (95% CI)	**891**	**885**		**100.0 %**	**0.60 [0.37, 0.95]**
Total events: 96 (Levosimendan), 131 (Control)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 6.20$, df = 4 (P = 0.18); $I^2 = 35\%$					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 Levosimendan versus placebo					
Adamopoulos 2006	2/23	4/23		77.6 %	0.50 [0.10, 2.47]
Husebye 2013	0/4	1/5		22.4 %	0.40 [0.02, 7.82]
Subtotal (95% CI)	**27**	**28**		**100.0 %**	**0.48 [0.12, 1.94]**
Total events: 2 (Levosimendan), 5 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.04 (P = 0.30)					
3 Levosimendan versus enoximone					
Fuhrmann 2008	5/16	10/16		100.0 %	0.50 [0.22, 1.14]
Subtotal (95% CI)	**16**	**16**		**100.0 %**	**0.50 [0.22, 1.14]**
Total events: 5 (Levosimendan), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.098)					

Analysis 1.2. Comparison 1 Levosimendan versus control, Outcome 2 All-cause short-term mortality: subgroup analysis.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 2 All-cause short-term mortality: subgroup analysis

Study or subgroup	Levosimendan n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Levosimendan versus dobutamine: males					
Mebazaa (SURVIVE) 2007	59/493	61/463		100.0 %	0.91 [0.65, 1.27]
Subtotal (95% CI)	**493**	**463**		**100.0 %**	**0.91 [0.65, 1.27]**
Total events: 59 (Levosimendan), 61 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.57)					
2 Levosimendan versus dobutamine: females					
Mebazaa (SURVIVE) 2007	20/171	30/200		100.0 %	0.78 [0.46, 1.32]
Subtotal (95% CI)	**171**	**200**		**100.0 %**	**0.78 [0.46, 1.32]**
Total events: 20 (Levosimendan), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
3 Levosimendan versus dobutamine: age < 65 years					
Mebazaa (SURVIVE) 2007	20/237	22/264		100.0 %	1.01 [0.57, 1.81]
Subtotal (95% CI)	**237**	**264**		**100.0 %**	**1.01 [0.57, 1.81]**
Total events: 20 (Levosimendan), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
4 Levosimendan versus dobutamine: age ≥ 65 years					
Mebazaa (SURVIVE) 2007	59/427	69/399		100.0 %	0.80 [0.58, 1.10]
Subtotal (95% CI)	**427**	**399**		**100.0 %**	**0.80 [0.58, 1.10]**
Total events: 59 (Levosimendan), 69 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
5 Levosimendan versus dobutamine: LCOS due to HF					
Adamopoulos 2006	2/23	5/23		8.9 %	0.40 [0.09, 1.86]
Follath(LIDO) 2002	8/103	17/100		25.8 %	0.46 [0.21, 1.01]
Mebazaa (SURVIVE) 2007	79/664	91/663		65.2 %	0.87 [0.65, 1.15]
Subtotal (95% CI)	**790**	**786**		**100.0 %**	**0.69 [0.42, 1.11]**
Total events: 89 (Levosimendan), 113 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.00, df = 2 (P = 0.22); I^2 =33%					

(*Continued* . . .)

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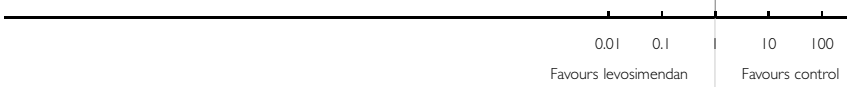
Study or subgroup	Levosimendan n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.52 (P = 0.13)					
6 Levosimendan versus dobutamine: LCOS due to cardiac surgery					
Alvarez 2006	1/21	1/20		9.4 %	0.95 [0.06, 14.22]
Levin 2008	6/69	17/68		90.6 %	0.35 [0.15, 0.83]
Subtotal (95% CI)	**90**	**88**		**100.0 %**	**0.38 [0.17, 0.87]**
Total events: 7 (Levosimendan), 18 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.28 (P = 0.023)					
7 Levosimendan versus placebo: LCOS due to HF					
Adamopoulos 2006	2/23	4/23		100.0 %	0.50 [0.10, 2.47]
Subtotal (95% CI)	**23**	**23**		**100.0 %**	**0.50 [0.10, 2.47]**
Total events: 2 (Levosimendan), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
8 Levosimendan versus placebo: CS due to AMI					
Husebye 2013	0/4	1/5		100.0 %	0.40 [0.02, 7.82]
Subtotal (95% CI)	**4**	**5**		**100.0 %**	**0.40 [0.02, 7.82]**
Total events: 0 (Levosimendan), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
9 Levosimendan versus dobutamine: LCOS with no history of CHF					
Mebazaa (SURVIVE) 2007	20/78	13/78		100.0 %	1.54 [0.82, 2.87]
Subtotal (95% CI)	**78**	**78**		**100.0 %**	**1.54 [0.82, 2.87]**
Total events: 20 (Levosimendan), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
10 Levosimendan versus dobutamine: LCOS with history of CHF					
Mebazaa (SURVIVE) 2007	59/586	78/585		100.0 %	0.76 [0.55, 1.04]
Subtotal (95% CI)	**586**	**585**		**100.0 %**	**0.76 [0.55, 1.04]**
Total events: 59 (Levosimendan), 78 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.084)					

