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Repeated or intermittent levosimendan treatment in advanced heart failure: An updated meta-analysis

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ABSTRACT

Introduction: Advanced heart failure is a malignant disease characterized by a debilitating late course, with increasingly frequent hospitalisations and high rate of mortality.
Levosimendan, an inodilator developed for the treatment of acutely decompensated chronic heart failure, has been recently proposed also as a repetitive treatment of advanced heart failure.
Several studies on the use of levosimendan in this settings report mortality data. Independent meta-analyses on the effect on mortality of repetitive or intermittent levosimendan administration in advanced heart failure has been published but were criticized in regard to the selection of the studies. Meanwhile new data became available. We therefore updated the selection of studies and re-analyzed all the available data.
Methods & results: Data from seven randomized trial and a total of 438 adult patients using intermittent levosimendan in a cardiological setting were included in the present analysis. The average follow-up period was 8 ± 3.8 months. The use of levosimendan was associated with a significant reduction in mortality at the longest follow-up available [41 of 257 (16%) in the levosimendan group vs. 39 of 181 (21.5%) in the control arm, OR = 0.54 (95% CI 0.32–0.91), p for effect = 0.02, p for heterogeneity = 0.64, I2 = 0%].
Conclusions: The updated results suggest that repetitive or intermittent levosimendan administration in advanced heart failure is associated with a significant reduction in mortality at the longest follow-up available. There is therefore a strong rationale for a randomized clinical trial with adequate power on mortality.
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1. Introduction

Advanced heart failure (AdHF) is one of the presentations of the complex syndrome of heart failure [1]. Usually it represents a late stage of heart failure characterized by high morbidity and mortality, hemodynamical and neurohormonal derangement and frequent hospitalizations. Patients with AdHF often need some sort of inotropic support [2]. Evidence is lacking, however, on the long term prognosis of such therapies [3]. It was recently proposed that levosimendan, an inodilator with a unique mechanism of action [4], could offer to AdHF patients both a hemodynamic improvement and a long term benefit [5]. Levosimendan has been used in several settings [6] from the beginning of the 2000, and has been described in literature as belonging to a new category of cardiotonic agents [7].

In 2014, two independent meta-analyses were published on the effect on mortality of repetitive or intermittent doses of levosimendan in advanced heart failure [5,8]. Both analyses arrived to the same conclusions despite the fact that the lists of included studies were different. Those papers were commented in an editorial by De Luca [9] in which a criticism was made regarding the studies included in the analyses. According to De Luca, in fact, Nieminen and coworkers should not have included the data by Nanas et al. [10] because that study was not randomized; while Silvetti and coworkers should not have included the data by Levin et al. [11] because that work has not been published as a full paper several years after the data collection.

These criticisms left open the question if a treatment with repeated or intermittent levosimendan doses is or not safe and effective for patients with advanced heart failure (AdHF). The need for further evidence was advocated for changing clinical practice.

Recently Comín Colet and coworkers disclosed the data of the LION-HEART study (Levosimendan Intermittent administration in Outpatients: effects on Natriuretic peptides in advanced chronic HEART failure — NCT01536132), a multicenter, double-blind, randomized, parallel group, placebo-controlled trial evaluating the efficacy and safety of intravenous administration of intermittent doses of levosimendan in outpatients with advanced chronic heart failure [12]. In this study 69 patients were randomized in a 2:1 ratio to receive either levosimendan or placebo and, among other parameters, also the effects on mortality were reported.

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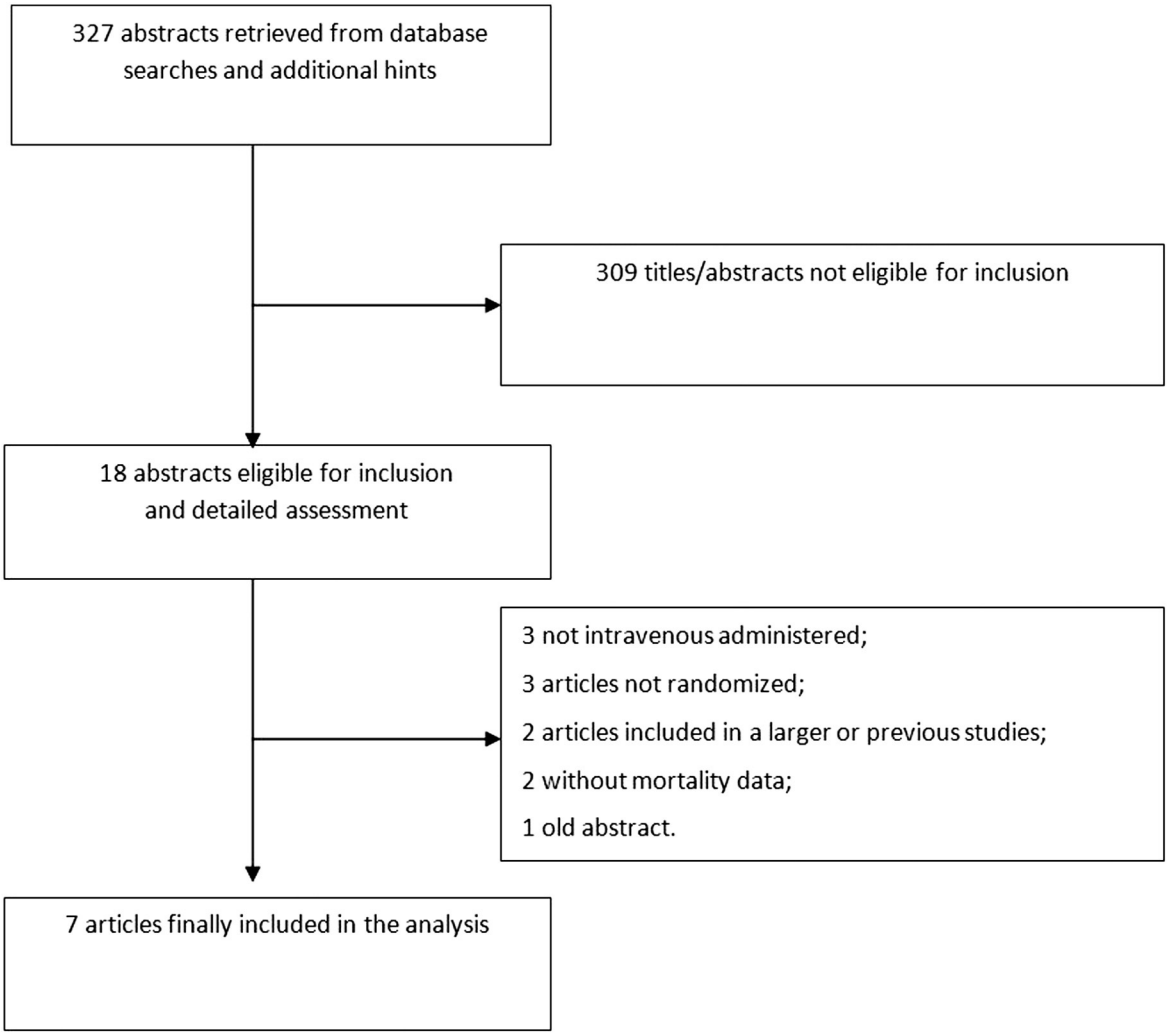


Fig. 1. Flow diagram for selection of articles.

We thus decided to re-analyze all the available data on the effects of repeated or intermittent levosimendan treatment in advanced heart failure, and update the meta-analysis on mortality by leaving our the data previously criticized in the editorial by de Luca [9] and adding recently published data.

2. Methods

2.1. Search strategy

Pertinent studies were independently searched in CENTRAL, Google Scholar MEDLINE/PubMed, Scopus and the Cochrane Central Register of clinical trials (updated May 30th, 2015) by the two authors. In addition, we employed backward snowballing (i.e., scanning of references of retrieved articles and pertinent reviews) and contacted international experts and the manufacturer for further studies. No language restriction was enforced.

The full PubMed search strategy [13], aimed to include any randomized study ever performed with intermittent levosimendan intravenous administration in patients with chronic heart failure, was: ((levosimendan OR simdax) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR crossover studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt]))

2.2. Studies' selection

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

2.3. Data abstraction

Baseline and outcome data were independently abstracted by the two authors, with divergences resolved by consensus. Specifically, we extracted potential sources of significant clinical heterogeneity, such as study design, sample size, clinical setting/indication, levosimendan bolus dose, infusion dose and duration, control treatment, and follow-up duration, as well as mortality data. If a trial reported multiple comparisons, the control group was considered as a whole in the overall analysis and single groups were considered separately in subset analysis. At least two separate attempts to contact original authors were made in cases of missing data. The primary endpoint of the present review was mortality at the longest follow-up available.

2.4. Internal validity and assessment of risk of bias

The internal validity and risk of bias of included trials was appraised according to Cochrane Collaboration methods [14], with divergences resolved by consensus.

Table 1
Description of characteristics of the studies, including setting, control treatment, loading and continuous infusion dose of the patients receiving levosimendan.

First author	Year	Setting	Control	N[a]	Loading dose	Continuous infusion	Length of administration	Lapse	End of administration	Longest follow-up
Altenberger J [33]	2014	Chronic heart failure	Placebo	63 vs. 57	No	0.2 μg/kg/min	6 h	Every 2 weeks	2 months	6 months
Berger R [29]	2007	Chronic heart failure	PGE1[a]	39 vs. 36	12 μg/kg in 10 min	0.1 μg/kg/min	24 h	Every month	3 months	1 year
Bonios MJ [30]	2012	Chronic heart failure	Levo-simendan + dobutamine OR dobutamine	42 vs. 21	No	Levosimendan group: 0.3 μg/kg/min Levosimendan + dobutamine group: 0.2 μg/kg/min and 10 μg/kg/min	6 h	Weekly	6 months	6 months
Comin-Colét [12]	2015	Chronic heart failure	Best of care	48 vs. 21	No	0.2 μg/kg/min	6 h	Every 2 weeks		1 year
Kleber FX [28]	2009	Pulmonary hypertension	Placebo	18 vs. 10	12 μg/kg in 10 min	0.1 μg/kg/min for 50 min followed by 0.2 μg/kg/min for 23 h	First infusion 24 h, following infusions 6 h	Every 2 weeks	2 months	12 weeks
Malfatto G [31]	2012	Chronic heart failure	Furosemide	22 vs. 11	No	0.1–0.4 μg/kg/min	24 h	Every month	4 months	1 year
Mavrogeni S [32]	2007	Chronic heart failure	Best available treatment	25 vs. 25	6 μg/kg	0.1–0.2 μg/kg/min	24 h	Every month	6 months	6 months

[a] N, number of patients; PGE1, prostaglandin E1.

Publication bias was assessed by visually inspecting funnel plots and by analytical appraisal based on the Begg adjusted-rank correlation test [15] and Egger's linear regression test [16]. According to the Begg or Egger methods for publication bias evaluation, a two-sided p value of 0.10 or less was regarded as significant. Sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining dataset (producing a new analysis for each study removed) and by analyzing data from studies with moderate and low risk of bias.

2.5. Data analysis and synthesis

Computations were performed with Stata (Stata Statistical Software: Release 11, College Station, TX). Hypothesis of statistical heterogeneity was tested by means of Cochran Q test, with statistical significance set at the two-tailed 0.10 level, whereas extent of statistical consistency was measured with I^2, defined as 100% (Q − df) / Q, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Binary outcomes from individual studies were analyzed to compute individual and pooled risk ratio with pertinent 95% confidence intervals, by means of inverse variance method and with a fixed-effect model in the case of low statistical inconsistency ($I^2 < 25\%$) or by means of Dersimonian–Laird and with random-effect model (which better accommodates clinical and statistical variations) in the case of moderate or high statistical inconsistency ($I^2 > 25\%$). In addition, we computed the number needed to treat. Statistical significance was set at the two tailed 0.05 level for hypothesis testing. Unadjusted p values are reported throughout. This study was performed in compliance with The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [17,18].

3. Results

Database searches, snowballing, and contacts with experts yielded a total of 327 titles (Fig. 1). Excluding 309 nonpertinent titles or abstracts, we retrieved in a complete form and assessed 18 studies according to the selection criteria. Specifically, three studies were excluded because levosimendan was not administered intravenously [19–21], three studies because they were not randomized [10,22,23], two studies because data were included in a larger or previous publication [24,25], two because lacking mortality data [26,27] and one because abstract without subsequent publication [11]. Ultimately, therefore, we identified seven eligible randomized clinical trials for inclusion in the analysis [12, 28–33].

3.1. Studies' characteristics

The seven included trials randomized 438 patients (257 to levosimendan and 181 to control) and are reported in Table 1. All studies used intermittent levosimendan in patients with advanced chronic heart failure and one [28] in chronic heart failure due to pulmonary hypertension, all in a cardiological setting. The mean length of follow-up was 8 ± 3.8 months. Clinical heterogeneity was mostly due to control treatment and studied drug infusion as dosage, length of infusion, interval and end of administration. Four studies [12,30,31,33] used a continuous infusion without the bolus dose. The length of infusion ranged between 6 and 24 h. The interval of administration was weekly for one study, every 2 weeks for three studies and every month for three studies. Dose varied between 6 and 12 μg/kg as intravenous bolus and between 0.1 and 0.4 μg/kg/min as a continuous infusion. The total range of administration was between 2 and 6 months. Two of the studies were multicentered [12,33]. Study quality appraisal indicated that the studies were of variable quality (Table 2) and that five of them had a moderate risk of bias while two had a low risk of bias.

3.2. Patients' characteristics

All 438 enrolled patients (257 to levosimendan and 181 to control) had an ejection fraction less than 35% and a NYHA class III or IV at randomization.

3.3. Quantitative data synthesis

Forest plot (Fig. 2) shows that the use of levosimendan was associated with a significant reduction in mortality at the longest follow-up

Table 2
Methodological quality summary. Review authors' judgments about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment used?	Blinding?	Concurrent therapies similar?	Complete outcome data addressed?	Uniform and explicit outcome definitions?	Free of selective outcome reporting?	Free of other bias?	Overall risk of bias?
Altenberger J [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Berger R [29]	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Moderate
Bonios MJ [30]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	Moderate
Comin-Colét[a] [12]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Moderate
Kleber FX [28]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Moderate
Malfatto G [31]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	Moderate
Mavrogeni S [32]	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Low

[a] Study published recently as abstract only.

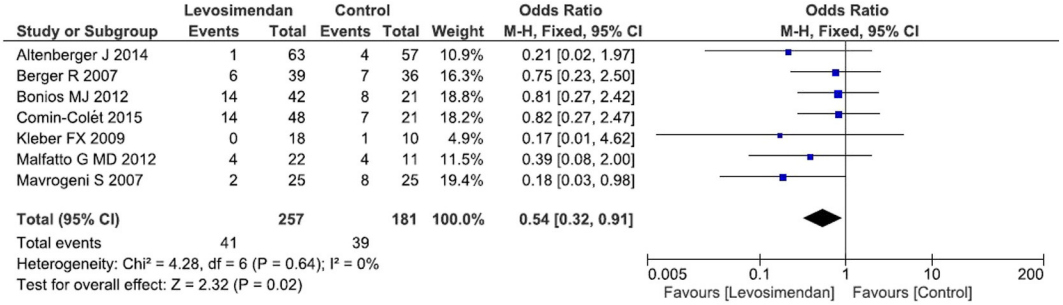


Fig. 2. Forest plot.

available [41 of 257 (16%) in the levosimendan group vs. 39 of 181 (21.5%) in the control arm, OR = 0.54 (95% CI 0.32–0.91), p for effect = 0.02, p for heterogeneity = 0.64, I2 = 0%].

Visual inspection of funnel plot (Fig. 3) identifies a skewed and asymmetrical shape, and quantitative evaluation suggests a presence of publication bias, Egger's test (p = 0.017) or Begg test (p = 0.072).

3.4. Sensitivity analysis

The significant reduction in mortality at the longest follow-up available using levosimendan was confirmed fitting a random effect model [OR = 0.56 (95% CI 0.33–0.96), p for effect = 0.037, p for heterogeneity = 0.6, I2 = 0%].

The sensitivity analysis performed by sequentially removing each study at time and reanalyzing the remaining dataset is shown in Table 3 The significant result is lost only by removing the Mavrogeni's trial (p = 0.1).

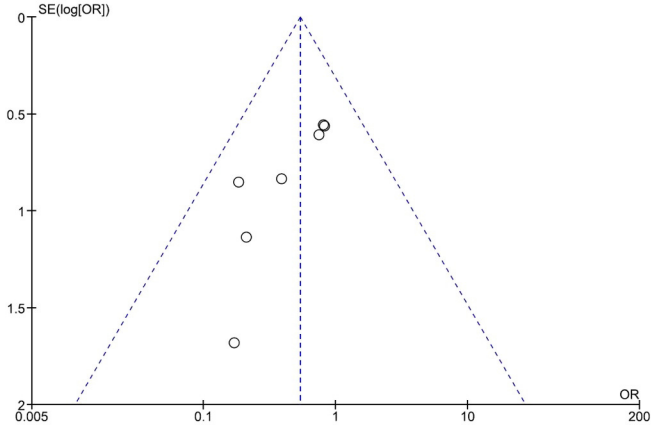


Fig. 3. Funnel plot.

4. Discussion

In AdHF the patient experiences repeated episodes of cardiac decompensation and frequent and prolonged hospitalization, which result in a severely compromised quality of life [34]. Furthermore, society is now undergoing an increased burden of AdHF due to the aging of the population and use of improved life-prolonging treatment options [35]. As well as being associated with substantial morbidity and mortality, the repeated hospitalization of these patients remains the main cause for the associated significant healthcare expenditure [36,37]. Indeed, following each successive admission of a patient for exacerbation of their heart failure, they will then generally leave the hospital with a further decreased cardiac function and a thus a higher probability of more frequent rehospitalisation and death [38].

Studied carried out over the past 15 years have indicated that continuous or intermittent infusion of parenteral dobutamine or milrinone as an inotropic support could provide favorable effects to support the circulation and heart function in the long-term therapy of end-stage heart failure [39–45]. However, there were early reports that continuous or intermittent use of these traditional inotropic drugs might be associated with an increased risk of mortality [46]. Indeed, the use of dobutamine and phosphodiesterase inhibitors was specifically investigated in two focused meta-analyses by Tacon et al. [47] and by Nony et al. [48], respectively, where continuous or intermittent use of these traditional inotropic drugs did not show any patient benefits. Over

Table 3
Sensitivity analysis.

Excluded trial	OR, 95% CI	p value
Altenberger J [33]	0.58 [0.33, 0.99]	0.05
Berger R [29]	0.50 [0.28, 0.89]	0.02
Bonios MJ [30]	0.47 [0.26, 0.87]	0.02
Comin-Colét [12]	0.47 [0.26, 0.87]	0.02
Kleber FX [28]	0.56 [0.33, 0.95]	0.03
Malfatto G [31]	0.56 [0.32, 0.97]	0.04
Mavrogeni S [32]	0.62 [0.35, 1.09]	0.1
All included trials	0.54 [0.32, 0.91]	0.02

the same period, however, the inodilator levosimendan became available for the treatment of acutely decompensated heart failure [4]. Levosimendan was shown to combine positive inotropic, vasodilatory, and cardioprotective effects without any increase in the oxygen consumption of myocardial tissue (for a recent review see [6]). This has also led to several independent reports of meta-analyses on the clinical data for levosimendan with positive indications of the advantages of levosimendan in cardiology settings [49–51]. Very recently, a series of case reports were published [52] in which pulsed levosimendan therapy is described as a viable solution in patients with heart disease, at the stage where all surgical, device and traditional therapeutic options have been exhausted. We cite, for the sake of completeness, a meta-analysis — which we found in literature after our manuscript was finalized — by Yi et al. [53] in which the authors conclude that intermittent or repetitive levosimendan infusion might be a promising strategy to reduce mortality and improve LVEF in patients with advanced chronic, but not necessarily acutely decompensated, heart failure to maintain disease stability. Finally, a recent consensus paper reviewed the beneficial effects of levosimendan on Quality of Life in AdHF patients, and suggested that treatment strategies at this stage should be planned taking into account the 'patient perspective' [34].

The present meta-analysis gives a clear signal (p for effect = 0.02) on the effect of repeated treatment with levosimendan on mortality in patients with AdHF and low EF (≤35%) on an average follow-up period of 8 ± 3.8 months. The heterogeneity of the results in the seven studies is low (p for heterogeneity = 0.6), but a sign of possible bias is shown by the Begg's test of the data (p = 0.072). The latter sign, however, has to be interpreted with caution since our meta-analysis is small, and Begg's test is fairly powerful only for large meta-analyses [15].

5. Conclusion

The present updated meta-analysis supports the hypothesis that repetitive or intermittent levosimendan administration for patients with advanced heart failure is associated with reduction in mortality. There is therefore a strong rationale for a randomized clinical trial to be designed and carried out that has adequate power to investigate patient mortality.

Author contributions

The authors (MSN, SS) independently performed the preliminary searches for the relevant publications, contributed substantially to the discussions of the existing literature and to the text of the recommendations, and reviewed the manuscript before submission.

Conflict of interest

The authors do not have conflict of interest.

Acknowledgments

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References

[1] A.F. Kirkwood Jr., F. Zannad, Clinical definition and epidemiology of advanced heart failure, Am. Heart J. 135 (6 part 2) (1998) S204–S215.
[2] M. Metra, L. Bettari, V. Carubelli, L.D. Cas, Old and new intravenous inotropic agents in the treatment of advanced heart failure, Prog. Cardiovasc. Dis. 54 (2) (2011) 97–106.
[3] M. Metra, L. Bettari, V. Carubelli, S. Bugatti, A. Dei Cas, F. Del Magro, V. Lazzarini, C. Lombardi, Cas L. Dei, Use of inotropic agents in patients with advanced heart failure: lessons from recent trials and hopes for new agents, Drugs 71 (5) (2011) 515–525.
[4] Z. Papp, I. Édes, S. Fruhwald, S.G. De Hert, M. Salmenperä, H. Leppikangas, A. Mebazaa, G. Landoni, E. Grossini, P. Caimmi, A. Morelli, F. Guarracino, R.H. Schwinger, S. Meyer, L. Algotsson, B.G. Wikström, K. Jörgensen, G. Filippatos, J.T. Parissis, M.J. González, A. Parkhomenko, M.B. Yilmaz, M. Kivikko, P. Pollesello, F. Follath, Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan, Int. J. Cardiol. 159 (2) (2012 Aug 23) 82–87.
[5] M.S. Nieminen, J. Altenberger, T. Ben-Gal, A. Böhmer, J. Comin-Colet, K. Dickstein, I. Edes, F. Fedele, C. Fonseca, M.J. García-González, G. Giannakoulas, Z. Iakobishvili, P. Jääskeläinen, A. Karavidas, J. Kettner, M. Kivikko, L.H. Lund, S.T. Matskeplishvili, M. Metra, F. Morandi, F. Oliva, A. Parkhomenko, J. Parissis, P. Pollesello, G. Pölzl, R.H. Schwinger, J. Segovia, M. Seidel, B. Vrtovec, G. Wikström, Repetitive use of levosimendan for treatment of chronic advanced heart failure: clinical evidence, practical considerations, and perspectives: an expert panel consensus, Int. J. Cardiol. 174 (2) (2014) 360–367.
[6] M.S. Nieminen, S. Fruhwald, L.M. Heunks, P.K. Suominen, A.C. Gordon, M. Kivikko, P. Pollesello, Levosimendan: current data, clinical use and future development, Heart Lung Vessels 5 (4) (2013) 227–245.
[7] H. Haikala, P. Pollesello, Calcium sensitivity enhancers, IDrugs 3 (10) (2000) 1199–1205.
[8] S. Silvetti, T. Greco, A.L. Di Prima, M. Mucchetti, C.M. de Lurdes, L. Pasin, M. Scandroglio, G. Landoni, A. Zangrillo, Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials, Clin. Res. Cardiol. 103 (7) (2014) 505–513.
[9] L. De Luca, Inotropic agents in advanced heart failure: repetita iuvant? Int. J. Cardiol. 176 (1) (2014) 6–7.
[10] J.N. Nanas, P. Papazoglou, E.P. Tsagalou, A. Ntalianis, E. Tsolakis, J.V. Terrovitis, J. Kanakakis, S.N. Nanas, G.P. Alexopoulos, M.I. Anastasiou-Nana, Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone, Am. J. Cardiol. 95 (6) (2005) 768–771.
[11] R. Levin, R. Porcile, E. Tanus, M. Degrange, Abstract 3815: the intermittent infusion of levosimendan reduces mortality and re-admissions in patients with advanced heart failure, Circulation 120 (2009) S865.
[12] J. Comín-Colet, Multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of intermittent levosimendan in outpatients with advanced chronic heart failure: the LION Heart Study, At "Late Breaking Trials II: Heart Failure Management"/Heart FAILURE 2015 Congress of the ESC-HFA, Seville, May 24, 2015 (Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1077&sessId=14858#.VWatraM3ups Accessed 25 May, 2015).
[13] G.G. Biondi-Zoccai, P. Agostoni, A. Abbate, L. Testa, F. Burzotta, A simple hint to improve Robinson and Dickersin's highly sensitive PubMed search strategy for controlled clinical trials, Int. J. Epidemiol. 34 (2005) 224–225.
[14] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0, Updated March 2011, http://www.cochranehandbook.org (4 January 2011).
[15] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics 50 (1994) 1088–1101.
[16] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (1997) 629–634.
[17] G. Biondi-Zoccai, M. Lotrionte, G. Landoni, M.G. Modena, The rough guide to systematic reviews and meta-analyses, HSR Proc. Intensive Care Cardiovasc. Anesth. 3 (3) (2011) 161–173.
[18] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ 339 (2009) b2700.
[19] M.S. Nieminen, J.G.F. Cleland, J. Eha, Y. Belenkov, M. Kivikko, P. Põder, T. Sarapohja, Oral levosimendan in patients with severe chronic heart failure—the PERSIST study, Eur. J. Heart Fail. 10 (2008) 1246–1254.
[20] V.P. Harjola, L. Oikarinen, L. Toivonen, R. Jurkko, J. Puttonen, T. Sarapohja, S. Sundberg, M.S. Nieminen, The hemodynamic and pharmacokinetic interactions between chronic use of oral levosimendan and digoxin in patients with NYHA classes II–III heart failure, Int. J. Clin. Pharmacol. Ther. 8 (2008) 389–399.
[21] P. Põder, J. Eha, S. Sundberg, S. Antila, M. Heinpalu, I. Loogna, U. Planken, S. Rantanen, L. Lehtonen, Pharmacodynamics and pharmacokinetics of oral levosimendan and its metabolites in patients with severe congestive heart failure: a dosing interval study, J. Clin. Pharmacol. 44 (2004) 1143–1150.
[22] N.M. Parle, M.D. Thomas, L. Dembo, M. Best, G.O. Driscoll, Repeated infusions of levosimendan: well tolerated and improves functional capacity in decompensated heart failure—a singlecentre experience, Heart Lung Circ. 17 (2008) 206–210.
[23] P.O. Tuomainen, J. Magga, P. Timonen, K. Miettinen, M. Kurttila, E. Vanninen, T. Laitinen, K. Timonen, K. Punnonen, I. Parviainen, A. Uusaro, O. Vuolteenaho, M. Kivikko, K. Peuhkurinen, Intermittent levosimendan treatment in patients with severe congestive heart failure, Clin. Res. Cardiol. 102 (2013) 485–493.
[24] M. Jalanko, M. Kivikko, V.P. Harjola, M.S. Nieminen, M. Laine, Oral levosimendan improves filling pressure and systolic function during long-term treatment, Scand. Cardiovasc. J. 45 (2011) 91–97.
[25] M. Bonios, J. Terrovitis, J. Drakos, I. Pozios, E. Tseliou, L. Katsaros, E. Kaldara, G. Alexopoulos, J. Kanakakis, J. Nanas, Intermittent inotropic infusions for the treatment of refractory end stage heart failure: a randomized clinical study, Abstract Presented at ESC Congress, 2010.
[26] Y.H. Zhang, E.M. Qing, J. Zhang, Y. Huang, R. Lü, Q. Zhou, B.Q. Wei, T. An, P. Qing, C.H. Zou, Hemodynamic and efficacies of domestic levosimendan versus dobutamine in patients with acute decompensated heart failure, Zhonghua Yi Xue Za Zhi 92 (2012) 555–558.
[27] J.T. Parissis, S. Adamopoulos, D. Farmakis, G. Filippatos, I. Paraskevaidis, F. Panou, E. Iliodromitis, D.T. Kremastinos, Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure, Heart 92 (2006) 1768–1772.

[28] F.X. Kleber, T. Bollmann, M.M. Borst, A. Costard-Jackle, M. Ewert, R. Kivikko, T. Petterson, P. Pohjanjousi, S. Sonntag, G. Wikström, Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study, J. Clin. Pharmacol. 49 (2009) 109–115.
[29] R. Berger, D. Moertl, M. Huelsmann, A. Bojic, R. Ahmadi, I. Heissenberger, R. Pacher, Levosimendan and prostaglandin E1 for uptitration of beta-blockade in patients with refractory, advanced chronic heart failure, Eur. J. Heart Fail. 9 (2007) 202–208.
[30] M.J. Bonios, J.V. Terrovitis, S.G. Drakos, F. Katsaros, C. Pantsios, S.N. Nanas, J. Kanakakis, G. Alexopoulos, S. Toumanidis, M. Anastasiou-Nana, J.N. Nanas, Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure, Int. J. Cardiol. 159 (2012) 225–229.
[31] G. Malfatto, F. Della Rosa, A. Villani, V. Rella, G. Branzi, M. Facchini, G. Parati, Intermittent levosimendan infusions in advanced heart failure: favourable effects on left ventricular function, neurohormonal balance and one-year survival, J. Cardiovasc. Pharmacol. 60 (2012) 450–455.
[32] S. Mavrogeni, G. Giamouzis, E. Papadopoulou, S. Thomopoulou, A. Dritsas, G. Athanasopoulos, E. Adreanides, I. Vassiliadis, K. Spargias, D. Panagiotakos, D.V. Cokkinos, 6-Month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure, J. Card. Fail. 13 (2007) 556–559.
[33] J. Altenberger, J.T. Parissis, A. Costard-Jaeckle, A. Winter, C. Ebner, A. Karavidas, K. Sihorsch, E. Avgeropoulou, T. Weber, L. Dimopoulos, H. Ulmer, G. Poelzl, Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial, Eur. J. Heart Fail. 16 (2014) 898–906.
[34] M.S. Nieminen, K. Dickstein, C. Fonseca, J.M. Serrano, J. Parissis, F. Fedele, G. Wikström, P. Agostoni, S. Atar, L. Baholli, D. Brito, J.C. Colet, I. Édes, J.E. Gómez Mesa, V. Gorjup, E.H. Garza, J.R. González Juanatey, N. Karanovic, A. Karavidas, I. Katsytadze, M. Kivikko, S. Matskeplishvili, B. Merkely, F. Morandi, A. Novoa, F. Oliva, P. Ostadal, A. Pereira-Barretto, P. Pollesello, A. Rudiger, R.H. Schwinger, M. Wieser, I. Yavelov, R. Zymliński, The patient perspective: quality of life in advanced heart failure with frequent hospitalisations, Int. J. Cardiol. 191 (2015) 256–264.
[35] V.L. Roger, Epidemiology of heart failure, Circ. Res. 113 (2013) 646–659.
[36] F. Braunschweig, M.R. Cowie, A. Auricchio, What are the costs of heart failure? Europace 13 (2011) ii13–ii17.
[37] L.E. Rohde, E.G. Bertoldi, L. Goldraich, C.A. Polanczyk, Cost-effectiveness of heart failure. therapies, Nat. Rev. Cardiol. 10 (2013) 338–354.
[38] M. Gheorghiade, L. De Luca, G.C. Fonarow, G. Filippatos, M. Metra, G.S. Francis, Pathophysiologic targets in the early phase of acute heart failure syndromes, Am. J. Cardiol. 96 (Suppl.) (2005) 11G–17G.
[39] S.G. Drakos, J.V. Kanakakis, S. Nanas, M. Bonios, E. Kaldara, F. Katsaros, C. Pantsios, J.N. Nanas, Intermittent inotropic infusions combined with prophylactic oral amiodarone for patients with decompensated end-stage heart failure, J. Cardiovasc. Pharmacol. 53 (2) (2009) 157–161.
[40] J.F. Price, J.A. Towbin, W.J. Dreyer, B.S. Moffett, N.J. Kertesz, S.K. Clunie, S.W. Denfield, Outpatient continuous parenteral inotropic therapy as bridge to transplantation in children with advanced heart failure, J. Card. Fail. 12 (2006) 139–143.
[41] V.D. Moga, C. Luca, C.T. Luca, H. Branea, S.I. Drăgulescu, The value of intermittent inotropic therapy in unhospitalized patients with refractory heart failure, Rom. J. Intern. Med. 37 (1999) 25–29.
[42] S. Upadya, F.A. Lee, C. Saldarriaga, et al., Home continuous positive inotropic infusion as a bridge to cardiac transplantation in patients with end-stage heart failure, J. Heart Lung Transplant. 23 (2004) 466–472.
[43] R.M. Oren, W.G. Cotts, C.J. Pies, M.L. Duncan, Difficult cases in heart failure: importance of patient selection in the use of intermittent inotrope infusions for advanced heart failure, Congest. Heart Fail. 5 (1999) 86–90.
[44] A.W. Friedman, S.J. Silver, R.A. Minella, R.C. Lipman, An overview of intermittent inotropic therapy for severe congestive heart failure, Congest. Heart Fail. 5 (1999) 63–73.
[45] B.S. Levine, Intermittent positive inotrope infusion in the management of end-stage, low-output heart failure, J. Cardiovasc. Nurs. 14 (2000) 76–93.
[46] C. Rapezzi, G. Bracchetti, A. Branzi, B. Magnani, The case against outpatient parenteral inotropic therapy for advanced heart failure, J. Heart Lung Transplant. 19 (2000) S58–S63.
[47] C.L. Tacon, J. McCaffrey, A. Delaney, Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials, Intensive Care Med. 38 (2012) 359–367.
[48] P. Nony, J.P. Boissel, M. Lievre, A. Leizorovicz, M.C. Haugh, S. Fareh, B. de Breyne, Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients. A meta-analysis, Eur. J. Clin. Pharmacol. 46 (1994) 191–196.
[49] A. Delaney, C. Bradford, J. McCaffrey, S.M. Bagshaw, R. Lee, Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials, Int. J. Cardiol. 138 (2010) 281–289.
[50] G. Koster, J. Wetterslev, C. Gluud, J.G. Zijlstra, T.W. Scheeren, I.C. van der Horst, F. Keus, Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis, Intensive Care Med. 41 (2) (2015 Feb) 203–221.
[51] G. Landoni, G. Biondi-Zoccai, M. Greco, et al., Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies, Crit. Care Med. 40 (2012) 634–646.
[52] I. Rafiq, L.J. Freeman, Pulsed levosimendan therapy in the management of chronic end stage cardiac failure in 'adult congenital heart disease', Int. J. Cardiol. 195 (2015) 283–284.
[53] G.Y. Yi, J.X. Li, J. Zhang, L.L. Niu, C.Y. Zhang, Repetitive infusion of levosimendan in patients with chronic heart failure: a meta-analysis, Med. Sci. Monit. 21 (2015) 895–901.