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ORIGINAL ARTICLE

# Intermittent inotropic support with levosimendan in advanced heart failure as destination therapy: The LEVO-D registry

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## Abstract

**Aim** Patients with advanced heart failure (AHF) who are not candidates to advanced therapies have poor prognosis. Some trials have shown that intermittent levosimendan can reduce HF hospitalizations in AHF in the short term. In this real-life registry, we describe the patterns of use, safety and factors related to the response to intermittent levosimendan infusions in AHF patients not candidates to advanced therapies.

**Methods and results** Multicentre retrospective study of patients diagnosed with advanced heart failure, not HT or LVAD candidates. Patients needed to be on the optimal medical therapy according to their treating physician. Patients with de novo heart failure or who underwent any procedure that could improve prognosis were not included in the registry. Four hundred three patients were included; 77.9% needed at least one admission the year before levosimendan was first administered because of heart failure. Death rate at 1 year was 26.8% and median survival was 24.7 [95% CI: 20.4–26.9] months, and 43.7% of patients fulfilled the criteria for being considered a responder lo levosimendan (no death, heart failure admission or unplanned HF visit at 1 year after first levosimendan administration). Compared with the year before there was a significant reduction in HF admissions (38.7% vs. 77.9%; $P < 0.0001$), unplanned HF visits (22.7% vs. 43.7%; $P < 0.0001$) or the combined event including deaths (56.3% vs. 81.4%; $P < 0.0001$) during the year after. We created a score that helps predicting the responder status at 1 year after levosimendan, resulting in a score summatory of five variables: TEER (+2), treatment with beta-blockers (+1.5), Haemoglobin >12 g/dL (+1.5), amiodarone use (−1.5) HF visit 1 year before levosimendan (−1.5) and heart rate >70 b.p.m. (−2). Patients with a score less than −1 had a very low probability of response (21.5% free of death or HF event at 1 year) meanwhile those with a score over 1.5 had the better chance of response (68.4% free of death or HF event at 1 year). LEVO-D score performed well in the ROC analysis.

**Conclusion** In this large real-life series of AHF patients treated with levosimendan as destination therapy, we show a significant decrease of heart failure events during the year after the first administration. The simple LEVO-D Score could be of help when deciding about futile therapy in this population.

**Keywords** Inotropes; Levosimendan; Palliative care; Advanced heart failure

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# Introduction

Patients with advanced heart failure (AHF) who are not heart transplant (HT) or durable left ventricular assist device (LVAD) candidates have a poor prognosis.[1] Unfortunately, when this stage is reached[2] therapeutic opportunities are scarce, patients are usually highly symptomatic with poor quality of life and have frequent hospital admissions. Continuous ambulatory inotropic support with milrinone or dobutamine are not frequently used because of their cumbersome administration and high rate of side effects.[3] On the other hand, levosimendan appears to be more attractive as inotropic drug for outpatients because of the length of the effect of its metabolites, allowing intermittent ambulatory dosing of the drug. Some small, randomized clinical trials have shown that intermittent levosimendan can reduce HF hospitalizations in AHF in the short term.[4] However, there is no real-life data in the literature about the use of this drug repeatedly and intermittently during long-term follow-up as the last resource in end-stage HF patients. In this real-life registry, we describe the patterns of use, safety and factors related to the response to intermittent levosimendan infusions in AHF patients not candidates to advanced therapies, as well as their prognosis in the current heart failure era of newer therapies.

# Methods

The LEVO-D is a multicentre retrospective study of patients over 18-year-old diagnosed with advanced heart failure, not HT or LVAD candidates. Twenty-three tertiary hospitals in Spain participated in the registry, including patients who received at least one dose of ambulatory levosimendan between 1 January 2015 and 1 September 2020. Patients needed to be on the optimal medical therapy (OMT) according to their treating physician. Patients with de novo heart failure or who underwent any procedure that could improve prognosis or clinical outcome (coronary revascularization, valve repair or replacement, CRT device implantation or any other procedure that under investigator criteria could improve prognosis or quality of life) after levosimendan was started, were not included in the registry. OMT was defined according to current guidelines and did not include iSGLT2 as patients of this registry came from a pre-iSGLT2 era.

## Data collection

Baseline data were collected the day of the first dose of levosimendan, with blood pressure and heart rate measured before the drug was administered. Laboratory parameters not usually performed in an urgent blood sample were allowed if the sample was taken up to 21 days before first levosimendan administration. Routine urgent laboratory data as haematinics, renal function or NT-proBNP were from the day of the first programmed infusion. Echocardiographic data were the closest before the first infusion. Data were collected in an anonymous database and analysed after the approval of the regional ethic committee. Patients were followed under their clinician's judgement. Follow-up events were updated up to June 2021.

## Levosimendan

We analysed 'levosimendan strategy' as well as the drug dose per administration. We classified the variable 'levosimendan strategy' in to one of these categories: bailout, fixed number and 'sine die'. Bailout was defined as levosimendan administration after clinical judgement of deterioration without a pre-specified protocol. Fixed number was defined as a fixed number of doses during a pre-specified period. 'Sine die' was considered when the drug was started and given intermittently with a pre-specified period between doses without the plan of stopping it at any time. We analysed the initial strategy and if strategy changed to other one during the follow-up. We explored how this drug was given in each administration. As we found this was very diverse among centres, we defined 'high dose' when the patient received at least 6.25 mg of the drug per administration, and 'low dose' when less than 6.25 mg was given during one infusion.

## Endpoints

We analysed death due to all causes, cardiovascular death, urgent HF hospitalizations and unplanned HF visits without needing admission during the entire follow-up period. We also analysed these endpoints at 1 year after receiving at least one dose of levosimendan and compared HF hospitalizations and unplanned HF visits with those during the previous year. We defined as 'responders' those who were alive 1 year after levosimendan treatment without urgent HF admissions or unplanned hospital visit due to HF. As a safety endpoint,

we analysed ICD therapies (shocks or ATP) during the year before and after receiving at least one dose of levosimendan. We also documented levosimendan withdrawal due to side effects, futility, or any other reason. We defined 'withdrawal' when it was actively decided to give no more doses of levosimendan independently of clinical situation.

### Statistical analysis

Results were expressed as mean ± standard deviation, medians (interquartile range [IQR]) or percentages, depending on each variable. Statistical differences were analysed with Student's *t*-test (gaussian distribution), nonparametric Mann–Whitney *U* (non-Gaussian distribution), nonparametric McNemar or chi-square as appropriate. Simple survival analysis was performed with Kaplan–Meier curves and long-rank test was used to evaluate statistical significance. Univariate logistic regression analysis was used to analyse relationship to clinical outcomes. Variables with a value of $P < 0.10$ in a univariate logistic regression analysis entered the multivariate analysis and a Cox regression model was created to predict the three outcomes measured: Overall survival, 1 year survival and 1 year response. Quantitative variables were dichotomized to create the LEVO-D score with those variables significant in the multivariate analysis. Dichotomization was based mainly on clinical relevance. The relative magnitude of the model regression coefficients from statistically significant variables in the final multivariable model was used to calculate the LEVO-D score. Missing data were managed by performing multiple imputations of all relevant parameters in the entire population. SPSS version 25 was used for multiple imputations using the automated function. A 20% limit for the missing data were set to exclude variables with excessive missing data. Results were expressed as hazard ratio (HR) with 95% confidence interval (95% CI). A *P*-value $<0.05$ was considered as significant.

## Results

### Demographics and baseline

Four hundred three patients with AHF, optimally treated and not candidates to advanced HF therapies were included (*Table 1*), and 77.9% needed at least one hospital admission the year before levosimendan was first administered because of heart failure (44.5% two or more times). Echocardiogram was performed a median of 64 [IQR 22, 218] days and laboratory data a median of 0 [IQR 0, 14] days before levosimendan was firstly administered. Mean heart rate was over 70 b.p.m., but it should be considered that 60.9% of the patients were on permanent atrial arrhythmia. Median MAGGIC score was 27, which confirmed the high risk of LEVO-D population.

### Events

There are 52.6% of patients who died during a median follow-up of 15.3 [IQR 7.5–28.2] months (*Tables 1* and *2*, *Figure 1*). Death rate at 1 year was 26.8% and 73.9% of all deaths were of cardiovascular cause. Median survival was 24.7 [95% CI: 20.4–26.9] months. At 1 year after levosimendan, 38.7% of patients needed at least one hospital admission and 22.3% at least one unplanned hospital attendance because of decompensated heart failure. Cardiovascular death rate was 24.1 per 100 patients-year and HF hospitalization rate was 30.1 per 100 patients-year. Differences in medical treatment were less marked than probably expected, as only less beta-blockade (74.9% vs. 83.2%; $P = 0.04$) was found in those who died. Deceased individuals already had more previous hospitalizations due to HF and showed signs of more advanced disease with higher heart rate and NT-proBNP, lower sodium, albumin, and cholesterol and poorer LVEF.

*Table 2* shows the profile of those who died within the first year as well as responders; 43.7% of patients fulfilled the criteria for being considered a responder lo levosimendan. Compared with the year before (*Figure 1*), there was a significant reduction in HF admissions (38.7% vs. 77.9%; $P < 0.0001$), unplanned HF visits (22.7% vs. 43.7%; $P < 0.0001$) or the combined event including deaths (56.3% vs. 81.4%; $P < 0.0001$) during the year after. The total number of HF admissions (1.12 ± 1.8 vs. 1.69 ± 1.7; $P < 0.001$) and unplanned HF visits (0.68 ± 1.7 vs. 1.37 ± 3.2; $P < 0.0001$) were also reduced comparing the year before and after levosimendan. Age was not found to be related to the probability of response to levosimendan at 1 year. Only beta-blockers were more frequent in responders (85.2% vs. 73.9%; $P = 0.006$) but treatment with amiodarone was more frequent in non-responders (27.1% vs. 17.7%; $P = -0.03$). Signs of advanced disease and comorbidities (higher heart rate and NT-proBNP, lower haemoglobin, higher urea, and lower cholesterol), but no the degree of structural heart disease, were related to worse response rate.

### Safety

Compared with the year before levosimendan, the percentage of patients experiencing any kind of ICD therapy was the same (percentage over the number of patients with an ICD, 16.2% vs. 14.9%; $P = 0.39$) (*Figure 2*). The total number of VT/VF therapies neither was increased (episodes per year, before 0.87 ± 3.1 vs. 0.91 ± 7.1 after; $P = 0.94$). In 40.4% of patients, levosimendan was actively withdrawn during the

**Table 1** Demographics and baseline data of the whole cohort and comparison between alive and deceased individuals during the follow-up

| | Full cohort (403) | Alive (191) | Death (212) | *P* value |
|---|---|---|---|---|
| Age (years) | 71.5 [64–78] | 71 [63–79] | 73 [67–79] | 0.02 |
| Death during FU | | | | |
| Total | 52.6% | - | - | - |
| Cardiovascular | 73.9% | - | - | - |
| Non cardiovascular | 17.5% | - | - | - |
| Unknown | 8.5% | - | - | - |
| BMI (kg/m$^2$) | 26.3 ± 4.9 | 26.5 ± 5.1 | 26.0 ± 4.6 | 0.30 |
| Male sex | 79.5% | 75.9% | 82.5% | 0.10 |
| Smoker | 7.4% | 7.3% | 7.7% | 0.24 |
| Hypertension | 68.8% | 64.4% | 72.6% | 0.07 |
| Dyslipidaemia | 65.6% | 67.5% | 64.2% | 0.47 |
| Diabetes Mellitus 2 | 49% | 41.4% | 56.1% | 0.003 |
| COPD | 23.8% | 20.9% | 26.4% | 0.20 |
| Atrial fibrillation/flutter | 60.9% | 56% | 65.1% | 0.06 |
| New AF in previous year | 14.7% | 13.7% | 15.5% | 0.32 |
| Aetiology | | | | |
| Dilated cardiomyopathy | 27% | 24.1% | 29.2% | 0.52 |
| Ischaemic heart disease | 52.5% | 56% | 49.5% | |
| Pulmonary hypertension | 2.2% | 2.6% | 1.9% | |
| Others | 18.3% | 17.3% | 19.3% | |
| VT ablation | 6.2% | 5.8% | 6.6% | 0.73 |
| Anticoagulation | 69.7% | 67.5% | 71.6% | 0.38 |
| Beta-blockers | 78.7% | 83.2% | 74.9% | 0.04 |
| ACE-i/ARB | 39.4% | 34.4% | 44.5% | 0.04 |
| ARNI | 33.4% | 41.8% | 26.5% | 0.001 |
| ACE-i/ARB/ARNI | 70.7% | 72.6% | 68.9% | 0.41 |
| MRA | 69.3% | 71.1% | 68.4% | 0.56 |
| Statins | 69.6% | 73.8% | 69% | 0.29 |
| Loop diuretics | 96% | 95.6% | 96.2% | 0.83 |
| Daily furosemide dosing | | | | |
| <40 mg | 25.5% | 28% | 23.3% | 0.57 |
| > 41–80 mg | 35,7% | 34.4% | 36.9% | |
| >80 mg | 38,8% | 37.6% | 39.8% | |
| Thiazides | 26.5% | 28.9% | 24.1% | 0.27 |
| Digoxin | 19.1% | 16.8% | 21.2% | 0.25 |
| Amiodarone | 22.8% | 21.7% | 24.2% | 0.56 |
| Hydralazine–nitrate combination | 9.2% | 11.1% | 7.5% | 0.22 |
| Ivabradine | 17.2% | 19.4% | 15.3% | 0.28 |
| CRT device | 30.9% | 26.2% | 35.1% | 0.05 |
| ICD | 55.2% | 55.5% | 54.7% | 0.87 |
| ICD shocks in previous year | 18.4% | 11.3% | 24.8% | 0.01 |
| ICD VT therapies previous year | 14.8% | 7.5% | 21.4% | 0.004 |
| Levosimendan in previous admission | 27% | 25.1% | 28.8% | 0.41 |
| TEER | 7.9% | 9.5% | 6.6% | 0.29 |
| Number HF admissions in previous year | | | | |
| 0 | 22.1% | 27.8% | 16.6% | 0.004 |
| 1 | 33.4% | 36.7% | 30.7% | |
| 2 | 22.6% | 16.7% | 28.1% | |
| 3 or more | 21.9% | 18.9% | 24.6% | |
| Number of HF visits in previous year | | | | |
| 0 | 45.8% | 55.2% | 46.8% | 0.20 |
| 1 | 17.3% | 20.1% | 18.6% | |
| 2 | 9.7% | 9.8% | 11.7% | |
| 3 or more | 16.7% | 14.9% | 22.9% | |
| NYHA class | | | | |
| II | 8.4% | 7.9% | 9% | 0.20 |
| III | 78.7% | 82.2% | 75.5% | |
| IV | 12.9% | 9.9% | 15.6% | |
| MAGGIC Score (median, IQR) | 27 [23–32] | 26 [22–30] | 29 [25–33] | <0.0001 |
| Systolic blood pressure (mmHg) | 106.6 ± 15.5 | 107.8 ± 16.1 | 105.3 ± 14.9 | 0.12 |
| Heart rate (b.p.m.) | 73.3 ± 13.6 | 71.2 ± 13.0 | 75.2 ± 13.9 | 0.005 |
| Haemoglobin (g/dL) | 12.6 ± 1.9 | 12.7 ± 2.1 | 12.5 ± 1.8 | 0.44 |
| Lymphocytes (%) | 19.8 ± 9.4 | 21.0 ± 8.2 | 18.8 ± 10.4 | 0.04 |
| Urea (mg/dL) | 91.7 ± 51.2 | 88.4 ± 52.4 | 94.4 ± 50.1 | 0.28 |
| Creatinine (mg/dL) | 1.6 ± 0.7 | 1.6 ± 0.8 | 1.6 ± 0.6 | 0.96 |

(*Continues*)

**Table 1** (continued)

| | Full cohort (403) | Alive (191) | Death (212) | *P* value |
|---|---|---|---|---|
| CrCl (mL/min) | 51.9 ± 24.1 | 53.2 ± 24.8 | 50.9 ± 23.4 | 0.34 |
| Sodium (mEq/L) | 138.6 ± 4.2 | 139.1 ± 3.9 | 138.1 ± 4.4 | 0.02 |
| Potassium (mEq/L) | 4.2 ± 0.6 | 4.3 ± 0.6 | 4.2 ± 0.6 | 0.32 |
| Bilirubin (mg/dL) | 1.2 ± 0.9 | 1.1 ± 0.7 | 1.2 ± 0.9 | 0.16 |
| Albumin (mg/dL) | 3.9 ± 0.5 | 4.0 ± 0.5 | 3.8 ± 0.6 | 0.01 |
| Uric Acid (mg/dL) | 8.2 ± 2.8 | 8.4 ± 2.8 | 7.9 ± 2.7 | 0.24 |
| Total cholesterol (mg/dL) | 134.2 ± 39.5 | 142.7 ± 42.4 | 126.1 ± 35.1 | 0.01 |
| NT-proBNP (median, IQR, pg/mL) | 6168 [3008, 12 904] | 5880 [2457–11 979] | 7090 [3616–13 616] | 0.001 |
| LVEF (%) | 27.5 ± 9.43 | 28.7 ± 9.7 | 26.4 ± 9.1 | 0.02 |
| LVEDD (mm) | 63.2 ± 9.3 | 63.1 ± 8.2 | 63.3 ± 10.2 | 0.78 |
| RVEF mod-severely reduced | 27.4% | 36.8% | 39.9% | 0.52 |
| TAPSE (mm) | 15.0 ± 4.3 | 15.6 ± 4.4 | 14.6 ± 4.2 | 0.06 |
| sPAP (mmHg) | 51.2 ± 15.8 | 51.4 ± 16.5 | 51.1 ± 15.2 | 0.88 |
| MR III-IV | 26.2% | 30.7% | 22.1% | 0.05 |
| TR III-IV | 21.4% | 22.8% | 20.3% | 0.54 |

Abbreviations: FU, follow-up; BMI, body mass index; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation or flutter; VT, ventricular tachycardia; ACE-i; angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonists; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; TEER, transcatheter edge-to-edge repair; HF, heart failure; NYHA, New York Heart Association; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; MR, mitral regurgitation; TR, tricuspid regurgitation.

follow-up; in 48.7% of them because of clinical improvement; and in 43.4% due to futility and only in 7.9% (3.7% of the whole cohort) because of adverse events or side effects (seven ventricular arrhythmias, one hypotension, and seven others not specified). Patients in which levosimendan was withdrawn because of clinical improvement showed the best survival (median of 54.6 months), followed by those that continued with levosimendan (median of 24.7 months, 95% CI: 19.3–29.9). Patients in which levosimendan was stopped due to futility (median, months, 11.8 95% CI: 6.5–17.1) or side effects (median, months, 10.8 95% CI: 4.5–17) showed the worst survival ($P < 0.0001$).

## Levosimendan

One hundred nine patients already had received at least one previous dose as inpatients (27%) (*Table 3*). Administration was very heterogeneous between centres. The most common initial strategy was bailout (40.2%) and when a fixed number of doses was the one selected (33.3%), in 95.5% of the cases six doses were given, in 72.3% every 2 weeks, resembling the LION-HEART protocol [4]. Most of the patients remained within the same strategy during follow-up. Patients in the sine die group received more doses. Initial or final levosimendan strategy did not influence the outcomes and the three groups were quite homogeneous, without significant differences in the risk profile considering the MAGGIC score. Patients treated as sine die protocol since the beginning showed the lowest sodium (mg/dL, 137.8 ± 4.3 vs. 138.8 ± 4.2; $P = 0.04$) and albumin (mg/dL, 3.8 ± 0.4 vs. 4.0 ± 0.6; $P = 0.02$) and a strong tendency to lower total cholesterol (mg/dL, 128.6 ± 35 vs. 136.4 ± 41.6; $P = 0.06$) and percentage of lymphocytes (%, 18.6 ± 8.2 vs. 20.6 ± 10; $P = 0.07$), all of them related to more advanced disease, frailty and malnutrition.

Regarding the dose at each administration, the most common approaches were 6.25 mg (38%) and 0.2 mcg/kg/min for 6 h (28%). As per our definitions, 61.5% of patients received high dose of levosimendan and 38.5% low dose. Those patients receiving the high dose showed better survival at 1 year and long-term, but no higher probability of being a responder. Dosing also reflected different clinical profile but with mixed results, as those with lower doses had worst MAGGIC score (median, IQR, 29 [24.5–33.5] vs. 26 [21.5–30.5] $P < 0.0001$), lower blood pressure (mmHg, 103.6 ± 14.3 vs. 108.5 ± 15.9; $P = 0.002$) and were older (years, 71.3 ± 11.3 vs. 68.2 ± 11.3; $P = 0.007$) but also had better LVEF (%, 28.8 ± 5.9 vs. 26.3 ± 5.8; $P = 0.05$) and percentage of lymphocytes (%, 21.1 ± 10.5 vs. 18.6 ± 8.2; $P = 0.02$).

## Multivariate analysis

We analysed factors related to overall survival, 1 year survival and responder status, including levosimendan dosing per administration (low or high) as it was strongly related to better outcomes in the univariate analysis (*Table 4*). Treatment with beta-blockers (HR 1.44, 95% CI: 1.03–2.06; $P = 0.04$) and haemoglobin over 12 g/dL (HR 1.52; 95% CI: 1.11–2.08; $P < 0.008$) and previous treatment with TEER (HR 2.06; 95% CI: 1.01–4.27; $P = 0.04$), were independently related to 1-year levosimendan response, whereas previous HF unplanned visit (HR 1.97; 95% CI: 1.43–2.71; $P < 0.0001$), heart rate over 70 b.p.m. (HR 1.43; 95% CI: 1.04–1.96; $P = 0.02$), and treatment with amiodarone (HR 1.45; 95% CI: 1.01–

**Table 2** Demographics and baseline data comparing 1-year outcomes (death and responder status)

| | Survival at 1 year (295) | Death at 1 year (108) | *P* value | Responders at 1 year (176) | Non-responders at 1 year (227) | *P* value |
|---|---|---|---|---|---|---|
| Age (years) | 71 [14] | 74 [12] | 0.02 | 71 [14] | 72 [14] | 0.30 |
| BMI (kg/m$^2$) | 26.5 ± 5.0 | 25.6 ± 4.3 | 0.11 | 26.4 ± 5.2 | 26.1 ± 4.6 | 0.28 |
| Male sex | 79.3% | 79.6% | 0.94 | 79.5% | 79.3% | 0.95 |
| Smoker | 6.5% | 10.3% | 0.44 | 5.7% | 8.9% | 0.48 |
| Hypertension | 66.8% | 74.1% | 0.16 | 61.9% | 74% | 0.009 |
| Dyslipidaemia | 66.8% | 63% | 0.47 | 66.5% | 65.2% | 0.79 |
| Diabetes mellitus 2 | 46.1% | 57.4% | 0.04 | 43.8% | 53.3% | 0.05 |
| COPD | 23.4% | 25% | 0.74 | 22.2% | 25.1% | 0.49 |
| Atrial fibrillation/flutter | 60.3% | 62% | 0.75 | 58.5% | 62.6% | 0.41 |
| New AF previous year | 13.3% | 18.2% | 0.10 | 14.4% | 14.9% | 0.65 |
| Aetiology | | | | | | |
| Dilated cardiomyopathy | 24.7% | 32.4% | 0.31 | 24.4% | 28.6% | 0.66 |
| Ischaemic heart disease | 55.3% | 45.4% | | 55.7% | 50.2% | |
| Pulmonary hypertension | 2.4% | 1.9% | | 1.7% | 2.6% | |
| Others | 17.6% | 20.4% | | 18.2% | 18.5% | |
| VT ablation | 5.1% | 9.3% | 0.12 | 5.7% | 6.6% | 0.70 |
| Anticoagulation | 68.8% | 72% | 0.54 | 69.3% | 69.9% | 0.89 |
| Beta-blockers | 81.7% | 71% | 0.02 | 85.2% | 73.9% | 0.006 |
| ACE-i/ARB | 28.5% | 43% | 0.41 | 37.9% | 41.1% | 0.53 |
| ARNI | 36.5% | 26.2% | 0.05 | 38.5% | 30.1% | 0.08 |
| ACE-i/ARB/ARNI | 71.9% | 67.3% | 0.37 | 73.9% | 66.4% | 0.10 |
| ARM | 72.4% | 62% | 0.04 | 73.6% | 68.4% | 0.26 |
| Statins | 73% | 66.3% | 0.20 | 71.6% | 71.1% | 0.91 |
| Loop diuretics | 95.9% | 96.3% | 0.86 | 97.2% | 95.2% | 0.31 |
| Daily furosemide dose | | | | | | |
| <40 mg | 28% | 18.4% | 0.14 | 30.6% | 21.5% | 0.06 |
| >41–80 mg | 33.9% | 40.8% | | 35.8% | 35.6% | |
| >80 mg | 38.1% | 40.8% | | 33.5% | 42.9% | |
| Thiazides | 28.2% | 21.3% | 0.16 | 26.3% | 26.4% | 0.97 |
| Digoxin | 19.7% | 17.6% | 0.64 | 20.5% | 18.1% | 0.54 |
| Amiodarone | 21.6% | 27% | 0.26 | 17.7% | 27.1% | 0.03 |
| Hydralazine–nitrate combination | 9.2% | 9.3% | 0.98 | 8% | 10.1% | 0.46 |
| Ivabradine | 17.7% | 16% | 0.70 | 18.2% | 16.5% | 0.66 |
| CRT device | 32.3% | 26.9% | 0.29 | 33.1% | 29.1% | 0.38 |
| ICD | 59.3% | 43.5% | 0.005 | 55.1% | 55.1% | 0.99 |
| ICD shocks | 17.1% | 22.9% | 0.36 | 18.6% | 18.3% | 0.94 |
| ICD VT therapies previous year | 11.4% | 27.6% | 0.007 | 14.4% | 15.1% | 0.89 |
| Levosimendan in previous admission | 27.1% | 26.9% | 0.96 | 26.7% | 27.3% | 0.89 |
| TEER | 8.2% | 7.4% | 0.79 | 10.9% | 5.8% | 0.06 |
| Number HF admissions in previous year | | | | | | |
| 0 | 16.8% | 23.7% | 0.06 | 25.7% | 18.9% | 0.03 |
| 1 | 32.7% | 33.8% | | 37.7% | 30.2% | |
| 2 | 31.7% | 19.4% | | 16.8% | 27.4% | |
| 3 or more | 18.8% | 23% | | 19.8% | 23.6% | |
| Number of HF visits in previous year | | | | | | |
| 0 | 45.2% | 52.8% | 0.33 | 64.4% | 40.1% | <0.0001 |
| 1 | 22.6% | 18.2% | | 18.8% | 19.8% | |
| 2 | 8.6% | 11.5% | | 5% | 15.3% | |
| 3 or more | 23.7% | 17.5% | | 11.9% | 24.8% | |
| NYHA class | | | | | | |
| II | 8.8% | 7.4% | 0.003 | 9.7% | 7.5% | 0.06 |
| III | 81.7% | 70.4% | | 81.8% | 76.2% | |
| IV | 9.5% | 22.2% | | 8.5% | 16.3% | |
| MAGGIC score (median, IQR) | 26 [21.5–30.5] | 29 [25.5–32.5] | <0.0001 | 26 [22–30] | 29 [25–33] | 0.001 |
| Systolic blood pressure (mmHg) | 107.2 ± 16.1 | 104.7 ± 13.8 | 0.16 | 105.8 ± 16.4 | 107.2 ± 14.8 | 0.33 |
| Heart rate (b.p.m.) | 71.9 ± 12.5 | 77.0 ± 15.6 | 0.001 | 71.3 ± 11.9 | 74.8 ± 14.6 | 0.01 |
| Haemoglobin (g/dL) | 12.7 ± 1.9 | 12.5 ± 1.9 | 0.42 | 13.0 ± 1.9 | 12.3 ± 1.9 | 0.001 |
| Lymphocytes (%) | 19.7 ± 8.1 | 20.1 ± 12.1 | 0.79 | 20.8 ± 7.9 | 19.1 ± 10.4 | 0.13 |
| Urea (mg/dL) | 87.3 ± 49.8 | 102.9 ± 53.3 | 0.01 | 83.5 ± 48.9 | 97.7 ± 52.1 | 0.01 |
| Creatinine (mg/dL) | 1.6 ± 0.7 | 1.7 ± 0.7 | 0.15 | 1.6 ± 0.8 | 1.6 ± 0.7 | 0.41 |
| CrCl (mL/min) | 52.9 ± 23.3 | 49.4 ± 26.1 | 0.19 | 53.3 ± 22.7 | 50.9 ± 25.1 | 0.33 |
| Sodium (mEq/L) | 138.8 ± 4.1 | 138.0 ± 4.4 | 0.10 | 138.5 ± 4.2 | 138.6 ± 4.3 | 0.95 |
| Potassium (mEq/L) | 4.3 ± 0.6 | 4.2 ± 0.6 | 0.14 | 4.3 ± 0.6 | 4.2 ± 0.6 | 0.09 |
| Bilirubin (mg/dL) | 1.2 ± 0.9 | 1.1 ± 0.7 | 0.85 | 1.2 ± 1.0 | 1.1 ± 0.7 | 0.24 |
| Albumin (mg/dL) | 3.9 ± 0.5 | 3.9 ± 0.6 | 0.45 | 4.0 ± 0.5 | 3.9 ± 0.6 | 0.19 |
| Uric Acid (mg/dL) | 8.5 ± 2.8 | 7.5 ± 2.5 | 0.04 | 8.5 ± 2.8 | 8.0 ± 2.7 | 0.19 |

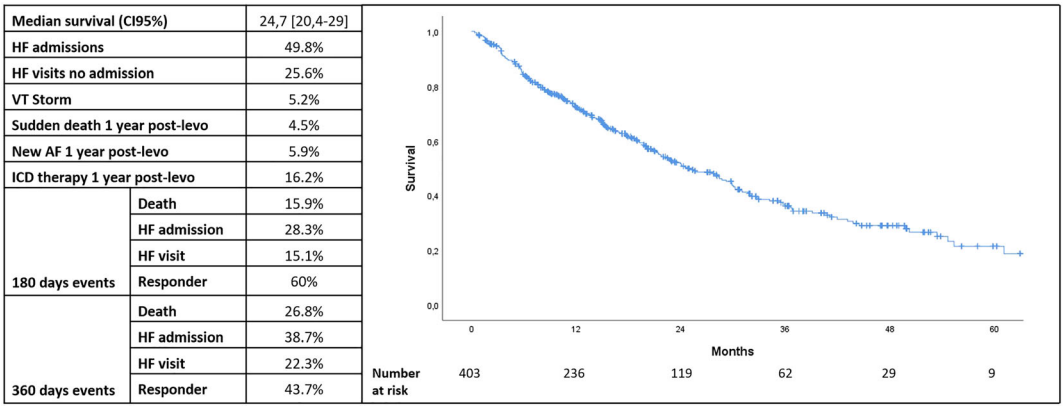
(*Continues*)

**Table 2** (continued)

| | Survival at 1 year (295) | Death at 1 year (108) | *P* value | Responders at 1 year (176) | Non-responders at 1 year (227) | *P* value |
|---|---|---|---|---|---|---|
| Total cholesterol (mg/dL) | 137.4 ± 40.0 | 125.5 ± 37.3 | 0.03 | 140.4 ± 40.1 | 129.7 ± 38.1 | 0.03 |
| NT-proBNP (median, IQR, pg/mL) | 5874 [2626, 11 975] | 9361 [4281, 14 906] | 0.001 | 5871 [2536–11 464] | 6951 [3614–14 000] | 0.001 |
| LVEF (%) | 27.8 ± 9.8 | 26.5 ± 8.3 | 0.19 | 28.0 ± 10.0 | 27.1 ± 8.9 | 0.31 |
| LVEDD (mm) | 63.5 ± 9.0 | 62.3 ± 9.9 | 0.25 | 63.9 ± 9.1 | 62.7 ± 9.4 | 0.24 |
| RVEF mod-severely reduced | 38.2% | 38.8% | 0.92 | 39.6% | 37.4% | 0.66 |
| TAPSE (mm) | 15.2 ± 4.3 | 14.7 ± 4.5 | 0.36 | 14.9 ± 4.2 | 15.1 ± 4.4 | 0.85 |
| sPAP (mmHg) | 51.0 ± 15.9 | 51.8 ± 15.4 | 0.69 | 52.4 ± 16.7 | 50.4 ± 15.1 | 0.30 |
| MR III-IV | 26.1% | 26.4% | 0.95 | 28.5% | 24.4% | 0.36 |
| TR III-IV | 21.8% | 20.8% | 0.83 | 22.5% | 20.7% | 0.67 |

Abbreviations: FU, follow-up; BMI, body mass index; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation or flutter; VT, ventricular tachycardia; ACE-i, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonists; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; TEER, transcatheter edge-to-edge repair; HF, heart failure; NYHA, New York Heart Association; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; MR, mitral regurgitation; TR, tricuspid regurgitation.

**Figure 1** Main outcomes and events of the full cohort during the follow-up. VT, ventricular tachycardia; AF, atrial fibrillation/flutter; ICD, implantable cardioverter defibrillator; HF, heart failure.




2.11; *P* = 0.04) were related to decrease probability of response to levosimendan. Levosimendan dosing per administration (high or low) did not influence 1 year response rate (HR 1.13; 95% CI: 0.82–1.56; *P* = 0.45), 1 year mortality (HR 0.73; 95% CI: 0.47–1.13; *P* = 0.16) or overall all-cause mortality, although high dose showed a tendency that was close to reach statistical significance (HR 0.70; 95% CI: 0.50–1.01; *P* = 0.05).

## LEVO-D score

We created a simple score that helps predicting the 'responder' status at 1 year after levosimendan with the use of the relative magnitude of the coefficient of regression in the multivariable model (*Figures 3* and *4*). Points were assigned to the covariates and values were rounded to the nearest integer or .5, resulting in a score summatory of five variables (*Figure 3*). LEVO-D score ranged from −5 to + 5. We created three groups: Low probability of response (LEVO-D Score −5 to −1.5, 24.3% of the cohort), intermediate (−1 to +1.5, 60.2% of the cohort) and high (2 to 5, 15.4% of the cohort). Probability of response was significantly higher in the first group (68.4%) versus the other two (50.9% and 21.5% respectively; $P < 0.0001$). The LEVO-D score performed well when examining its prediction power in the ROC analysis (*Figure 4*, AUC 0.71), better than the MAGGIC score (AUC 0.60) in this cohort.

# Discussion

In this report, we present the largest multi-centre real-life series of end-stage heart failure on optimal therapy not candidates to advanced therapies, treated with ambulatory period-


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**Figure 2** Heart failure events the year before and after first ambulatory levosimendan infusion. HFH, Heart failure hospitalizations; UVHF, unplanned visits due to heart failure; HF, heart failure; ICD, implantable cardioverter defibrillator.

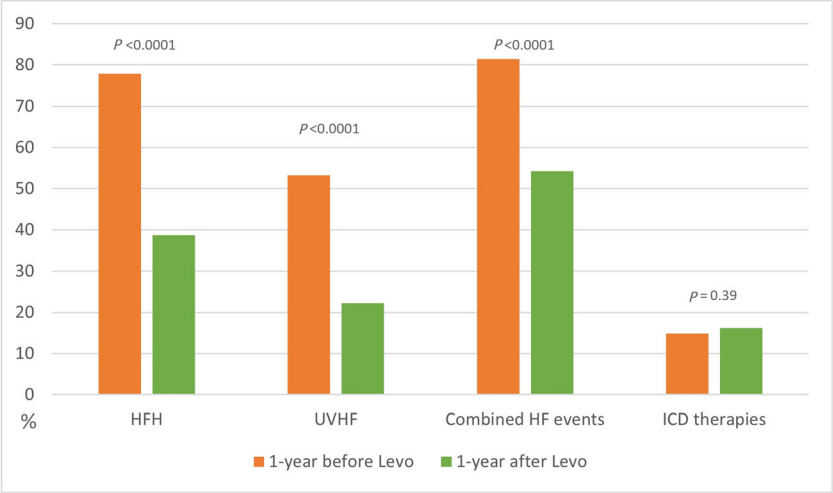



**Table 3** Characteristics and outcomes depending on strategy and levosimendan dosing per administration

| | Bailout | Fixed number | Sine die | *P* value | High dose | Low dose | *P* value |
|---|---|---|---|---|---|---|---|
| Initial strategy | 40.2% | 33.3% | 26.5% | - | - | - | - |
| Final strategy | 35.8% | 30.8% | 33.4% | - | - | - | - |
| Risk profile MAGGIC (median, IQR) | 27 [22.5–31.5] | 28 [24, 32] | 27 [23, 31] | 0.55 | 26 [21.5–30.5] | 29 [24.5–33.5] | <0.0001 |
| Number doses (median, IQR) | 4 [2, 6] | 6 [3,9] | 11 [3, 19] | <0.0001 | 6 [2, 10] | 6 [1, 12] | <0.0001 |
| Median survival (95% CI) | 27.7 [21.4–34] | 23.3 [15.5–31.1] | 22.8 [14.9–30.7] | 0.73 | 29.9 [25–34.7] | 18.9 [14.4–23.5] | 0.003 |
| 1 year survival | 74.2% | 73.5% | 69.5% | 0.68 | 78.6% | 64.5% | 0.002 |
| 1-year HFH | 34% | 42.4% | 40% | 0.31 | 39.5% | 37.4% | 0.67 |
| Responder | 45.3% | 41.7% | 43.8% | 0.82 | 44.4% | 42.6% | 0.73 |

Abbreviations: IQR, interquartile range; HFH, heart failure hospitalizations.

ical levosimendan infusions. We show that in this elderly and high-risk population, 1 year mortality was high (26.8%) and levosimendan was able to decrease the rate of HF hospitalization or unplanned HF visits from more than 80% the year before to 56% the year after, which is very significant as in this 56% of non-responders, those who died—26.8% at 1 year—were also included. Levosimendan was able to decrease the total number of HF hospitalizations (by 33%) and unplanned HF visits (by 50%). This was achieved without increasing the number of ICD therapies and with a low rate of side effects.

The impact of levosimendan on HF decompensations requiring medical assistance shown in this report it is in consonance with data from small, randomized trials[4,5] and a small number of retrospective works[6,7] in the whole spectrum of AHF, but our cohort focus specifically in those not candidates to advanced therapies. LEVO-REP trial[8] did not show improved outcomes with levosimendan, but the subsequent LION-HEART trial[4] using a similar protocol but in six doses, was able to reduce the risk of death/HF hospitalization (mainly due to HF hospitalizations) similarly to the results we show and LAICA trial,[5] which used a different levosimendan protocol of 24-h infusions. These trials included younger patients and candidates for advanced therapies. The RELEVANT-HF registry[7] with intermittent levosimendan shows some similarities to our work, but the population studied was smaller, of less risk, younger and, around 40% candidate to advanced therapies. Despite this, the comparable death/heart transplant/LVAD 1 year rate was 24%, very similar to LEVO-D.

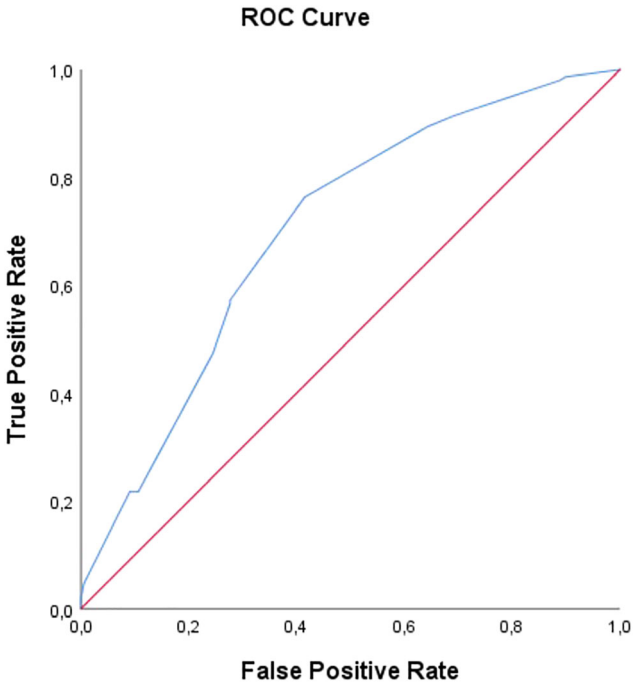
LEVO-D population showed great similarity to the high risk (over 8000 NT-proBNP) cohort of the VICTORIA trial[9]; MAGGIC score, LVEF or NT-proBNP were very similar. Comparing outcomes, the LEVO-D showed a rate of 24.1 cardiovascular death and 30.1 HF hospitalization events per 100 patients-year. This higher risk VICTORIA cohort showed a rate between (placebo and vericiguat, respectively) 22.9 and 26.5 cardiovascular death and between 51.6 and 60.7 HF hospitalization events per 100 patients-year. Death rates are similar, but LEVO-D showed significantly lower HF hospitalization rates after levosimendan. This helps discarding that the decrease in HF events observed in our work was related to more medical consultations, as patients included in VICTORIA had

**Table 4** Multivariate analysis: Overall and 1 year survival

| Variable | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| Overall mortality | | |
| Age (per year increase) | 1.02 (1.004–1.039) | 0.02 |
| Diabetes Mellitus 2 | 1.49 (1.08–2.08) | 0.02 |
| VT ablation | 1.93 (1.01–3.67) | 0.046 |
| Atrial arrhythmias | 1.20 (0.84–1.69) | 0.32 |
| Beta-blockers | 0.90 (0.77–1.11) | 0.55 |
| CRT device | 0.75 (0.74–1.06) | 0.11 |
| ICD therapies year before | 2.10 (1.23–3.59) | 0.006 |
| HF hospitalization year before | 1.24 (0.80–1.90) | 0.32 |
| Heart rate (b.p.m.) | 1.02 (1.011–1.03) | 0.03 |
| Lymphocyte percentage (%) | 1.01 (0.98–1.03) | 0.35 |
| Sodium (mEq/L) | 1.03 (1.01–1.07) | 0.04 |
| Total cholesterol (mg/dL) | 0.99 (0.98–0.99) | 0.01 |
| NT-proBNP (per 1000 pg/mL increase) | 1.02 (1.01–1.03) | 0.03 |
| LVEF (%) | 0.97 (0.95–0.99) | 0.008 |
| TAPSE (mm) | 0.97 (0.93–1.03) | 0.36 |
| Levosimendan dosing (low/high) | 0.70 (0.50–1.01) | 0.05 |
| NYHA class IV | 1.17 (0.75–1.83) | 0.47 |
| MR grades III-IV | 1.25 (0.88–1.80) | 0.21 |
| Ischaemic heart disease | 1.84 (1.31–2.57) | <0.0001 |
| 1 year mortality | | |
| Age (per year increase) | 1.016 (0.99–1.04) | 0.21 |
| Diabetes mellitus 2 | 1.36 (0.88–2.12) | 0.16 |
| VT ablation | 2.84 (1.18–5.95) | 0.01 |
| Beta-blockers | 0.71 (0.44–1.15) | 0.17 |
| MRA | 0.86 (0.54–1.37) | 0.53 |
| ICD device | 0.63 (0.38–0.98) | 0.04 |
| ICD therapies year before | 2.27 (1.09–4.76) | 0.03 |
| HF hospitalization year before | 1.16 (0.66–2.06) | 0.59 |
| Heart rate (b.p.m.) | 1.02 (1.002–1.03) | 0.03 |
| Urea (mEq/L) | 1.006 (0.99–1.003) | 0.56 |
| Total cholesterol (mg/dL) | 0.99 (0.98–1.002) | 0.12 |
| NT-proBNP (per 1000 pg/mL increase) | 1.02 (0.99–1.03) | 0.15 |
| Levosimendan dosing (low/high) | 0.73 (0.47–1.13) | 0.16 |
| NYHA class IV | 1.26 (0.73–2.19) | 0.39 |
| Ischaemic heart disease | 1.87 (1.21–2.90) | 0.005 |

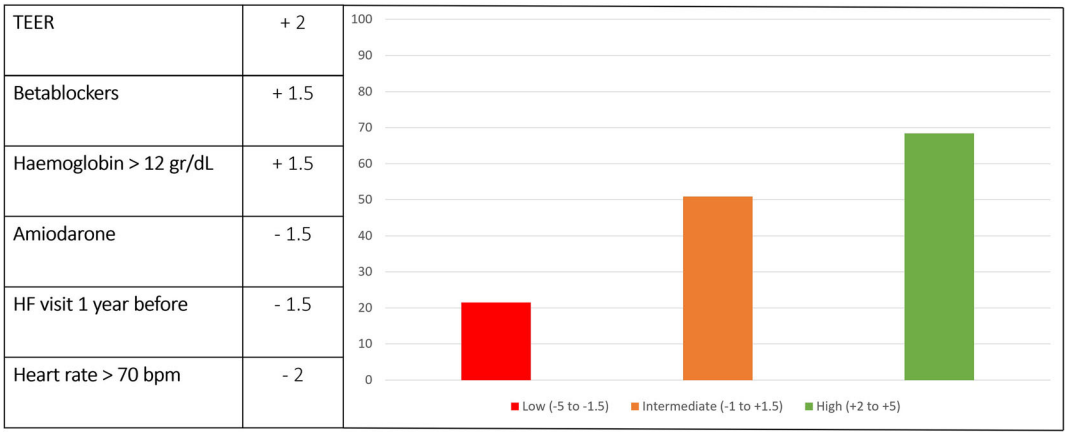
Abbreviations: VT, ventricular tachycardia; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; MR, mitral regurgitation.

**Figure 4** ROC curve of the LEVO-D score for discriminating 1-year levosimendan response.




also frequent clinical visits as part of the trial and access to rapid medical evaluation if decompensation. The MedaMACS[10] also focused on patients with true AHF and (at least initially) medical management; MedaMACS 1-year death/Trasplant/LVAD rate in MedaMACS was not so different to our cohort (34% vs. 26.8%) and again 1 year HF hospitalization was higher (57% vs. 38.7%), but patients were significantly younger (more than 10 years), with poorer LVEF (21% vs. 27%) and less comorbid, which makes comparisons more difficult.

**Figure 3** LEVO-D score and the probability of response to levosimendan of the three categories (low, intermediate and high probability of response). TEER, transcatheter edge-to-edge repair; HF, heart failure.



## Strategy and dosing

We show that in real life, levosimendan is used in a very heterogenous manner during a mean time of treatment of around 10 months. We could not find that the strategy of how to use it or the number of doses given were related to better outcomes, suggesting that a bailout approach might be enough for this population. A sine die approach in our cohort was used in patients with signs of more advanced general disease (mainly malnutrition), thus clinician perception of disease severity probably led to the decision of giving the drug indefinitely, but this population did not have worse HF profile and did not get benefit of the higher number of doses given. The way levosimendan was administered in this cohort was even more heterogeneous than in other experiences published[7] as each centre followed their own criteria and protocols.

In the univariate analysis, higher dose per administration was related to better 1 year and overall survival; this was not significant in the multivariate analysis. There is no clear data in the literature about ideal levosimendan dosing for outpatients. Pivotal clinical trials of in-hospital acute heart failure patients used doses ranging between 0.05 and 0.2 mcg/kg/min in 24 h, being 0.2 mcg/kg/min the most commonly used,[11] but it was 0.1 mcg/kg/min in the LAICA[5] for outpatients who required hospital admission to receive the infusion. Outpatient LION-HEART and LEVO-Rep protocols[4,8] used 0.2 mcg/kg/min for 6 h, which allows treatment of the patients in a fully ambulatory way in a day hospital. This approach in most of patients results in less dosing per administration than 24-h infusions at 0.1 or 0.2 mcg/kg/min. In most of the patients under levosimendan protocols as an outpatient, one vial of 12.5 mg is used for two patients, thus a 'half vial' dose (6.25 mg) is commonly used, and this was the case in 40% of our cohort. Again, most of the patients using LION-HEART or LEVO-Rep protocols received less than 6.25 mg per administration (the lower limit for the 'high dose group'). Low number of administrations was blamed to be the cause of the lack of effect of the drug in the LEVO-Rep and the increase to six doses in the LION-HEART may have resulted in the significant effect observed in reducing HF hospitalizations. Our cohort received a median of six doses of the drug. The results of this work might raise the question if 0.2 mcg/kg/min for 6 h is enough for most of the patients when receiving at least six doses of levosimendan. Furthermore, we did not find a signal that dosing correlates with HF events, as the response rate at 1 year was not related to dosing, which might suggest that even low doses could be beneficial in terms of reducing HF events.

## LEVO-D score and mortality

The LEVO-D score we show might be of help for the clinician to decide whether levosimendan infusions may be futile in certain patients, especially when clinical judgement is concordant with a low probability of achieving a favourable response to levosimendan. Age was not related to 1-year outcomes and maybe more modestly than expected to overall mortality. This reflects the short survival expectancy of this population, but also that age should not be a decisive factor to be considered when deciding to start intermittent treatment with levosimendan.

Factors related to overall mortality in the multivariate analysis were the usual ones described in other cohorts of heart failure. Neurohormonal blockade was not related to reduced overall or 1 year mortality, which is in consonance with the scarce data we have about its use in this population. Bucindolol[12] was not able to reduce all-cause mortality but HF hospitalizations, but these patients were not true AHF as their risk profile and mortality rates were low.[10] In the most recent LIFE trial in true AHF,[13] sacubitril-valsartan did not reduce NT-proBNP values compared with valsartan. Even not going into AHF, NYHA III patients are clearly underrepresented in pivotal heart failure trials. Subgroup's analysis suggests that effects on hard endpoints are at least attenuated in NYHA III-IV.[14–16] On the other hand, we have retrospective data[17,18] that correlates HF drug down titration to worse outcomes, although it cannot be ascertained how much of this deterioration is because of the decrease in HF drugs, or if the decrease of HF drugs is mainly a marker of disease progression.

## Limitations

This is a retrospective study thus it is subject to bias by its nature, data were not obtained at pre-specified times and every centre used its own levosimendan protocols for administration and patient follow-up.

## Conclusion

In this large real-life series of AHF patients treated with levosimendan as destination therapy, we show a significant decrease of heart failure events during the year after the first administration. The simple LEVO-D Score could be of help when deciding about futile therapy in this population. More evidence is needed to refine the dosing and administration protocols of ambulatory levosimendan infusions.

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## Conflict of interest

D.D., J.G.C., J.J.B., and J.F. received speaker fees from Orion.

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