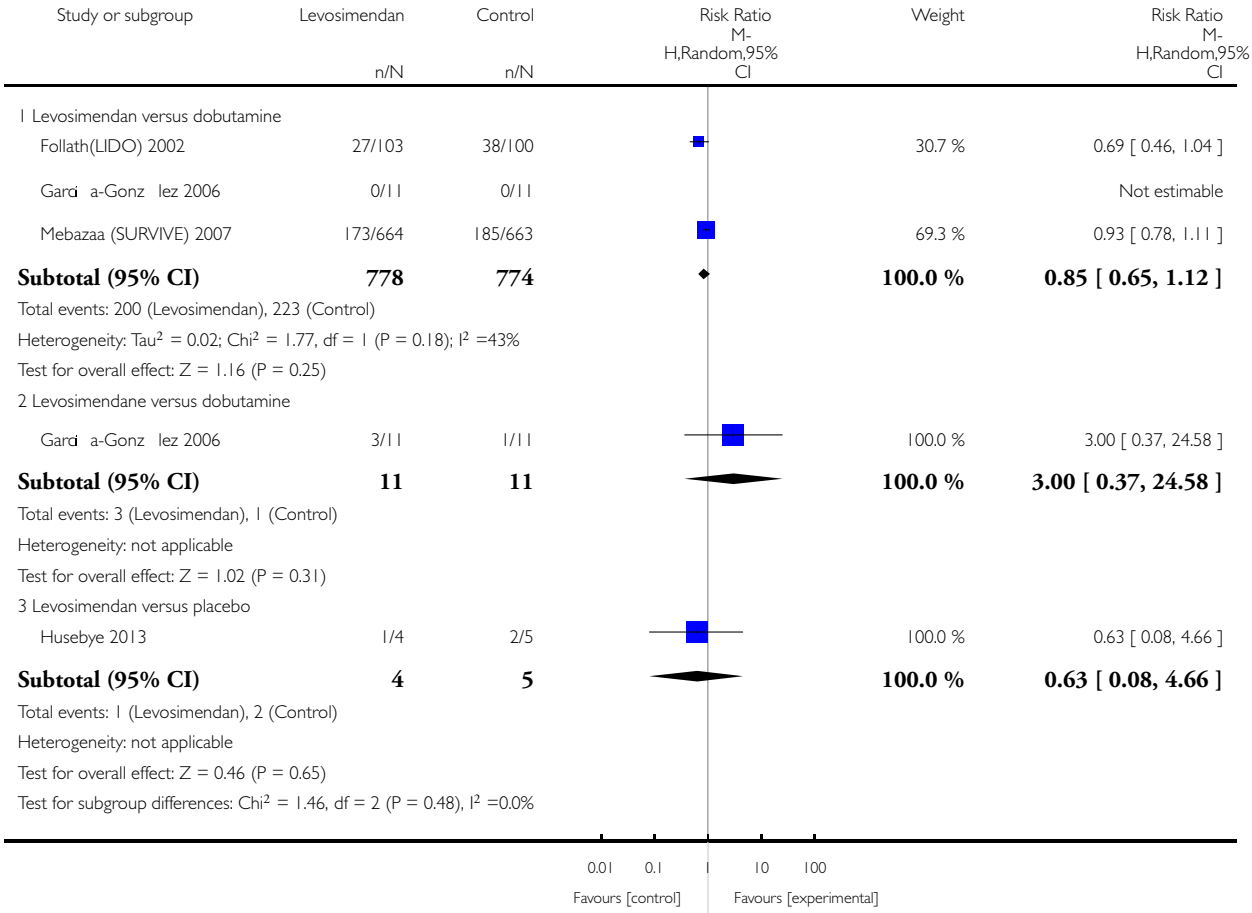


Analysis 1.3. Comparison 1 Levosimendan versus control, Outcome 3 All-cause long-term mortality.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 3 All-cause long-term mortality



Analysis 1.4. Comparison 1 Levosimendan versus control, Outcome 4 All-cause long-term mortality:subgroup analysis.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 4 All-cause long-term mortality:subgroup analysis

Study or subgroup	Levosimendan n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Levosimendan versus dobutamine: males				
Mebazaa (SURVIVE) 2007	128/493	127/463		0.95 [0.77, 1.17]
2 Levosimendan versus dobutamine: females				
Mebazaa (SURVIVE) 2007	45/171	58/200		0.91 [0.65, 1.26]
3 Levosimendan versus dobutamine: age < 65 years				
Mebazaa (SURVIVE) 2007	54/237	56/264		1.07 [0.77, 1.49]
4 Levosimendan versus dobutamine: age ≥ 65 years				
Mebazaa (SURVIVE) 2007	119/427	129/399		0.86 [0.70, 1.06]

Analysis 1.5. Comparison 1 Levosimendan versus control, Outcome 5 Cardiac index.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 5 Cardiac index

Study or subgroup	Levosimendan N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Levosimendan versus dobutamine						
Adamopoulos 2006	23	1.9 (0.1)	23	1.8 (0.04)		0.10 [0.06, 0.14]
Alvarez 2006	21	2.8 (0.3)	20	2.3 (0.2)		0.50 [0.34, 0.66]
Garcı a-Gonz lez 2006	11	2.9 (0.4)	11	2.4 (0.2)		0.50 [0.24, 0.76]
Levin 2008	69	3.4 (0.2)	68	2.7 (0.1)		0.70 [0.65, 0.75]
2 Levosimendan versus placebo						
Adamopoulos 2006	23	1.9 (0.1)	23	1.8 (0.1)		0.10 [0.04, 0.16]
3 Epinephrine versus norepinephrine-dobutamine						
Levy 2011	15	2.9 (0.5)	15	2.8 (0.4)		0.10 [-0.22, 0.42]
4 Dopexamine versus dopamine						
Rosseel 1997	29	3.1 (0.7)	30	2.8 (0.5)		0.30 [-0.01, 0.61]

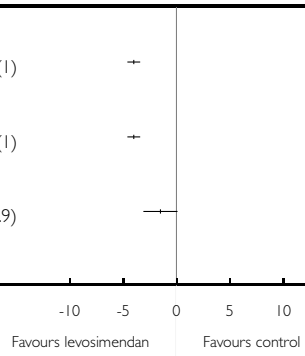
Analysis 1.6. Comparison 1 Levosimendan versus control, Outcome 6 Pulmonary capillary wedge pressure.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 6 Pulmonary capillary wedge pressure

Study or subgroup	Levosimendan N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Levosimendan versus dobutamine						
Adamopoulos 2006	23	19 (1)	23	23 (1)		-4.00 [-4.58, -3.42]
2 Levosimendan versus placebo						
Adamopoulos 2006	23	19 (1)	23	23 (1)		-4.00 [-4.58, -3.42]
3 Dopexamine versus dopamine						
Rosseel 1997	29	9.3 (3.2)	30	10.8 (2.9)		-1.50 [-3.06, 0.06]

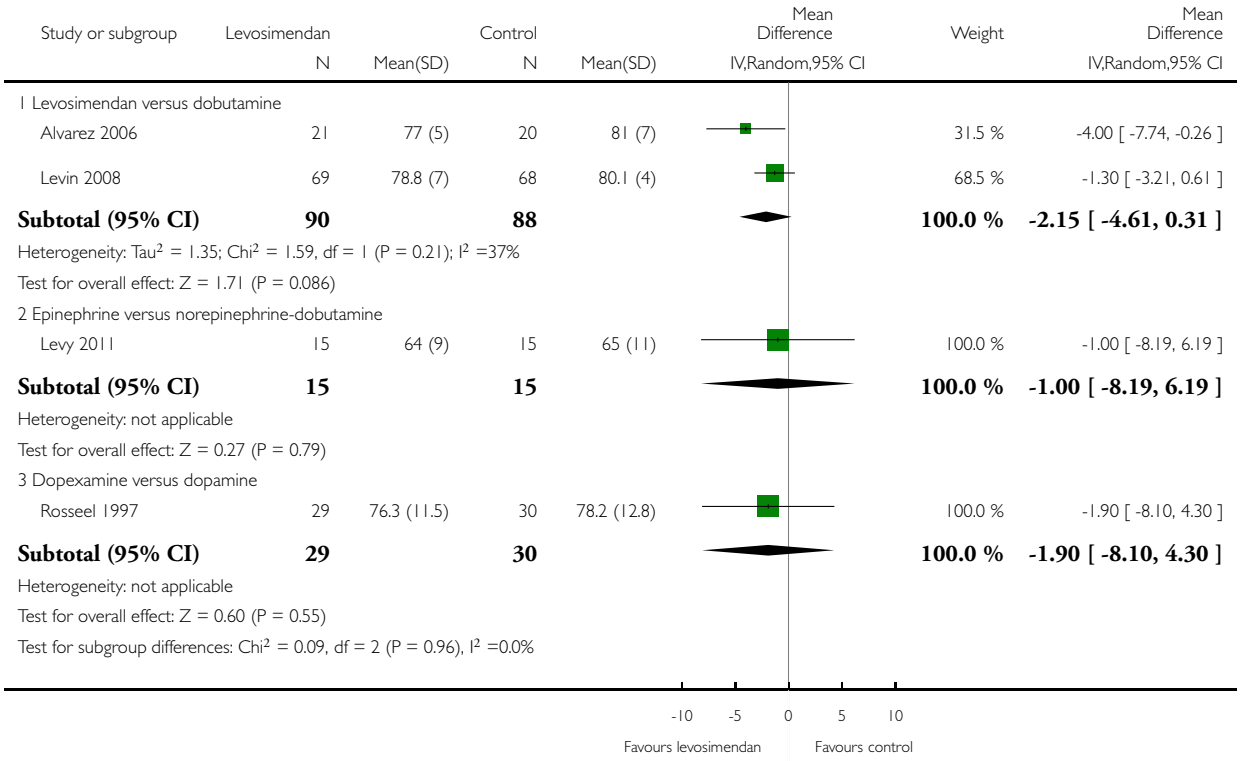


Analysis 1.7. Comparison 1 Levosimendan versus control, Outcome 7 Mean arterial pressure.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 1 Levosimendan versus control

