Medizinische Fakultät der

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Inotropic Agents and Vasodilator Strategies for the Treatment of Cardiogenic Shock or Low Cardiac Output Syndrome in Patient with Heart Failure

Dissertation

zur Erlangung des akademischen Grades Doktor der Medizin (Dr. Med.)

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geboren am 06.06.1992 in Herbolzheim

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12.07.2021

06.04.2022

Abstract

Heart failure (HF) is a common reason to be admitted to the hospital. Cardiogenic shock (CS) and low cardiac output syndrome (LCOS) are complications of HF with a high mortality rate. To treat these complications positive inotropic and vasodilative medicines are often used to reduce the cardiac load and stabilise the circulatory system. The objective of this systematic review is to collect the existing evidence for these therapeutic strategies and to summarise and evaluate the results. For this purpose a systematic search of randomised controlled trials was conducted. The last search was performed October 24, 2019. To assess the effectiveness of the treatment the primary outcome mortality was investigated. Secondary outcomes studied were haemodynamic parameters, major adverse cardiovascular events (MACE), Adverse Events (AEs), length of hospital stay, quality of life and costs.

A total of 3,986 papers were identified and 140 potentially relevant full-text paper were read. Nine finally published and one ongoing study met the predefined inclusion criteria and were incorporated in the systematic review. The included studies investigated the efficacy of the drugs levosimendan, dobutamine, PGE1, enoximone, epinephrine, norepinephrine, milrinone and dopamine. In seven different comparisons, 1,836 participants were included. No statistically significant reduction of mortality for any of the included drugs could be shown. In a meta-analysis of five studies, with a total of 1,724 participants suffering from CS or LCOS, levosimendan showed a positive trend with a reduction in mortality compared to the different control groups not reaching statistical significance. Levosimendan showed compared to dobutamine for short-term mortality a Risk Ratio (RR) of 0.7 with a 95% confidence interval (CI) of 0.39 to 1.27; compared to dobutamine showed a RR for long-term mortality a RR of 0.83 with a 95% CI of 0.64 to 1.09; levosimendan compared to placebo/no specific treatment for long-term mortality a RR of 0.34 with a 95% CI of 0.12 to 1.00.

Larger placebo-controlled trials are needed to evaluate the true effect of levosimendan in patients with HF.

Kurzreferat

Herzinsuffizienz ist ein häufiger Grund für Krankenhausaufenthalte. Kardiogener Schock (CS) und Low Cardiac Output Syndrome (LCOS) sind Komplikationen einer Herzinsuffizenz mit einer hohen Mortalität. In der Therapie dieser Komplikationen kommen positiv inotrope und vasodilatative Medikamente zum Einsatz, um das Herz zu entlasten und den Kreislauf zu stabilisieren. Das Ziel der vorliegenden systematischen Übersichtsarbeit ist es, die existierende Evidenz für diese Therapieoptionen zu sammeln, zusammenzufassen und zu bewerten. Hierzu wurde systematisch nach geeigneten randomisiert kontrollierten klinischen Studien gesucht. Letztes Suchdatum war der 24. Oktober 2019. Zur Beurteilung der Wirksamkeit wurde als primärer Endpunkt die Mortalität untersucht. Als sekundäre Endpunkte wurden hämodynamische Parameter, schwere kardiale Komplikation (englisch: major adverse cardiovascular events, MACE), unerwünschte Ereignisse, die Länge des Krankenhausaufenthaltes, Lebensqualität und Kosten der Therapie untersucht.

Es wurden insgesamt 3 986 Referenzen gesichtet. Neun Studien erfüllten die vordefinierten Einschlusskriterien und wurden in der Übersichtsarbeit mit aufgenommen. In den ausgewerteten Studien wurde die Wirksamkeit der Medikamente Levosimendan, Dobutamin, PGE1, Enoximon, Adrenalin, Noradrenalin, Milrinon und Dopamin in der beschriebenen Patientengruppe miteinander verglichen. Die Daten von 1 836 Patienten sind in diesen Analysen ausgewertet worden. Es konnte in keinem der Vergleiche eine statistisch signifikante Reduktion der Mortalität gezeigt werden. In Metaanalyen von fünf Studien, in denen insgesamt 1 724 Patienten mit CS oder LCOS eingeschlossen wurden, zeigte Levosimendan einen positiven Trend mit einer Reduktion der Mortalität im Vergleich zu den Kontrollgruppen ohne statistische Signifikanz zu erreichen. Im Vergleich mit Dobutamine für Kurzzeitmortalität zeigte Levosimendan eine Risk Ratio (RR) von 0.7 mit einem 95% Konfidenzintervall (KI) von 0.39 bis 1.27; für Langzeitmortalität RR = 0.83; 95% KI: 0.64 - 1.09; Levosimendan verglichen mit Placebo/ ohne spezifische Therapie für Langzeitmortalität RR = 0.34; 95% KI: 0.12 - 1.00.

Größere Placebo-kontrollierte Studien werden benötigt, um den tatsächlichen Effekt von Levosimendan in Patienten mit Herzinsuffizienz und kardiogenem Schock oder Low Cardiac Output Syndrom zu bestätigen.

Feige, Hellen: Wirksamkeit von Vasodilatatoren und Inotropika bei Patienten mit kardiogenem Schock oder geringem Herzauswurfvolumen bedingt durch Herzinsuffizienz – eine systematische Übersichtsarbeit Halle (Saale), Univ., Med. Fak., Diss., 88 Seiten, 2021

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Abbreviations

AHF	acute heart failure
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AMI	acute myocardial infarction
BNP	Brain natriuretic peptide
CHF	Chronic Heart Failure
CI	Confidence interval
CrI	cardiac index
CS	cardiogenic shock
DBP	diastolic blood pressure
EFICA	European Association of Preventive Cardiology
ESC	European Society of Cardiology
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	heart rate [bpm = beats per minute]
Hrs	hours
HF	heart failure
ICU	intensive care unit
ITT	intention-to-treat
i.v.	intravenous
LCOS	low cardiac output syndrome
LIDO	study Levosimendan Infusion versus Dobutamin
LVEF	left ventricular ejection fraction

MACE	major adverse cardiovascular events
MAP	mean arterial pressure [mmHg]
MBP	mean blood pressure [mmHg]
MD	mean differences
mmHg	millimeter of mercury column (1mmHg = 0,001333 bar)
N	number of studies
NYHA	New York Heart Association
NVL	Nationale Versorgungs Leitlinie (englisch: National Disease Management Guidelines)
PCWP	pulmonary capillary wedge pressure [mmHg]
PDE	phosphodiesterase enzyme
PGE1	prostaglandin E 1
PICO-criteria	participants, interventions, comparisons and outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RR	relative risk
SAQ	Self Assessment Questionaire
SBP	systolic blood pressure
SVR	systemic vascular resistance

1 Introduction

Heart failure (HF) is a common cause of hospital admission. Even though therapeutic strategies improved over the last years mortality rates are still high (Bytyçi and Bajraktari 2015). In Germany more than 500 out of 100 000 inhabitants develop HF during one year and their number is increasing (Deutsche Herzstiftung 2019). While mortality in HF patients decreases, it is still one of the most common causes of death in Germany (Deutsche Herzstiftung 2019). Two of the most common causes for high mortality in HF patients are cardiogenic shock (CS) and low cardiac output syndrome (LCOS) (Spinar et al. 2011). In 2020 an estimated number of about 64 million people worldwide suffered from HF and their number is increasing due to an aging population (Lippi and SanchiGomar 2020). It is estimated to cost approximately $108 billion per year worldwide, around 60% direct and 40% indirect costs (Cook et al. 2014). The prognosis for HF changes with the development of CS or LCOS. In the AHEAD study (Spinar et al. 2011) patients admitted for acute heart failure (AHF) developed CS in 15% and LCOS in 4% of the cases. The in-hospital mortality of patients with CS was at 63% and 17% in patients with LCOS (Spinar et al. 2011). Finding the right treatment strategy therefore plays an important role in the management of these patients.

For patients with hypotension or signs of hypoperfusion inotropic agents are recommended by the European Society of Cardiology (ESC) whereas vasodilators should only be considered in patients with systolic blood pressure (SBP) > 90 mmHg (Ponikowski et al. 2016). However, the national disease management guideline of Germany only recommends the use of inotropic agents in patients with CS or when diuretics alone cannot achieve a sufficient amount of volume reduction (Arzneimittelkommission der Deutschen Apotheker et al. 2017). In severe cases of shock evidence suggests that adding vasodilators to a vasopressor medication might be useful (Pirracchio et al. 2013), therefore not restricting the use of vasodilators for patients without hypotension. To optimize haemodynamic effects and to minimize the likelihood of adverse effects it may be helpful to match the medication to the underlying pathophysiology due to which the patient develops the CS (Jentzer et al. 2015). As the guidelines do not differentiate between the cause of CS or LCOS in their treatment recommendations this systematic review tries to find the best treatment strategy for patients with HF as underlying cause.

1.1 Description of the Condition

HF is a clinical syndrome that can be characterised by symptoms such as breathlessness, ankle swelling and fatigue, as well as by signs such as elevated jugular venous pressure, pulmonary crackles and peripheral oedema. The fast onset or worsening of these symptoms is called AHF and is a life-threatening condition (Ponikowski et al. 2016). AHF can be subdivided into different forms which should be treated accordingly (Metra et al. 2008). These subgroups may be defined as LCOS and CS (John R. Teerlink 2010).

Shock in general might be difficult to classify into a scheme under clinical conditions because two or more causes of shock frequently occur in patients (Braunwald et al. 2001). No consensus on the criteria that should be used to define CS has been found at present (Reyentovich et al. 2016). In the guidelines for acute and chronic heart failure (CHF) provided by the ESC the definition of CS is the presence of signs for hypoperfusion and hypotension despite adequate filling status (Ponikowski et al. 2016).

CS can also be described as an extreme form of forward failure in which the systemic perfusion is reduced by the failure to pump sufficiently it is described with low blood pressure, reduced cardiac output and higher filling pressure. The mortality for this condition is very high (> 70-80%) (Marx et al. 2018)

As in CS, the causes of LCOS are diverse. LCOS may be described as a less severe form of CS with tissue hypoperfusion as a result of HF (John R. Teerlink 2010). Spinar et al. describe right heart failure as a form of LCOS with increased jugular venous pressure, increased liver size and hypotension (Spinar et al. 2011). Signs and symptoms that help to assess a state of LCOS are tachycardia, hypotension, narrow pulse pressure, poor perfusion (cold extremities, weak pulses, slow capillary refill time) and oliguria or anuria (Massé et al. 2005).

1.2 Description of the Intervention

1.2.1 Positive Inotropic Agents

Positive inotropic agents increase the force with which the cardiac muscle contracts and thereby leading to an increase in cardiac output (Palmer and Pennefather 2009). Different inotropes have different effects and side effects. The combination of different inotropes may be used to achieve a desired result (Parry 2011). Positive Inotropic agents can be further divided into inodilators and inopressors. Inodilators combine positive inotropic and vasodilative qualities for example dobutamine and milrinone. Inoconstrictors

combine positive inotropic and vasoconstrictive qualities for example norepinephrine, epinephrine and dopamine (Jentzer et al. 2015).

1.2.2 Vasodilative Agents

Vasodilators are used in AHF for symptomatic relief and constitute the second most frequently used agents under this condition but without robust evidence confirming their beneficial effects (Ponikowski et al. 2016).

Vasodilators (e.g. nitroglycerine, nitroprusside) reduce the systemic vascular resistance without direct inotropic effects. By reducing the systemic vascular resistance, cardiac filling pressure is decreased. (Jentzer et al. 2015)

1.3 How the Intervention might Work

The ESC recommends vasodilators and inotropic agents for patients with AHF (Ponikowski et al. 2016). One of the main goals in patients who are in a stage of volume overload and display signs of hypoperfusion, is to alleviate systemic perfusion and increase renal blood flow. This may be achieved by using intravenous vasodilator or inotropic agents (Desai et al. 2016).

Inotropic agents are used to lift the coronary perfusion pressure in case of systemic hypotonic pressure and to enhance contractility of the heart in case of myocardial stunning (Störk et al. 2005). Patients treated with intravenous inotropes have been associated with higher in-hospital mortality (Mebazaa et al. 2011). The use of intravenous (i.v.) inotropic agents should be considered, if despite adequate filling status, a patient presents hypotension or hypoperfusion. In case of beta blockade causing hypotension with hypoperfusion, levosimendan or phosphodiesterase (PDE) III inhibitors may be considered (Ponikowski et al. 2016).

In patients with pulmonary oedema vasodilators can improve poor oxygenation, if used in the absence of hypotension (Felker et al. 2015). The use of i.v. vasodilators was associated with lower in-hospital mortality in patients with AHF in the ALARM-HF registry, even in patients with low-normal blood pressure. (Mebazaa et al. 2011)

1.4 Outcome measurements

To estimate treatment effects the most reliable endpoint is all-cause mortality. This might not be the endpoint with the highest effect, especially in a study setting where follow-up times could be too short to see any small effects. As intermediate markers the haemodynamic parameters systolic, diastolic and mean blood pressure (SBP, DBP, MBP), heart rate (HR), cardiac index (CrI), pulmonary capillary wedge pressure (PCWP), left ventricular ejection fraction (LVEF) and systemic vascular resistance (SVR) are used, to help estimate therapeutic effects.

2 Objectives

In their HF guidelines the European Society of Cardiology (ESC) (Ponikowski et al. 2016), the American College of Cardiology Foundation in cooperation with the American Heart Association (ACCF/AHA) (Yancy et al. 2017) and the German Medical Association (GMA) (Arzneimittelkommission der Deutschen Apotheker et al. 2017) state that inotropic therapy may be considered for patients with CS. The ESC and the ACCF/AHA guidelines both grade the level of evidence for this strategy as level C, indicating that it is based on consensus of opinion or small studies, retrospective studies or registries (Ponikowski et al. 2016). The German Medical Association lists solely expert opinions as evidence (Arzneimittelkommission der Deutschen Apotheker et al. 2017). All three guidelines also state that inotropic agents should not be used in AHF patients who do not meet specific criteria, such as low blood pressure, as they might be harmful in this group of patients.

Although there is a long history of usage for vasodilators in AHF nevertheless the evidence remains limited (Metra et al. 2008).They are often used to reduce pre- and afterload in AHF and might thereby increase stroke volume. Even though that is the case, the ESC guidelines state that there is not enough evidence to prove the benefit of this line of therapy. As vasodilators can also cause hypotension, they are not recommended in patients already presenting with low blood pressure (Ponikowski et al. 2016). No recommendation on dosage or length of treatment is made in the current guidelines of the ACC, ESC or the Nationale Versorgungs Leitlinien (NVL) (Yancy et al. 2017; Ponikowski et al. 2016; Arzneimittelkommission der Deutschen Apotheker (AMK) et al. 2019).

In 2014 Unverzagt et al. published a Cochrane-Review looking at inotropic and vasodilator strategies in patients with myocardial infarction complicated by CS or LCOS (Unverzagt et al. 2014). This systematic review was updated in 2018 regarding the same treatment strategies but looking at all patients with CS or LCOS without distinction of cause (Schumann et al. 2018)

The analyses of small subgroups of patients with AHF might amend the outcome by improving therapeutic strategies (Follath et al. 2011).The objective of this thesis is to summarise all randomized controlled trials (RCTs) existing that investigate the efficacy of vasodilator or positive inotropic strategies in patients with HF experiencing CS or LCOS, by means of a systematic review.

The aim of this review is to collect all existing evidence and to give a clear picture of what we know about these treatment strategies so far and how reliable recommendations based on this evidence are. It also aims to form a good foundation for future trials by showing which evidence is missing, to improve practice guidelines and evidence based medical care.

3 Methods

This theses is based on a systematic review published in the Cochrane Library (Schumann et al. 2018).Cochrane is a not-for-profit organization which aims to improve evidencebased health decision-making. For this goal evidence is summed up in systematic reviews, based on the methods published in the Cochrane Handbook for Systematic Reviews of Interventions. The review question was based on the systematic Cochrane review "Inotropic Agents and Vasodilator Strategies for CS or LCOS" by Schumann et al. published in 2018. In contrast to the initial paper, this thesis aims to work out a more detailed view for the mentioned treatment strategies including long-term treatment with respect to HF patients who develop CS or LCOS.

3.1 Inclusion criteria

As suggested by the Cochrane Handbook for the inclusion criteria: participants, interventions, comparisons and outcomes (PICO-criteria) were predefined as shown in Table 1.

Table 1 Inclusion criteria

Criteria	Description
Study design	RCT
Patient population	18 years or older HF With either CS or LCOS
Intervention	Inotropic agents or vasodilators
Comparison	Placebo, no treatment, other inotropic agents or vasodilators
Outcome	All-cause mortality

All studies had to be RCTs to be considered for this review. The RCTs had to be of parallel group design and report results on efficacy and safety, and on mortality. Crossover trials were excluded, as an intention to treat (ITT) analysis was planned and it was expected that a cross-over would have an influence on the primary outcome mortality. Prevention trials were also excluded, to focus this review on acute settings.

