

Rehospitalization after intermittent levosimendan treatment in advanced heart failure patients: a meta-analysis of randomized trials

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Abstract

Aims Intermittent levosimendan administration has been suggested to improve survival in patients with advanced heart failure (AdHF). Quality of life is a key issue for AdHF patients and is negatively affected by frequent hospitalizations.

Methods and results CENTRAL, Google Scholar, MEDLINE/PubMed, Scopus, and the Cochrane Central Register of clinical trials (updated 15/1/2017) were searched for randomized controlled trials investigating the effect of intermittent levosimendan administration in patients with AdHF. The primary outcome was the number of patients requiring rehospitalization 3 months after the end of treatment. A total of 319 patients from six trials were included. Overall pooled analysis showed that the use of levosimendan was associated with a significant reduction in the number of rehospitalizations at 3 months: 33/207 (16%) vs. 39/113 (35%), risk ratio 0.40, 95% confidence interval 0.27–0.59, $P < 0.001$, $I^2 = 0\%$. This result was confirmed by sensitivity analyses.

Conclusions Within the limitations of this meta-analysis including also studies in which endpoints were not independently adjudicated and not clearly specified, repetitive or intermittent administration of levosimendan for patients with AdHF was associated with a reduction in the rehospitalization rate at 3 months. Large, high-quality randomized controlled trials are needed to confirm this finding.

Keywords Advanced heart failure; Intermittent; Repetitive; Levosimendan; Meta-analysis; Rehospitalization

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Introduction

Use of the calcium-sensitizer and inodilator levosimendan in intermittent cycles has been shown to benefit patients with advanced heart failure (AdHF). The largest single trial of this intervention so far completed is the Levo-REP trial,¹ in which administration of four cycles of levosimendan therapy (0.2 µg/kg/min for 6 h) at 2-week intervals substantially improved event-free survival, defined as freedom from death from all causes, heart transplantation/implantation of a ventricular assist device, or acute heart failure. Previous studies with intermittent levosimendan in a range of patient populations, including those with AdHF, documented a range of haemodynamic and neuro-hormonal effects considered likely to be beneficial. In several instances, these were accompanied by an indication of

improved survival that was amplified in two separate meta-analyses.^{2,3}

These indications of a survival benefit from intermittent levosimendan in patients with AdHF offer a distinct contrast to experiences with traditional adrenergic inotropes such as dobutamine. Taken in conjunction with the proven utility of levosimendan in patients treated with beta-blockers,⁴ plus its ability to confer positive inotropic, vasodilatory, and cardioprotective effects without significant increases in myocardial oxygen requirements,^{5,6} this identifies levosimendan as a qualitatively distinct addition to the treatment options for late-stage heart failure (HF).

For many patients with AdHF, however, quality of life (QoL) is as much a priority as duration of life. One of the larger negative influences on QoL is the need for repeated hospitalizations to stabilize a condition that is prone to

clinical exacerbations and deterioration despite maximal use of first-line therapies such as diuretics, beta-blockers, and drugs that target the renin–angiotensin system. With this in mind, we undertook, as part of an ongoing evaluation of intermittent levosimendan therapy, an analysis of the impact of this intervention on rehospitalization events during a total treatment period of 3 months.

Methods

Search strategy

Pertinent studies were independently searched for in CENTRAL, Google Scholar, MEDLINE/PubMed, Scopus, and the Cochrane Central Register of clinical trials (updated 15/1/2017) by two of the authors. Our search strategy aimed to include any randomized controlled trials (RCTs) ever performed in which levosimendan was intermittently administered in patients with AdHF. In addition, we contacted international experts and employed backward snowballing (i.e. scanning of references from the retrieved articles and other pertinent reviews) to obtain further studies. The full PubMed search strategy⁷ is available in the Supporting Information. No language restriction was enforced.