Outcome: 7 Mean arterial pressure



Analysis 2.1. Comparison 2 Levosimendan versus control: sensitivity analyses, Outcome 1 All-cause short-term mortality: fixed-effect model.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 2 Levosimendan versus control: sensitivity analyses

Outcome: 1 All-cause short-term mortality: fixed-effect model

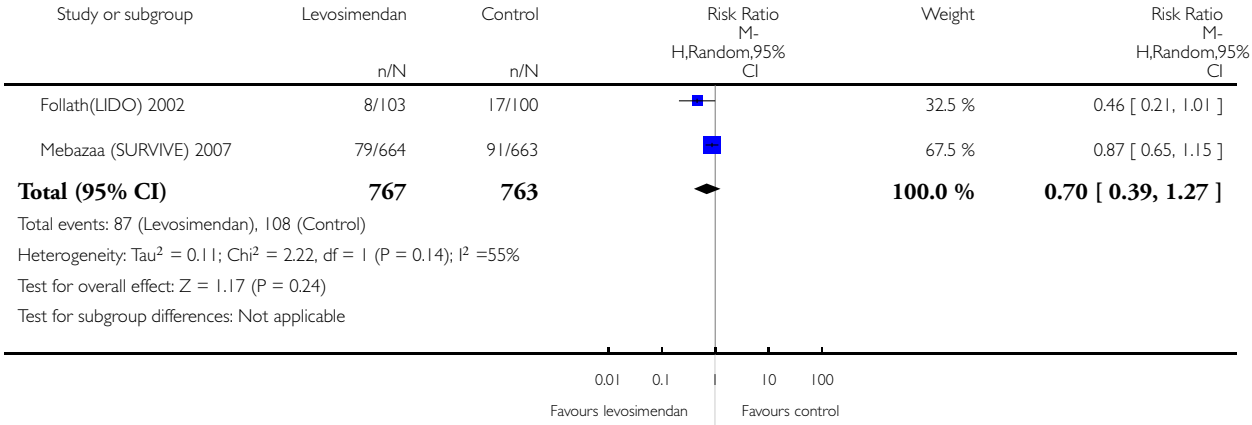
Study or subgroup	Levosimendan n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Levosimendan versus dobutamine					
Adamopoulos 2006	2/23	5/23		3.8 %	0.40 [0.09, 1.86]
Alvarez 2006	1/21	1/20		0.8 %	0.95 [0.06, 14.22]
Follath(LIDO) 2002	8/103	17/100		13.1 %	0.46 [0.21, 1.01]
Garcı a-Gonz lez 2006	0/11	0/11			Not estimable
Levin 2008	6/69	17/68		13.0 %	0.35 [0.15, 0.83]
Mebazaa (SURVIVE) 2007	79/664	91/663		69.3 %	0.87 [0.65, 1.15]
Subtotal (95% CI)	**891**	**885**		**100.0 %**	**0.73 [0.57, 0.93]**
Total events: 96 (Levosimendan), 131 (Control)					
Heterogeneity: Chi^2 = 6.20, df = 4 (P = 0.18); I^2 =35%					
Test for overall effect: Z = 2.52 (P = 0.012)					
2 Levosimendan versus placebo					
Adamopoulos 2006	2/23	4/23		74.6 %	0.50 [0.10, 2.47]
Husebye 2013	0/4	1/5		25.4 %	0.40 [0.02, 7.82]
Subtotal (95% CI)	**27**	**28**		**100.0 %**	**0.47 [0.12, 1.93]**
Total events: 2 (Levosimendan), 5 (Control)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Chi^2 = 0.35, df = 1 (P = 0.56), I^2 =0.0%					

Analysis 2.2. Comparison 2 Levosimendan versus control: sensitivity analyses, Outcome 2 All-cause short-term mortality: low risk of bias.

Review: Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome

Comparison: 2 Levosimendan versus control: sensitivity analyses

Outcome: 2 All-cause short-term mortality: low risk of bias



ADDITIONAL TABLES

Table 1. Major adverse cardiac events (MACE) (no deaths) in hospital

Comparison	Primary studies	MACE	Intervention		Control		RR (95% CI)
			events	total	events	total	
Levosimendan vs dobutamine	Levin 2008	Perioperative infarction	1 (1.4%)	69	8 (11.8%)	68	0.12 (0.02 to 0.96)
	García-González 2006	Re-infarction	0 (0%)	11	0 (0%)	11	Not estimable
	Levin 2008	Cerebrovascular accidents	2 (2.9%)	69	6 (8.8%)	68	0.33 (0.07 to 1.57)
	García-González 2006	Cerebrovascular accidents	0 (0%)	11	0 (0%)	11	Not estimable

Table 1. Major adverse cardiac events (MACE) (no deaths) in hospital (*Continued*)

Levosimendan vs placebo	Husebye 2013	MACE (death, non-fatal myocardial infarction, revascularisation of the infarct-related artery)	2 (50.0%)	4	2 (40.0%)	5	1.25 (0.29 to 5.35)
		Repeat PCI	1 (25.0%)	4	0 (0%)	5	3.60 (0.18 to 70.34)
Amrinone vs dobutamine	Dupuis 1992	Re-infarction (2 h)	0 (0%)	15	6 (40.0%)	15	0.08 (0.00 to 1.25)
Dopexamine vs dopamine	Rosseel 1997	Perioperative infarction	3 (8.6%)	35	2 (5.7%)	35	1.50 (0.27 to 8.43)
Nitric oxide vs placebo	Baldassarre 2008	Myocardial infarction	1 (50.0%)	2	1 (100%)	1	0.67 (0.17 to 2.67)

CI: confidence interval; PCI: percutaneous coronary intervention; RR: risk ratio

Table 2. Length of hospital stay

Comparison	Primary studies	Reported information	Intervention		Control	
			Events/time	Total	Events/time	Total
Levosimendan vs dobutamine	Levin 2008	Stay in ICU (hours, median with IQR)	66 (58-74)	69	158 (106-182)	68
Levosimendan vs enoximone	Fuhrmann 2008	Stay in ICU (days, median with IQR)	10 (5-23)	16	13 (7-19)	16
Enoximone vs dobutamine	Atallah 1990	Stay in ICU (hours, mean)	92 ± 37	18	155 ± 129	19

