



Repetitive use of levosimendan in advanced heart failure: need for stronger evidence in a field in dire need of a useful therapy



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ABSTRACT

Patients in the latest stages of heart failure are severely compromised, with poor quality of life and frequent hospitalizations. Heart transplantation and left ventricular assist device implantation are viable options only for a minority, and intermittent or continuous infusions of positive inotropes may be needed as a bridge therapy or as a symptomatic approach. In these settings, levosimendan has potential advantages over conventional inotropes (catecholamines and phosphodiesterase inhibitors), such as sustained effects after initial infusion, synergy with beta-blockers, and no increase in oxygen consumption. Levosimendan has been suggested as a treatment that reduces re-hospitalization and improves quality of life. However, previous clinical studies of intermittent infusions of levosimendan were not powered to show statistical significance on key outcome parameters. A panel of 45 expert clinicians from 12 European countries met in Rome on November 24–25, 2016 to review the literature and envision an appropriately designed clinical trial addressing these needs. In the earlier FIGHT trial (daily subcutaneous injection of liraglutide in heart failure patients with reduced ejection fraction) a composite Global Rank Score was used as primary end-point where death, re-hospitalization, and change in N-terminal-prohormone-brain natriuretic peptide level were considered in a hierarchical order. In the present study, we tested the same end-point post hoc in the PERSIST and LEVOREP trials on oral and repeated i.v. levosimendan, respectively, and demonstrated superiority of levosimendan treatment vs placebo. The use of the same composite end-point in a properly powered study on repetitive levosimendan in advanced heart failure is strongly advocated.

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1. Heart failure, chronic heart failure, and advanced heart failure

Heart failure (HF) is the result of various clinical conditions, all of which have the common characteristic of reduced myocardial function either in terms of contractility or in terms of ventricular compliance and relaxation. Moreover, HF affects not only the heart itself, but may be considered as a systemic condition in which neurohormonal and inflammatory activation mediates cardiac remodeling and disease progression [1]. The number of patients suffering from chronic HF is increasing over the years, due several factors, i.e. to advances in medicine and science leading to improved survival from previously life-threatening scenarios, the high prevalence of serious comorbidities among the ageing population, and not least the growing life expectancy itself [2]. HF has become the leading cause of adult hospitalization in the industrialized world, with an estimated 26 million people suffering from the disease.

Prognostically effective treatments for HF recommended in the current guidelines include inhibitors of the renin–angiotensin–aldosterone system (comprising angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and angiotensin-receptor/neprilysin inhibitors), beta-adrenergic blockers, ivabradine, and devices (either cardiac resynchronization therapy or implantable cardioverter defibrillators) [3]. These strategies are flanked by symptomatic treatment, in particular diuretics.

Hospitalization for acute HF is a significant predictor of increased mortality risk, with registries consistently demonstrating high rates of all-cause 1-year mortality both for acute and chronic HF [4]. Each time a patient is hospitalized for acute decompensation, there is a risk for a further worsening of myocardial function, leading to recurring episodes of hospitalizations for HF (Fig. 1). Moreover, each successive hospitalization carries a higher probability of death [5], and impacts on health economics, due to the high costs of HF-related hospitalization [4,6,7].

Although strict adherence to the recommended treatment is essential for favorably shaping both general welfare and outcome of patients with severe HF, many do not tolerate all of the currently available therapies, due to hypotension or co-morbidities (renal impairment, COPD, etc.). The advent of CRT represented a milestone in cardiovascular medicine, since it greatly reduced the re-hospitalization rate and mortality in a relatively large (though necessarily selected) cohort of patients [8], whereas heart transplantation or left ventricular assist devices (LVAD) were (and remain) a possibility for only a limited number of patients.

The later stages of HF are often referred to either as advanced (AdHF) or end-stage HF. A distinction between the two terms has to be made, however, according to the criteria established in 2007 by the

European Society of Cardiology and endorsed in 2013 by the American College of Cardiology Foundation/American Heart Association. Both societies define AdHF as a condition in which cardiac dysfunction and symptoms are still potentially reversible, whereas in end-stage HF they are not [9,10]. AdHF represents a major challenge for both patients and physicians, as patients experience a severely compromised quality of life with easily worsening clinical conditions, requiring frequent and prolonged hospitalizations [11].