Study selection

References obtained from database and literature searches were first independently examined at a title/abstract level by the two authors, with divergences being resolved by consensus. Then, if potentially pertinent, they were retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment; comparison of levosimendan vs. any control; studies performed in AdHF patients; use of intravenous repetitive administration; and no restrictions on dose or time of administration. The exclusion criteria were as follows: duplicate publications either acknowledged or not (in this case we referred to the article with the longest follow-up period available); non-RCT; non-adult studies; and oral administration of levosimendan. Two investigators independently assessed compliance with selection criteria and selected studies for the final analysis, with divergences being resolved by consensus.

Data abstraction and study

Baseline and outcome data were independently abstracted by the two authors, with divergences being resolved by consensus. Specifically, we extracted potential sources of

significant clinical heterogeneity, such as study design, sample size, clinical setting/indication, bolus and infusion doses of levosimendan, and duration of treatment, control treatment, and follow-up duration, as well as rehospitalization data. At least two separate attempts to contact the original authors were made in cases of missing data. The primary endpoint of our meta-analysis was the number of rehospitalizations 3 months after the end of treatment.

Internal validity and risk of bias assessment

The internal validity of and risk of bias in the included trials was appraised by two independent investigators according to the latest version of the 'Risk of bias assessment tool' developed by The Cochrane Collaboration,⁸ with divergences being resolved by consensus. Visual inspection of a funnel plot was performed to assess the presence of publication bias.

Data analysis and synthesis

Dichotomous data were extrapolated to compute the individual and pooled risk ratio (RR) with pertinent 95% confidence interval (CI) using the Mantel–Haenszel method. For continuous outcomes, the mean difference (MD) was computed using the inverse variance method. We used a fixed-effects model in cases of low statistical inconsistency ($I^2 \leq 25\%$) and a random-effects model (which better accommodates clinical and statistical variations) in cases of high statistical inconsistency ($I^2 > 25\%$). Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. The hypothesis of statistical heterogeneity was tested by means of the Cochran Q test, with statistical significance set at the two-tailed 0.10 level, whereas the extent of statistical consistency was measured with I^2 , defined as $100\% \times (Q - df)/Q$, where ' Q ' is Cochran's heterogeneity statistic and ' df ' is the degrees of freedom. In addition to the principal analysis in which all the studies that fulfilled the inclusion criteria were considered, we performed secondary analyses to assess the effect of different control treatment and levosimendan infusion schemes on the primary outcome. The effect of intermittent levosimendan administration on left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) class was also assessed. Sensitivity analyses were performed by sequentially removing each study and reanalysing the remaining dataset (performing a new analysis after removal of each study) and by changing the summary statistics (from RR to odds ratio and risk difference) and analysis method (from Mantel–Haenszel to inverse variance and Peto). Unadjusted P -values are reported throughout. All data were

analysed according to the intention-to-treat principle whenever possible. Data were analysed using Review Manager version 5.3 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

This study was performed in compliance with appendix S1 of The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^{9–12}

Results

Study characteristics

Our search strategy yielded a total of 362 articles. After exclusion of 344 non-pertinent titles or abstracts, 18 papers were retrieved in complete form and assessed according to the selection criteria (*Figure 1*). Of these, a total of 12 papers were excluded because of non-compliance with the pre-specified selection criteria, leaving six studies^{13–18} for the final analysis. A complete list of the excluded studies, together with the reasons for exclusion, is provided in *Table S1*.

The six included studies randomized a total of 319 enrolled patients: 207 to levosimendan and 113 to control (*Table 1*).

Different comparators were used: placebo in three studies,^{14,17,18} standard treatment in one study,¹³ dobutamine in one study,¹⁵ and furosemide in one study.¹⁶ Three studies were multicentre.^{14–16}

Data on 3-month rehospitalization rates were available for three studies. We obtained further data from the authors in three cases.^{13,14,16} Quality appraisal of the studies indicated that three of them were judged to have an unclear risk of bias^{14,17,18} and three to have a high risk of bias^{13,15,16} (*Table S2*).

Patient characteristics and levosimendan regimen

The cardiac conditions of the enrolled patients are reported in *Table 2*, and some available not cardiologic variables are reported in *Table S3*. Most of the trials enrolled chronic heart failure (CHF) patients with a severely depressed LVEF, NYHA class III or IV, and who were experiencing frequent decompensation.