ICU: intensive care unit; IQR: intra-quartile-range

Table 3. Haemodynamics

Comparison	Primary studies	Haemodynamics	Intervention		Control		MD (95% CI)
Intervention vs control		**last measurements**	**mean ± SD or median (IQR)**	**total**	**mean ± SD or median (IQR)**	**total**	
Levosimendan vs dobutamine	Adamopoulos 2006	Cardiac index (after 72 h, L/min/m^2)	1.9 ± 0.1	23	1.8 ± 0.04	23	0.10 (0.06 to 0.14)
	Alvarez 2006	Cardiac index (after 48 h, L/min/m^2)	2.8 ± 0.3	21	2.3 ± 0.2	20	0.50 (0.34 to 0.66)
	Garc a-González 2006	Cardiac index (after 30 h, L/min/m^2)	2.9 ± 0.4	11	2.4 ± 0.2	11	0.50 (0.24 to 0.76)
	Levin 2008	Cardiac index (after 48 hrs, L/min/m^2)	3.4 ± 0.2	69	2.7 ± 0.1	68	0.70 (0.65 to 0.75)
	Adamopoulos 2006	PCWP (after 72 h, mmHg)	19.0 ± 1	23	23.0 ± 1.0	23	-4.00 (-4.60 to -3.40)
	Alvarez 2006	MAP (after 48 h, mmHg)	77.0 ± 5	21	81.0 ± 7.0	20	-4.00 (-7.70 to -0.30)
	Levin 2008	MAP (after 48 h, mmHg)	78.8 ± 7	69	80.1 ± 4	68	-1.30 (-3.20 to 0.60)
Levosimendan vs placebo	Adamopoulos 2006	Cardiac index (after 72 h, (L/min/m^2)	1.9 ± 0.1	23	1.8 ± 0.1	23	0.10 (0.04 to 0.16)
	Adamopoulos 2006	PCWP (after 72 h, mmHg)	19.0 ± 1	23	23.0 ± 1.0	23	-4.00 (-4.60 to -3.40)
Levosimendan vs enoximone	Fuhrmann 2008	Cardiac index (after 48 h, L/min/m^2)	3.1 (2.5-3.5)	16	3.1 (2.8-3.3)	16	Not estimable
	Fuhrmann 2008	MAP (after 48 h (mmHg)	75.0 (58.0-79.0)	16	70.0 (63.0-83.0)	16	Not estimable
Epinephrine vs norepinephrine-	Levy 2011	Cardiac index (after 24 h, L/	2.9 ± 0.5	15	2.8 ± 0.4	15	0.10 (-0.22 to 0.42)

Table 3. Haemodynamics (*Continued*)

dobutamine		min/m^2)					
	Levy 2011	MAP (after 24 h, mmHg)	64 ± 9	15	65.0 ± 11.0	15	-1.00 (-8.20 to 6.20)
Dopexamine vs dopamine	Rosseel 1997	Cardiac index (after 6 h, L/min/m^2)	3.1 ± 0.7	29	2.8 ± 0.5	30	0.30 (-0.01 to 0.61)
	Rosseel 1997	PCWP (after 6 h, mmHg)	9.3 ± 3.2	29	10.8 ± 2.9	30	-1.50 (-3.10 to 0.10)
	Rosseel 1997	MAP (after 6 h, mmHg)	76.3 ± 11.5	29	78.2 ± 12.8	30	-1.90 (-8.10 to 4.30)

CI: confidence interval; IQR: intra-quartile-range; MAP: mean arterial pressure; MD: mean difference; PCWP: pulmonary capillary wedge pressure; SD: standard deviation

Table 4. Adverse events

Comparison	Primary studies	Adverse events (no MACE)	Intervention		Control	
			events	total	events	total
Levosimendan vs**dobutamine**	Alvarez 2006, Levin 2008, Mebazaa (SURVIVE) 2007	Atrial fibrillation	78 (10.4%)	750	71 (9.5%)	748
	Mebazaa (SURVIVE) 2007	Ventricular fibrillation	15 (2.3%)	660	19 (2.9%)	660
	Alvarez 2006, Follath(LIDO) 2002, Levin 2008	Ventricular arrhythmias	7 (3.6%)	193	25 (13.3%)	188
	Mebazaa (SURVIVE) 2007	Ventricular tachycardia	52 (7.9%)	660	48 (7.3%)	660
		Ventricular extrasystoles	40 (6.1%)	660	24 (3.6%)	660
		Tachycardia	33 (5.0%)	660	33 (5.0%)	660

Table 4. Adverse events (*Continued*)

	Bradycardia	8 (1.2%)	660	17 (2.6%)	660
Follath(LIDO) 2002, Mebazaa (SURVIVE) 2007	Headache	69 (9.0%)	763	36 (4.7%)	760
	Cardiac failure	91 (11.9%)	763	127 (16.7%)	760
Mebazaa (SURVIVE) 2007	Congestive cardiac failure	26 (3.9%)	660	22 (3.3%)	660
	Cardiac arrest	20 (3.0%)	660	26 (3.9%)	660
Follath(LIDO) 2002, Mebazaa (SURVIVE) 2007	Disorder aggravated	17 (2,2%)	763	27 (3.6%)	760
	Gastrointestinal disorders	54 (7.1%)	763	52 (6.8%)	760
Levin 2008, Mebazaa (SURVIVE) 2007	Acute kidney failure	29 (4.0%)	729	43 (5.9%)	728
Levin 2008	Need for dialysis	2 (2.9%)	69	8 (11.9%)	68
Levin 2008, Mebazaa (SURVIVE) 2007	Pneumonia	34 (4.7%)	729	34 (4.7%)	728
Garcı a-González 2006	Multiple organ failure	0 (0%)	11	0 (0%)	11
	Stroke	0 (0%)	11	0 (0%)	11
Levin 2008	Vasoplegia	1 (1.4 %)	69	9 (13.2%)	68
	Dyspnoea	1 (1.4%)	69	4 (5.8%)	68
	Inflammatory response syndrome	4 (5.8%)	69	15 (22.1%)	68
	Sepsis	1 (1.4%)	69	9 (13.2%)	68
	Prolonged ventilatory assistance	6 (8.7%)	69	22 (32.3%)	68

Table 4. Adverse events (*Continued*)

	Mebazaa (SURVIVE) 2007	Hypokalaemia	62 (9.4%)	660	39 (5.9%)	660
		Hyperkalaemia	15 (2.3%)	660	16 (2.4%)	660
		Hypotension	102 (15.5%)	660	92 (13.9%)	660
		Nausea	45 (6.8%)	660	49 (7.4%)	660
		Insomnia	37 (5.6%)	660	29 (4.4%)	660
		Chest pain	32 (4.8%)	660	47 (7.1%)	660
		Constipation	26 (3.9%)	660	28 (4.2%)	660
		Pyrexia	22 (3.3%)	660	19 (2.9%)	660
		Urinary tract infection	21 (3.2%)	660	30 (4.5%)	660
		Anexiety	20 (3.0%)	660	19 (2.9%)	660
		Pulmonary oedema	20 (3.0%)	660	18 (2.7%)	660
		Dizziness	19 (2.9%)	660	16 (2.4%)	660
		Cough	19 (2.9%)	660	21 (3.2%)	660
		Pain in extremity	18 (2.7%)	660	10 (1.5%)	660
		Pruritus	16 (2.4%)	660	7 (1.1%)	660
		Anaemia	15 (2.3%)	660	17 (2.6%)	660
		Epistaxis	14 (2.1%)	660	7 (1.1%)	660
		Back pain	13 (2.0%)	660	18 (2.7%)	660
		Angina pectoris	12 (1.8%)	660	18 (2.7%)	660
		Muscle spasms	12 (1.8%)	660	13 (2.0%)	660
		Dyspnoea	9 (1.4%)	660	17 (2.6%)	660
		Hypertension	9 (1.4%)	660	15 (2.3%)	660
		Cataract	7 (1.1%)	660	14 (2.1%)	660