Various attempts have been made to identify suitable therapies for AdHF patients in addition to the first-line agents identified above. The use of continuous or intermittent infusions of intravenous inotropes was tested, but concern was raised about increased mortality with such treatments, notwithstanding favorable hemodynamics and symptomatic improvements in small clinical studies (see Upadya et al. [12]). Larger trials and meta-analysis appeared to confirm a trend towards higher mortality risk and did not identify any beneficial impact on hospitalizations [13].

In the early 2000s, a new perspective on the treatment of HF was opened by the introduction of the inodilator levosimendan, a calcium sensitizer and potassium channel opener [14]. This drug combines positive inotropic, vasodilatory, and cardioprotective effects, without increasing oxygen demand. Levosimendan is the most studied inotrope

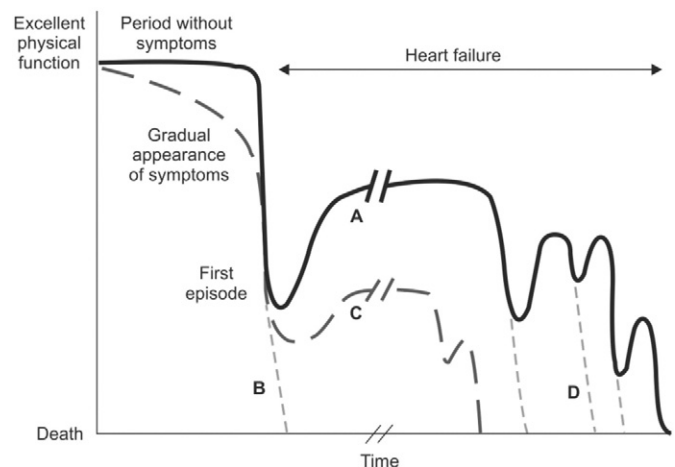


Fig. 1. Functional capacity and worsening events during the progression of heart failure (freely from Cowie MR et al. [5]). A, recovery after first episode followed by stable period of variable length; B, non-surviving the first episode; C, poor recovery after first episode followed by deterioration; D, ongoing deterioration with intermittent crises (advanced heart failure) and unpredictable death point.

indicated for HF, and multiple meta-analyses have shown possible advantages of levosimendan in various clinical settings [15–18]. In particular, the intermittent use of i.v. levosimendan in chronic AdHF has been suggested to prevent acute decompensation and frequent re-hospitalization, and possibly to improve other outcomes [15].

2. Aim of the expert consensus meeting

A panel of 45 clinical experts from 12 European countries (Austria, Denmark, Finland, Germany, Greece, Hungary, Italy, Poland, Slovenia, Spain, Sweden, and Switzerland) convened in Rome on November 24th–25th, 2016 to (a) review the current data on repetitive levosimendan studies, (b) profile the patient groups most likely to benefit from repetitive intermittent treatment with i.v. levosimendan, (c) compare end-points from previous clinical trials in the same settings, and (d) discuss the end-points and the protocol of an adequately powered trial designed to evaluate efficacy and safety of intermittent i.v. levosimendan therapy started during the vulnerable phase after a recent hospitalization for HF. This consensus paper presents the conclusions of the expert panel.

3. Levosimendan

Levosimendan is a calcium sensitizer and potassium channel opener indicated for the treatment of acute HF [14]. Levosimendan has one active metabolite, coded OR-1896. Both the parent drug and OR-1896 have similar effects, but levosimendan has a half-life of about 1 h, whereas OR-1896 reaches its peak plasma concentration 2–3 days after levosimendan infusion, thus prolonging therapeutic effects beyond the infusion period [19–22]. The drug was formulated for a 24-hour infusion, after which its pharmacodynamic effects (i.e., increase in cardiac output and reduction of pulmonary capillary wedge pressure) persist for at least one week [23]. However, some research groups have obtained interesting results with limited duration of the infusion (i.e., 6 to 8 h), although pharmacokinetic information is limited. Of note, the reduction in pulmonary vascular resistance after a 6-hour infusion in patients with pulmonary hypertension does not seem to persist for 2 weeks as is seen with the 24-hour infusion [24].