The dose regimen and schedule for levosimendan administration varied between studies and are detailed in *Table 1*. A loading dose of 6 or 12 µg/kg was administered in two trials, while a continuous infusion (dose range 0.1–0.4 µg/kg/min) was administered in all trials. The infusion

Figure 1 Flow diagram for selection of articles.

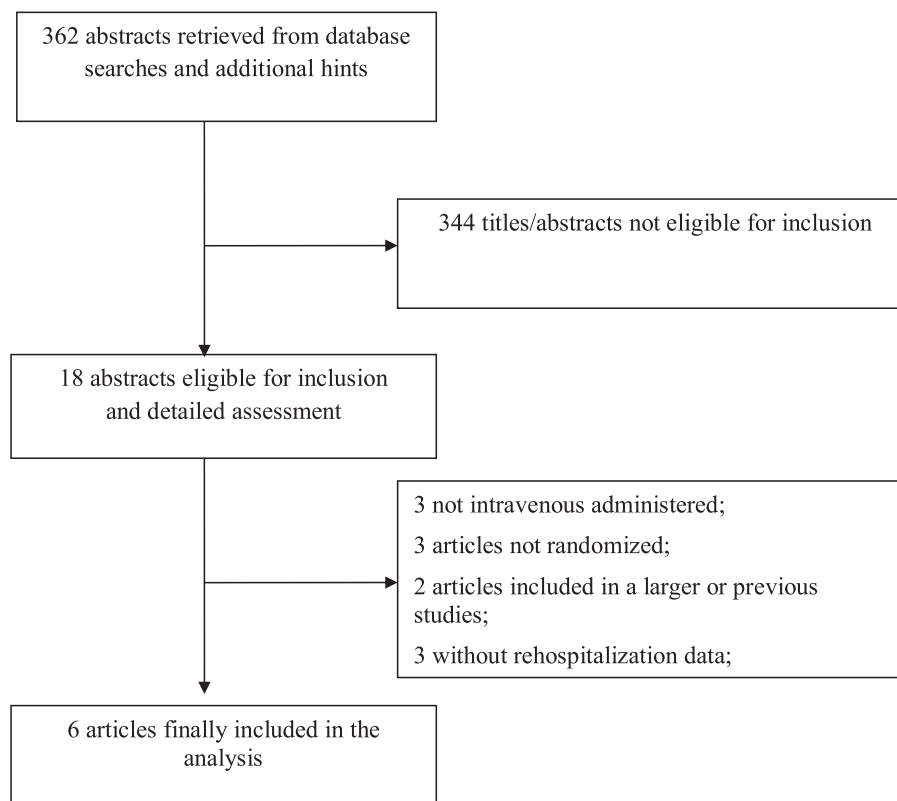


Table 1 Characteristics of the studies

Reference	Year	Multicentre?	Control	No. of patients		Loading dose?	Continuous infusion dose ($\mu\text{g}/\text{kg}/\text{min}$)	Duration of administration (h)	Dosing interval
				Treatment group	Control group				
Mavrogeni et al. ¹³	2007	No	Best available treatment	30	30	6 $\mu\text{g}/\text{kg}$	0.1–0.2	24	Every month
Kleber et al. ¹⁴	2009	Yes	Placebo	18	9	12 $\mu\text{g}/\text{kg}$ over 10 min	0.1 for 50 min followed by 0.2 for 23 h	24 (first infusion); 6 (subsequent infusions)	Every 2 weeks
Bonios et al. ¹⁵	2012	No	Dobutamine	19	15	No	Levosimendan: 0.3; dobutamine: 10	6	Every week
Malfatto et al. ¹⁶	2012	No	Furosemide	22	11	No	0.1–0.4	24	Every month
Comin-Colet et al. ¹⁷	2015	Yes	Placebo	48	21	No	0.2	6	Every 2 weeks
García-González et al. ¹⁸	2016	Yes	Placebo	70	27	No	0.1	24	Every 30 days