Table 4. Adverse events (*Continued*)

		Agitation	7 (1.1%)	660	0 (0%)	660
Levosimendan vs**placebo**	Husebye 2013	Non-sustained ventricular tachycardia	1 (25.0%)	4	3 (60.0%)	5
		Atrial fibrillation	1 (25.0%)	4	0 (0%)	5
		Episodes of hypotension during drug infusion (MAP fall > 10 mmHg)	2 (50.0%)	4	1 (20.0%)	5
Levosimendan vs**enoximone**	Fuhrmann 2008	Need of mechanical ventilation	13 (81.3%)	16	15 (93.8%)	16
		Acute renal failure	5 (31.3%)	16	8 (50.0%)	16
		Need of continuous renal replacement therapy	5 (31.5%)	16	8 (50.0%)	16
		New onset atrial fibrillation	7 (43.8%)	16	9 (56.3%)	16
		Ventricular tachycardia or fibrillation	8 (50.0%)	16	11 (68.8%)	16
		Development of systemic inflammatory response	8 (50.0%)	16	13 (81.3%)	16
		Pneumonia	7 (43.8%)	16	7 (43.8%)	16
		Urinary infections	0 (0%)	16	2 (12.5%)	16
		Sepsis	3 (18.8%)	16	2 (12.5%)	16
Epinephrine vs. norepinephrine-dobutamine	Levy 2011	Supraventricular arrhythmia	2 (13.3%)	15	0 (0%)	15

Table 4. Adverse events (*Continued*)

		Sustained ventricular tachycardia	1 (6.7%)	15	0 (0%)	15
Amrinone vs. dobutamine	Dupuis 1992	Cardiac arrhythmias during treatment	0 (0%)	15	4 (26.7%)	15
		Myocardial ischemias (within 16 to 20 hrs)	4 (26.7%)	15	4 (26.7%)	15
Dopexamine vs. dopamine	Rosseel 1997	Cardiac events	19 (54.3%)	35	22 (62.9%)	35
		Abnormal blood loss	2 (5.7%)	35	1 (2.9%)	35
		Kidney failure	1 (2.9%)	35	1 (2.9%)	35
		Other adverse events	5 (14.3%)	35	1 (2.9%)	35
		Major adverse events	0 (0%)	35	0 (0%)	35

MACE: major adverse cardiac events; MAP: mean arterial pressure

APPENDICES

Appendix 1. Search strategy

CENTRAL

#1 MeSH descriptor: [Shock, Cardiogenic] this term only
#2 (cardiogenic* shock)
#3 MeSH descriptor: [Cardiac Output, Low] this term only
#4 (low near/2 cardiac output)
#5 ((instab* or unstab*) next h?emodynamic)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Drug Therapy] this term only
#8 ((drug or medica* or pharmacological) next (therap* or treatment))
#9 MeSH descriptor: [Drug Administration Routes] explode all trees
#10 drug administ*
#11 MeSH descriptor: [Drug Administration Schedule] this term only

#12 #7 or #8 or #9 or #10 or #11
#13 MeSH descriptor: [Cardiotonic Agents] explode all trees
#14 cardiotonic
#15 ((myocardial or cardiac) next stimula*)
#16 inotrope*
#17 inotropic agent*
#18 cardioprotective agent*
#19 acetyldigitoxin*
#20 acetyldigoxin*
#21 adrenomedullin
#22 amrinone
#23 carbachol
#24 cardiac glycoside*
#25 cymarine
#26 deslanoside
#27 digitalis glycoside*
#28 digitoxin
#29 digoxin
#30 dobutamine
#31 dopamine
#32 enoximone
#33 etilefrine
#34 isoproterenol
#35 lisinopril
#36 medigoxin
#37 milrinone
#38 ouabain
#39 oxyfedrine
#40 phenylephrine
#41 prenalterol
#42 proscillaridin
#43 strophanthin*
#44 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43
#45 MeSH descriptor: [Vasodilator Agents] explode all trees
#46 vasodilators
#47 vasodilator drug*
#48 vasodilator agent*
#49 vasorelaxant*
#50 vasoactive antagonist*
#51 acetylcholine
#52 adenosine*
#53 adrenomedullin
#54 alprostadil
#55 amlodipine
#56 amyl nitrite
#57 bencyclane
#58 bepridil
#59 betahistine
#60 bradykinin
#61 celiprolol
#62 chromonar
#63 cromakalim

#64 cyclandelate
#65 diazoxide
#66 dihydroergocristine
#67 dihydroergocryptine
#68 dilazep
#69 diltiazem
#70 dipyridamole
#71 dyphylline
#72 ergoloid mesylate*
#73 erythrityl tetranitrate
#74 felodipine
#75 fenoldopam
#76 flunarizine
#77 hexobendine
#78 hydralazine
#79 iloprost
#80 isosorbide dinitrate
#81 isoxsuprine
#82 isradipine
#83 kallidin
#84 lidoflazine
#85 mibefradil
#86 minoxidil
#87 molsidomine
#88 moxisylyte
#89 nafronyl
#90 niacin
#91 nicardipine
#92 nicergoline
#93 nicorandil
#94 nicotinyl alcohol
#95 nifedipine
#96 nimodipine
#97 nisoldipine
#98 nitrendipine
#99 nitroglycerin
#100 nitroprusside
#101 nonachlazine
#102 nylidrin
#103 oxprenolol
#104 oxyfedrine
#105 papaverine
#106 pentaerythritol tetranitrate
#107 pentoxifylline
#108 phenoxybenzamine
#109 pinacidil
#110 pindolol
#111 (Pituitary Adenylate Cyclase-Activating Polypeptide)
#112 prenylamine
#113 propranolol
#114 (S-Nitroso-N-Acetylpenicillamine)
#115 S-Nitrosoglutathione
#116 S-Nitrosothiols

#117 Suloctidil
#118 Theobromine
#119 Tolazoline
#120 Trapidil
#121 (Vasoactive Intestinal Peptide)
#122 Verapamil
#123 Vincamine
#124 (Xanthinol Niacinate)
#125 #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121 or #122 or #123 or #124
#126 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
#127 Epoprostenol
#128 Ketanserin
#129 #126 or #127 or #128
#130 MeSH descriptor: [Phosphodiesterase Inhibitors] this term only
#131 ((phosphodiesterase2 or phosphodiesterase-2 or phosphodiesteraseII or "phosphodiesterase-II") next (antagonist*))
#132 ((phosphodiesterase2 or phosphodiesterase-2 or phosphodiesteraseII or phosphodiesterase-II) next (inhibitor*))
#133 antiphosphodiesterase*
#134 Caffeine
#135 "calcium sensitiser*"
#136 Levosimendan
#137 #130 or #131 or #132 or #133 or #134 or #135 or #136
#138 tilarginine
#139 #12 or #44 or #125 or #129 or #137 or #138
#140 #6 and #139