Efficacy and safety of levosimendan have been described in the medical literature. The hemodynamic effects of the drug have been convincingly demonstrated in acute HF patients in two regulatory studies, i.e. the LIDO [25] and RUSSLAN [26] clinical trials. Moreover, in the regulatory clinical trial REVIVE [27] levosimendan induced marked relief from symptoms. Several meta-analyses evaluating approximately 5000 patients of 50 randomized controlled trials demonstrated a reduction in mortality with levosimendan in different clinical scenarios [28].

Levosimendan also exhibits neurohormonal and anti-inflammatory effects, reducing brain natriuretic peptide (BNP) level, as well as tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and proapoptotic factors sFas and Fas-ligand levels [29–32]. In addition, levosimendan improves both right ventricular function [33] and endothelial function, and has a beneficial effect on coronary blood flow [34,35].

This profile renders intermittent repetitive administration of levosimendan a potentially valuable treatment option for patients with AdHF. In fact, levosimendan has several theoretical advantages over the other commonly used inotropes [14,16], such as the synergy with beta-blockers and the beneficial effect on renal function and peripheral organ perfusion.

A panel of international experts recently proposed criteria for the identification of the patients most likely to benefit from repetitive use of levosimendan in chronic AdHF [36]. Among those were patients listed for heart transplantation or LVAD implantation, as well as patients with similar clinical profiles but not eligible to LVAD or transplantation due to other causes (i.e. mental illness), in whom intermittent repetitive levosimendan infusions may be viewed as “destination treatment”.

4. Clinical studies on the effects of levosimendan in AdHF

Several studies on the repetitive or intermittent administration of levosimendan in AdHF have already been published and subjected to meta-analysis [37]. Evidence of clinical benefit was brought forward [36,37] although data on the subject are heterogeneous both in terms of methodology and of results: the comparator of levosimendan varied from placebo to diuretics, or dobutamine; the dosages and interval of levosimendan administration differed among centers; there was marked variation in these study design, as the primary and secondary outcomes.

The safety and efficacy of levosimendan infused every two weeks in patients refractory to i.v. dobutamine in addition to standard therapy was tested by the group of Nanas et al. [38] in an open-label comparison between daily dobutamine plus levosimendan versus daily dobutamine infusions alone. A total of 36 patients with cardiac decompensation were enrolled. Half of them were treated with 24-hour infusions of dobutamine followed by 8-hour infusions for up to three days and then weekly dobutamine infusions: the other 18 patients received a 24-hour infusion of levosimendan every two weeks in addition to daily dobutamine. The authors found that levosimendan infusions were useful to stabilize the majority of patients, and to improve their clinical and hemodynamic status. Patients' survival improved with this sequential treatment, whereas higher mortality was reported in the group treated by dobutamine infusions alone.

Parissis et al. [39] tested the efficacy of five levosimendan infusions, administered once every three weeks, in a series of 25 patients with chronic AdHF. Their patients were randomized 2:1 to levosimendan and placebo respectively, and all of them underwent echocardiographic as well as biochemical evaluations before and after each cycle of treatment and at the final visit. Left ventricular ejection fraction (LVEF), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and IL-6 levels significantly improved after levosimendan therapy.

LVEF was also assessed in a study by Mavrogeni et al. [40], who additionally evaluated other echocardiographic parameters such as end-diastolic and end-systolic volumes and dimensions. All these echocardiographic indices were significantly improved following monthly levosimendan infusions for a 6-month-period, and besides, the authors demonstrated significant symptoms improvement and reduction in mortality with levosimendan, compared to standard care.