Papers were included as CS trials if they specifically used the term CS to describe the condition of their participants, or if their participants had systolic blood pressure (SBP) of less than 90 mm Hg (Pressure [mm HG] = 133,322 Pascal [Pa]) for at least 30 minutes or required supportive measures to maintain a SBP of 90 mm Hg or more, and end-organ

hypoperfusion (cool extremities, less than 30 ml per hour of urine output, altered mental status or elevated serum lactate). These criteria are adapted from Reyentovich et al. (Reyentovich et al. 2016)

To be accepted as LCOS trial a study had to pre-define a cardiac index < 2.5 L/min/m2 for all patients included. Additionally, either symptoms of low peripheral perfusion, or failure to be weaned from catecholamine support, were required. The studies were also included if study authors used the term low cardiac output. If cardiac index or indicators of the peripheral perfusion were not given, the judgement was made individually, based on the condition described.

3.2 Primary and Secondary Endpoints

The primary outcome was mortality. Mortality was subdivided into short-term all-cause mortality for up to three month and long-term all-cause mortality for any period longer than 3 months after diagnosis of CS or LCOS.

As secondary outcome haemodynamic parameters, major adverse cardiac events (MACE), adverse events (AEs), length of hospital stay, quality of life and costs of treatment were examined. As haemodynamic indicators of the therapeutic effect

→ systolic, diastolic and mean blood pressure (SBP, DBP, MBP),

→ heart rate (HR),

→ cardiac index (CrI),

→ pulmonary capillary wedge pressure (PCWP),

→ left ventricular ejection fraction (LVEF) and

→ systemic vascular resistance (SVR) were used.

MACE was defined as in-hospital death, stroke or transient ischaemic attack or acute myocardial infarction (AMI) (Schumann et al. 2018). All AEs, including MACE were summarised under the secondary outcome adverse events.

3.3 Search methods for identification of studies

3.3.1 Electronic search

The systematic search was conducted by the Cochrane Heart Group for the systematic reviews in 2016 (Schumann et al. 2018) and updated in 2019. Dates of the last search are added in parenthesis. The following databases were searched:

- CENTRAL (The Cochrane Library 2016, Issue 5 of 12) (searched June 9, 2016, updated on Oktober 24, 2019)
- MEDLINE Ovid (Epub Aheadof Print, In-Process& Other Non-Indexed Citations, Daily MEDLINE, OVID 1946 to June 9, 2016, updated on October 24, 2019)
- Embase Classic (searched 9 June 2016, updated on October 24, 2019)
- ISI Web of Science (Conference Proceedings Citation Index-Science, Thomson Reuters 1990 to June 9, 2016, updated on October 24, 2019)

3.3.2 Manual search

In a manual search references from other systematic reviews identified during the systematic search as well as from the included studies were screened for eligible paper.

3.4 Data collection and analysis

3.4.1 Selection of studies

Four authors each screened half of the abstracts that were identified by the Cochrane Group. Two groups were then formed, each responsible for one half of the identified papers, so that all papers were screened twice. Articles collected were sorted by title, author and by date published, in that order. The abstracts were screened for the following criteria according to the inclusion criteria from table 1.:

- Is the study an RCT?
- Was primary data used?
- Are inotropic agents or vasodilator strategies compared to a comparison group either with placebo or a different type of inotropic agent or vasodilator strategy?
- Are patients included with CS or with LCOS?

Two new groups were formed so that two people from different abstract groups now cooperated to screen the papers identified in the abstract screening, in full text. For this review the systematic search was updated by one author with the renewed search by Cochrane in 2019. The papers were sorted by cause of CS/LCOS. For this thesis only those papers investigating patients with HF as cause of CS or LCOS were included.

Papers evaluating long-term treatment were initially excluded in the Cochrane review, but were included in this thesis. In case of uncertainty at any point of the screening process a second author was consulted. For this thesis all studies that had been identified in the

abstract screening, then were screened a second time, by one author, now including longterm treatment.

3.4.2 Data extraction and management

The characteristics of studies included were extracted from the identified papers into a table of study characteristics. The reasons for exclusion were identified for all papers that passed the abstract screening but were not included in the review. Baseline characteristics regarding age, sex, and haemodynamic parameters were extracted from the papers. The primary and secondary outcomes as reported in the included studies were collected in tables.

3.4.3 Assessment of risk of bias in included studies

To assess the risk of bias the risk of bias tool from the Cochrane Handbook was used (Higgins 2008). Six specific domains, as described in the Cochrane Handbook, were judged for risk of bias as high, low or unclear:

1. Random sequence generation
2. Allocation concealment
3. Double blinding of participants, personnel and outcome assessment
4. Incomplete outcome data addressed
5. Selective reporting
6. 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)

The quality of evidence on adverse effects was assessed using the following items (Higgins 2008):

→ Are definitions of registered AEs given?

→ Were methods reported that were used for monitoring AEs (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 detailed by the investigators?

3.4.4 Measures of treatment effect

Effect measures for the primary endpoint all-cause mortality of the included RCTs are presented as risk ratio (RR) with their 95% confidence intervals (CIs). Sub analyses were planned for the different timelines in-hospital mortality, short-term and long-term mortality. Short-term mortality was defined as a 3-month period after diagnosis of CS or LCOS. Long-term mortality was defined as any period longer than 3 months after diagnosis of CS or LCOS. For haemodynamic parameters mean differences (MDs) and 95% CI as effect measures was calculated.

For the statistical calculations Review manager 5.3 was used (RevMan 2014).

3.4.5 Data synthesis

The data was analysed based on the ITT. Results were planned to be evaluated according to the initially intended group assignment to uphold the randomisation. The studies were expected to be heterogeneous and the results therefore not identical, so a random-effectsmodel was used. To calculate the RR the Mantle-Haenzle-equation was used, with a random effects model and a CI of 95%. According to the study protocol, participants schedules for drug intervention and standard therapies were expected to differ in the studies and the use of a random-effects model was planned (Barili et al. 2018).

3.4.6 Assessment of heterogeneity

To assess the plausibility of chance in the differences of study results a Chi-Squared test was planned (Higgins 2008). To quantify heterogeneity an I2-test (Higgins et al. 2003) and to calculate the variance of the true effect a τ2-test (Barili et al. 2018) was planned. The following aspects are possibly sources of heterogeneity:

- the application schedule for the interventional drug (differences in dose and timings)
- duration of the treatment (short-term versus long-term)
- variation in control group treatment
- variation in standard therapies
- differences in the baseline characteristics of the participants (age, sex, co-

morbidities, etc.)

- variations in the definition of the indication
- and differences in the quality of the studies

3.4.7 Subgroup analysis

Analyses of subgroups were planned for all-cause mortality, for the factors sex and age.

3.4.8 Sensitivity analysis

To estimate whether an effect is caused by high risk of bias in the studies, if possible, a sensitivity analysis was planned to evaluate the results in case low quality evidence was excluded compared to the results in case of inclusion. Low quality evidence was predefined as low risk of bias in at least six of seven domains for risk of bias (Higgins 2008) (Chapter 8.8.3.1). To lower the risk of small-study effects leading to an overestimation of the outcome, the results calculated with a random-effects model were compared to results with a fixed-effect model (Higgins 2008) (Chapter 10.4.4.1).

3.4.9 Summary of findings table and GRADE assessment

The GRADE program was used (GRADEpro GDT 2015) to estimate the strength of confidence that can be placed in the evidence of the results of specific outcomes and categorized as (Balshem et al. 2011):

- high quality: in case of strong confidence in that the estimated effect is close to the true effect
- moderate quality: in case of moderate confidence in the estimated effect, meaning that it is likely that the true effect is close to the estimated, but there is a possibility that the true effect is substantially different
- low quality: in case of limited confidence that the true effect lies close to the estimated effect, the true effect and the estimated effect might differ substantially
- very low quality: in case of very little confidence in the estimated effect, the estimated and the true effect are likely to differ substantially

To sum up the main results a `Summary of findings´ table was created. The quality of evidence was estimated using the six domains proposed by GRADE (study design, risk of bias, inconsistency, indirectness, imprecision, other factors). According to the recommendations of the GRADE guidelines the six domains were evaluated for the

primary outcome short-term and long-term mortality (Guyatt et al. 2011a). For better comparability the number of events was calculated for 1.000 participants using the percentage of events in relation to participants in the described group.

Only RCTs were included in this review. They were graded as high quality of evidence in case no limitations that might lower the quality of evidence were identified. Risk of bias was rated across all outcomes for each study individually for the risk of bias table as described in chapter 1.4.3. For the GRADE evaluation the risk of bias was rated for the individual outcome for each study. The risk of bias was then summarised across studies reporting results concerning this outcome (Langer et al. 2013). Inconsistency was judged based on the I2 -test on heterogeneity. (Guyatt et al. 2011b). The criteria for indirectness included differences between the inclusion criteria of our review and studies on patients, intervention or outcome. Only in case of deviation from the prespecified criteria a downgrading could be necessary (Guyatt et al. 2011c). As this systematic review aims to summarise the existing evidence but is not the basis for decision making, the grading of imprecision was aimed to show the confidence in the effect estimate. For an informed decision making as presented in guidelines, the effect estimate would have to be evaluated for support of a decision making. Imprecision was therefore downgraded in case the CI was judged to be insufficient, being narrow or including no difference between groups (RR=1). In case of more than one reason for downgrading, it was considered to downgrade for one or two levels of confidence (Balshem et al. 2011).

4 Results

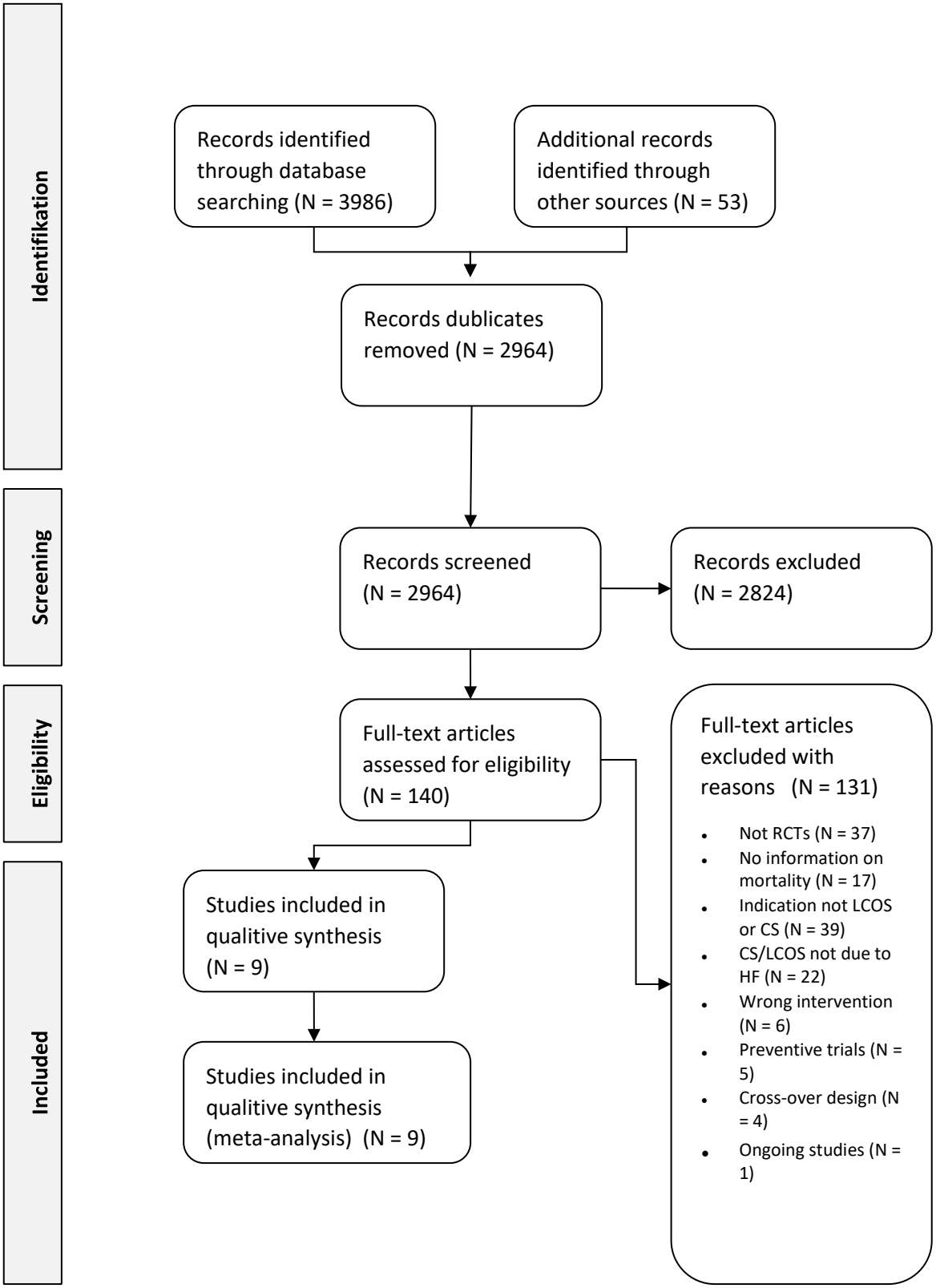
4.1 Results of the search

A total of 3,986 references were identified by the systematic search, after duplicates had been removed. Another 53 papers were identified through manual search. In total 140 full-text papers were of relevance and assessed against the inclusion and exclusion criteria previously established. Nine studies met the inclusion criteria. The remaining 131 studies were excluded in the full-text screening.

In this systematic review five short-term studies (Adamopoulos et al. 2006; Follath et al. 2002; Levy et al. 2011; Mebazaa et al. 2007; Meissner et al. 1996) and four studies that investigated long-term treatment (Berger et al. 2007; Mavrogeni et al. 2007; Jondeau et al. 1994; Oliva et al. 1999) were included.

Schumann 2018 included nine more trials, four were excluded in this systematic review as they investigated patients with AMI (Baldassarre 2008; Fuhrmann et al. 2008; Dominguez-Rodriguez et al. 2006; Husebye et al. 2013) and five trials were excluded as they investigated surgical patients (Alvarez et al. 2006; Atallah et al. 1990; Dupuis et al. 1992; Levin et al. 2008; Rosseel et al. 1997). The result of the systematic search is presented in a flow chart as suggested by the PRISMA-Statement (Moher et al. 2009).

Figure 1 Results of data collection (N = number of studies)



4.1.1 Included studies

Nine trials met the inclusion criteria:

- Effects of levosimendan versus dobutamine on inflammatory and apoptotic pathways in acutely decompensated chronic heart failure (Adamopoulos, 2006)
- Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial (Follath, 2002)
- Comparison of norepinephrine-dobutamine to epinephrine for haemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomised pilot study (Levy, 2011)
- Levosimendan vs dobutamine for patients with acute decompensated heart failure the SURVIVE randomized trial (Mebazaa, 2007)
- Combined haemodynamic effects of dopamine/milrinone as compared to dopamine/dobutamine in cardiogenic shock (Meißner, 1996)
- Levosimendan and prostaglandin E1 for up titration of beta-blockade in patients with refractory, advanced chronic heart failure (Berger, 2006)
- Oral enoximone as a substitute for intravenous catecholamine support in end-stage congestive heart failure (Jondeau, 1994)
- A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure (Mavrogeni, 2007)
- Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicentre Trial (Oliva, 1999)

  Four different interventions were used in these studies additional to standard therapies. Levosimendan, norepinephrine-dobutamine, dopamine-milrinone and enoximone were compared to established therapy strategies. The data found entail different comparisons of treatment. For three comparisons were investigated in more than one study and were summarised in meta-analysis. Three trials compared levosimendan with dobutamine (Adamopoulos et al. 2006; Follath et al. 2002; Mebazaa et al. 2007). Two trials, one comparing levosimendan to placebo and

one to non-specific treatment, were also summed up. The strategies for the control group seem to be comparable (Adamopoulos et al. 2006; Mavrogeni et al. 2007). Two trials compared dobutamine and placebo and could therefore also be summarised in one meta-analysis (Adamopoulos et al. 2006; Oliva et al. 1999). One of these trials (Adamopoulos et al. 2006) being three-armed, comparing levosimendan with dobutamine and placebo and was included in three metaanalyses. For the treatment strategies of the other four trials (Berger et al. 2007; Jondeau et al. 1994; Levy et al. 2011; Meissner et al. 1996) an individual analysis of data was performed.

4.1.2 Participants

Study group size varied between 20 participants (Meissner et al. 1996) and 1,320 participants (Mebazaa et al. 2007). The biggest group of participants that could be summed up was in the levosimendan group with 849 participants over all studies. The age ranged from a median of 54 years (Berger 2006) to 71 years (Adamopoulos 2006). All studies included more men, lowest amount 66% (Levy 2011) and the highest amount, 90% (Meißner 1996). Comorbidities were only reported indirectly through the concomitant medication at baseline as shown in Table 6.

4.1.3 Condition described in the trials

Four studies solely described participants in LCOS (Adamopoulos et al. 2006; Berger et al. 2007; Jondeau et al. 1994; Mavrogeni et al. 2007), two studies described only participants showing symptoms of CS (Levy et al. 2011; Meissner et al. 1996)and three studies included participants with either LCOS or CS (Follath et al. 2002; Mebazaa et al. 2007; Oliva et al. 1999).