MEDLINE Ovid

1. Shock, Cardiogenic/
2. cardiogenic* shock*.tw.
3. Cardiac Output, Low/
4. (low adj2 cardiac output).tw.
5. ((instab* or unstab*) adj h?emodynamic*).tw.
6. or/1-5
7. Drug Therapy/
8. ((drug or medica* or pharmacological) adj (therap* or treatment)).tw.
9. exp Drug Administration Routes/
10. drug administ*.tw.
11. Drug Administration Schedule/
12. or/7-11
13. exp Cardiotonic Agents/
14. cardiotonic.tw.
15. ((myocardial or cardiac) adj stimula*).tw.
16. inotrope*.tw.
17. inotropic agent*.tw.
18. cardioprotective agent*.tw.
19. acetyldigitoxin*.tw.
20. acetyldigoxin*.tw.
21. adrenomedullin.tw.
22. amrinone.tw.

23. carbachol.tw.
24. cardiac glycoside*.tw.
25. cymarine.tw.
26. deslanoside.tw.
27. digitalis glycoside*.tw.
28. digitoxin.tw.
29. digoxin.tw.
30. dobutamine.tw.
31. dopamine.tw.
32. enoximone.tw.
33. etilefrine.tw.
34. isoproterenol.tw.
35. lisinopril.tw.
36. medigoxin.tw.
37. milrinone.tw.
38. ouabain.tw.
39. oxyfedrine.tw.
40. phenylephrine.tw.
41. prenalterol.tw.
42. proscillaridin.tw.
43. strophanthin*.tw.
44. or/13-43
45. exp Vasodilator Agents/
46. vasodilators.tw.
47. vasodilator drug*.tw.
48. vasodilator agent*.tw.
49. vasorelaxant*.tw.
50. vasoactive antagonist*.tw.
51. acetylcholine.tw.
52. adenosine*.tw.
53. adrenomedullin.tw.
54. alprostadil.tw.
55. amlodipine.tw.
56. amyl nitrite.tw.
57. bencyclane.tw.
58. bepridil.tw.
59. betahistine.tw.
60. bradykinin.tw.
61. celiprolol.tw.
62. chromonar.tw.
63. cromakalim.tw.
64. cyclandelate.tw.
65. diazoxide.tw.
66. dihydroergocristine.tw.
67. dihydroergocryptine.tw.
68. dilazep.tw.
69. diltiazem.tw.
70. dipyridamole.tw.
71. dyphylline.tw.
72. ergoloid mesylate*.tw.
73. erythrityl tetranitrate.tw.
74. felodipine.tw.
75. fenoldopam.tw.

76. flunarizine.tw.
77. hexobendine.tw.
78. hydralazine.tw.
79. iloprost.tw.
80. isosorbide dinitrate.tw.
81. isoxsuprine.tw.
82. isradipine.tw.
83. kallidin.tw.
84. lidoflazine.tw.
85. mibefradil.tw.
86. minoxidil.tw.
87. molsidomine.tw.
88. moxisylyte.tw.
89. nafronyl.tw.
90. niacin.tw.
91. nicardipine.tw.
92. nicergoline.tw.
93. nicorandil.tw.
94. nicotinyl alcohol.tw.
95. nifedipine.tw.
96. nimodipine.tw.
97. nisoldipine.tw.
98. nitrendipine.tw.
99. nitroglycerin.tw.
100. nitroprusside.tw.
101. nonachlazine.tw.
102. nylidrin.tw.
103. oxprenolol.tw.
104. oxyfedrine.tw.
105. papaverine.tw.
106. pentaerythritol tetranitrate.tw.
107. pentoxifylline.tw.
108. phenoxybenzamine.tw.
109. pinacidil.tw.
110. pindolol.tw.
111. Pituitary Adenylate Cyclase-Activating Polypeptide.tw.
112. prenylamine.tw.
113. propranolol.tw.
114. S-Nitroso-N-Acetylpenicillamine.tw.
115. S-Nitrosoglutathione.tw.
116. S-Nitrosothiols.tw.
117. Suloctidil.tw.
118. Theobromine.tw.
119. Tolazoline.tw.
120. Trapidil.tw.
121. Vasoactive Intestinal Peptide.tw.
122. Verapamil.tw.
123. Vincamine.tw.
124. Xanthinol Niacinate.tw.
125. or/45-124
126. exp Platelet Aggregation Inhibitors/
127. Epoprostenol.tw.
128. Ketanserin.tw.

129. or/126-128
130. Phosphodiesterase Inhibitors/
131. ((phosphodiesterase2 or phosphodiesterase-2 or phosphodiesteraseII or phosphodiesterase-II) adj (antagonist* or inhibitor*)).tw.
132. antiphosphodiesterase*.tw.
133. Caffeine.tw.
134. calcium sensitiser*.tw.
135. Levosimendan.tw.
136. or/130-135
137. tilarginine.tw.
138. 12 or 44 or 125 or 129 or 136 or 137
139. 6 and 138
140. randomized controlled trial.pt.
141. controlled clinical trial.pt.
142. randomized.ab.
143. placebo.ab.
144. drug therapy.fs.
145. randomly.ab.
146. trial.ab.
147. groups.ab.
148. or/140-147
149. exp animals/ not humans.sh.
150. 148 not 149
151. 139 and 150

Embase Ovid

1. Shock, Cardiogenic/
2. cardiogenic* shock*.tw.
3. Cardiac Output, Low/
4. (low adj2 cardiac output).tw.
5. ((instab* or unstab*) adj h?emodynamic*).tw.
6. or/1-5
7. Drug Therapy/
8. ((drug or medica* or pharmacological) adj (therap* or treatment)).tw.
9. exp Drug Administration Routes/
10. drug administ*.tw.
11. Drug Administration Schedule/
12. or/7-11
13. exp Cardiotonic Agents/
14. cardiotonic.tw.
15. ((myocardial or cardiac) adj stimula*).tw.
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17. inotropic agent*.tw.
18. cardioprotective agent*.tw.
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20. acetyldigoxin*.tw.
21. adrenomedullin.tw.
22. amrinone.tw.
23. carbachol.tw.
24. cardiac glycoside*.tw.
25. cymarine.tw.
26. deslanoside.tw.
27. digitalis glycoside*.tw.