Table 2 Cardiac conditions of the enrolled patients

Reference	Year	Setting	LVEF (%)	NYHA class	Proportion of patients with HF of ischaemic aetiology (%)
Mavrogeni et al. ¹³	2007	CHF (LVEF <30%)	22 \pm 6 (levosimendan group); 22 \pm 5 (control group)	III–IV	50
Kleber et al. ¹⁴	2009	Pulmonary hypertension with signs of right HF in the previous 6 months	Not reported	III–IV	Not available
Bonios et al. ¹⁵	2012	Chronic systolic HF with recent decompensation	23 \pm 7 (levosimendan group); 21 \pm 5 (control group)	IV	50
Malfatto et al. ¹⁶	2012	CHF (LVEF <35%) requiring at least two hospitalizations in the previous 6 months	26 \pm 5 (levosimendan group); 28 \pm 8 (control group)	3 \pm 0.4 (levosimendan group); 3 \pm 0.4 (control group)	72
Comin-Colet et al. ¹⁷	2015	CHF (LVEF <35%) with decompensation in the previous 12 months	25 \pm 7 (levosimendan group); 25 \pm 6 (control group)	III–IV	61
García-González et al. ¹⁸	2016	CHF with decompensation in the previous 6 months	25 \pm 8 (levosimendan group); 26 \pm 10 (control group)	III–IV	Not available

CHF, chronic heart failure; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

was continued for 6 h in two trials and for 24 h in three trials. In one trial, levosimendan was initially infused for 24 h and for 6 h in the subsequent administrations. The time lag between infusions varied from 1 week (one trial) to 2 weeks (two trials) and 1 month (three trials). Infusions were repeated for at least 2 months and for up to 12 months.

Quantitative data synthesis

The overall pooled analysis showed that the use of levosimendan was associated with a significant reduction in the number of rehospitalizations at 3 months: 33/207 (16%) vs. 39/113 (35%), RR 0.40, 95% CI 0.27–0.59, $P < 0.001$, $I^2 = 0\%$ (Table 3, Figure 2). These results were confirmed when analysing the only three multicentre studies^{14,17,18} in which placebo was used as comparator [25/136 (18%) vs. 27/57 (47%), RR = 0.40, 95% CI = 0.26 to 0.62, $P < 0.001$, $I^2 = 0\%$ (Table 3, Figure 2).

In addition, the results were confirmed when analysing only studies in which levosimendan was administered every 2 weeks or less, every month, for less than 6 months, or for at least 6 months.

Statistical significance was lost when analysing studies in which a loading dose was administered but was evident when analysis was restricted to studies in which only continuous infusion was administered (Table 3).

Removing each trial and reanalysing the remaining dataset, and changing the analysis method or summary

statistics did not change either the significance or magnitude of the results (Table 3).

Visual inspection of the funnel plot did not suggest the presence of publication bias (Figure S1).

LVEF was significantly different between the two groups after treatment with levosimendan (MD 3.87, 95% CI 0.15–7.60, $P = 0.04$, $I^2 = 62\%$; three studies included; Figure S2), but no significant difference in NYHA class was observed (MD –0.30, 95% CI –1.03 to 0.42, $P = 0.41$, $I^2 = 80\%$; two studies included; Figure S3).

Discussion

The intermittent use of levosimendan infusions as a bridge to heart transplantation/implantation of a ventricular assist device, as well as its use as a destination therapy in palliative care for advanced/end-stage HF patients, has increased in importance over the years since the first attempts to evaluate the efficacy of such therapy for improving the outcome and QoL of patients. Among other properties of levosimendan, the persistence of its haemodynamic effects for ≈ 2 weeks is obtained in particular with the active metabolite OR-1896,¹⁹ which is mainly responsible for the efficacy of the intermittent repetitive infusion scheme of treatment.²

The papers regarding the repetitive intermittent administration of levosimendan selected for this

Table 3 Secondary and sensitivity analyses

Analysis	No. of trials included	No. of events		RR	95% CI	P for effect	P for heterogeneity	I^2 (%)
		Levosimendan group	Control group					
Overall	6	33/207	39/113	0.40	0.27–0.59	<0.001	0.79	0
Placebo-controlled trials	3	25/136	27/57	0.40	0.26–0.62	<0.001	0.62	0
Multicentre trials	3	25/136	27/57	0.40	0.26–0.62	<0.001	0.62	0
Lapse ≤ 2 weeks	3	17/85	21/45	0.39	0.23–0.65	<0.001	0.58	0
Lapse > 2 weeks	3	16/122	18/68	0.42	0.23–0.74	0.003	0.55	0
Study period < 6 months	3	23/88	24/41	0.45	0.29–0.69	<0.001	0.46	0
Study period ≥ 6 months	3	10/119	15/72	0.32	0.15–0.68	0.003	0.77	0
Loading dose used	2	5/48	7/39	0.43	0.16–1.19	0.10	0.31	2
Loading dose not used	4	28/159	32/74	0.39	0.26–0.59	<0.001	0.75	0
Excluding studies providing data via personal communication	3	21/137	26/63	0.35	0.22–0.57	<0.001	0.94	0
Analysis using inverse variance	6	33/207	39/113	0.42	0.29–0.61	<0.001	0.80	0
Analysis using Peto	6	33/207	39/113	0.24 ^a	0.14–0.44 ^a	<0.001	0.83	0
Analysis using OR	6	33/207	39/113	0.25 ^b	0.14–0.46 ^b	<0.001	0.85	0
Analysis using RD	6	33/207	39/113	–0.20 ^c	–0.31 to –0.08 ^c	<0.001	0.17	36 ^d
Analysis removing each trial and reanalysing the dataset	$P < 0.001$, 95% CI < 1 , and $I^2 = 0\%$ for all							

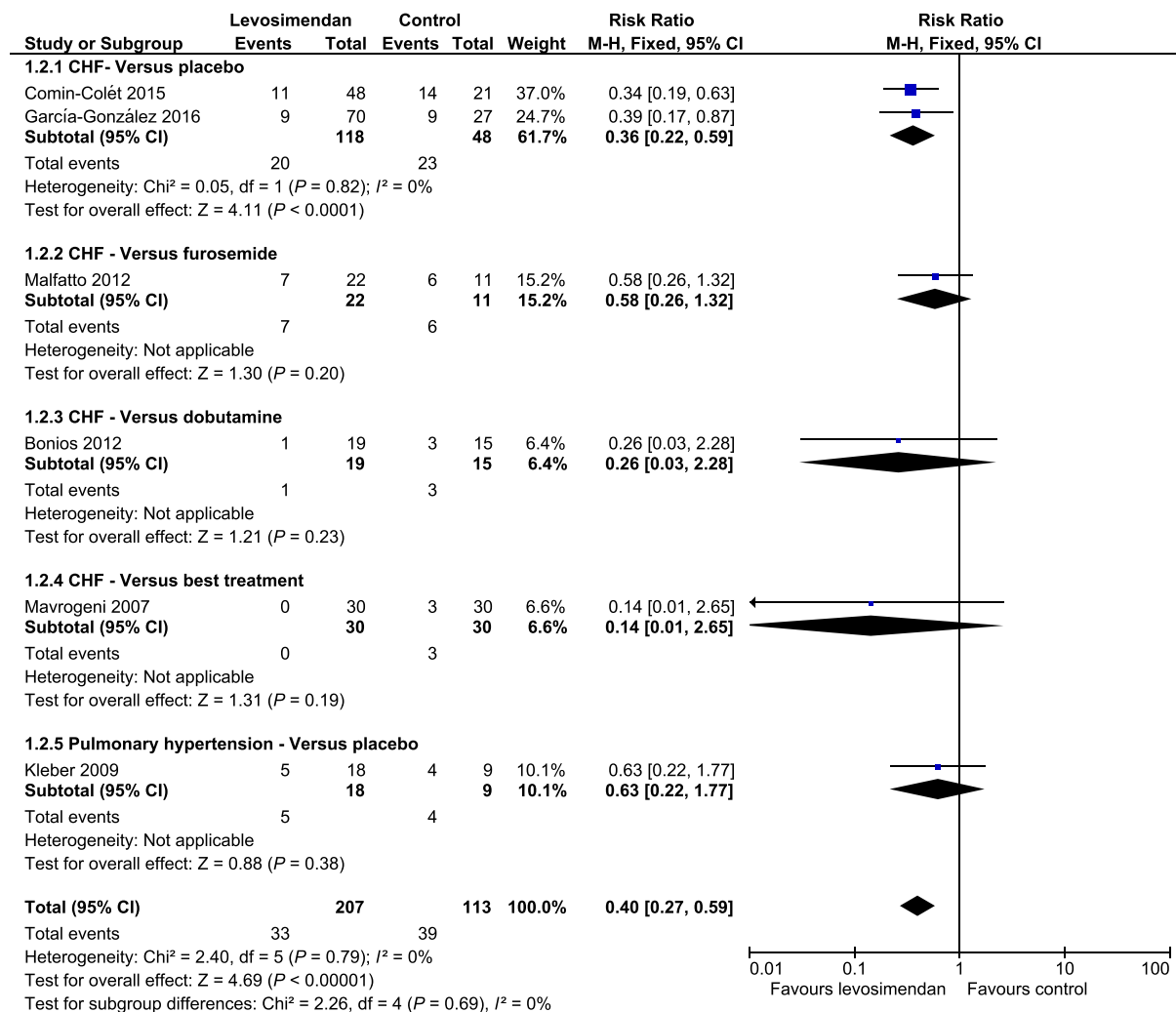
CI, confidence interval; OR, odds ratio; RD, risk difference; RR, risk ratio.

^aPeto OR and 95% CI for Peto OR are shown.

^bOR and 95% CI for OR are shown.

^cRD and 95% CI for RD are shown.

^dData analysed with random-effects model.

Figure 2 Forest plot. CI, confidence interval; CHF, chronic heart failure; M-H, Mantel–Haenszel.

meta-analysis exhibited a heterogeneous methodology and variable results. In particular, there were significant differences between study designs, levosimendan comparators, levosimendan dosages, the duration of the infusions, and the frequency of repetitive treatment, not to mention endpoints were independently adjudicated and not clearly specified in several cases. This notwithstanding, all of the studies showed some beneficial effects of levosimendan in these clinical settings.

Mavrogeni *et al.*¹³ assessed the effects of monthly levosimendan infusions on LVEF, end-diastolic and end-systolic volumes, and diameters. In addition to the good echocardiographic results obtained, the authors also demonstrated an improvement in symptoms and a reduction in mortality.

Echocardiographic indices and QoL were also the outcomes of the study by Malfatto *et al.*¹⁶: compared with furosemide, they obtained significant reductions in NYHA

class, ventricular volumes, and N terminal pro brain natriuretic peptide (NT-proBNP) levels, and an increase in LVEF, with monthly levosimendan infusions. One-year mortality did not reach statistical significance, although a positive trend towards a reduction with levosimendan was noted.

The study by Kleber *et al.*¹⁴ evaluated both the short-term and long-term (8 weeks) effects of levosimendan on pulmonary vascular resistance and other haemodynamic parameters in patients with various forms of pulmonary hypertension. The decrease in pulmonary vascular resistance observed differed significantly between the levosimendan and placebo groups (*P* = 0.009), with the best results obtained 6 h after the start of the infusion. The authors also reported that repeated infusions maintained the clinical effects without the development of tolerance to the drug and concluded that shorter dosing intervals might render even better results.

Bonios *et al.*¹⁵ randomized 63 patients to levosimendan, dobutamine, or the combination of both. The investigators found a significant benefit on event-free survival with levosimendan, with 6-month mortality lowered to 19%, as opposed to 38% with dobutamine ($P = 0.037$ vs. levosimendan) and 48% in the combination group ($P = 0.009$ vs. levosimendan).

Two new studies in this clinical setting were presented during the 2015 and 2016 European Society of Cardiology–Heart Failure Association Congresses.

The first is the LION-Heart study,¹⁷ a multicentre, randomized, double-blind, parallel group, placebo-controlled trial. It aimed to evaluate the efficacy and safety of intermittent 6-h administrations of levosimendan every 2 weeks in 69 outpatients with CHF. The primary endpoint of the study was changes in NT-proBNP levels assessed bi-weekly, and the results were significantly in favour of levosimendan ($P < 0.005$). This is consistent with the results of levosimendan trials in acute HF,^{4,19} and has not been reported with any other inodilator.

The LAICA study^{18,20} aimed to test the effects of monthly 24-h infusions of levosimendan on the incidence of in-hospital admissions for acute decompensated HF in 97 patients in the advanced stages of the disease. This was a multicentre, prospective, randomized, double-blind, placebo-controlled, parallel-group trial, with several additional secondary endpoints. Although statistical significance for the primary endpoint was missed, fewer admissions for acute decompensated HF, as well as lower mortality rates, were recorded among the levosimendan-treated patients.

Within the limitations of this meta-analysis on rehospitalization including few studies, in which endpoints were not clearly specified, at least three reasons exist to support the repetitive levosimendan treatment of AdHF patients, at least three reasons exist to support this repetitive treatment in selected patients. Firstly, it has been demonstrated that repeated levosimendan administrations improve the haemodynamic stability of patients; secondly, this treatment improves symptoms; and thirdly, it reduces episodes of acute decompensation.

We noticed that in the studies in which a loading dose of levosimendan was administered,^{13,14} the statistical significance in the advantages of levosimendan vs. comparators is lost. This observation matches well with the analysis by Landoni *et al.*²¹ Indeed, in that previous meta-analysis of 45 randomized levosimendan clinical trials in all settings, a trend towards a lesser reduction in mortality in the bolus subset ($P = 0.2$) was observed. One may speculate that the pronounced haemodynamic effects/adverse effects (i.e. reduction of blood pressure) induced by a loading dose of levosimendan in hypotense or hypovolemic patients could be the cause of the observed reduction of benefits.

Rehospitalizations and quality of life

Advanced heart failure is characterized by potentially and partially reversible symptoms and cardiac dysfunction,² together with frequent episodes of acute decompensation requiring prolonged hospitalization,²² and thus, a severely compromised QoL. Each exacerbation of the condition is characterized by worsening of symptoms, greater limitation of functional capacity, and deterioration of QoL.²³ Moreover, the repeated hospitalizations also contribute to a further decrease in cardiac function in a circular fashion towards progressive decline of the patient's clinical condition, which ends with death.²⁴

Rehospitalization is an important marker of the QoL of AdHF patients, although it is rarely evaluated when QoL is measured. Registries and administrative data have shown that early HF-related readmission after discharge from hospital is associated with worse long-term outcomes and a decline in QoL, with ≈25% of preventable readmission cases happening within 1 month of the initial phase.^{25,26} For this reason, the possibility of including rehospitalization in future HF studies as a composite endpoint, along with death and other indices of clinical stability (such as NT-proBNP), has evoked some interest. Recently, such an attempt was made by Margulies *et al.*²⁷ In their study, the primary endpoint was a global rank score that assigned a numerical value to each patient on the basis of their clinical condition, considering clinical events first (death and/or acute decompensation) and changes in NT-proBNP levels thereafter. This endpoint was then analysed in hierarchical categories, with the first being time to death, the second time to HF hospitalization, and the third time-averaged proportional change in NT-proBNP.

A surrogate to measure QoL can be the assessment of functional capacity by NYHA classes, although QoL encompasses much more than functional capacity alone. Indeed, it is commonly perceived that in the advanced NYHA classes III or IV, QoL is very low. As it regards the effects of levosimendan on QoL, a recent review²² listed and discussed encouraging data present in the literature. In parallel, some recent papers show promising effects by levosimendan on NYHA in acute heart failure patients.²⁸ We hypothesize that the lack of improvement of NYHA class with the repetitive treatment with levosimendan observed in some of the studies utilized for the present meta-analysis may be due to the subjectivity of assessing such parameter, as compared with the more objective improvements in ejection fraction (EF) and NT-proBNP.

Limitations

This study has several limitations. First of all, the relatively small number of studies and patients included in the

meta-analysis and the heterogeneous population involved should be taken into consideration when interpreting the results. This is a common and intrinsic limitation of meta-analyses.⁹ Data on rehospitalizations were available in the original publications only for three trials, while data from the remaining three were provided by trials' authors. However, a sensitivity analysis including only studies with published data confirmed magnitude and directions of results. A further limitation is the heterogeneous selection of comparators in the six studies. A clear definition of a strategy for readmission in the individual studies was lacking, and in several cases, there was an uncertain adjudication of reason for readmissions. A time-dependent analysis for readmission was lacking in the majority of included trials. Moreover, the heterogeneous dosing and interval of administration of levosimendan can also be seen as a severe limitation. Last but not least, the assessment of the patients was non-blinded in some studies: both Bonios *et al.*¹⁵ and Malfatto *et al.*¹⁶ adopted randomized assignment but open-label protocols, while Mavrogeni *et al.*¹³ run an open labeled study. The remaining three studies by Comin-Colet *et al.*,¹⁷ Garcia-Gonzalez *et al.*,¹⁸ and Kleber *et al.*¹⁴ (accounting for 72% of the weight in this meta-analysis) were double-blind trials. However, because the performance of a meta-analysis is meant to shed light on the overall safety and efficacy of a drug and to help in powering future clinical trials, we consider our results useful as providing a strong rationale for a properly powered study on the effect of levosimendan on rehospitalization.

Future steps

In the light of our results, and taking into due account all the limitations of our study, it appears that a repeated administration of levosimendan to patients with AdHF brings advantages as less frequent rehospitalization. The present meta-analysis is based on data from clinical trials where levosimendan was compared with other treatments mainly on top of standard of care (e.g. diuretics). Often the rationale of those studies was the hypothesis that levosimendan would bring additional advantages as sustained improvements of haemodynamics and symptoms due to its prolonged pharmacokinetics. Still open is the question if levosimendan would be more beneficial in patients with HF with reduced EF or HF with preserved EF, and future studies should tackle also this aspect. Certainly, our analysis supports the use of rehospitalization as one of the endpoints.

The fact that recent studies of new drugs developed as treatments of acute and AdHF failed to show benefits (see the fate of intravenous omecamtiv mecarbil,²⁹ ularitide,³⁰ serelaxin,³¹ and liraglutide²⁸) brings this field in focus again. In fact, despite effective new drugs contributing to prolong the life of CHF patients, the rate of hospitalization for acute

events is not decreasing at all in the developed countries,^{32,33} making AdHF an even greater burden. A properly powered clinical trial on repetitive levosimendan use in these patients is thus strongly advocated.

Conclusions

This meta-analysis supports the hypothesis that repetitive or intermittent administration of levosimendan for patients with AdHF is associated with a reduction in rehospitalization rate at 3 months. There is therefore a strong rationale for an RCT with levosimendan in these settings to be designed and carried out that has adequate power to investigate patient rehospitalization within its endpoints.

Conflict of interest

A.F. and P.P. are employed by the company that discovered and developed levosimendan. None of the other authors have any conflict of interest.

Author contributions

A.B. and S.S. independently performed the preliminary searches for the relevant publications. P.P. and A.F. contributed substantially to the discussions of the existing literature and to the final text. All authors reviewed the manuscript before submission.

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None.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. List of the 12 excluded studies, together with reason for exclusion.

Table S2. Assessment of the risk of bias of included studies.

Table S3. Analysis of the serum electrolytes.

Figure S1. Funnel Plot.

Figure S2. Forest plot for LVEF after study drug administration.

Figure S3. Forest plot for NYHA after study drug administration.

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