4.1.4 Interventions

The interventions compared in the studies included are

→ levosimendan vs dobutamine (Adamopoulos et al. 2006; Follath et al. 2002; Mebazaa et al. 2007)

→ levosimendan vs. placebo/no treatment (Adamopoulos et al. 2006; Mavrogeni et al. 2007)

→ levosimendan vs PGE1 (Berger et al. 2007)

→ dobutamine vs. placebo (Adamopoulos et al. 2006; Oliva et al. 1999)

→ enoximone vs. placebo (Jondeau et al. 1994)

→ epinephrine vs norepinephrine-dobutamine (Levy et al. 2011), and

→ dopamine/dobutamine vs dopamine/milrinone (Meissner et al. 1996)

In case of dopamine/dobutamine vs dopamine/milrinone a co-medication with nitroglycerin was administered to the participants. The interventions varied in dose administered, as well as in administration and treatment period.

4.1.5 Excluded studies

The studies excluded during the full-text screening are listed in Table 5 together with the reason for exclusion. A total of 37 studies were excluded as they did not meet the criteria of an RCT and were therefore either missing a control group or the adequate randomisation. If the inclusion criteria did not meet the definition of CS or LCOS or the reason for CS or LCOS was something other than HF the study was excluded for wrong indication (N=61). In case the treatment strategies did not include positive inotrope or vasodilative strategies the trials were excluded for wrong intervention (N=6). If mortality was not reported, the trials were excluded as they could not be compared for the primary endpoint of this review (N=17). Study designs that were preventive or cross-over trials were also excluded (N=9). If one criterion for exclusion was found, they were not tested for other criteria. All studies excluded are therefore only listed once in Table 5.

4.1.6 Ongoing studies

One ongoing study was identified, investigating sodium nitroprusside versus dobutamine in participants suffering from HF exacerbated by LCOS (NCT02767024 2016). The study was stopped before enrolling the first participants. The characteristics of this study are listed in Table 2.

Table 2 Characteristics of ongoing study ((NCT02767024 2016)

Planned enrolment	148	
Planned intervention	Nitroprusside	Dobutamine
Both groups were planned to be comedicated with furosemide	Start of titration at 24 µg/min increased every 5 min up to 400 µg/min Continued infusion	Start of titration at 2.5 µg/kg/min increased to 5, 7.5 and a maximum dose of 10 µg/kg/min
Inclusion criteria	Exclusion criteria	Description of the condition
• HF with reduced EF, NYHA class IV, LVEF ≤ 40% during the last six months • Hospitalization for ADHF with requirement of iv. therapy anticipated • Suspicion of LCOS clinically • SBP ≥ 90 mmHg and < 120 mmHg • CI ≤ 2.2 l/min/m^2 and PCWP ≥ 20 mmHg • Randomization during the first 24 h from the presentation	• ACS current or during the prior 30 days • left ventricular outflow track obstruction • Severe mitral stenosis • Severe aortic insufficiency, severe mitral regurgitation • Restrictive amyloid myocardiopathy, acute myocarditis, hypertrophic obstructive, restrictive or constrictive cardiomyopathy • Complex congenital heart disease • Significant arrhythmia • high temperature or sepsis or required anti-microbial treatment • history of malignancy or terminal illness • major surgery or neurologic event	• LVEF ≤ 40%, • CI ≤2.2 l/min/m^2, • PCWP ≥ 20 mmHg, • SBP ≥90 mmHg and < 120 mmHg
Primary outcome	Secondary outcome	
Arrhythmia incidence Serum troponin T release Hypotension incidence	• Improvement in the Likert dyspnea scale • Improvement in the global patient assessment scale • cardiac care unit length of stay reduction • in-hospital length of stay reduction • in the echocardiogram assessment difference in restrictive filling pattern	

4.2 Levosimendan vs. dobutamine

One single-centre trial from Greece (Adamopoulos et al. 2006) and two international multi-centre trials (Follath et al. 2011; Mebazaa et al. 2007) compared levosimendan with dobutamine. One international multi-centre trial was conducted in Switzerland, the United Kingdom, Germany, Hungary, and Finland (Follath et al. 2011). The other international multi-centre trial was conducted in Austria, Finland, France, Germany, Latvia, Poland, the United Kingdom, Israel, and Russia (Mebazaa et al. 2007). All three studies investigated short-term treatment. In total 731 participants were randomised to the levosimendan group and 780 participants to the dobutamine group. The group sizes in each study are listed in Table 7 (see appendix).

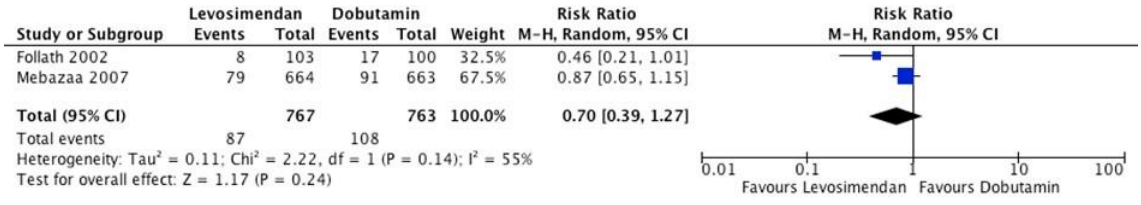
Baseline characteristics: The three trials varied in participants' age between 58 in Follath 2002 and 71 years in Adamopoulos 2006 as median age, all other parameters were similar between all groups. Detailed baseline characteristics as reported are listed in Table 8 (see appendix). The reported comorbidities are listed in Table 9 (see appendix).

Intervention: Variation in the interventions were mainly the initial loading dose of levosimendan and the protocol for inadequate haemodynamic response as can be seen in Table 10 (see appendix).

Inclusion/exclusion criteria: Inclusion and exclusion criteria varied between groups, but all three trials included patients with LCOS, Mebazza 2007 also included CS patients. The detailed inclusion and exclusion criteria are listed in Table 11 (see appendix).

Outcomes reported: Results were reported on the outcomes mortality, haemodynamic and biochemical measurements. The predefined outcomes are listed in Table 12 (see appendix). Time of follow-up varied between one day and 180 days. Different haemodynamic measurements were conducted at different time intervals and could not be summarised.

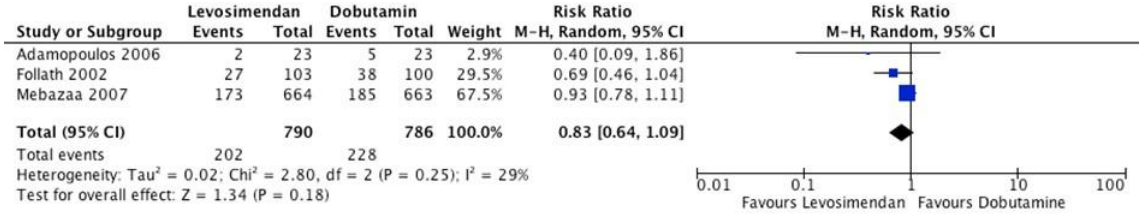
Short-term mortality: The short-term mortality was reported at 31 days in Follath 2002 and Mebazaa 2007 (see Figure 2). No short-term mortality was reported in Adamopoulos 2006. A total of 1,530 participants were included. The heterogeneity between the results of both studies was moderate with I2 = 55%. In the levosimendan group 87 out of 767 (11.3%) died during short-term follow up compared to 108 out of 763 (14.1%) participants in the dobutamine group. The RR is calculated as 0.70 favouring levosimendan, with a 95% CI of 0.39 to 1.27 that crosses the line of no difference. *Figure 2 Forest plot levosimendan vs. dobutamine, all-cause short-term mortality*



Long-term mortality: Long-term mortality was reported for a total of 1,576 participants in 3 studies. In Adamopoulos 2006 long-term mortality was reported at four months, in Follath 2002 and Mebazaa 2007 at 180 days. During this period 202 out of 790 participants died (25.6%) in the levosimendan group and 228 out of 786 participants

(29%) in the dobutamine group. The heterogeneity between the studies was low (I2 = 29%). Long-term mortality also favours the levosimendan group with a RR 0.83 and a 95% CI of 0.64 to 1.09, also crossing the line of no difference (RR=1) as shown in Figure 3.

Figure 3 Forest plot levosimendan vs dobutamine, all-cause long-term mortality



Haemodynamic parametrs: Adamopoulos 2006 reported an improvement in LVEF, CrI and PCWP in the levosimendan group compared to dobutamine at 48 hours (hrs) following randomisation. No differences were found for SBP, DBP and heart rate. Follath 2002 found an improvement of haemodynamics (cardiac output, PCWP, Pulmonaryartery diastolic pressure, systemic vascular resistance) within 24 hrs in the levosimendan group compared to dobutamine. Mebazaa 2006 reported an initially stronger drop of SBP and DBP during the first 24 hrs in the levosimendan group which than elevated again to the dobutamine level over the next days. Heart rate was more elevated in the levosimendan group and remained constant till the end of follow-up at 180 days.

In Adamopoulos 2006 LVEF and CrI was improved in the levosimendan group and not significantly different in the dobutamine group. PCWP was reduced in the levosimendan group and unchanged in the dobutamine group. SBP, DBP and heart rate remained similar in both groups. No information was available on systemic vascular resistance. Follath 2002 reported more participants improved in the haemodynamic performance in the levosimendan group than in the dobutamine group. Median change for PCWP was reported with -3 mmHg in the dobutamine and -7 mmHg in the levosimendan group, systemic vascular resistance with -4.6 mmHg/L/min in the dobutamine and -5.8 mmHg/L/min.

Subgroup and sensitivity analyses: Subgroup analyses were reported in only one study. The effect depended on history of congestive HF (Mebazaa et al. 2007). Lower efficacy was observed 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) in short-term mortality. About the same but less pronounced result was shown in

long-term mortality where participants with no history of congestive HF (RR 1.25, 95% CI 0.76 to 2.06) compared to participants with a history of congestive HF (RR 0.87, 95% CI 0.71 to 1.05) had a higher mortality rate in the levosimendan group compared to the dobutamine group.

The sensitivity analysis showed no relevant differences. A random-effect model showed a pooled result of RR 0.69, 95% CI 0.42 to 1.11 and an analysis including only trials with low risk of bias (Follath et al. 2002; Mebazaa et al. 2007) showed a RR of 0.70, 95% CI 0.39 to 1.27.

MACE: Adamopoulos 2006 provided no information on MACE. Follath 2002 reported more cases of angina pectoris and myocardial ischemia in the dobutamine-group, not specifying MACE or number of participants. Mebazaa 2007 described cardiac arrest in 3.0% of participants in the levosimendan group and 3.9% in the dobutamine group and CS in 2.3% of participants in the levosimendan group and 3.5% in the dobutamine group.

Adverse events: AEs were reported by Follath 2002 and Mebazaa 2007. Follath 2002 reported disorder aggravated, headache or migraine, cardiac and vascular disorders, angina pectoris, chest pain or myocardial ischaemia, hypotension, dizziness, flushing, rate and rhythm disorders, atrial fibrillation and others. Mebazaa 2007 reported hypotension, cardiac failure, hypokalemia, atrial fibrillation, headache, ventricular tachycardia, nausea, ventricular extrasystoles, insomnia and others. No difference in the safety profiles of the drugs was reported. In Adamopoulos 2006 mean event-free survival was reported to be greater in the levosimendan group (72±6 days) compared to (53±5 days) in the dobutamine group, not specifying events.

Quality of life: Quality of life was not investigated in any of the studies. In Follath 2002, dyspnoea and fatigue were reported and might be considered surrogate parameters. Dyspnoea and fatigue improved to a greater extend in the levosimendan group, but without significant difference.

In hospital stay, cost of treatment: None of the studies included information about length of hospital stay or cost of treatment.

4.3 Levosimendan vs. placebo/no specific treatment

Two single-centre trials from Greece (Adamopoulos et al. 2006; Mavrogeni et al. 2007) compared levosimendan with placebo (Adamopoulos et al. 2006) and no specific treatment (Mavrogeni, 2007). Adamopoulos 2006 investigated short-term treatment of

levosimendan, Mavrogeni 2007 investigated long-term treatment. In total 48 participants were randomised to the levosimendan group and 48 participants to the dobutamine as shown in Table 13 (see appendix).

Baseline characteristics: Mavrogeni 2007 included patients that were 10 years younger on average compared to Adamopoulos 2006. Sex ratio and LVEF were similar in both groups. All baseline characteristics reported in the papers are listed in Table 14 (see appendix). Comorbidities as reported in the trials are listed in Table 15 (see appendix).

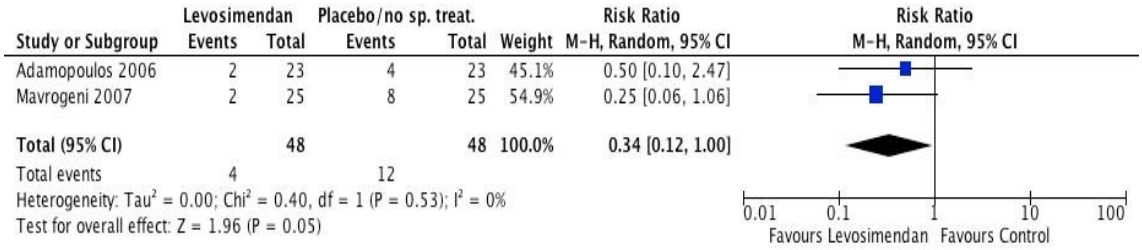
Intervention: The initial loading dose was the same in both trials. Up-titration to a higher infusion rate was performed in Mavrogeni 2007 but not in Adamopoulos 2006. The control group was treated with placebo in the trial of Adamopoulos 2006 and with no specific treatment in Mavrogeni, 2007. The treatment plans are listed in Table 16 (see appendix).

Inclusion/exclusion criteria: The inclusion and exclusion criteria were similar in both trials, Mavrogeni included only patients with LVEF <30 %, Adamopoulos 2006 defined no restrictions regarding LVEF. The criteria are listed in Table 17 (see appendix).

Outcomes reported: Mavrogeni 2007 investigated long-term treatment, repeating the initial treatment plan every month whereas Adamopoulos 2006 investigated short-term treatment only giving a one-time treatment. The outcomes specified in the trials are listed in Table 18 (see appendix).

Long-term mortality: Long-term mortality was reported for a total of 96 participants in 2 studies. In both studies, long-term mortality was reported for a four-month follow-up period. During this period 4 out of 48 participants died (17.4%) in the levosimendan group and 12 out of 48 participants (25%) in the dobutamine group. The heterogeneity between the results of both studies was low (I2 = 0%). Long-term mortality favoured the levosimendan group with a RR 0.34 and a 95% CI of 0.12 to 1.00 as shown in Figure 4.

Figure 4 Forest plot all-cause long-term mortality levosimendan vs control



Haemodynamic parameters: Time of follow-up for haemodynamic parameters were at 48 hrs in Adamopoulos 2006 and at 6 months in Mavrogeni 2007. In Adamopoulos 2006 haemodynamic parameters improved after three days in the levosimendan group and remained constant in the placebo group. LVEF improved from 24±2% to 28±2% compared to a declining of LVEF in the placebo group from 27±1% to 26±1%. CrI improved from 1.7±0.04 L/min/m2 to 1.9±0.1 L/min/m2 in the levosimendan group and remained at 1.8±0.1 L/min/m2 in the placebo group. PCWP improved from 24±1 mmHg to 19±1 mmHg in the levosimendan group and stayed at 23±1 mmHg in the placebo group. No differences were found for SBP, DBP, and heart rate. Mavrogeni 2007 found an increase in LVEF in the levosimendan group at 6 months from 22±6 % at baseline to 28±7 %. In the control group the LVEF decreased from 22±5 % to 21±4 %. No significant changes in heart rate were reported. They also included a self-assessment questionnaire (SAQ) to estimate the activities of daily life that is possible without symptoms. No significant differences were found between the two groups, even though a larger portion of the levosimendan group reported that the symptoms improved.

Subgroup and sensitivity analyses: No subgroup analyses were reported in either study. In the sensitivity analysis a random-effect model showed RR 0.34, 95% CI 0.12 to 1.00 compared to a fixed effect model RR 0.33, 95% CI 0.12 to 0.96.

MACE: Neither study provided information on MACE.

Adverse events: In Adamopoulos 2006 mean event-free survival was reported to be greater in the levosimendan group (72±6 days) compared to (54±5 days) in the placebo group, not specifying events. Mavrogeni 2007 reported temporary hypotension in two patients receiving levosimendan.

Quality of life: Quality of life was not investigated in any of the studies. Mavrogeni 2007 used a specific activity questionnaire which could be used as a surrogate marker for

quality of live. They reported an improvement in the levosimendan group, but without significant difference to the control group.

In hospital stay, cost of treatment: None of the studies included information about length of hospital stay or cost of treatment.

4.4 Levosimendan vs. PGE1

One trial from Austria, Berger 2007, investigated levosimendan compared to PGE1. Details of this trial are shown in Table 19 (see appendix). 75 participants were randomised into two groups 39 to levosimendan and 36 to the PGE1 group.

Baseline characteristics: There were no differences in baseline characteristics or comorbidities reported between the two groups. As shown in Table 20 and 21 (see appendix).

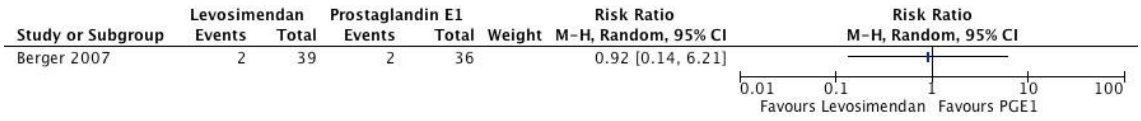
Intervention: The levosimendan group received a loading dose, depending on their initial blood pressure, followed by continuous infusion rate, whereas the PGE1 group only received a continuous infusion without a loading dose. As described in Table 22 (see appendix).

Inclusion/exclusion criteria: Inclusion and exclusion criteria are listed in Table 23 (see appendix).

Outcomes reported: The primary endpoint was exacerbation of HF. Death was reported as secondary endpoint as listed in Table 24 (see appendix).

Short-term mortality: From a total of 85 participants 2 out of 39 (5.1%) died during short-term 12-week follow-up in the levosimendan group compared with two of 36 participants (5.6%) in the Prostaglandin E1 group. This results in a RR of 0.92 favouring levosimendan but leaves a wide 95% CI between 0.14 and 6.21 including the line of no difference. The results are shown in Figure 5.

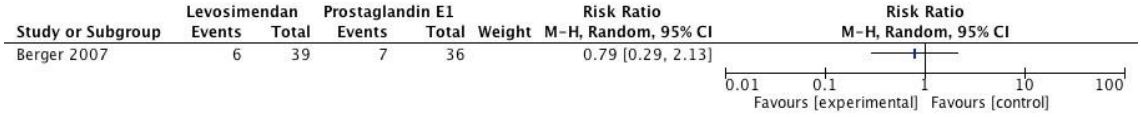
Figure 5 Forest plot all-cause short-term mortality: levosimendan vs PGE1



Long-term mortality: Six out of 39 (15.4%) participants died during the long-term oneyear follow-up in the levosimendan group compared with seven of 36 participants

(19.4%) in the Prostaglandin E1 group. The RR of 0.79 favouring levosimendan was not significant as the 95% CI lies between 0.29 and 2.13 as shown in Figure 6.

Figure 6 Forest plot all-cause long-term mortality: legomena vs PGE1



Haemodynamic parameters: The haemodynamic parameters SBP, DBP, HR and LVEF were reported in this trial. No marked differences between the groups were reported. In both groups a decrease in heart rate and an increase of LVEF was detected at 12 weeks follow-up.

Subgroup analyses: No subgroups were reported by Berger 2007. Sensitivity analyses were therefore not possible.

AEs: HF exacerbation was described in 74% of the levosimendan group and 44% in the PGE1 group, dose reduction and withdrawal due to hypotension was reported for the levosimendan group, hypotension, cholecystits, back-pain, problems with the catheter, diarrhoea and prostaglandin side effects were reported in the PGE1 group.

Quality of life: MACE, length of hospital-stay, quality of life and costs were not described in the study.

4.5 Dobutamine vs. placebo/no specific treatment

One single-centre trial conducted in Greece investigating dobutamine vs. placebo was identified in the search from 2016 (Adamopoulos et al. 2006). In the update from 2019 one multi-centre trial conducted in Italy was identified comparing levosimendan vs. no specific treatment (Oliva et al. 1999). Adamopoulos 2006 investigated short termtreatment and Oliva 1999 investigated long-term-treatment. A total of 84 patients was randomised 42 in each the dobutamine and the control group. The group sizes in each study are listed in Table 25 (see appendix).

Baseline characteristics: Not all haemodynamic parameters are reported at baseline for both studies and therefore the comparability is limited. The three trials varied in age between 65 in Oliva 1999 and 71 in Adamopoulos 2006 as median age, all other parameters as reported were similar among all groups. Detailed baseline characteristic as

reported are listed in Table 26 (see appendix). Only diabetes and ischaemic heart failure were listed as co-morbidities as shown in Table 27 (see appendix).

Intervention: The interventions between the two trials differed greatly. In Adamopoulos 2006 a continuous infusion with 5µg/kg/min was infused for 24h and adapted in case of inadequate haemodynamic response. In Oliva 1999 maximal oral therapy was combined with intermittent ambulatory infusions for six months as described in Table 28 (see appendix).

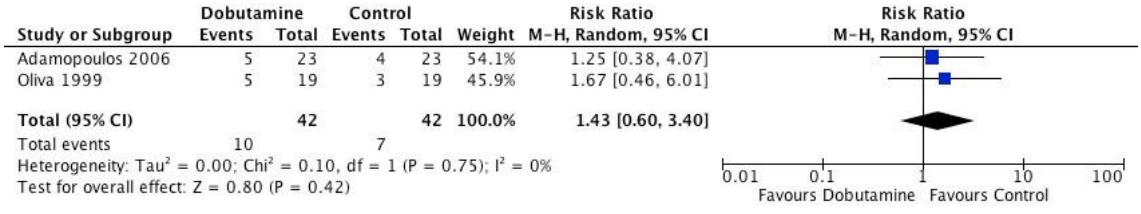
Inclusion/exclusion criteria: Both trials investigated LCOS in patients with prior New York Heart Association (NYHA) class III or IV. The detailed inclusion and exclusion criteria are listed in Table 29 (see appendix).

Outcomes reported: Both trials reported worsening of the disease in form of rehospitalization and all-cause mortality. The predefined outcomes are listed in Table 30 (see appendix).

Long-term mortality: Mortality was a predefined outcome in both trials and reported at long-term intervals of four months in Adamopoulos 2006 and six months in Oliva 1999. Adamopoulos also investigated haemodynamic and biochemical measurements. Oliva 1999 included exacerbation of CHF, change in NYHA class and change in the 6 min walking test. An improvement of CrI was reported by Oliva 1999 but not in Adamopoulos 2006. Neither of the trials found any changes in other haemodynamic parameters.

A total of 84 participants was included in both trials. The heterogeneity between the studies was low with I2 = 0%. 10 out of 42 participants in the dobutamine group died (23,8 %) and 7 out of 42 in the control group (16,7 %) during long-term follow-up. The RR shows no difference between groups (RR 1.43; 95% CI 0.60 to 3.43) as shown in Figure 7.

Figure 7 Forest plot all-cause long-term mortality: dobutamine vs placebo/no specific treatment



Haemodynamic parameters: Adamopoulos 2006 found no significant difference between the two groups in systolic LV function, PCWP, SAB, DAB and HR. No haemeodynamic differences between the two treatment arms were found in OIiva 1999.

Subgroup analyses: No subgroup analyses were reported in either study. In the sensitivity analysis a random-effect model showed RR 1.43, 95% CI 0.60 to 3.40 and stayed the same with a fixed-effect model.

MACE: Neither study provided information on MACE.

AEs: In Adamopoulos 2006 mean event-free survival did not differ between the two groups and was reported with 53±5 days in the dobutamine group compared to 54±5 days in the placebo group, not specifying events. No information on AEs were given in Oliva 1999.

Quality of life: Quality of life was not investigated in any of the studies.

In hospital stay, cost of treatment: None of the studies included information about length of hospital stay or cost of treatment.

4.6 Enoximone vs. placebo

Only one small, single-centre, long-term treatment trial from France investigated enoximone versus placebo in participants with LCOS (Jondeau, 1994). More participants in the placebo group experienced a relapse in chronic HF. One participant in the placebo group died from septic shock, one developed a ventricular tachycardia and one in the enoximone group developed a thoracic cutaneous rash. Overall, there were more AEs in the placebo group. A total of 24 participants was included in the trial, 12 in each studyarm, as described in Table 31 (see appendix).

Baseline characteristics: The baseline characteristics reported were age, sex, MBP and HR and are reported in Table 32 (see appendix). Comorbidities as reported are listed in Table 33 (see appendix).

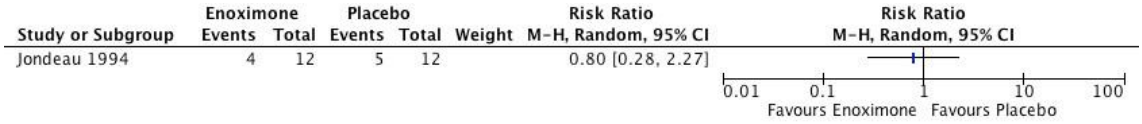
Intervention: Patients received either 100mg Enoximone or 100mg placebo three times a day as described in Table 34 (see appendix).

Inclusion/exclusion criteria: Included were patients with LCOS requiring i.v. inotropic support in case of severe congestive HF. The detailed inclusion and exclusion criteria are listed in Table 35 (see appendix).

Outcomes reported: The primary outcome reported was successful weaning from dobutamine. Mortality was reported as secondary outcome, as described in Table 36 (see appendix).

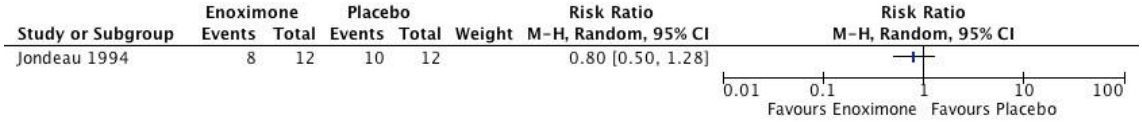
Short-term mortality: Four out of 12 participants (33.3%) died in the enoximone group and five out of 12 participants (41.7%) died in the placebo group in a three-month followup. These results favour the enoximone group with a RR of 0.80 but are not statistically significant as the 95% CI lies between 0.28 and 2.27 as shown in Figure 9.

Figure 9 Forestplot all-cause short-term mortality: enoximone vs. placebo



Long-term mortality: 24 participants were included and 8 out of 12 (66.6%) died in the enoximone group compared to 10 out of 12 (83.3%) who died in the placebo group in a one-year follow-up. The RR showed no difference between both groups (RR 0.80 with a 95% CI between 0.50 and 1.28) as shown in Figure 8.

Figure 8 Forestplot all-cause long-term mortality: enoximone vs. placebo



Haemodynamic parameters: Haemodynamic parameters were reported at baseline day 4 and day 28. No significant changes in heart rate and MBP could be detected. There was a significant increase in LVEF in the enoximone group whereas LVEF remained unchanged in the placebo group. LVEF was improved in the enoximone group and unchanged in the placebo group. No information was available on blood pressure, heart rate, CrI, PCWP or systemic vascular resistance.

MACE: Ventricular tachycardia requiring electrical cardioversion was reported in one patient from the placebo group.

AEs: Eight patients from the placebo group and two patients from the enoximone group suffered from a relapse of chronic HF during the trial. One participant in the placebo group died of septic shock during the trial, one was withdrawn due to the development of ventricular tachycardia that required electrical cardioversion. One participant in the

enoximone group developed a thoracic cutaneous rash that disappeared after treatment was discontinued.

Subgroup analysis, in-hospital stay, quality of life, cost of treatment: No results on subgroups, length of hospital stay, quality of life or costs were available from the study.

4.7 Epinephrine vs. norepinephrine-dobutamine

Only one trial from France investigated epinephrine compared with norepinephrinedobutamine in the context of acute HF complicated by LCOS (Levy, 2011). This was a small, single-centre study with 30 participants and with very low-quality evidence. A total of 30 participants was included in the trial, 15 in each study-arm, as described in Table 37 (see appendix).

Baseline characteristics: Baseline characteristics included age, sex, MBP, HR, CI, LVEF and prior AMI or vascular interventions. All were similar between the two treatment groups. As shown in Table 38 (see appendix). Comorbidities as reported are listed in Table 39 (see appendix).

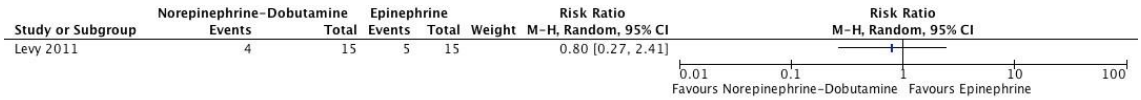
Intervention: Both intervention groups initially received dobutamine. In case of insufficient results under this treatment they were randomized to receive either epinephrine or norepinephrine. In the epinephrine group dobutamine was then discontinued. In the norepinephrine group dobutamine was continued. The detailed intervention protocol is described in Table 40 (see appendix).

Inclusion/exclusion criteria: Patients were included in case of CS due to acute or chronic HF and excluded in case of MI. The more detailed criteria are listed in Table 41 (see appendix).

Outcomes reported: Outcomes reported included mortality and changes in haemodynamic measurements as listed in Table 42 (see appendix).

Short-term mortality: 30 participants were included in this study. 5 out of 15 participants (33.3%) died in the epinephrine group during short-term follow-up of 28 days and 4 out of 15 participants (26.7%) died in the norepinephrine-dobutamine group. An RR of 1.25 was calculated favouring the norepinephrine-dobutamine group but with a 95% CI between 0.41 and 3.77 this presents no statistical significance. The results are shown in Figure 10.

Figure 10 Forest plot all-cause short-term mortality: epinephrine vs. norepinephrinedobutamine



Haemodynamic parameters: The haemodynamics reported showed no difference for MAP and CrI between the two groups. The HR was significantly higher in the epinephrine group. PCWP, LVEF and systemic vascular resistance were not reported. There was an increase in MAP and CrI in all participants without differences between groups. In the epinephrine group HR was significantly higher compared to the norepinephrinedobutamine group.

AEs: Two participants in the epinephrine (13.3%) group developed a supraventricular arrhythmia and one developed sustained ventricular arrythmia (6.7%). None from the norepinephrine-dobutamine group showed such AEs. In the epinephrine group ten (66.6%) participants and in the norepinephrine-dobutamine group thirteen participants (86.6%) suffered from oliguria, which was reversed.

In hospital stay: No results were available on subgroups, MACE, length of hospital stay, quality of life or costs from the studies included.

4.8 Dopamine/dobutamine vs. dopamine/milrinone

Only one small, single-centre trial from Germany with 20 participants (Meißner, 1996) investigated dopamine-milrinone versus dopamine-dobutamine in people with CS. A total of 20 participants was included in the trial, 10 in each study-arm, as described in Table 43 (see appendix).

Baseline characteristics: Baseline characteristics included age, sex, SBP, MBP, HR, CI, LVEF and PCWP as reported in Table 44 (see appendix). Comorbidities as reported are listed in Table 45 (see appendix).

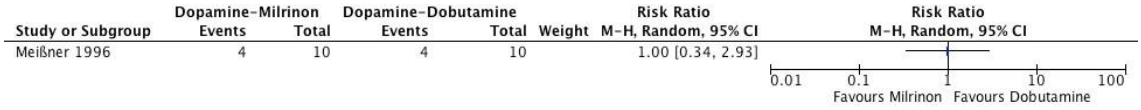
Intervention: In the dopamine/dobutamine group a continued infusion was administered. In the dopamine/milrinone group a bolus injection was administered first. The detailed interventions are listed in Table 46 (see appendix).

Inclusion/exclusion criteria: Included were patients with LCOS due to acute decompensated HF, that were dopamine dependent. One of the reasons for exclusion was MI. The detailed criteria are listed in Table 47 (see appendix).

Outcomes reported: Mortality and haemodynamic measurements were reported as described in Table 48 (see appendix).

Short-term mortality: From a total of 20 participants in each group 4 out of 10 died during their stay in the ICU (40%). This results in an RR of 1.0 with a 95% CI between 0.34 and 2.93. These results are shown in Figure 11:

Figure 11 Forest plot all-cause short-term mortality: dopamine/milrinone vs. dopamine/dobutamine



Haemodynamic parameters: MBP decreased in the dopamine-milrinone group and remained the same in the dopamine-dobutamine group. HR stayed constant in the dopamine-dobutamine group and increased slightly in the dopamine-milrinone group. CrI improved more in the dopamine-dobutamine group than in the dopamine-milrinone group. PCWP decreased more in the dopamine-milrinone group, but differences detected were not significant. No information was provided on LVEF or systemic vascular resistance. At 60 min the SBP was significantly higher in the dopamine/dobutamine group and no significant difference was found in the PCWP.

AEs: Ventricular extrasystoles did not increase during either therapy. There was no ventricular tachycardia or ventricular extrasystoles. No further information was given concerning AEs.

Subgroup analyses, MACE, in-hospital stay, quality of life, cost of treatment: No results were available on subgroups, MACE, length of hospital stay, quality of life or costs from the included study.

4.9 Risk of Bias

Five trials (Adamopoulos et al. 2006; Berger et al. 2007; Jondeau et al. 1994; Levy et al. 2011; Oliva et al. 1999), did not give a description of their method of randomisation. Three studies (33 %) were judged as low risk of bias: Follath 2002 used blocked random tables by means of a computer random number generator; Mavrogeni 2007 used a sequence of random binary numbers, using a special software to create the randomisation system; Mebazaa 2007 used a biased coin algorithm. One trial was evaluated at a high

risk of bias: Meißner 1996 generated the sequence by odd or even date of birth (figure 12 and 13).

Five studies (Adamopoulos et al. 2006; Berger et al. 2007; Jondeau et al. 1994; Levy et al. 2011; Oliva et al. 1999), provided no information on allocation concealment. Three trials were graded low risk of bias for allocation concealment: Follath 2002 and Mebazaa 2007 performed allocation by a blinded investigator according to a pre-determined list, Mavrogeni 2007 allocation concealment was insured by randomization software. No allocation concealment was possible in Meißner 1996 due to sequence generation by odd or even date of birth, it was therefore graded as high risk of bias.

Risk of performance bias was graded low in Follath 2002, Mavrogeni 2007 and Mebazaa 2007. In Adamopoulos 2006, Berger 2007, Meißner 1996 and Oliva 1999 blinding was not possible due to different timing of administration of the study drugs and were therefore graded high risk for performance bias. In two studies the blinding of participants and personnel was not described, they were rated with an unclear risk: Levy 2011 was described as an open-label study and as a double-blind study, but no further information was provided. Jondeau 1994 gave no information to blinding of personnel or outcome assessment.

No information on blinding of outcome assessment was provided for Adamopoulos 2006, Jondeau 1994 and Oliva 1999. Berger 2007 reports blinding in outcome assessment for the measurement of brain natriuretic peptide (BNP) and LVEF no information was given for the other outcomes. These three studies were judged to have an unclear risk of detection bias. Three studies were graded with low risk of detection bias: Follath 2002 was a double-blinded study in which only 4 out of 199 participants remained blinded until the end of the study. Mavrogeni 2007 reported that the personnel was blinded to the treatment group. In Mebazaa 2007 the results were reviewed in a blinded manner. Two studies were graded with high risk of bias: Levy 2011 was an open study neither patients nor physicians were blinded. In Meißner 1996 the personnel was not blinded.

Seven of the studies included reported all-cause mortality for all participants at the study endpoint and were judged with low risk of attrition bias (Adamopoulos et al. 2006; Levy et al. 2011; Follath et al. 2002; Mavrogeni et al. 2007; Mebazaa et al. 2007; Meissner et al. 1996; Oliva et al. 1999). Berger 2007 and Jondeau 1994 reported participants being lost to follow up and were therefore graded with a high risk for attrition bias.

All prespecified outcomes were reported in the studies included, therefore all studies were rated with low risk of reporting bias.

No other risk of bias was found in four of the studies and these were graded with low risk of other bias (Adamopoulos et al. 2006; Berger et al. 2007; Levy et al. 2011; Mavrogeni et al. 2007). For two studies no information was available on other bias. Follath 2002, Mebazaa 2007 and Oliva 1999 were graded high risk of other bias due to reports of interruptions of study drug administration. Follath 2002 and Mebazaa 2007 also reported connections to the pharma industry, which also would give reason for down-grading for other risk of bias.

Six studies were evaluated with high risk of bias for the reported AEs. Adamopoulos 2006, Berger 2007, Jondeau 1994, Mavrogeni 2007, Meißner 1996 and Oliva 1999 provided neither definitions of AEs, nor reported the monitoring of AEs and no analysis of numerical data by intervention was given. Levy 2011 only reported numerical data by intervention. Two studies were graded low risk of bias for AEs: in Follath 2002 AEs are listed for each patient. In Mebazaa 2007 for 31 days following initial study drug administration and during all blinded drug re-administrations the AEs were reported. Numerical data by intervention was collected.

The risk of bias for all included studies is presented in figure 12 and summarized in figure 13.

Figure 12 Risk of bias summary

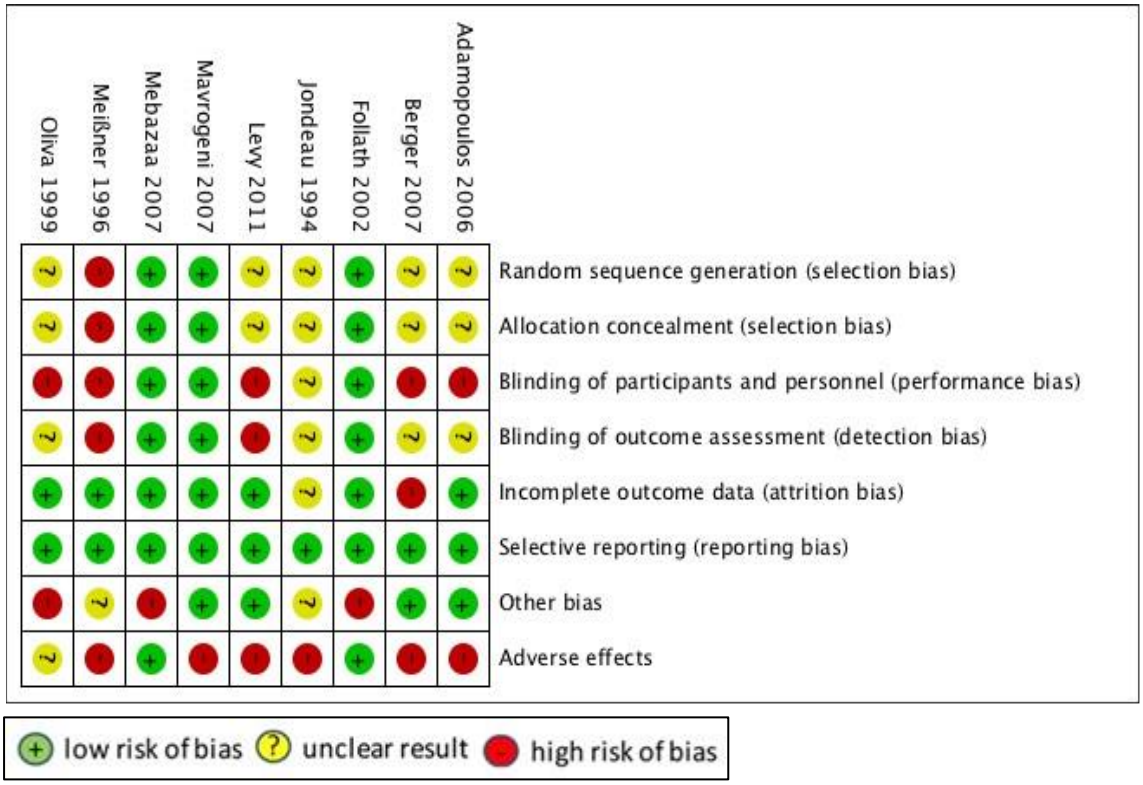
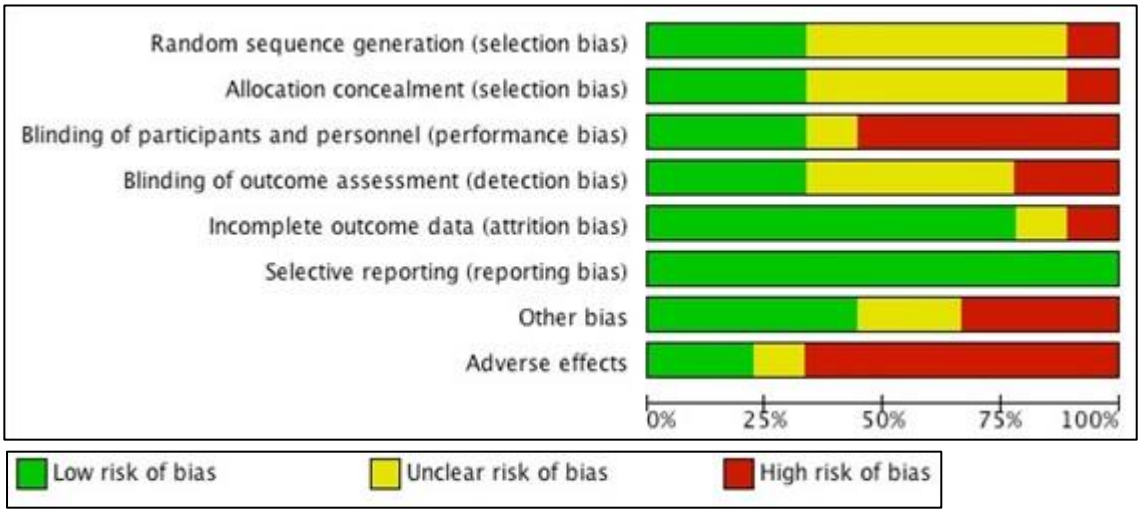


Figure 13 Risk of bias graph



4.10 Summary of evidence on all-cause mortality

There were no results showing any statistically significant difference in all-cause mortality in any of these studies. Thus, for all comparisons the CI included the one (RR=1).

The main results that could be summed up in a meta-analysis were the comparison of

- levosimendan vs. dobutamine for the endpoint long-term and short-term all-cause mortality
- levosimendan vs. placebo/no treatment for the endpoint long-term all-cause mortality
- dobutamine vs placebo/no treatment for the endpoint long-term all-cause mortality

To estimate the confidence that can be placed in these results "summary of findings tables", as suggested by the GRADE guidelines were created.

Results on the comparison of the efficacy of levosimendan and dobutamine on short-term mortality were reported from two studies (Follath 2002 and Mebazaa 2006) with a total of 1530 participants. From the two included studies 108 of 763 patients died when treatment with dobutamine, this is means 14.2%. Therefore if patients with LCOS or CS would be treated with dobutamine, 142 of 1000 might die, as shown in Table 3. According to the RR of 0.70 (95%CI 0.39 to 1.27), a total of 99 of 1000 patients (between 55 and 180) would die within three months with levosimendan (see Table 3). The certainty of the evidence of these results was graded low. It was downgraded for imprecision one step as the CI includes the RR=1 and both treatment strategies might be beneficial. Evidence was downgraded one further step due to reported conflicts of interest because of connections to the pharma industry in both trials.

Results on the comparison of the efficacy of levosimendan and dobutamine on long-term mortality were reported from three studies (Adamopoulos 2006, Follath 2002 and Mebazaa 2006), with a total of 1576 participants. If patients with LCOS or CS would be treated with dobutamine, 290 of 1.000 patients might die, as shown in Table 3 (three included studies, 228 of 786 patients died in the dobutamine group = 29%). According to the RR of 0.83 (95%CI 0.64 to 1.09), a total of 241 of 1.000 patients would die after more than three months with levosimendan (see Table 3). The certainty of the evidence of these results was also graded low. It was downgraded for imprecision one step as the CI includes the RR=1 and both treatment strategies might be beneficial. Two of the three trials (Follath 2002, Mebazaa 2006) reported conflicts of interest due to connections to the pharma industry and was therefore downgraded another step.

Results on the comparison of the efficacy of levosimendan and on long-term mortality were reported from two trials (Adamopoulos 2006 and Mavrogeni 2007) with a total of 96 participants. If patients with LCOS/CS would be treated with placebo or no specific treatment, 250 of 1.000 patients might die, as shown in Table 3 (two included studies, 12 of 48 patients died in the control group = 25%). According to the RR of 0.34 (95% CI 0.12 to 1.00), a total of 85 of 1.000 patients would die after more than three months with levosimendan (see Table 3). The certainty of the evidence of these results was graded moderate. It was downgraded one step for imprecision as the CI included RR=1.

Table 3 Levosimendan compared to control for HF complicated by LCOS

Outcome **all-cause mortality**	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of the participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with control	**Risk with levosimendan**			
short-term: l**evosimendan versus dobutamine**	142 per 1.000	99 per 1.000 (55 to 180)	RR 0.70 (0.39 to 1.27)	1530 (2 RCTs)	⊕⊕⊖⊖ LOW[1, 2]
long-term: l**evosimendan versus dobutamine**	290 per 1.000	241 per 1.000 (186 to 316)	RR 0.83 (0.64 to 1.09)	1576 (3 RCT)	⊕⊕⊖⊖ LOW[1,2]
long-term: l**evosimendan versus placebo/ no treatment**	250 per 1.000	85 per 1.000 (30 to 250)	RR 0.34 (0.12 to 1.00)	96 (2 RCT)	⊕⊕⊕⊖ MODERATE[1]
* The risk in the intervention group (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% confidence interval).					
[1]Downgraded one step for imprecision because the confidence interval crosses the line of no difference and includes possible benefit from both approaches [2]Downgraded one step for reporting bias due to sponsoring by pharma industry [3]Downgraded one step for bias due to lack of blinding participants and physicians					

Results on the comparison of the efficacy of dobutamine and placebo or no treatment on long-term mortality were reported from two trials Adamopoulos 2006 and Oliva 1999, with a total of 84 participants. If patients with LCOS would be treated with placebo/no treatment, 167 of 1.000 patients might die (two included studies, 7 of 42 patients died in the control group = 16,7 %), as shown in Table 4. According to the RR of 1.43 (95% CI 0.60 to 3.40), a total of 238 of 1.000 patents would die after more than three months with dobutamine (see Table 4). The confidence in the evidence was graded low. It was

downgraded two steps due to imprecision, as the CI entailed RR=1 and is very wide. *Table 4 Dobutamine vs placebo/no treatment for CHF complicated by LCOS*

Outcomes **all-cause mortality**	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of the participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with control	**Risk with dobutamine**			
long-term: **dobutamine versus placebo/ no treatment**	167 per 1.000	238 per 1.000 (100 to 567)	RR 1.43 (0.60 to 3.40)	84 (2 RCT)	⨁⨁⨀⨀ LOW[1]
* The risk in the intervention group (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% confidence interval).					
[1]Downgraded two steps for imprecision because the confidence interval is very wide, crosses the line of no difference and includes possible benefit from both approaches					

5 Discussion

In this systematic review nine RCTs with a total of 1,771 participants with CS or LCOS were included. The drugs investigated were levosimendan, dobutamine, PEG1, enoximone, epinephrine and the combinations norepinephrine-dobutamine, dopaminedobutamine and dopamine-milrinone. All trials reported results on the primary endpoint mortality. Six trials reported results on short-term mortality of up to three months and seven trials reported results on long-term mortality. None of the trials reported results on in-hospital mortality. The secondary endpoints haemodynamic parameters as a secondary marker for morbidity were reported in seven trials. MACE were reported in two trials and AEs were reported by four trials. None of the trials reported any information on length of hospital stay/ICU stay, quality of life or costs.

Only three of the comparisons included more than one trial and a meta-analysis could be performed. Due to differences in mechanism of action and resulting differences of intervention and control groups, other studies could not be summarised. An intervention with levosimendan was compared to dobutamine in three trials, levosimendan was compared to placebo or no specific treatment and dobutamine was compared to placebo/no specific treatment in two. This review is based on RCTs to reduce the risk of systematic baseline differences between the treatment groups for known and unknown confounder. Therefore, it shows the highest level of evidence as defined by the Oxford Centre for Evidence-based Medicine (Howick et al. 2009). Main study limitations include risk of bias due to unreported AEs, lack of blinding and low to moderated level of confidence that can be placed in the evidence for the main outcome all-cause mortality according to the GRADE system.

The quantitatively most investigated study drug was levosimendan. For all five studies comparing levosimendan with a control group a reduction of mortality in the levosimendan group was found, not reaching statistical significance neither in individual studies nor in the pooled results compared to other effective drugs. Evidence was graded low to moderate for the studies included.

Levosimendan showed a beneficial effect on mortality compared to all control groups including placebo and dobutamine. The quality of evidence was graded low-quality for levosimendan vs dobutamine for short- and long-term mortality. The evidence for levosimendan vs placebo/ no treatment was also graded low-quality due to imprecision

with different possible recommandations considering the upper versus lower boundary of the CI and a potential reporting bias due to sponsoring by the pharma industry.

In two small trials dobutamine was compared to placebo, with a total of 84 participants. The quality of evidence was graded low and downgraded as the CI included the one and the study group was small. No difference was shown between the two groups (RR 1.43; 95% CI 0.60 to 3.40). A harmful effect of dobutamine cannot be ruled out. When compared to another drug this could lead to an overestimation of the treatment effect, of the drug compared to dobutamine.

Haemodynamic parameters seemed to improve under the treatment with levosimendan in all included trials. Mebazaa 2007 found a higher rate of atrial fibrillation reported in the levosimendan group possibly due to an initial drop in BP and an elevation in HR in the levosimendan treatment group compared to dobutamine. Mavrogeni 2007 found an improvement of LVEF and a reduction of mean pulmonary artery pressure in the levosimendan group compared to the control group. This might be responsible for the reported reduction of symptoms, that improved more in the levosimendan group than the control group but did not reach statistical significants.

All other comparisons, levosimendan vs PGE1, enoximone vs placebo, epinephrine vs. norepinephrine- dobutamine, dopamine/dobutamine vs dopamine/milrinone, are based on single RCTs.

The GRADE guidelines recommend to include the differences of resource use and to rate the quality of economic evidence for decision making (Brunetti et al. 2013). None of the included studies reported data on treatment costs. However, in a secondary analysis the treatment costs from Mebazaa 2007 were estimated using the case reports from the trial, in hospital stay, ICU stay and readmission were also reported (Lissovoy 2008). Little difference was found between the treatment groups for mean length of stay after the index hospital admission with 14.3 days for levosimendan compared to 14.5 days for doutamine ($p = 0.98$). ICU stay was reported as mean days also similar between the groups with 4.6 days in the levosimendan group and 4.5 days in the dobutamine group ($p=0.27$). Readmission rates were slightly lower in the levosimendan group with 0.73 compared to 0.86 in the dobutamine group at 180 days of follow-up ($p = 0.23$). Per diem costs were estimated using national payment schedules from France, Germany and the UK. For the follow-up periode the costs of in hospital stay were astimated with a mean of 5,396€ for

the levosimendan group and 5,275€ for the dobutamine group (p = 0.96) excluding the study drug costs. The cost of the study drugs was calculated between 600 and 800 € for levosimendan compared to relatively low costs for dobutamine. A cost-effectiveness analysis was performed to estimate the cost per life-year gained as patients in the levosimendan group had a lower mortality rate compared to doutamine. The authors concluded, that if willing to pay equal or greater than 15,000 € per life year gained, with an acquisition cost of 600€ per vial levosimendan there is a 50% likelihood that levosimendan is cost effective compared to dobutamine. These cost estimates are based on differences between the treatment groups that did not reach statistical significance and are therefore of limited informative value.

5.1 Analysis of heterogeneity

Expected reasons for heterogeneity were differences in standard of care depending on time and place of study conduction, as well as differences in time of follow-up.

The search was not restricted to a timeframe. The trials were conducted between 1994 and 2011. During this time advances in chronic HF therapy were made, especially with respect to the influence of neurohormonal pathways lessening the risk of morbidity and mortality for patients in ambulatory settings (Gheorghiade et al. 2016). Even though all countries that were involved in these trials today are members of the ESC (Russia, Switzerland, Hungary, Greece, Israel, Austria, Finland, France, Germany, Latvia, Poland, and the United Kingdom) common guidelines for HF were first published in 2016 (Ponikowski et al. 2016). Since all trials were set prior to the publication, a difference in the basic treatment of HF can be expected among the trials. From the reported data no significant baseline differences can be concluded. However, the standard of care is not reported in any of the trials.

The studies summarised for long-term mortality comparing levosimendan vs. dobutamine had follow-up periods that differed between four and six months. As there is little data on the epidemiology of acute decompensated HF, Zannad et al. performed a prospective cohort study. In this EFICA study 50% of CS patients died during the first four weeks, of those who survived the first four weeks another 25% died during the following eleven months (Zannad et al. 2006). This means patients with CS are most likely to die during the first month, with mortality rates decreasing among the survivors after that time and are represented in the short-term mortality. The mortality rates at the follow-up time

between four and six months were therefore expected to be low enough to be summarised as long-term mortality.

The mortality rates varied between the studies. Short-term mortality (up to three-month follow-up) was reported between 5.3% (Berger 2007) and 40% (Meißner 1996). Both studies investigated LCOS with a CI < 2.5 l/min/m2 and PCWP > 15 mm Hg. Berger investigated Levosimendan vs PGE1 whereas Meißner investigated dopamine in combination with either dobutamine or milrinone. This might explain a difference in mortality rates. Additionally, both trials also differed in inclusion and exclusion criteria. Meißner 1996 included acutely decompensated patients whereas Berger 2007 included patients with NYHA IIIb or IV and no change in therapy for two weeks prior to randomisation. Berger 2007 excluded patients that suffered from SBP lower than 90 mm Hg or renal impairment. In Meißner 1996 the follow-up period reported was ICU-stay, in Berger 2007 short-term follow-up was reported at 12 weeks. This also suggest a more severely sick patient group investigated by Meißner 1996.

The follow-up period, summarised as long-term mortality, included a range from four months to one year and are therefore expected to vary. The lowest mortality rate was reported at four months by Adamopoulos 2006. The highest mortality-rate was reported by Jondeau 1994 at one year. Adamopoulos 2006, Follath 2002, Mebazaa 2007, Mavrogeni 2007 and Oliva 1999 reported similar mortality rates between 16% and 26%. These were all reported at four to six months. Berger 2007 and Jondeau 1994 both reported mortality at one-year follow-up. Berger 2007 reported a 17% mortality-rate whereas Jondeau 1994 reported a 75% mortality-rate. Berger 2007 excluded all patients with SBP lower than 90 mm Hg, MI and other acute settings. Jondeau 1994 did not prespecify exclusion criteria, this might therefore have led to a difference in severity of illness due to a different degree of acute and chronic organ failure between the two trials. In the AHEAD Main study one year-mortality was reported with around 20% for acute decompensated HF and CS and is therefore closer to the mortality rates found in Berger 2007 (Parenica et al. 2013).

5.2 Potential bias

Different sources for bias that might influence the results of this review are publication bias, differences in inclusion and exclusion criteria as well as differences in treatment strategies.

To minimise publication bias, no language barrier was restricted. The search was conducted in different data bases. Trials are more likely to be published in case of positive results, statistical significance and when showing a large effect leading to the risk of publication bias (Higgins et al. 2008). Only RCTs were included to reduce the risk of structural differences between intervention groups.

For this review the definition of LCOS and CS was based on the measurement of haemodynamic parameters and symptoms. Not all trials reported these parameters. To decide the inclusion of a study the criteria reported by the authors were evaluated and it was relied on the described definitions. It might be possible that, as a result, not all participants included in this review suffered from LCOS or CS as defined for this review.

Only studies, which reported mortality, were included. This might lead to a less informational value for all other outcomes such as haemodynamics.

In 2010 the CONSORT Statement was published leading to an improvement in the quality of research publication (Shulz et al. 2010). However, all except one study included in this review were published prior to 2010. The evaluation of the quality of evidence was therfore, in part, difficult due to missing reported information data from the studies. This led to a high number of unclear risks of bias estimations, the conduct of the trial might, however, not be reflected by this (Soares et al. 2004). The effect of these risks on the meta-analyses cannot be approximated. As the oldest study is more than 25 years old the standard of care is likely to differ from studies today since the management of HF has significantly changed over the last 30 years (Pellicori et al. 2020).

The application method of the drugs differed among the trials. In most cases a bolus injection was administered followed by a continues infusion rate. Other trials adapted the infusion rate according to haemodynamic parameters. This might lead to differences in result and distort the conclusions based on these results (Nieminen et al. 2000).

5.3 Safety of dobutamine

From the drugs that were compared to placebo all but dobutamine showed a positive tendency.

A harmful effect of dobutamine in patients with LCOS/CS and underlying HF could not be ruled out, the included studies showed no difference between the treatment groups (RR 1.43; 95% CI 0.60 to 3.40). One possible risk factor when treating with dobutamine might be comedication with a betablocker in HF patients, possibly leading to an interaction of

medication. Epinephrine, norepinephrine, dobutamine and dopamine all depend on adrenal receptors in their mechanism of action (Palmer and Pennefather 2009). They therefore interact with beta-blockers and might have a reduced beta-adrenal effect due to competitive mechanism of action. Beta-blockers by themselves lower mortality in HF patients (Foody et al. 2002) and are part of the first line therapy in HF (Ponikowski et al. 2016). The Euro Heart Failure Survey II (EHFS II) found that 61% of HF patients were taking beta-blockers (Nieminen et al. 2006). Two trials from this review conducted a subgroup analysis on participants receiving beta-blockers. Follath 2002 found that the haemodynamic effect of dobutamine was weakened by beta-blockade and had no negative influence on the effect of levosimendan. No significant effect on mortality was detected but an apparent emphasis on the hemodynamic advantage of levosimendan. A secondary subgroup analysis of the data from the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial (Mebazaa et al. 2007) was performed to evaluate the effect of beta-blocker therapy among participants. For participants receiving beta-blockers a significantly lower mortality was found in the levosimendan treatment group compared to the dobutamine group (Mebazaa et al. 2009). A possible explanation for this difference might be that the effect of levosimendan as calcium sensitiser does not depend on beta-receptors opposed to dobutamine. The ESC recommends preferring levosimendan over dobutamine in patients with hypotention if beta-blockers might contribute to the low blood pressure (Ponikowski et al. 2016).

Further investigations should examine the effect of dobutamine under comedication with beta-blockers which seems to be dependent on the kind of betablocker taken. In a randomised cross-over trial Bollano et al. showed a significant difference to dobutamine in chronic HF patients receiving metoprolol compared to those receiving carvedilol. Under the treatment with carvedilol, dobutamine showed an increase in arterial pressure without altering the HR or cardiac output, whereas under metoprolol heart rate and cardiac output were increased without changing mean arterial pressure (Bollano et al. 2003). Further studies are needed to evaluate the effect of these findings on outcome in patients receiving dobutamine in HF.

5.4 Comparison to other reviews

The review by Schumann et al. was used as basis for this review. Five additional systematic reviews (Delaney et al. 2010, Landoni et al. 2012, Ribeiro et al. 2009, Leopold

et al. 2018, Belletti et al. 2015) investigated positive inotrope and vasodilative strategies to treat patients in acute HF.

The systematic review conducted by Schumann et al. included patients with LCOS and CS due to any causes including AMI, cardiac surgery and HF. In conclusion, the review found no superiority of any drug except an improvement of haemodynamic measurements in levosimendan patients. Whether this is an advantage for the patient or not, could not be concluded. The authors hypothesised that it might be more important to reach quick haemodynamic stability rather than using a specific drug (Schumann et al. 2018).

A systematic review investigating the treatment with levosimendan in patients with acute severe HF was published in 2010 by Delaney et al. (Delaney et al. 2010). CS or LCOS were no inclusion criteria and mortality did not need to be reported as outcome, if one of the other prespecified outcomes was reported. 19 RCTs with 3,650 patients were identified in the study including Adamopoulos 2006, Follath 2002 and Mebazaa 2007. The results reported included haemodynamic factors and mortality. Levosimendan was compared to placebo or dobutamine. The results showed an improvement in haemodynamic parameters in the levosimendan group. Mortality was not significantly lower than in the placebo group (Delaney 2010: OR 0.83, 95%CI 0.62-1.10, p=0.20) but reduced when compared to dobutamine (Delaney 2010: OR 0.75, 95%CI, 0.61-0.92, p=0.005). These results are in accordance with the findings of this systematic review. This indicates a positive effect of levosimendan on haemodynamic parameters and possibly a reduction in mortality.

Delaney et al. also compared dobutamine with placebo and noticed an increase of mortality in the dobutamine group (Delaney 2010: OR 1.82; 95% CI 1.06-3.12; p=0.03). These findings support the thesis that dobutamine might be potentially harmful in patients with CS/LCOS due to HF.

Landoni et al. conducted a meta-analysis to evaluate the effect that the use of levosimendan has on mortality (Landoni et al. 2012). A systematic search was performed. All RCTs comparing levosimendan with a control group were included. 45 RCTs were identified, including 5,480 participants. Overall a mortality rate of 17.4% was found in the levosimendan group and 23.3% in the control group. The reduction could also be found in a subgroup investigating cardiology settings. The authors concluded that levosimendan might reduce mortality in this setting (Landoni 2012: RR 0.75, CI 0.630.91,

p=0.003). This review did not explicitly investigate LCOS or CS, and CS was an exclusion-criteria in some of the studies included. This might lead to lower mortality rates. No subgroup analysis showed the different control groups in the setting of cardiology and the effect might therefore be imprecise due to differences between the interventions in the control groups. Overall, this review also showed a reduction in mortality in the levosmiendan group compared to the control group.

A systematic review published in 2009 investigated levosimendan in acute decompensated HF (Ribeiro et al. 2009). Medline database was searched for RCTs that investigated CHF treatment with levosimendan. The predefined outcomes included allcause mortality and length of hospital stay. 7 trials (including Adamopoulos 2006) compared levosimendan with placebo, including 1,652 participants. The results showed a RR of 0.87 with a 95% CI of 0.75-1.02. Levosimendan was compared to dobutamine in 10 trials (including Adamopoulos 2006, Mebazaa 2007 and Follath 2002), including 2,067 participants. A RR of 0.87 and a 95% CI of 0.75-1.02 was found. The AEs reported for levosimendan showed an increase in atrial fibrillation and ventricular tachycardia. The author concluded that, from the existing data, no benefit on survival was found for levosimendan. The review did not only include CS and LCOS, therefore it is likely that less severe settings were included. MI was not excluded from the search. The overall results, however, were close to the results of this thesis.

A meta-analysis of individual data was conducted by Leopold et al. in 2018 (Leopold et al. 2018). A systematic search was performed in 2017. Included were non-surgical CS patients, treated with inotropes and/or vasopressors, of which at least 15% were treated with epinephrine. The investigated outcome was short-term mortality. 16 cohorts were identified, leading to 2,583 participants being included in the meta-analysis. Mortality rates varied between 21-69%. The risk of death was found to be higher in patients treated with epinephrine compared to other drugs (OR=3.3, CI 2.8-3.9). One limit of the review was, that 14 out of the 16 studies included were observational trials. Only one of the included trials aimed to assess epinephrine in CS, for all other studies the data was reevaluated regarding epinephrine. Not only HF patients were included by Leopold et al. but also patients with other non-surgical reasons for CS, such as MI. 18% of the included participants suffered from CS after resuscitation of cardiac arrest. Regardless of these differences Leopold et al. found an increase of mortality in almost every study across different levels of illness severity in the epinephrine treatment group. The study included

in this review that investigated norepinephrine-dobutamine vs. epinephrine by Levy et al. found a RR of 0.8 with a wide 95% CI between 0.27 and 2.41. This trial was small, only including 30 participants. The tendency shown in the results are, however supported by the larger meta-analysis by Leopold et al. In the one small trial included in this review comparing epinephrine to norepinephrine-dobutamine, epinephrine had a slightly higher mortality. This is in accordance with the findings by Leopold et al.

The systematic review by Belletti et al. investigated the effect of inotropes and vasoconstrictors on mortality (Belletti et al. 2015). A difference in mortality could not be found in the overall population. In the review 177 randomised controlled trials were included by the authors which led to a total of 28,280 participants. The reason for the drug use was not prespecified. Trials showing an association between an increased mortality and the use of inotropic agents focused on chronic and stable HF patients. The authors concluded that a therapy with inotropes in HF patients should not be recommended. This differs from the results of this thesis as inotropes such as levosimendan seem to have a beneficial effect. Belletti et al. did not differentiate between different inotropic drugs, this might lead to negative effects cancelling out beneficial effects. Another difference to this review is the less acute setting of stable HF. These variations may explain the difference in result.

Some of the reviews included trials that were also included in this thesis. None of the trials investigated CS and LCOS in patients with pre-existing HF. They either included other reasons for CS and LCOS as well or they investigated HF in less acute settings. The literature search for this thesis was updated in 2019 and is therefore more up-to date than any of the reviews mentioned above. Not only one drug, such as levosimendan, was investigated but all inotrope and vasodilative drugs. The data from other reviews was in accordance with this thesis except for Belletti et al. which can be explained by the differences in the review question.

5.5 Implications for clinical practice and research

There is not enough evidence available to determine, whether any inotropic or vasodilator drug is superior to the others. Therefore, no clear recommendation can be derived for treatment recommendations of patients with pre-existing HF complicated by CS or LCOS.

In patients with HF, who suffer a CS or LCOS, levosimendan might lead to a reduction in mortality and positive effects on the haemodynamic stability of the patients. Larger

placebo-controlled trials are needed to prove the effectiveness in this setting. Dobutamine might be harmful in patients with HF and should only be used after critical consideration.

The current guidelines published by the ESC, the ACCF/AHA, and the GMA recommend the consideration of inotropic therapy in patients with CS and in case of acute HF, and the consideration of vasodilators in patients with high blood pressure (Ponikowski et al. 2016; Yancy et al. 2017; Arzneimittelkommission der Deutschen Apotheker et al. 2019). In the ESC guidelines this is based on level C evidence (expert opinion). In the ACCF/AHA guidelines this is based on class 1, level C, meaning that this procedure is recommended as useful based on expert opinion, case studies or standard of care. The GMA gives a strong recommendation for inotropic agents as short-time treatment in case of CS, based on expert opinion. None of the guidelines differentiate between the reasons of AHF.

Studies that investigate the interaction of dobutamine and beta-blockers are needed to identify, which subgroups of patients might benefit from its use and for which patients it should be avoided.

As the data collected for this review was limited from low to moderate quality of evidence and none of the comparisons was able to state benefits or detriments regarding mortality it cannot be justified to base clinical strategies on these results. Larger RCTs with a higher sample size and resulting precision are necessary to determine which drugs should be recommended in CS/LCOS due to HF.

6 Summary

HF is a common disease with high mortality if complicated by CS or LCOS. Even with improving therapeutic strategies HF still is one of the most common causes of death in Germany. The current guidelines are based on expert opinion and case studies. Inotropic and vasodilative agents are recommended without differentiating between causes for CS or LCOS. The ESC guidelines recommend to prefer levosimendan over dobutamine if betablockers are likely to contribute to low blood pressure. It stays unclear if in different circumstances any drug is superior to other available medication.

This thesis summarieses the currently available RCTs on HF patients complicated by CS or LCOS comparing inotropic or vasodilative strategies with either placebo or established treatments. The aim of this thesis was to evaluate if there is evidence for a superior treatment strategy for HF patients with CS or LCOS. As primary endpoint short- and long-term mortality were investigated, secondary endpoints included haemodynamic parameters, major adverse cardiac events (MACE), adverse events (AEs), length of hospital stay, quality of life and costs of treatment.

The Cochrane group conducted a systematic search. The results of this search were then screened by a predefined protocol identifying all eligible studies. The data of nine studies with 1,836 participants were included in this review. The trials included seven different drug comparisons. For the primary endpoint mortality three meta-analyses could be performed and described in forest plots with the RR and a 95% CI.

None of the comparisons showed statistical significance. Levosimendan was favored compared to dobutamine at 31 days with a RR of 0.70 and a 95% CI of 0.39 to 1.27. Long-term mortality also favours the levosimendan group with a RR of 0.83 and a 95% CI of 0.64 to 1.09. In both comparisons the CI includes the RR = 1. Two trials found a negative effect of the comedication with beta-blockers in patients receiving dobutamine, but not in patients receiving levosimendan.

These results are in accordance with the current guidelines, recommending to prefer levosimendan over dobutamine in patients with HF in case of low blood pressure, that might be caused by beta-blockers.

Larger placebo-controlled trials are needed to evaluate the effect of different inotropic and vasodilative strategies in patients with HF complicated by CS and LCOS.

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8 Theses

1. In the systematic search about 4000 studies were identified. Nine studies were eligible for the systematic review, including a total of 1,771 participants with low cardiac output syndrome (LCOS) or cardiogenic shock (CS) due to chronic heart failure (CHF) and were evaluated in seven comparisons.

2. The quality of evidence was assessed using the GRADE-System (Grading of Recommendations, Assessment, Development and Evaluation) for the primary outcome mortality. The evidence of the included studies was classified as low to moderate.

3. None of the included studies was able to conform benefits or harms on the primary endpoint mortality. The evidence collected for this review is not enough to recommend any of the investigated drugs.

4. Low grade evidence suggests that levosimendan might decrease short- and longterm mortality in patients with LCOS or CS due to CHF. All included studies favoured levosimendan with non-significant results on mortality.

5. Levosimendan showed a positive effect on haemodynamic parameters in most of the trials with very different follow-up times. Levosimendan might improve haemodynamic parameters such as median arterial pressure (MAP), left ventricular ejection fraction (LVEF), cardiac index (CrI) and pulmonary capillary wedge pressure (PCWP).

6. Two very small trials investigating dobutamine did not show a positive effect on mortality with low grade evidence (RR 1.43; 95% CI 0.60 – 3.40). This might be caused by comedication with beta-blockers.

7. Further studies are necessary to investigate the potentially beneficial effect of levosimendan on patients with LCOS or CS due to pre-existing heart failure (HF).

8. Dobutamine should only be used very cautiously in patients suffering under LCOS or CS due to a pre-existing HF.

9 Appendices

9.1 Excluded studies

Table 5 Excluded studies

Reason for exclusion	Studies
No RCT(N=37)	Affronti et al. 2013; Andriange et al. 1971; Aronski et al. 1978; Belskii et al. 1987; Bussmann 1983; Caimmi et al. 2011; Coma Canella and López-Sendón 1981; Clark et al. 1983; Delle Karth et al. 2003; Dhainaut et al. 1990; Estanove et al. 1988; Fowler et al. 1980; Friedel et al. 1992; Gray et al. 1981; Hobbs 1998; Kaplan et al. 1980; Kones 1972; Lanfear et al. 2009; Lima et al. 2010; Lopez et al. 1997; Lvoff and Wilcken 1972; Mebazaa et al. 2009; Monte et al. 1986; Nadjmabadi et al. 1980; Orellano et al. 1991; Perret 1978; Poelzl et al. 2008; Russ et al. 2009; Santman 1992; Shah et al. 2014; Sterling et al. 1984; Tacon et al. 2012; Tritapepe et al. 1999; Tritapepe et al. 2009; Tzimas et al. 2009; Verma et al. 1992; Wright et al. 1992; Zerkowski et al. 1992
Wrong indication (N=61)	Al-Shawaf et al. 2006; Aldea-Perona et al. 2016; Altenberger et al. 2014; Comín, 2012; Garcia et al. 2016; Elsevier Ltd, 1990 Barisin et al. 2004; Biteker et al. 2011; Burger et al. 2002; Chen et al. 2013; Cotter et al. 1997; Cotter et al. 2003; Cowley and Skene 1994; Cuffe et al. 2002; Erb et al. 2014; Euctr 2010; Feldman et al. 2007; Felker et al. 2003; García-González et al. 2013; Giamouzis et al. 2010; Ikonomidis et al. 2007; Jia et al. 2015; Khand et al. 2003; Kleber et al. 2009; Kurt et al. 2010; Landoni et al. 2017; Levin et al. 2012; Lilleberg et al. 1998; Lilleberg et al. 2007; Llorens P 2012; Lowes et al. 2000; Malfatto et al. 2012; Metra et al. 2009; Mehta et al. 2017; Meng et al. 2016; Moiseyev et al. 2002; Nagai et al. 2013; Nanas et al. 2004; Nancy, Central Hospital, France, 2019; Nieminen et al. 2008; O'Connor et al. 1999; Packer et al. 2013; Parissis et al. 2007; Pasqui et al. 2011; Perry 2013; Siostrzonek et al. 2000; Trikas et al. 2006; Triposkiadis et al. 2014; Tziakas et al. 2005; Wimmer et al. 1999; Woodhouse et al. 1995; Zemljic et al. 2007
Wrong intervention (N=6)	**ß-blocker:** Genth-Zotz et al. 2000; **Sartan:** Ochiai et al. 2014; **ACE-inhibitor:** Karakas, 2019; Avanzini et al. 2002; Beller et al. 1995; Pouleur 1992;
No mortality (N=17)	Carmona et al. 2010; Duygu et al. 2008; Feneck et al. 2001; Galinier et al. 1990; George et al. 1989; Gunnicker et al. 1995; Kikura et al. 1997; Kikura and Sato 2002; Lancon et al. 1990; MacGregor et al. 1994; Nijhawan et al. 1999; Patel et al. 1993; Seino et al. 1996; Slawsky et al. 2000; Sunny et al. 2016; Timewell et al. 1990; Zwölfer et al. 1995
Cross-over trial (N=5)	Dominguez-Rodriguez et al. 2007; Ferrario et al. 1994; KielerJensen et al. 1995; Loeb et al. 1971; Richard et al. 1983
Preventive (N=5)	Butterworth et al. 1993; Hert et al. 2007; Hoffman et al. 2003; Lechner et al. 2012; Sharma et al. 2014

9.2 Concomitand medication at baseline

Table 6 Concomitand medication at baseline

Medication	**Trial in which medication is mentioned as co-medication**
Diuretics	7 (Adamopoulos et al. 2006; Berger et al. 2007; Follath et al. 2002; Jondeau et al. 1994; Levy et al. 2011; Mavrogeni et al. 2007; Mebazaa et al. 2007)
Aldosterone antagonist	4 (Adamopoulos et al. 2006; Levy et al. 2011; Mavrogeni et al. 2007; Mebazaa et al. 2007)
ACE inhibitors or AT1-blocker	7 (Adamopoulos et al. 2006; Berger et al. 2007; Follath et al. 2002; Jondeau et al. 1994; Levy et al. 2011; Mavrogeni et al. 2007; Mebazaa et al. 2007)
beta blocker	7 (Adamopoulos et al. 2006; Berger et al. 2007; Follath et al. 2002; Jondeau et al. 1994; Levy et al. 2011; Mavrogeni et al. 2007; Mebazaa et al. 2007)
nitrates	3 (Follath et al. 2002; Mavrogeni et al. 2007; Mebazaa et al. 2007)
digitalis	2 (Berger et al. 2007; Mavrogeni et al. 2007)
digoxin	2 (Follath et al. 2002; Jondeau et al. 1994)
Class III antiarrhythmic agents	3 (Adamopoulos et al. 2006; Follath et al. 2002; Jondeau et al. 1994)
Calciumchannel blockers	1 (Follath et al. 2002)
No data for medication before randomisation was given in Meißner 1994	

9.3 Levosimendan vs. dobutamine

Table 7 Group size levosimendan vs dobutamine

Study	**Group size levosimendan**	**Group size Dobutamin**	**Total**
Adamopoulos 2006	23	23	46
Follath 2002	102	97	199
Mebazaa 2007	606	660	1266

Table 8 Baseline characteristics levosimendan vs dobutamine

Age	**Sex (♂ %)**	**SBP (mmHg)**	**DBP (mmHg)**	**MAP (mmHg)**	**HR (bpm)**	**CI (l/min/m^2)**	**LVEF (%)**	**PCWP (mmHg)**
Adamopoulos 2006								
71±1/ 67±2	87/ 87	109±3/ 106±3	67±2/ 70±1	-	-	1.7±0.04/ 1.7±0.04	24±2/ 25±1	24±1/ 23±1
Follath 2002								
58±11/ 60±11	85/ 88	112±18/ 117±19	69±12/ 71±12	104±6.7/ 98±6.4	82±15/ 81±16	1.94±0.36/ 1.91±0.44	-	25±8/ 24±7

Age	Sex (♂ %)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	CI (l/min/m^2)	LVEF (%)	PCWP (mmHg)
Mebazaa 2007								
67±12/ 66±12	74/ 70	116±18/ 116±19	70±12/ 70±12	-	84±17/ 83±17	-	-	-

Table 9 Comorbidities levosimendan vs. dobutamine

Diabetes (%)	Hypertension (%)	Prior AMI/vascular intervention (%)
Adamopoulos 2006		
-	-	62/82
Follath 2002		
-	-	45/50
Mebazaa 2007		
31/34	61/65	68/69

Table 10 Interventions: levosimendan vs. dobutamine

Levosimendan	Dobutamine
Adamopoulos 2006	
loading dose: 6µg/kg for 10 min continues infusion: 0.1 µg/kg/min for 24h	5 µg/kg/min for 24 h In case of inadequate heamodynamic response: the dobutamine rate was gradually doubled
Follath 2002	
Loading dose: 24 µg/kg for 10 min Continues infusion: 0.1 µg/kg/min	5 µg/kg/min
In case of inadequate haemodynamic response after two hours: the rate was doubled	
Mebazaa 2007	
Loading dose: 12µg/kg over 10 min Continues infusion: 0.1 µg/kg/min for 50 min, then 0.2 µg/kg/min for 23 h as tolerated	5 µg/kg/min for at least 24 h (as long as appropriate, tapered according to clinical status) Could be increased up to a maximum of 40 µg/kg/min

Table 11 Inclusion/exclusion criteria: levosimendan vs. dobutamine

Inclusion criteria	Exclusion criteria	Description of the condition
Adamopoulos 2006		
• Systolic left ventricular dysfunction • NYHA III or IV • Admitted for acute decompensated heart failure	• Acute/chronic infection • inflammatory disease • Recent AMI (< 8 weeks) • Active ischemia • Hepatic / renal impairment (creatinine>2.5 mg/dl) • Immunosuppressive drugs in premedication • Serious arrhythmias • Supine SBP <85 mmHg	• LCOS: • CI ≤ 2.5 L/min/m2
Follath 2002		
• worsening of severe chronic HF despite of optimum vasodilating and diuretic oral therapy • including: • Participants awaiting cardiac transplantation • severe HF following cardiac surgery • acute HF of recent onset which are related to a cardiac or non-cardiac disorder	• CS • age < 21 years • childbearing potential • chest pain at time of randomization • second/third degree atrioventricular block • heart rate at rest > 120 beats/min • SBP < 85 mm Hg • severe renal failure with serum creatinine>450 mol/L • hepatic failure • cardiac tamponade • adult respiratory distress syndrome • septic shock • <u>reasons for HF:</u> • restrictive/hypertrophic cardiomyopathy • uncorrected stenotic valvular disease • <u>prohibited before baseline:</u> • sustained ventricular tachycardia within 2 weeks • ventricular fibrillation within 2 weeks • i.v. -adrenergic agonists within 30 min • i.v. vasodilators within 2 h • i.v. milrinone or enoximone within 12 h • i.v. amrinone within 2 days	• LCOS: • LVEF < 0,35 within one month previous • CI < 2,5 l/min/m2 • mean PCWP > 15 mm Hg.

Inclusion criteria	Exclusion criteria	Description of the condition
Mebazaa 2007		
• EF ≤ 30% within the 12 months prior • Requirement of i.v. inotropic support apparent as an insufficient response to i.v. diuretic and/or vasodilating strategies • at least one of the following symptoms at screening: • dyspnea at rest / mechanical ventilation for HF • oliguria not due to hypovolaemia • PCWP≥18 mmHg and/or CI≤2.2 l/min/m^2	• severe ventricular outflow obstruction • SBP<85 mmHg constantly • HR ≥ 130/min constantly • Use of i.v. inotropes at time of index hospitalisation (exceptions: dopamine≤2µg/kg/min, digitalis) • torsade de pointes in history • serum creatinine level >450µmol/l • dialysis	• LCOS/CS: • requirement of inotropic support due to: • EF ≤ 30% • PCWP≥18 mmHg and/or CI≤2.2 l/min/m^2

Table 12 Outcomes levosimendan vs dobutamine

Primary outcome	Secondary outcome	Safety protocol
Adamopoulos 2006		
• disease progression during a **four-month** follow-up: • all-cause mortality • rehospitalization due to decompensated HF	• **at48 h** and at **day one** in a subgroup of 13 patients per group: • echocardiographic and haemodynamic measurements: • LV stroke volume, EF, end-systolic wall stress (ESWS), • central haemodynamic measurements: • cardiac output, CI, PCWP, 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)	

Primary outcome	Secondary outcome	Safety protocol
Follath 2002		
• <u>haemodynamic improvement:</u> • ≥30% increase in cardiac output and • ≥ 25% (at least 4 mm Hg) decrease in PCWP at 24 h	• all-cause mortality: **day 31** and **day 180** after randomization • changes from baseline in haemodynamics **at 24 h** except cardiac output, PCWP • changes in symptoms of HF from baseline to **24 h** (described on a fourgrade HF scale) • quantity of patients with the necessity of i.v. rescue therapy during study drug infusion (positive inotropic drugs, vasodilators, diuretics) • number of days during which the patient is alive, out of hospital, not getting intravenous drugs for the first month • time until HF worsens or death occurs.	• reports of adverse reactions, • laboratory safety tests (blood and urine)
Mebazaa 2007		
• all-cause mortality for the period of **180 days** after randomization	• at **31 days**: all-cause mortality • change from baseline to **24 h**: in BNP level, patient assessed dyspnea, patient assessed global assessment • number of days alive and out of hospital during the 180 days • through **180 days**: cardiovascular mortality	• Collection of adverse events: • at 31 days after initial study drug administration • during all blinded drug re-administrations

9.4 Levosimendan vs. placebo/no specific treatment

Table 13 Group size levosimendan vs. control

Study	Group size levosimendan	Group size placebo	Total
Adamopoulos 2006	23	23	46
Mavrogeni 2007	25	25	50

Table 14 Baseline characteristics levosimendan vs control

Age	Sex (male, %)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	CI (l/min/m^2)	LVEF (%)	PCWP (mmHg)
Adamopoulos 2006							
71±1/ 71±2	87/78	109±3/ 113±4	67±2/ 71±2	-	1.7±0.04/ 1.8±0.1	24±2/ 27±1	24±1/ 23±1
Mavrogeni 2007							
62±20/ 61±19	80/80	-	-	78±13/ 80±13	-	22±6/ 22±5	-

Table 15 Comorbidities levosimendan vs. control

Diabetes (%)	Hypertension (%)	Prior AMI/vascular intervention (%)
Adamopoulos 2006		
-	-	62/82
Mavrogeni 2007		
-	-	-

Table 16 Interventions: levosimendan vs. control

Levosimendan	Placebo/no specific treatment
Adamopoulos 2006	
loading dose: 6 µg/kg for 10 min continues infusion: 0.1 µg/kg/min for 24h	continuous infusion for 24 h: 5% dextrose
Mavrogeni, 2007	
loading dose: 6 µg/kg for 10min continues infusion: 0.1 µg/kg/min initially, then up-titration to a maximum rate of 0.2 µg/kg/min or an event imitating the dose occurred for six months this protocol was repeated monthly in the levosimendan group The day of infusion the dos of diuretics was halved	No specific treatment

Table 17 Inclusion/exclusion criteria: levosimendan vs. control

Inclusion criteria	Exclusion criteria	Description of the condition
Adamopoulos 2006		
• Systolic left ventricular dysfunction • NYHA III or IV • Admitted for acute decompensated heart failure	• Acute/chronic infection • inflammatory disease • Recent AMI (< 8 weeks) • Active ischemia • Hepatic / renal impairment (creatinine>2.5 mg/dl) • Immunosuppressive drugs in premedication • Serious arrhythmias • Supine SBP <85 mmHg	• LCOS: • CI ≤ 2.5 L/min/m^2
Mavrogeni 2007		
• Systolic left ventricular dysfunction • NYHA III or IV • LVEF <30% • CI<2.5 L/min/m^2.	• Acute/chronic infection • inflammatory disease • Recent AMI (< 8 weeks) • Active ischemia • Hepatic / renal impairment (creatinine>2.5 mg/dl) • Immunosuppressive drugs in premedication • Serious arrhythmias • Supine SBP <85 mmHg	• LCOS/CS: • LVEF <30% • CI <2.5 L/min/m^2

Table 18 Outcomes: levosimendan vs control

Primary outcome	Secondary outcome	Safety protocol
Adamopoulos 2006		
disease progression during a **four-month** follow-up: all-cause mortality rehospitalization due to decompensated HF	• **at48 h** and at **day one** in a subgroup of 13 patients per group: • echocardiographic and haemodynamic measurements: • LV stroke volume, EF, end-systolic wall stress (ESWS), • central haemodynamic measurements: • cardiac output, CI, PCWP, pulmonary and systemic vascular resistance • biochemical measurements: • tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), soluble Fas (sFas), sFas ligand (sFasL), N-terminal-pro-Btype natriuretic peptide (NT-pro-BNP)	-
Mavrogeni, 2007		
• Specific activity questionnaire (SAQ) • echocardiography (ECHO)	• All-cause mortality during **6-month** follow-up • Haemodynamic parameters	-

9.5 Levosimendan vs. PGE1

Table 19 Group size: levosimendan vs PGE1

Group size		
Berger 2006		
Levosimendan	**PGE1**	**Total**
39	36	75

Table 20 Baseline characteristics: levosimendan vs. PGE1

Basline Characteristics						
Berger 2006						
Age	**Sex (male,%)**	**SBP (mmHg)**	**DBP (mmHg)**	**CI ($l/min/m^2$)**	**LVEF (%)**	**PCWP (mmHg)**
57±10/54±10	82/81	103±17/108±20	68±13/71±12	1.8±0.4/1.8±0.4	20±6/21±7	24±4/24±4

Table 21 Comorbidities levosimendan vs. control

dilated cardiomyopathy (%) (Levosimendan/PGE1)	**coronary artery disease (%) (Levosimendan/PGE1)**	**atrial fibrilation (%) (Levosimendan/PGE1)**	**pacemaker(%) (Levosimendan/PGE1)**
Berger 2006			
22/18	17/18	10/15	15/6

Table 22 Interventions: levosimendan vs. PGE1

Intervention	
Berger 2006	
Levosimendan	**PGE1**
Patients with blood pressure ≥95 mm Hg Loading dose:12 µg/kg for 10min continues infusion: 0.1 µg/kg/min for 24h. Patients with blood pressure <95 mm Hg and ≥90 mm Hg: Loading dose: none Continues infusion: 0.1 µg/kg/min for 24h	Infusion rate: 2.5 ng/kg/min (for continues infusion applied through a Hickman catheter with a portable pump)

Table 23 Inclusion/exclusion criteria: levosimendan vs. PGE1

Participants		
Berger 2006		
Inclusion criteria	**Exclusion criteria**	**Description of the condition**
• age 18 to 85 years, • NYHA IIIb or IV without edema, • LVEF <35% (determined within 3 months before inclusion by radionuclide ventriculography) • PCWP>15 mm Hg • CI<2.5 l/min/m^2, • Increase in BNP of >400 pg/ml or • increase in N-terminal atrial natriuretic peptide (N-ANP) of >6300 fmol/ml • the target dose of 10 mg of bisoprolol could not be reached • no change of therapy for 2 weeks prior to randomisation	• Supine SBP<90 mm Hg • renal impairment (creatinine>2.5 mg/dl) • severe reactive chronic obstructive pulmonary disease, • MI • 3 months prior: coronary revascularization • acute inflammatory reaction • signs of infection • hypertrophic cardiomyopathy • severe obstructive valvular disease	• **LCOS/CS:** • CI < 2.5 l/min/m^2 • PCWP > 15 mm Hg

Table 24 outcome: Levosimendan vs. PGE1

Outcome	
Berger 2006	
Primary outcome	**Secondary outcome**
• worsening of NYHA class • within 1 week: weight increase >2 kg • signs of cardiac decompensation	combined negative endpoint: • death • urgent heart transplantation • implantation of a ventricular assist device
Safety protocol	
Levosimendan: After each dose alteration, blood pressure was monitored. In case of blood pressure decrease to <90 mm Hg but ≥85 mm Hg, dose was reduced to half. In case of blood pressure <85 mm Hg infusion was stopped and restarted at half dose if the blood pressure recovered during the next 30 min. PGE1: dose was decreased by half (1.25 ng/kg/min): In case of blood pressure > 90 mm Hg but > 85 mm Hg, in case of side effects (if side effects disappeared dose was kept at half, in case of ongoing side effects it was stopped, according to side effects and patient re-start or increase of dose was performed) PGE1 was stopped and volume substituted: blood pressure < 85 mm Hg, creatinine increasing by more than 0.5 mg/ml in comparison to baseline Diuretics were reduced in case of absence of signs of decompensation. Reevaluation after 48 h of blood pressure, serum creatinine followed by adjustment of dose	

9.6 Dobutamine vs. placebo/no specific treatment

Table 25 Group size: dobutamine vs control

Study	**Group size Dobutamin**	**Group size control**	**Total**
Adamopoulos 2006	23	23	46
Oliva 1999	19	19	38

Table 26 Baseline characteristics: dobutamine vs control

Age	**Sex (male,%)**	**SBP (mmHg)**	**DBP (mmHg)**	**MAP (mmHg)**	**HR (bpm)**	**CI (l/min/m^2)**	**LVEF (%)**	**PCWP (mmHg)**
Adamopoulos 2006								
67±2/ 71±2	87/ 78	106±3/ 113±4	70±1/ 71±2	-	-	1.7±0.04/ 1.8±0.1	25±1/ 27±1	23±1/ 23±1
Oliva 1999								
65±2.8/ 66±1.4	89/ 74	-	-	78±2/ 87±2	77±3/ 82±4	1.9±0.1/ 1.9±0.1	21±1/ 24±1	21±2/ 25±2

Table 27 Comorbidities

Diabetes (%)	Hypertension (%)	Ischemic heart failure (%)
Adamopoulos 2006		
-	-	82/78
Oliva 1999		
47/26	-	42/53

Table 28 Interventions: dobutamine vs control

Dobutamine	Control
Adamopoulos 2006	
5 µg/kg/min for 24 h continuous infusion for 24 h: 5% In case of inadequate haewmodynamic response: the dobutamine rate was gradually doubled	dextrose
Oliva 1999	
Maximal oral therapy and intermittent ambulatory infusion of 2.5 µg/kg/min dobutamine increased to 5 and 7.5 µg/kg/min if tolerated for 48 hours per week or 72 hours per week if clinicly needed for 6 months	Maximal oral therapy

Table 29 Inclusion/Exclusion criteria: levosimendan vs. dobutamin

Inclusion criteria	Exclusion criteria	Description of the condition
Adamopoulos 2006		
• Systolic left ventricular dysfunction • NYHA III or IV • Admitted for acute decompensated heart failure	• Acute/chronic infection • inflammatory disease • Recent AMI (< 8 weeks) • Active ischemia • Hepatic / renal impairment (creatinine>2.5 mg/dl) • Immunosuppressive drugs in premedication • Serious arrhythmias • Supine SBP <85 mmHg	• LCOS: • CI ≤ 2.5 L/min/m2

Inclusion criteria	Exclusion criteria	Description of the condition
Oliva 1999		
• CHF • Age > 18 years old • NYHA III or IV requiring hospitalisation • The need for intravenous inotropes 6 months before evaluation	• Patients without automatic defibrillator and documented malignant arrhythmia • Short-term prognosis effecting neoplastic or systemic diseases • Unstable angina • Coronary stenosis that were angiographically documented and effective • Valvular heart diseases that are surgically curable • Prior to randomisation maximal oral therapy combined with a dobutamine infusion 2.5 µg/kg/min increased to 5 and 7.5 µg/kg/min if tolerated for 48 hours per week or 72 hours per week if clinically needed was administered and stopped in case of: o HR > 110 bpm o Atrial fibrillation o More than 6 ventricular ectopic beats per minute o Sustained ventricular tachycardia • In case the initial therapy was stopped participants were excluded from the study	• LCOS: • CI ≤ 2.2 L/min/m2 • LVEF ≤ 0.3

Table 30 Outcomes: levosimendan vs dobutamine

Primary outcome	Secondary outcome	Safety protocol
Adamopoulos 2006		
decompensated HF • LV stroke wall stress (ESWS),	• disease progression during a • **at48 h** and at **day one** in a subgroup of **four-month** follow-up: 13 patients per group: • all-cause mortality • echocardiographic and haemodynamic rehospitalization due to measurements: volume, EF, end-systolic • central haemodynamic measurements: • cardiac output, CI, PCWP, 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)	

Primary outcome	Secondary outcome	Safety protocol
Oliva 1999		
• worsening of CHF resulting in hospitalisation • defined as hospital stay of more than 24 hours and the need of inotropes and/or furosemide	• death occurs • change in NYHA class • change in 6 min walking test	• Control of electrolytes and renal function at weekly intervals

9.7 Enoximone vs. Placebo

Table 31 Group size: enoximone vs. placebo

Group size levosimendan	Group size placebo	Total
Jondeau 1994		
12	12	24

Table 32 Baseline characteristics: enoximone vs. placebo

Age	Sex (male,%)	MBP (mmHg)	HR (bpm)
Jondeau 1994			
64/64.5	79/79	74±10/77±12	38±14/88±18

Table 33 Comorbidities: enoximone vs. placebo

Coronary artery disease (%)	Dilated cardiomyopathy(%)
Jondeau 1994	
29%	71%

Table 34 Interventions: enoximone vs. placebo

Enoximone	Placebo
Jondeau 1994	
oral 100mg three times a day	oral 100mg three times a day

Table 35 Inclusion/exclusion criteria: enoximone vs. placebo

Inclusion criteria	Exclusion criteria	Description of the condition
Jondeau 1994		
patients requiring: • need for i.v. inotropic support in case of severe congestive HF • be weaning from i.v. dobutamine not possible despite progressive dosage decrease • decrease in dobutamine led to a state of LCOS if dobutamine infusion was continued this state would be reversed	Non given in the protocol	LCOS including: • hypotension, • congestive symptoms worsening • decrease in diuresis

Table 36 Outcomes: enoximone vs. placebo

Primary outcome	Secondary outcome
Jondeau 1994	
successful weaning from dobutamine	• clinical parameters (blood pressure, heart rate) • echocardiographic parameters, doppler signals, • mortality

9.8 Epinephrine vs. norepinephrine-dobutamine

Table 37 Group size: epinephrine vs. norepinephrine-dobutamine

Study	Group size epinephrine	Group size norepinephrine-dobutamine	Total
Levy, 2011	15	15	30

Table 38 Baseline characteristics: epinephrine vs. norepinephrine-dobutamine

Age	Sex (male,%)	MBP (mmHg)	HR(bpm)	CI (l/min/m^2)	LVEF (%)	Prior AMI/vascular intervention (%)
Levy, 2011						
66±12/ 64±10	66/ 73	55±9/ 54±8	121±19/ 125±15	1.6±0.4/ 1.6±0.4	24±5/ 24±5	53/ 66

Table 39 Comorbidities: epinephrine vs. norepinephrine-dobutamine

History of HF	Ischemic cardiomyopathy	Dilated cardiomyopathy	Valvular disease	Atrial fibrillation/ flutter	Previous intubation
Levy, 2011 (%)(epinephrine/ norepinephrine)					
86/93	53/66	33/20	13/13	40/47	13/13

Table 40 Interventions: epinephrine vs. norepinephrine-dobutamine

Epinephrine	Norepinephrine-dobutamine
Levy, 2011	
Both groups initially received dobutamine. In case of persisting hypoperfusion under dopamine dosage of up to 10 µg/kg/min, dopamine was added. Dopamine was administered in doses ranging form 2 to 20 µg/kg/min. The dopamine dose was increased 5 µg/kg/min every 10 min. Patients were eligible for the trial if this regime was not sufficient	
Infusion rate: 0.1µg/kg/min up titration based on MAP at 5-min intervals with target MAP > 65 and <70mm Hg and a stable or increased in CI when this was reached the infusion of dobutamine was stopped	Infusion rate: 0.1µg/kg/min up titration based on MAP at 5-min intervals with target MAP > 65 and < 70mm Hg and a stable or increased in CI, the dobutamine infusion was continued

Table 41 Inclusion/exclusion criteria: epinephrine vs. norepinephrine-dobutamine

Inclusion criteria	Exclusion criteria	Description of the condition
Levy, 2011		
• Acute or chronic HF • EF ≥ 30% • CI < 2.2 l/min/m^2 • no hypovolemia • SBP> 90 mm Hg or MAP> 60 mmHg or a drop in MAP of 30 mm Hg despite dopamine up to 20 g/kg/min • Urine output <0.5 ml/kg/h • lactate level ≥ 2 mmol/L • signs of hypoperfusion	• acute cardiac ischemia signs alternative: two negative troponin tests at 6h intervals (in case of left branch block) • CS secondary to acute ischemic events (MI, immediate indication of a ventricular assist device, acute and sustained atrial and ventricular arrhythmias, pulmonary embolism, pure right ventricular failure, septic shock, poisoning)	• **CS:** • evidence of tissue hypoperfusion (cold and/or clammy skin, liver dysfunction, or impaired mentation) • induced by heart failure after adequate correction of preload and major arrhythmia

Table 42 Outcomes: epinephrine vs. norepinephrine-dobutamine

Outcomes
Levy, 2011
• Mortality • changes in haemodynamic measurements (Vasopressor titration, MAP, CI, HR, pulmonary artery occlusion pressure, pulmonary artery pressure, right atrial pressure oxygen delivery index, mixed venous oxygen saturation, oxygen consumption index), • changes in metabolic parameters • splanchnic parameters • renal parameters (creatinine, lactate, lactate/pyruvate ratio, arterial pH, insulin, PCO_2 gap, diuresis,)

9.9 Dopamine/dobutamine vs. dopamine/milrinone

Table 43 Group size: dopamine/dobutamine vs. dopamine/milrinone

Study	Group size dopamine/dobutamine	Group size dopamine/milrinone	Total
Meißner, 1996	10	10	20

Table 44 Baseline characteristics: dopamine/dobutamine vs. dopamine/milrinone

Age	Sex (♂%)	SBP (mmHg)	MBP (mmHg)	HR (bpm)	CI (l/min/m^2)	LVEF (%)	PCWP (mmHg)
Meißner, 1996							
62±3.2/ 66±2.5	90/ 70	112±3.5/ 117±3.8	75±2.2/ 77±1.9	96±5.6/ 94±5.7	2.05±0.1/ 2.0±0.1		21±1.7/ 24±2.1

Table 45 Comorbidities: dopamine/dobutamine vs. dopamine/milrinone

Atrial fibrilation (%)
Meißner, 1996
40%

Table 46 Interventions: dopamine/dobutamine vs. dopamine/milrinone

Dopamine/dobutamine	Dopamine/milrinone
Meißner, 1996	
Infusion rate: 3 µg/kg/min, 6 µg/kg/min and 9µg/kg/min increased after 20 min each time	Bolus injection: 50 µg/kg over 10 min Continues infusion rate: 0.5 µg/kg/min
Dopamine (10-12 µg/kg/min) Nitroglycerin 33 µg/min	

Table 47 Inclusion/exclusion criteria: dopamine/dobutamine vs. dopamine/milrinone

Inclusion criteria	Exclusion criteria	Description of the condition
Meißner, 1996		
• acute decompensated HF, a • dopamine dependent in pressure elevating dose • CI < 2.5 l/min/m^2 • persistent PCWP > 15mmHg	• acute MI during the last two weeks, • pre-existing instable angina pectoris, • uncorrected valvular heart disease, • cardio muscular complications, • pre-existing severe liver and/or renal disfunctions	• **LCOS:** • CI < 2.5 l/min/m^2 • PCWP > 15mmHg after therapy

Table 48 Outcome: dopamine/milrinone vs dopamine/dobutamine

Primary outcome	Secondary outcome	Safty protocol
Meißner, 1996		
Mortality, haemodynamic measurements at 20 min, 40 min, 60 min and 120 min in the dobutamine group and at 15 min, 20 min, 45 min, 60 min milrinone group		

9.10 Search Strategy

MEDLINE Ovid

1. Shock, Cardiogenic/
2. cardiogenic* shock*.tw.
3. Cardiac Output, Low/
4. (low adj2 cardiac output).tw.
5. ((instab* or unstab*) adjh?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. expCardiotonic Agents/
14. cardiotonic.tw.
15. ((myocardial or cardiac) adjstimula*).tw.
16. inotrope*.tw.
17. inotropic agent*.tw.
18. cardioprotective agent*.tw.
19. acetyldigitoxin*.tw.
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22. amrinone.tw.
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27. digitalis glycoside*.tw.
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32. enoximone.tw.
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34. isoproterenol.tw.
35. lisinopril.tw.
36. medigoxin.tw.
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57. bencyclane.tw.
58. bepridil.tw.
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111. Pituitary AdenylateCyclase-Activating Polypeptide.tw.
112. prenylamine.tw.
113. propranolol.tw.
114. S-Nitroso-N-Acetylpenicillamine .tw.
115. S-Nitrosoglutathione.tw.
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117. Suloctidil.tw.
118. Theobromine.tw.
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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 phosphodiesteraseII) adj (antagonist* or inhibitor*)).tw.
132. antiphosphodiestera se*.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

Keywords: Dissertation Cardiogenic Shock - Kardiogener Schock – vasodilatataiv innotropische

Medikamente - Epinephrine - Levosimendan - Dobutamin - Enoximone - Norepinephrin – Milrinon

Declaration under Oath / Selbständigkeitserklärung

I declare under oath that this thesis is my own work entirely and has been written without any help from other people. I met all regulations of good scientific practice and I used only the sources mentioned and included all the citations correctly both in word or content.

Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommen Stellen als solche kenntlich gemacht.

Halle (Saale), Hellen Feige

Declaration / Erklärung

I declare that I have not completed or initiated a doctorate procedure at any other university.

Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen beziehungsweise eine Promotion begonnen habe.

Halle (Saale), Hellen Feige

Declaration Concerning the Truth of Information Given / Erklärung über frühere Promotionsversuche

I declare that all information given is accurate and complete. The thesis has not been used previously at this or any other university in order to achieve an academic degree.

Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

Halle (Saale), Hellen Feige

Danksagung

Hiermit möchte ich mich bei allen bedanken, die mich beim Schreiben dieser Arbeit unterstützt haben.

Insbesondere gilt mein Dank meiner Betreuerin Frau PD Dr. rer. nat. habil. Susanne Unverzagt für ihre lange, gute Unterstützung, die in Form von vielen wertvollen Ratschlägen und Anregungen das Fertigstellen der Arbeit begleitete, sowie meinem Betreuer PD Dr. med. Roland Prondzinsky für seine fachlichen Anmerkungen.

Meiner Familie danke ich für die mentale Unterstützung und das Schaffen von Freiräumen, die es mir ermöglichten, mich den spannenden Herausforderungen dieser Arbeit zu stellen.