28. digitoxin.tw.
29. digoxin.tw.
30. dobutamine.tw.
31. dopamine.tw.
32. enoximone.tw.
33. etilefrine.tw.
34. isoproterenol.tw.
35. lisinopril.tw.
36. medigoxin.tw.
37. milrinone.tw.
38. ouabain.tw.
39. oxyfedrine.tw.
40. phenylephrine.tw.
41. prenalterol.tw.
42. proscillaridin.tw.
43. strophanthin*.tw.
44. or/13-43
45. exp Vasodilator Agents/
46. vasodilators.tw.
47. vasodilator drug*.tw.
48. vasodilator agent*.tw.
49. vasorelaxant*.tw.
50. vasoactive antagonist*.tw.
51. acetylcholine.tw.
52. adenosine*.tw.
53. adrenomedullin.tw.
54. alprostadil.tw.
55. amlodipine.tw.
56. amyl nitrite.tw.
57. bencyclane.tw.
58. bepridil.tw.
59. betahistine.tw.
60. bradykinin.tw.
61. celiprolol.tw.
62. chromonar.tw.
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64. cyclandelate.tw.
65. diazoxide.tw.
66. dihydroergocristine.tw.
67. dihydroergocryptine.tw.
68. dilazep.tw.
69. diltiazem.tw.
70. dipyridamole.tw.
71. dyphylline.tw.
72. ergoloid mesylate*.tw.
73. erythrityl tetranitrate.tw.
74. felodipine.tw.
75. fenoldopam.tw.
76. flunarizine.tw.
77. hexobendine.tw.
78. hydralazine.tw.
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96. nimodipine.tw.
97. nisoldipine.tw.
98. nitrendipine.tw.
99. nitroglycerin.tw.
100. nitroprusside.tw.
101. nonachlazine.tw.
102. nylidrin.tw.
103. oxprenolol.tw.
104. oxyfedrine.tw.
105. papaverine.tw.
106. pentaerythritol tetranitrate.tw.
107. pentoxifylline.tw.
108. phenoxybenzamine.tw.
109. pinacidil.tw.
110. pindolol.tw.
111. Pituitary Adenylate Cyclase-Activating Polypeptide.tw.
112. prenylamine.tw.
113. propranolol.tw.
114. S-Nitroso-N-Acetylpenicillamine.tw.
115. S-Nitrosoglutathione.tw.
116. S-Nitrosothiols.tw.
117. Suloctidil.tw.
118. Theobromine.tw.
119. Tolazoline.tw.
120. Trapidil.tw.
121. Vasoactive Intestinal Peptide.tw.
122. Verapamil.tw.
123. Vincamine.tw.
124. Xanthinol Niacinate.tw.
125. or/45-124
126. exp Platelet Aggregation Inhibitors/
127. Epoprostenol.tw.
128. Ketanserin.tw.
129. or/126-128
130. Phosphodiesterase Inhibitors/
131. ((phosphodiesterase2 or phosphodiesterase-2 or phosphodiesteraseII or phosphodiesterase-II) adj (antagonist* or inhibitor*)).tw.
132. antiphosphodiesterase*.tw.
133. Caffeine.tw.

134. calcium sensitiser*.tw.
135. Levosimendan.tw.
136. or/130-135
137. tilarginine.tw.
138. 12 or 44 or 125 or 129 or 136 or 137
139. 6 and 138
140. random$.tw.
141. factorial$.tw.
142. crossover$.tw.
143. cross over$.tw.
144. cross-over$.tw.
145. placebo$.tw.
146. (doubl$ adj blind$).tw.
147. (singl$ adj blind$).tw.
148. assign$.tw.
149. allocat$.tw.
150. volunteer$.tw.
151. crossover procedure/
152. double blind procedure/
153. randomized controlled trial/
154. single blind procedure/
155. or/140-154
156. (animal/ or nonhuman/) not human/
157. 155 not 156
158. 139 and 157

CPCI-S Web of Science

#23 #22 AND #21
#22 TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))
#21 #20 AND #1
#20 #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
#19 TS=(Caffeine or "calcium sensitiser*" or Levosimendan or tilarginine)
#18 TS=("phosphodiesterase2 antagonist*" or "phosphodiesterase-2antagonist*" or "phosphodiesteraseII antagonist*" or "phosphodiesterase-II antagonist*" or "phosphodiesterase2 inhibitor*" or "phosphodiesterase-2 inhibitor*" or "phosphodiesteraseII inhibitor*"or "phosphodiesterase-II inhibitor*")
#17 TS=(platelet near/2 inhibitor* or Epoprostenol or Ketanserin)
#16 TS=(Vincamine or "Xanthinol Niacinate")
#15 TS=(S-Nitrosothiols or Sodium Azide or Suloctidil or Theobromine or Theophylline or Thiouracil or Tolazoline or Trapidil or Trimetazidine or "Vasoactive Intestinal Peptide" or Verapamil)
#14 TS=(S-Nitrosothiols or Suloctidil or Theobromine or Tolazoline or Trapidil or "Vasoactive Intestinal Peptide" or Verapamil)
#13 TS=(S-Nitrosothiols or Sodium Azide or Suloctidil or Theobromine or Theophylline or Thiouracil or Tolazoline or Trapidil or Trimetazidine or "Vasoactive Intestinal Peptide" or Verapamil)
#12 TS=("Pituitary Adenylate Cyclase-Activating Polypeptide" or prenylamine or propranolol or S-Nitrosoglutathione)
#11 TS=(nonachlazine or nylidrin or oxprenolol or oxyfedrine or papaverine or "pentaerythritol tetranitrate" or pentoxifylline or phenoxybenzamine or pinacidil or pindolol)
#10 TS=(nicorandil or "nicotinyl alcohol" or nifedipine or nimodipine or nisoldipine or nitrendipine or nitroglycerin or nitroprusside)
#9 TS=(lidoflazine or mibefradil or minoxidil or molsidomine or moxisylyte or nafronyl or niacin or nicardipine or nicergoline)
#8 TS=(fenoldopam or flunarizine or hexobendine or hydralazine or "isosorbide dinitrate" or isoxsuprine or isradipine or kallidin)
#7 TS=(dilazep or diltiazem or dipyridamole or dyphylline or "ergoloid mesylate*" or "erythrityl tetranitrate" or felodipine)
#6 TS=(celiprolol or chromonar or cromakalim or cyclandelate or diazoxide or dihydroergocristine or dihydroergocryptine)
#5 TS=(adrenomedullin or alprostadil or amlodipine or "amyl nitrite" or bencyclane or bepridil or betahistine or bradykinin)

#4 TS=(vasodilators or vasodilator drug* or vasodilator agent* or vasorelaxant* or vasoactive antagonist* or acetylcholine or adenosine*)
#3 TS=(cardiotonic or "myocardial stimula*" or "cardiac stimula*" or inotrope* or "inotropic agent*" or "cardioprotective agent*" or acetyldigitoxin* or acetyldigoxin* or adrenomedullin or amrinone or carbachol or cardiac glycoside* or cymarine or deslanoside or digitoxin or digoxin or dobutamine or enoximone or etilefrine or lisinopril or medigoxin or milrinone or ouabain or oxyfedrine or phenylephrine or prenalterol or proscillaridin or strophanthin*)
#2 TS=("drug treatment" or "medica* treatment "or "pharmacological treatment") OR TS=("drug therap*" or "medica* therap*" or "pharmacological therap*" or "drug administ*")
#1 TS=("cardiogenic* shock" OR low near/2 "cardiac output" OR "instab* h?emodynamic" or "unstab* h?emodynamic ")

Controlled trials (ISRCTN registry)

Search 1: cardiogenic shock
Search 2: low cardiac output

Centerwatch

search by Medical condition (cardiac ischemia, myocardial ischemia, heart failure) and therapeutic area (cardiogenic shock, low cardiac output)