Other studies such as those of Papadopoulou et al. [41] and Malfatto et al. [42] demonstrated improvements in both objective echocardiographic measurements and subjective quality of life measures with 24-h levosimendan. Patients in the Papadopoulou et al. study did not have a comparator group, whereas Malfatto et al. compared monthly levosimendan infusions to furosemide, resulting in a significant reduction in New York Heart Association (NYHA) class, and improvements in echocardiographic parameters and BNP levels. Again, a trend towards reduction in one-year mortality was seen with levosimendan, although it did not reach statistical significance.

Levosimendan was less effective than prostaglandin E1 in patients not tolerating the appropriate beta-blocker therapy in the trial by Berger et al. [43]. In this study, continuous treatment with prostaglandin E1 was more efficacious than 24-hour levosimendan infusions every 4-weeks in allowing up-titration of beta-blockers. Prostaglandin E1 performed better than levosimendan with regard to the composite endpoint of worsening HF, death, urgent heart transplantation, and/or implantation of LVAD, although mortality did not differ between the two groups.

Sixty-three patients with decompensated end-stage HF refractory to standard therapy were randomized by Bonios et al. [44] to receive levosimendan, dobutamine, or the combination of both drugs. Patients were first treated with inotropes for stabilization, and entered the study after successful weaning from i.v. inotropic support. Only the group of patients receiving levosimendan alone showed a significant benefit in event-free survival, whereas the group receiving the

combination of both drugs showed the worst results. At 6 months, mortality rate favored levosimendan both versus dobutamine alone (19% vs 38%, $p = 0.037$) and versus the combination group (19% vs 48%, $p = 0.009$). Similar improvements in the functional capacity of patients receiving repetitive levosimendan (from 2 to 26 times, with a mean dosing interval of 66.2 ± 12 days) were observed also in another single-centre, prospective, non-randomized study, by Parle et al. [45].

The largest trial on repetitive administration of inotropes for end-stage HF [46] in outpatients was the LEVOREP study, a prospective, multi-centre, randomised, placebo-controlled, double-blind, two-armed, parallel-group that enrolled 120 patients with chronic stable HF, in NYHA class III/IV for >3 months, with LVEF $\leq 35\%$, and performance of <350 m at the 6-minute walk test. The patients were randomized to placebo or 6-hour levosimendan infusions every 2 weeks for four times. The combined primary endpoint was improvement in functional capacity of $\geq 20\%$ by the 6-minute walk test, plus improvement in patient quality of life of $\geq 15\%$ as assessed by the Kansas City Cardiomyopathy Questionnaire score (KCCQ). Follow-up lasted 24 weeks, after which a trend in favour of levosimendan was evident but no significant difference was confirmed. It has been speculated that the primary endpoint was not reached due to under-dosing of the study drug, small sample size of the study population, and better care of the patients population also in the placebo group as compared to patients not enrolled in clinical studies, who apparently experience fewer improvements in functional capacity than the overall study population.

Regarding the secondary endpoint of event-free survival (freedom from death, heart transplantation/LVAD implantation, or acute HF) after 24 weeks, ambulatory treatment with levosimendan was more effective than placebo. Across both arms of the study, similar percentages of patients experienced adverse events.

Recently, intermittent levosimendan has been assessed in two double-blind, randomized, placebo-controlled trials, the LION-HEART and LAICA studies [47,48].

LION-HEART [47] was a multi-centre, randomized, double-blind, parallel group, placebo-controlled trial aiming to test the efficacy and safety of intravenous administration of repetitive doses of levosimendan in outpatients with AdHF. Levosimendan was administered in an ambulatory setting during a 6-h-period of observation, and repeated every two weeks. The study lasted 12 weeks (6 cycles of levosimendan for each patient), after which change in NT-proBNP from baseline was assessed as the primary endpoint. The reduction in NT-proBNP was significantly in favour of levosimendan, as was the probability of survival in the Kaplan-Meier curve at 180 days (all $p < 0.005$).

LAICA [48] was an Investigator Initiated Trial evaluating monthly 24-hour infusions of levosimendan for a year in addition to optimal medical therapy for reducing the incidence of hospitalization for acute decompensated HF in patients with advanced chronic AdHF. Secondary endpoints were cumulative incidence of hospitalization for acute decompensated HF and/or mortality at 30 days, and after 3, 6, and 12 month; the time-interval from randomization to first hospitalization for acute cardiac decompensation or death; incidence of adverse events; and changes in NYHA functional class over the one-year follow-up. Ninety-seven patients were randomized: 70 were allocated to levosimendan and 27 to placebo. Although many patients were lost to follow-up, statistical analysis was performed considering all 97 patients enrolled.

LAICA did not demonstrate statistical significance for the primary endpoint, but the results favoured levosimendan both in terms of fewer admissions for acute decompensated HF and in terms of lower mortality rates. The rate of adverse events was comparable between levosimendan and placebo. Ongoing studies are exploring treatment effects on renal function and cost-effectiveness.

Table 1 summarizes the total doses of levosimendan used in the 10 studies described. Although a trend in favour of the repetitive use of levosimendan is discernible in the majority of the studies, more robust

data on hospitalization and mortality rates associated with repetitive use of levosimendan are needed.

5. Primary end-points in AdHF clinical studies

The central clinical aims in the treatment of HF are to relieve symptoms, reduce the number and length of hospitalizations and reduce mortality. Symptomatic improvement has turned out to be an extremely elusive endpoint in such trials. There are confounding factors influencing its reliable measurement and – although clinically meaningful – symptoms may not be an ideal primary endpoint to test the efficacy of a treatment. A composite endpoint of mortality and re-hospitalisations would ensure wide acceptance. However, with this approach only a proportion of the patients participating in the trial would contribute to the endpoint unless the follow-up period were extended to years; with a more realistic (i.e. shorter) duration of follow-up, the size of the patient population would need to be markedly higher, and conducting such a study in a reasonable time-frame would be extremely difficult. Having all patient randomized contributing to the endpoint would optimise the needed sample size and the duration of the study.

Recently, a study with a primary endpoint combining deaths, re-hospitalizations and positive neurohormonal response (on NT-proBNP) has been published [49]. In the FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment Study) [49], Margulies et al. set as primary endpoint a Global Rank Score where each patient is assigned a numerical value corresponding to their stability index mirroring their respective clinical conditions.

Each patient is given a score value based on outcome during follow-up, and then analyzed in hierarchical categories of: (1) time to death; (2) time to HF hospitalization; and (3) time-averaged proportional change in NT-proBNP. In this way, deaths are the most important events, followed by re-hospitalizations and finally by NT-pro-BNP elevation. This approach was based on the consideration that changes in NT-proBNP levels over time well represent the severity of HF, and thus can be a surrogate endpoint for patients not experiencing a clinical endpoint. This score is easy to interpret: the higher the score value the more stable the clinical condition. The hierarchical approach increases the clinical validity of the endpoint, and this new statistical endpoint has received endorsement by competent regulatory authorities.

In order to compare this newly proposed end-point with the ones previously used in previous HF trials, we produced post-hoc analyses of the PERSIST study results on oral levosimendan in chronic heart failure, and of the LEVOREP study on repetitive levosimendan in AdHF.

The PERSIST study [50] evaluated the effects of oral levosimendan in patients with severe chronic HF (NYHA class IIIB-IV). PERSIST was a randomized, double-blind, placebo-controlled trial of levosimendan 1 mg once or twice daily versus placebo administered orally for at least 6 months. A total of 307 patients were enrolled. The endpoint of the study, called “Patient Journey”, was a composite consisting of repeated symptom assessments, worsening heart failure and mortality up to 60 days. Several repeated assessment of the Minnesota Living with Heart Failure quality of life (MLHFQoL) score and NT-proBNP levels were performed. However, a limitation of that study was that, due to an imperfect randomization, the lower dose of levosimendan was given to sicker patients. The results of PERSIST were inconclusive with no statistical difference on the primary endpoint although there was a numerical sign of mortality risk reduction with levosimendan, and both QoL and NT-proBNP levels improved.

A simulation performed with the FIGHT Global Rank Score on the results of the PERSIST study (Table 2) revealed that this composite parameter would have reached statistical significance for both the 1 and 2 mg doses of oral levosimendan ($p = 0.0187$ and $p = 0.0008$ respectively).

A similar statistical simulation was performed for the LEVOREP study [46] (Table 3). Again, significant results in favor of levosimendan were found when the Global Rank Score was used to test the statistical significance of the primary endpoint ($p = 0.0239$). While this analysis

Table 1

Summary of published trials of repetitive/intermittent levosimendan in advanced heart failure. See text for discussion.

Study name and characteristics	Patients enrolled	Levosimendan dose	Infusion duration	Infusion frequency	End-points
Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone [38]	36	Bolus of 6 mg/kg followed by 0.2 µg/kg/min infusion	24-h	2 weeks	Survival at 45-days, hemodynamics
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 [39]	25	Bolus of 6 mg/kg followed by 0.1 µg/kg/min infusion, uptitrated to 0.4 µg/kg/min	24-h	3 weeks	LVEF, LV dimensions and volumes, Nt-proBNP levels, tnt T levels, CRP levels, IL 6 levels
A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure [40]	50	Bolus of 6 mg/kg followed by 0.1 µg/kg/min infusion, uptitration to 0.2 µg/kg/min if tolerated	24-h	30 days	Symptoms/QoL, LVEF, LV volumes and dimensions, mitral regurgitation, RV systolic pressure
Assessment of quality of life using three different activity questionnaires in heart failure patients after monthly, intermittent administration of levosimendan during a six-month period [41]	20	0.1 µg/kg/min infusion without a loading dose	24-h	30 days	QoL and LVEF
Intermittent levosimendan infusions in advanced heart failure: favourable effects on left ventricular function, neurohormonal balance, and one-year survival [42]	33	Starting 0.1 µg/kg/min, without a loading dose, uptitration 0.1 µg/kg/min per hour up to 0.4 µg/kg/min	24-h	30 days	Hemodynamics and echocardiographic indices, BNP
Levosimendan and prostaglandin E1 for uptitration of beta-blockade in patients with refractory, advanced chronic heart failure [43]	75	Bolus of 12 mg/kg if blood pressure > 95 mm Hg, followed by 0.1 µg/kg/min infusion, or continuous infusion without loading dose if blood pressure < 95 mm Hg	24-h	4 weeks	Up-titration of beta-blockers, LVEF, BNP
Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure [44]	63	Either 0.2 µg/kg/min infusion in association with dobutamine or 0.3 µg/kg/min lone levosimendan infusion	6-h	weekly	Hemodynamics, survival/freedom from LVAD at 3 and 6 months
Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial [46]	120	0.2 µg/kg/min, without a loading dose	6-h	2 weeks	≥20% improvement in the 6 min walk test and a ≥ 15% score increase in the KCCQ; 8-weeks and 24-weeks survival
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 [47]	69	0.2 µg/kg/min, without a loading dose	6-h	2 weeks	NTproBNP changes from baseline, survival
A randomized, double-blind, placebo controlled multicenter trial to study efficacy, security, and long term effects of intermittent repeated levosimendan administration in patients with advanced heart failure: LAICA study [48]	97	0.1 µg/kg/min, without a loading dose	24 h	30 days	Reduction of AHF hospitalizations, short and long-term mortality changes in NYHA functional class over the one-year

did not change the interpretation of these trials, the results suggest that Global Rank Score might be an informative endpoint for a study in this particular patient population with advanced HF.

6. Recommendations

Past experience has shown that evaluation of symptoms as an objective end-point in HF trials is problematic. Symptoms cannot always be reliably measured, and may not represent an ideal primary endpoint to test the efficacy of a treatment. A composite endpoint combining death and re-hospitalizations would enjoy widespread acceptance, although it presents two interrelated drawbacks: follow-up needs to be long enough to enable a relevant number of patients to reach the

endpoint, and the sample size has to be adequately large in order to ascertain statistical power, which in turn extends the period of recruitment to an extent that may itself be infeasible.

We hypothesized that, compared to placebo, repetitive administration of levosimendan early in the period after discharge from an acute episode of worsening HF may be associated with greater clinical stability through 14 weeks, especially if assessed with the composite clinical end-point consisting of mortality, acute HF episodes and change in natriuretic peptide levels evaluated in hierarchical manner by Margulies et al. [49].

As secondary endpoints we suggest to consider all the individual components of the Global Rank Score at 14 weeks, changes in functional status (measured by NYHA class and 6-minute walking test at baseline and 14 weeks), symptoms (evaluated with Kansas City Cardiomyopathy

Table 2

PERSIST [50] result with the FIGHT [49] endpoint. Significant result in favor of intermittent levosimendan in the Global Rank Score.

	Global Rank Score ^a	p-Value ^b
Levosimendan 1 mg (n = 102)	159 (95)	0.0187
Levosimendan 2 mg (n = 103)	173 (90)	0.0008
Levosimendan 1 or 2 mg (n = 205)	166 (93)	0.0009
Placebo (n = 102)	130 (75)	

^a Mean (SD).^b Wilcoxon-Mann-Whitney Test.**Table 3**

LEVOREP [46] result with the FIGHT [49] endpoint. Significant result in favor of intermittent levosimendan in the Global Rank Score.

	Global Rank Score ^a	p-Value ^b
Levosimendan (n = 63)	67 (36)	0.0239
Placebo (n = 57)	53 (32)	

^a Mean (SD).^b Wilcoxon-Mann-Whitney Test.

Questionnaire from baseline to 14 weeks), combined events and cumulative numbers of events/hospital admissions/days alive out of hospital.

With the Global Rank Score as primary endpoint of a trial, every patient would contribute to the endpoint through one or more of the hierarchical categories: either if he/she experiences death or an episode of worsening HF or a change in NT-proBNP measurement. This approach would create an opportunity to recruit an advanced but fairly stable HF population that would be comparatively easy to enroll and should have a low rate of drop-out by virtue of the shorter treatment time per patient.

7. Conclusion

Although only a limited proportion of all HF patients belong to the sub-group of chronic AdHF, this population exerts a huge impact both in terms of health care resources and costs and in terms of emotional involvement for physicians and relatives. Despite being treated with all recommended evidence-based medications, these patients may experience clinical deterioration, need for re-hospitalization and further decline in the trajectory of their HF.

It appears that repetitive levosimendan may help patients to gain a longer stability period and a better QoL and postpone re-hospitalizations, easing the challenge of treating their failing heart. Intermittent use of levosimendan has been evaluated in 10 trials with a multitude of chronic AdHF patients treated with this approach (see Table 1). Differences among the various trials make it difficult to raise univocal and firm conclusion; nonetheless, repetitive infusions of levosimendan have demonstrated several benefits in terms of improved hemodynamics, symptoms, re-hospitalization rates, and biomarkers.

The panel recommends initiating an adequately powered clinical trial that utilizes as primary-end point a composite such the one used for the FIGHT trial on liraglutide [49]. Cardiac mortality and re-hospitalization are advocated as secondary end-points.

Conflicts of interest

This project did not receive any financial support, apart from logistic expenses related to the organization of the consensus meeting in Rome on 24–25 November 2016, which were covered by Orion Pharma. Attendees were invited by the chairman (GP) on the basis of their experience with repetitive use of levosimendan documented in the literature. The attendees did not receive any honorarium. In the past 5 years, FG, GP, JA, LB, JCC, JD, FF, ZP, and GW have received research grants or limited lectures honoraria from Orion Pharma. PP, MK, TS and AF are full-time employees of Orion Pharma. Orion Pharma follows the code of conduct of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

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PP and AF performed a preliminary search for the relevant publications. TS and MK performed the statistical analyses related to the endpoint discussion. All authors contributed substantially to discussions on the existing literature, and reviewed the manuscript before submission. AF drafted the first version of the manuscript on the basis of the discussion proceedings.

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