Clinicaltrials.gov

Search 1: Conditions: cardiogenic shock
Search 2: Conditions: low cardiac output

ICTRP

Search 1:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: acetyldigitoxin or acetyldigoxin or adrenomedullin or amrinone or carbachol or cardiac gycoside or cymarine or deslanoside or digitalis glycoside or digitoxin or digoxin or dobutamine
Search 2:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: enoximone or etilefrine.or isoproterenol or lisinopril or medigoxin or milrinone or ouabain or oxyfedrine or phenylephrine or prenalterol or proscillaridin or strophanthin
Search 3:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: acetylcholine or adenosine or adrenomedullin or alprostadil or amlodipine or amyl nitrite or bencyclane or bepridil or betahistine or bradykinin or celiprolol or chromonar or cromakalim or cyclandelate or diazoxide or dihydroergocristine
Search 4:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: dihydroergocryptine or dilazep or diltiazem or dipyridamole or dyphylline or ergoloid mesylate or erythrityl tetranitrate or felodipine or fenoldopam or flunarizine or hexobendine or hydralazine iloprost or isosorbide dinitrate or isoxsuprine or isradipine
Search 5:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: kallidin or lidoflazine or mibefradil or minoxidil or molsidomine or moxisylyte or nafronyl or niacin or nicardipine or nicergoline or nicorandil or nicotinyl alcohol or nifedipine or nimodipine or nisoldipine or nitrendipine or nitroglycerin
Search 6:
Condition: cardiogenic shock or low cardiac output

AND
Intervention: nitroprusside or nonachlazine or nylidrin or oxprenolol or oxyfedrine or papaverine or pentaerythritol tetranitrate or pentoxifylline or phenoxybenzamine or pinacidil or pindolol or Pituitary Adenylate or Cyclase-Activating Polypeptide or prenylamine
Search 7:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: propranolol or S-Nitroso-N-Acetylpenicillamine or S-Nitrosoglutathione or S-Nitrosothiols or Suloctidil or Theobromine or Tolazoline or Trapidil or Vasoactive Intestinal Peptide or Verapamil or Vincamine or Xanthinol Niacinate
Search 8:
Condition: cardiogenic shock or low cardiac output
AND
Intervention: Epoprostenol or Ketanserin or Phosphodiesterase Inhibitor or phosphodiesterase2 or phosphodiesterase-2 or phosphodiesteraseII or phosphodiesterase-II or antiphosphodiesterase or Caffeine or calcium sensitiser or Levosimendan or tilarginine

WHAT'S NEW

Last assessed as up-to-date: 22 June 2017.

Date	Event	Description
22 June 2017	New search has been performed	The searches were updated in June 2017. We identified nine additional studies for inclusion, which leads to a total of 13 studies included in this review update
5 December 2016	New citation required and conclusions have changed	In this update, we expanded the review to all people with AMI, HF or cardiac surgery and CS or LCOS and included trials with a subgroup of eligible participants. We used the RR to measure treatment effects on mortality, MACE and adverse events instead of HRs and ORs

CONTRIBUTIONS OF AUTHORS

Julia Schumann (contact author): co-ordination of the review, data collection for the review (screening, appraisal of inclusion criteria and quality of papers, extracting data from papers, screening data on unpublished studies), writing the review

Eva Henrich: data collection for the review (screening, appraisal of inclusion criteria and quality of papers, extracting data from papers, screening data on unpublished studies)

Hellen Strobl: data collection for the review (screening, appraisal of inclusion criteria and quality of papers, extracting data from papers, screening data on unpublished studies)

Roland Prondzinsky: writing the protocol and conclusions, appraisal of inclusion criteria and quality of papers, interpretation of data from a clinical and consumer perspective

Sophie Weiche: data collection for the review (screening, appraisal of inclusion criteria and quality of papers, extracting data from papers, screening data on unpublished studies), providing general advice from a clinical perspective

Holger Thiele: screening data on unpublished studies, contacting authors, providing general advice from a clinical perspective

Karl Werdan: providing general advice from a clinical and a policy perspective

Stefan Frantz: appraisal of inclusion criteria and quality of papers, screening data on unpublished studies, writing the introductory part of the review, providing general advice from a clinical perspective

Susanne Unverzagt: design and co-ordination of the review, design and organisation of the search strategy, data collection for the review (screening, appraisal of inclusion criteria and quality of papers, extracting data from papers, contacting authors, data management, methodological interpretation of data), analysis of data, writing the review

DECLARATIONS OF INTEREST

Julia Schumann: no relevant conflicts of interests

Eva Henrich: no relevant conflicts of interests

Hellen Strobl: no relevant conflicts of interests

Roland Prondzinsky: no relevant conflicts of interests

Sophie Weiche: no relevant conflicts of interests

Holger Thiele has received research funding (Maquet Cardiovascular, Teleflex Medical, Terumo, Lilly Germany, The Medicines Company), honoraria for advisory board activities (Lilly, Maquet Cardiovascular), honoraria for lectures (AstraZeneca, Lilly, Daiichi Sankyo, The Medicines Company, Terumo, Maquet Cardiovascular, Bayer, Boehringer Ingelheim).

Karl Werdan has received honoraria for lectures (Abbott, Biogen, Biotest, Boston scientific, Brahms, Datascope, Maquet, Novartis, Roche, Servier), honoraria for advisory board activities (Abbott, Baxter, Biotest, Datascope, Servier), took part in clinical trials (Arrows, Datascope, MSD, Novartis, Servier) and has received research funding from Biotest, Bayer, Datascope, Novartis Roche, Servier.

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Susanne Unverzagt: no relevant conflicts of interests.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Handsearching in the annual conference proceedings was planned from 1960 to the present but proceedings were not available in Germany for this period. Due to the first publication of eligible trials in 2003 we restricted our search to the available proceedings in Halle, Leipzig and Munich.

In the update, we expanded the review to all people with CS or LCOS. We included trials with a subgroup of eligible participants. We used the risk ratio to measure treatment effects on mortality, major adverse cardiac events (MACE) and adverse events instead of hazard ratios and odds ratios.

We searched for conference proceedings in ISI Web of Science (Conference Proceedings Citation Index-Science, Thomson Reuters 1990 to 22 June 2017) and did no separately handsearch in the annual conference proceedings of the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), European Society of Intensive Care (ESICM) and Deutsche Gesellschaft für Kardiologie (DGK) for the years 2013 to 2016.

We excluded trials on children.

We excluded trials not reporting on the acute setting, that is, prevention trials and long-term studies (treatment lasting one month or more).

We excluded studies that did not report on our primary outcome (all-cause mortality). We plan to change this in future updates of this review.

We added 'Summary of findings' tables with GRADE rating.

We added adverse events as a secondary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiac Output, Low [*drug therapy; etiology]; Cardiotonic Agents [*therapeutic use]; Dobutamine [therapeutic use]; Enoximone [therapeutic use]; Hydrazones [therapeutic use]; Myocardial Infarction [*complications]; Nitric Oxide [therapeutic use]; Pyridazines [therapeutic use]; Randomized Controlled Trials as Topic; Shock, Cardiogenic [*drug therapy; etiology]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans