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Intermittent levosimendan infusions in advanced heart failure: a real world experience

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Abstract

Objective: To analyse the effects of levosimendan infusions in advanced heart failure.

Methods: Patients with advanced heart failure treated with repeated levosimendan infusions were retrospectively compared with controls. Clinical, blood and echocardiographic parameters were obtained at baseline and after 12 months, and before and after each levosimendan infusion. Hospitalizations for heart failure and in-hospital length of stay in the 6 months before enrolment and after 6 and 12 months were recorded, along with 1-year mortality.

Results: Twenty-five patients treated with levosimendan and 25 controls were studied. After each levosimendan infusion, ventricular function and various clinical and metabolic parameters were improved. After 12 months, left ventricular ejection fraction (LVEF) had improved compared with baseline in the levosimendan group. The 1-year mortality rate was similar in both groups. During the 6 months before enrolment, hospitalizations were fewer in controls compared with the levosimendan group; after 6 and 12 months they increased in controls and decreased in the levosimendan group. Seven patients were super-responders to levosimendan, with LVEF improving more than 20% and hospitalizations being reduced at 12 months compared with the rest of the levosimendan group.

Conclusion: Intermittent levosimendan improved LVEF and decreased hospitalizations in advanced heart failure and represents a therapeutic option for patients whose disease is worsening.

Keywords

Advanced chronic heart failure, intermittent levosimendan, inotropic drugs

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Introduction

The advanced stages of heart failure are associated with a poor quality of life, with frequent hospitalizations and the need for inotropic support.[1,2] Unlike other intropes, the calcium sensitizer levosimendan does not increase intracellular calcium concentration but facilitates calcium binding to troponin C,[3] thus improving myocardial contractility without an increase in oxygen consumption.[4] Moreover, levosimendan also acts as a vasodilator through its effects on adenosine triphosphate-activated potassium channels[5] and has an intriguing pharmacokinetic profile due to its long-acting metabolites.[6] Apart from its use in acute heart failure in selected patients as suggested in the European Society of Cardiology (ESC) guidelines,[1] many single centre studies investigating the effects of pulsed levosimendan infusions in chronic heart failure have reported encouraging results.[7–11] In the Heart Failure Unit at San Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy, a clinical protocol has been developed to allow the use of levosimendan in patients with New York Heart Association (NYHA) class III heart failure, long-standing disease and frequent hospitalizations,[10,12] that is, the 'frequent flyers' of the INTERMACS classification.[13] The aim of this retrospective study was to present a real-world experience in the intermittent administration of levosimendan, assessing its effects on morbidity, mortality and hospitalizations in an open comparison with patients not treated with the drug.

Patients and methods

Patients

Patients with chronic systolic heart failure of >2 years' duration treated in the Heart Failure Unit at San Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy, from January 2013 to December 2014 whose treatment was optimized following ESC guidelines[1] (including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II type 2 receptor inhibitors, aldosterone inhibitors and diurectics) and who had been treated with repeated levosimendan infusions in accordance with the institutional protocol[10,12] were included in the study. Patients with arterial hypotension or severe renal failure (estimated glomerular filtration rate <30 ml/min) were excluded, as treatment with levosimendan is not indicated in such patients.[7–10] Patients with similar clinical characteristics who, despite being eligible, did not receive repeated levosimendan infusions, either because they were not referred by their physicians or because they refused the treatment for personal or logistical reasons, were used as controls.

Echocardiographic and blood parameters were evaluated at baseline and after 12 months; during this period all patients were treated according to the ESC guidelines.[1] In addition, some patients from both groups underwent intermittent outpatient infusions of furosemide, and patients in the levosimendan group followed an additional programme of levosimendan infusions, echocardiograms and blood tests.[10]

All patients provided written informed consent. The study formed part of an institutional clinical protocol[10,12] approved by the Ethical Committee of the Istituto Auxologico Italiano IRCCS (LEVOrep 09C716_2007) and conformed to the principles of the Declaration of Helsinki.

Levosimendan treatment

The protocol for levosimendan infusion has been described in detail elsewhere.[10] Briefly, levosimendan (Simdax®, Abbott Laboratories, Abbott Park, IL, USA) was administered intravenously without an initial loading dose, as a continuous infusion at 0.1–0.2 μg/kg per min, to a total dose of

12.5 mg, which usually occurs within 24–48 h. The number of infusions and the interval between them were set for each patient according to their clinical condition. In line with previous experience,[8,9,11] a cycle of three infusions at 28-day intervals was performed in all patients, with additional infusions being given if a patient showed clinical worsening at monthly follow-up visits.

Echocardiographic assessment

Echocardiographic examination, including Doppler and tissue Doppler imaging analysis, was performed at baseline and at the end of the 12-month follow-up period in all patients. In addition, echocardiography was performed in the levosimendan group within 12 h before and within 12 h after each infusion of levosimendan,[10,14] in accordance with the recommendations of the American Society of Echocardiography.[15] At each echocardiographic examination, left ventricular ejection fraction (LVEF), estimated systolic pulmonary artery pressure and left ventricular end-diastolic volume were recorded. Pulsed Doppler was used to assess transmitral and pulmonary venous flow in the apical four-chamber view. Tissue Doppler velocities were acquired at the septal and lateral annular sites. Mitral inflow measurements included peak early (E) and peak late (A) velocities, the E/A ratio and the deceleration time of E velocity. Pulmonary venous flow measurements included peak systolic, diastolic, atrial reversal velocities, systolic filling fraction and duration of atrial reversal. The early diastolic (E′) velocity at the septal and lateral annular sites was measured using tissue Doppler, and the E/E′ ratio was calculated using the mean of the septal and lateral E′ values. The severity of mitral regurgitation was graded semi-quantitatively from minimal (grade 1) to severe (grade 4) using colour-flow Doppler images of the apical four-chamber view.

Assessment of blood parameters

Blood samples were taken to assess serum creatinine (with the glomerular filtration rate being estimated using the Cockroft–Gault formula), serum electrolytes, haemoglobin and plasma B-type natriuretic peptide (BNP) levels (measured using the Triage BNP Test®, Biosite, San Diego, CA, USA, according to the manufacturer's instructions) at baseline and at the end of the 12-month follow-up period in all patients. In addition, blood samples were obtained within 12 h before and within 12 h after each infusion of levosimendan for the measurement of the same set of parameters in the levosimendan group.

Assessment of outcomes

The primary endpoints considered were mortality at 12 months and hospitalizations for heart failure in the 0–6 month period and the 0–12 month period of follow up. Both the total number of hospitalizations and the length of stay in hospital were recorded; admissions to the Emergency Department were not included. The number of hospitalizations and in-hospital length of stay in the 6 months before the baseline evaluation were used for comparison. Changes in clinical, blood and echocardiographic parameters over the same observation periods were used as secondary endpoints. All-cause mortality was assessed at 12 months after baseline.

Statistical analyses

Categorical variables were expressed as the number of patients and percentages and compared using the χ^2-test. Continuous variables were expressed as the mean ± SD and compared using either the paired or unpaired Student's t-test. A P-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using

OriginPro software version 7.0 (OriginLab, Northampton, MA, USA).

Results

A total of 25 patients who had received repeated levosimendan infusions were included in the study, along with 25 patients with similar clinical characteristics who were eligible for levosimendan treatment but did not receive it because they were not referred by their physicians ($n = 10$) or because treatment was refused for personal or logistical reasons ($n = 15$) as controls. Baseline patient characteristics are given in Table 1. No statistically significant differences were observed between the levosimendan and control groups with regard to age, clinical history, heart failure aetiology, comorbidities, NYHA class, renal function, haemoglobin level, medical treatment or the cardiac and comorbid condition heart failure (3C-HF) score.[16]

A total of 16 patients received intermittent outpatient infusions of furosemide, six in the levosimendan group and 10 in the control group.

Acute effects of levosimendan

The mean infusion time for levosimendan was 32.8 h. A total of 147 infusions were performed. Patients underwent a mean of 4.12 infusions (range 3–5), with a mean interval between infusions of 56 days (range 28–90 days) and a mean interval between the baseline and last infusion of 7.1 months (range 3–10 months). No side effects were observed apart from asymptomatic hypotension requiring a lower infusion rate, which occurred in nine patients.

In the patients receiving levosimendan, there was a statistically significant improvement from baseline in both systolic and diastolic function after the first infusion (Table 2). There was also a reduction in BNP levels, a clear improvement in renal function, and a slight decrease in haemoglobin and potassium levels (Table 2). Similar effects were seen after each subsequent levosimendan infusion (data not shown).

Follow-up results

After 12 months' follow-up, NYHA class had remained stable in the levosimendan group (2.75 ± 0.26 at 12 months compared with 2.96 ± 0.32 at baseline), but had significantly worsened in the control group (3.23 ± 0.21 at 12 months compared with 2.86 ± 0.40 at baseline, $P = 0.047$). At baseline there were no differences between the two groups with regard to echocardiographic data (Table 1). However, after 12 months follow-up, there was a slight improvement in LVEF ($P = 0.018$) compared with baseline in the levosimendan group and a worsening of estimated pulmonary pressure ($P = 0.02$) in the control group (Table 3). In the levosimendan group, serum creatinine and estimated glomerular filtration rate worsened compared with baseline values, but did not differ from the values observed in the control group (Table 3). In the 43 patients for whom data were available, BNP levels did not change significantly in the levosimendan group ($n = 23$) but were higher at follow-up in the control group ($n = 20$) ($P = 0.046$).

Mortality and hospitalization

After 12 months, mortality was similar in the two groups: two patients in the control group and three patients in the levosimendan group had died (mortality rates of 8% and 12%, respectively). In both groups the mortality rate was lower than that predicted by the baseline 3C-HF score (Table 1). In the 6 months preceding the baseline analysis, the number of hospitalizations and the in-hospital length of stay were lower in the

Table 1. Baseline characteristics in patients with chronic systolic heart failure who received (levosimendan group) or did not receive (control group) treatment with intermittent levosimendan infusions.

	Levosimendan group $n = 25$	Control group $n = 25$
Gender		
Male	19 (76)	17 (68)
Female	6 (24)	8 (32)
Aetiology		
Ischaemic	21 (84)	17 (68)
Non-ischaemic	4 (16)	8 (32)
Age, years	72.5 ± 7.4	77.9 ± 9.6
NYHA class	2.96 ± 0.32 (2–4)	2.86 ± 0.40 (2–4)
Left ventricular ejection fraction, %	26.8 ± 5.6	33.1 ± 8.9
Systolic blood pressure, mmHg	108 ± 19	116 ± 20
Diastolic blood pressure, mmHg	64 ± 9	63 ± 10
Hypertension	14 (56)	17 (68)
Diabetes mellitus	6 (24)	10 (40)
Obesity	5 (20)	5 (20)
Haemoglobin, g/dl	10.8 ± 1.6	11.0 ± 1.2
B-type natriuretic peptide, ng/l	900.4 ± 380.5	655.7 ± 513.9
Creatinine, mg/dl	1.7 ± 0.7	1.7 ± 0.9
Estimated glomerular filtration rate, ml/min	45.6 ± 19.4	42.9 ± 32.4
Atrial fibrillation	5 (20)	5 (20)
Left bundle branch block	6 (24)	4 (16)
Implantable cardioverter defibrillator therapy or cardiac resynchronization therapy	18 (72)	23 (92)
β-Blockers	21 (84)	19 (76)
Angiotensin-converting enzyme inhibitors and/or angiotensin II type 2 receptor blockers	22 (88)	18 (72)
Mineralocorticoid drugs	7 (28)	10 (40)
Loop diuretics	25 (100)	25 (100)
3C-HF score 1-year mortality, %	28.36 ± 18.93	29.88 ± 17.54

NYHA, New York Heart Association; 3C-HF score, cardiac and comorbid conditions heart failure score.
Data presented as number of patients (%), mean ± SD or mean ± SD (range).
No statistically significant between-group differences ($P \geq 0.05$) using χ^2-test or unpaired Student's *t*-test.

control group than in the levosimendan group ($P = 0.05$ and $P = 0.02$, respectively) (Table 4). After 6 months' follow-up, the number of hospitalizations and the length of stay in hospital were reduced in the levosimendan group, both in comparison with the 6 months before baseline ($P = 0.006$ and $P = 0.012$, respectively) and with the control group ($P = 0.012$ and $P = 0.044$, respectively). There was an opposite trend seen in the control group, with a progressive increase in the number of hospitalizations and the length of stay in hospital from 6 months before baseline to after 6 and 12 months' follow-up ($P < 0.001$ and $P = 0.002$, respectively) (Table 4). After 12 months' follow-up, the number of hospitalizations in the levosimendan group remained significantly lower than in the control group ($P < 0.009$).

Table 2. Echocardiographic and blood parameters in patients with chronic systolic heart failure before and after the first levosimendan infusion ($n = 25$).

	Before infusion	After infusion	Statistical significance[a]
Left ventricular ejection fraction, %	26.8 ± 5.6	29.2 ± 5.6	$P < 0.0001$
Left ventricular end-diastolic volume, ml	193.4 ± 53.2	187.2 ± 42.3	$P = 0.005$
E/E′ ratio	18.40 ± 8.23	14.10 ± 5.10	$P < 0.0001$
Mitral regurgitation index	2.63 ± 0.63	2.43 ± 0.65	$P = 0.0001$
Systolic pulmonary artery pressure, mmHg	54.36 ± 17.78	49.03 ± 17.07	$P < 0.0001$
B-type natriuretic peptide, ng/l	900.4 ± 380.5	489.50 ± 451.96	$P < 0.0001$
Haemoglobin, g/dl	11.11 ± 1.29	10.82 ± 1.29	$P < 0.0001$
Creatinine, mg/dl	1.98 ± 0.92	1.82 ± 0.71	$P = 0.003$
Estimated glomerular filtration rate, ml/min	37.44 ± 18.61	38.49 ± 17.74	$P = 0.0001$
Potassium, mEq/l	4.05 ± 0.42	3.88 ± 0.37	$P = 0.0003$

E/E′ ratio, ratio of peak early mitral inflow velocity (E) and mean of septal and lateral early diastolic velocity (E′).
Data presented as mean ± SD.
[a]Using paired Student's t-test.

Table 3. Echocardiographic and blood parameters at baseline and after 12 months' follow-up in patients with chronic systolic heart failure who received (levosimendan group) or did not receive (control group) treatment with intermittent levosimendan infusions.

	Levosimendan group n = 25		Control group n = 25	
	Baseline	After 12 months	Baseline	After 12 months
Left ventricular ejection fraction, %	26.8 ± 5.6	28.8 ± 6.5[a]	33.1 ± 8.9	33.0 ± 9.6
Left ventricular end-diastolic volume, ml	214.2 ± 56.3	195.5 ± 58.1	182.7 ± 53.4	190.0 ± 73.3
E/E′ ratio	20.3 ± 8.5	15.8 ± 5.6	15.5 ± 9.6	14.0 ± 5.1
Mitral regurgitation index	2.77 ± 0.61	2.47 ± 0.77	2.02 ± 0.81	2.02 ± 0.73
Systolic pulmonary artery pressure, mmHg	55.7 ± 17.6	52.4 ± 18.4	47.9 ± 13.4	53.5 ± 14.4[a]
B-type natriuretic peptide, ng/l	900.4 ± 380.5	872.3 ± 605.3[b]	655.7 ± 513.9	807.1 ± 755.4[a,b]
Haemoglobin, g/dl	10.8 ± 1.6	10.9 ± 1.4	11.0 ± 1.2	11.6 ± 1.4
Creatinine, mg/dl	1.7 ± 0.7	2.0 ± 0.1[a]	1.7 ± 0.9	1.8 ± 0.9
Estimated glomerular filtration rate, ml/min	45.6 ± 19.4	39.7 ± 16.3[a]	42.9 ± 32.4	38.8 ± 30.4
Potassium, mEq/l	3.84 ± 0.36	4.04 ± 0.41	4.07 ± 0.55	4.29 ± 0.54

Data presented as mean ± SD.
[a]$P < 0.05$ compared with baseline using paired Student's *t*-test.
[b]Data available for 23 patients in levosimendan group and 20 patients in control group.

Super-responders

In the levosimendan group, the LVEF increased by more than 20% after 12 months' follow-up with respect to baseline in seven patients (28%), who were termed super-responders. Since two of these patients had undergone mitral valve

Table 4. Number of hospitalizations and in-hospital length of stay in the 6 months before baseline and after 6 and 12 months' follow-up in patients with chronic systolic heart failure who received (levosimendan group; $n = 25$) or did not receive (control group; $n = 25$) treatment with intermittent levosimendan infusions.

	6 months before baseline		After 6 months' follow up		After 12 months' follow up	
	Levosimendan group	Control group	Levosimendan group	Control group	Levosimendan group	Control group
No. of hospitalizations	26	13	6	21	17	43
No. of hospitalizations/patient	0.84 ± 0.80^{a}	0.40 ± 0.70	$0.24 \pm 0.52^{a,b}$	0.83 ± 1.02	0.68 ± 0.80^{a}	1.72 ± 1.42^{b}
Length of stay in hospital, days	126	62	46	200	152	399
Length of stay in hospital/patient, days	9.2 ± 13.1^{a}	2.5 ± 5.1	$1.8 \pm 4.7^{a,b}$	8.0 ± 14.1^{b}	8.9 ± 17.0^{a}	15.9 ± 19.9^{b}

Data presented as number or mean ± SD.
[a]$P < 0.05$ compared with control group using unpaired Student's *t*-test.
[b]$P < 0.05$ compared with 6 months before baseline using paired Student's *t*-test.

repair, it was not possible to evaluate whether a similar favourable change had also occurred in diastolic function. Clinical, echocardiographic blood parameters, and the number of hospitalizations and the in-hospital length of stay in these patients compared with the rest of the levosimendan group are showed in Table 5. The super-responder patients were significantly younger than the remaining patients and in all of them chronic systolic heart failure had been diagnosed < 3 years before the start of the study. Super-responders underwent fewer drug infusions (3.86 ± 0.90 in the super-responders compared with 5.15 ± 0.31 in the remaining patients; $P = 0.045$), had lower BNP levels ($P = 0.019$), and had fewer hospitalizations ($P < 0.05$) and a shorter length of stay ($P < 0.05$) both at 6 and 12 months of follow-up compared with the remaining patients in the levosimendan group (Table 5); none of the super-responders died during the study period.

Discussion

In this retrospective analysis, experience with the repeated use of levosimendan in an ordinary heart failure unit is presented. These results follow up on a randomized, open-label, prospective study comparing repeated infusions of levosimendan and furosemide in advanced heart failure.[10] In both studies, although severely ill, the patients were not those in whom temporary inotropic support is considered,[1] but they fulfilled the criteria followed in most studies for the use of levosimendan in chronic advanced heart failure.[8–10]

In the population of unselected patients in the present study, the acute effects of levosimendan were similar to those reported in randomized studies,[8–12] with improved left ventricular systolic and diastolic function and reduced BNP levels; moreover, the effects were seen after every infusion of levosimendan, with no apparent tolerance

Table 5. Patient characteristics, echocardiographic and blood parameters, number of hospitalizations and in-hospital length of stay in patients with chronic systolic heart failure who received levosimendan treatment in those classified as super-responders and remaining patients.

	Super-responders $n = 7$	Remaining patients $n = 18$
Gender		
Male	3 (43)	16 (89)
Female	4 (57)	2 (11)
Aetiology		
Ischaemic	4 (57)	17 (94)
Non-ischaemic	3 (43)	1 (6)
Age, years	64.75 ± 5.60[a]	74.82 ± 8.42
NYHA class	2.79 ± 0.39	3.11 ± 0.38
Hypertension	2 (29)	14 (78)
Diabetes mellitus	1 (14)	4 (22)
Obesity	1 (14)	6 (33)
Atrial fibrillation	1 (14)	6 (33)
Left bundle branch block	1 (14)	14 (78)
Implantable cardioverter defibrillator therapy or cardiac resynchronization therapy	5 (71)	13 (72)
β-Blockers	7 (100)	14 (78)
Angiotensin-converting enzyme inhibitors and/or angiotensin II type 2 receptor blockers	7 (100)	15 (83)
Mineralocorticoid drugs	2 (29)	5 (28)
Loop diuretics	7 (100)	18 (100)
3C-HF score 1-year mortality, %	24.57 ± 23.96	31.16 ± 13.89
Blood parameters		
B-type natriuretic peptide, ng/l	677.2 ± 280.5[a]	1007.9 ± 773.4
Creatinine, mg/dl	1.7 ± 0.7	1.7 ± 0.9
Estimated glomerular filtration rate, ml/min	48.8 ± 16.4	41.8 ± 35.5
Echocardiographic parameters		
Left ventricular ejection fraction, %	28.8 ± 7.6	26.9 ± 6.0
Left ventricular end-diastolic volume, ml	199.3 ± 53.5	209.5 ± 52.2
E/E′ ratio	N/A	21.7 ± 7.7
Mitral regurgitation index	N/A	2.24 ± 0.8
Systolic pulmonary artery pressure, mmHg	49.7 ± 7.8	56.3 ± 6.9
No. of hospitalizations/patient		
6 months before baseline	1.42 ± 0.79	0.88 ± 0.75
After 6 months' follow-up	—[a]	0.31 ± 0.10
After 12 months' follow-up	1.12 ± 0.39[a]	2.02 ± 0.08
Length of stay in hospital/patient, days		
6 months before baseline	11.28 ± 10.78	8.19 ± 10.12
After 6 months' follow-up	—[a]	9.19 ± 13.12
After 12 months' follow-up	1.82 ± 0.51[a]	6.16 ± 9.19

NYHA, New York Heart Association; 3C-HF score, cardiac and comorbid conditions heart failure score; N/A, not available. Data presented as number of patients (%) or mean ± SD.

[a] $P < 0.05$ compared with remaining patients using unpaired Student's *t*-test.

developing over time. In the present study, similar to previous studies,[8–10] a trend towards a better clinical state was observed at follow-up in patients treated with levosimendan: their NYHA class remained stable, while it worsened in the control group, and there was a slight improvement in LVEF. Levels of BNP were not available in every patient; although they did not change in patients treated with levosimendan, they worsened over time in the control group. Taken together, despite the inherent weaknesses of a retrospective analysis, these results are coherent with the hypothesis that levosimendan might slow the progression of advanced heart failure.[17,18]

In the present study the mortality rate was lower than that predicted by the baseline 3C-HF score, and therefore a similar survival rate in the two groups of patients was not surprising. To date, a reduction in mortality with levosimendan treatment in chronic heart failure has been shown only in meta-analyses[17,18] and has not been confirmed in randomized studies.[19] In the present study, the number of hospitalizations and the length of stay in hospital were reduced in the levosimendan group 6 months after the beginning of treatment, when patients were still undergoing repeated infusions. After 12 months of follow-up, most patients were no longer being treated with regular infusions of the drug, which may explain the trend towards relapse at that time; however, both the number of hospitalizations and the length of stay in hospital were still lower than in the control group, which is in line with the results reported by Bartesaghi et al.[20] who studied levosimendan treatment in outpatients with end-stage chronic heart failure and who thus were more seriously ill than the patients in the present study. The initial higher number of hospitalizations and in-hospital length of stay in patients treated with levosimendan compared with patients who did not undergo this treatment suggests the two groups may be two different populations. However, levosimendan infusions were offered to the majority of control patients (some eligible patients were not referred by their attending physicians), and there were no significant differences in clinical characteristics between the two groups at baseline (Table 1). During the follow-up period, the trends in the number of hospitalizations and in-hospital length of stay in the two groups diverged and became reversed. It is worth noting that many of the patients treated with levosimendan would not have been eligible for the drug after 6 months since they did not require hospitalization during that time.

In a few patients, repeated infusions of levosimendan was associated with an improvement in LVEF, a long-lasting decrease in BNP levels and a reduction in the number and length of hospitalizations at 6 and 12 months; these patients were termed super-responders. With respect to the other patients in the levosimendan group, the ventricles of these younger patients might have carried a lesser degree of fibrosis and a greater amount of viable myocardium that was more responsive to the calcium-sensitizing action of levosimendan.

The present study had a number of limitations. First, it was a retrospective analysis of data derived from the clinical registry of single heart failure unit, so the number of patients to be studied could not be defined in advance. Moreover, the control group was chosen on the basis of the more relevant clinical characteristics rather than treatment being randomized. Finally, the number of levosimendan infusions was not predetermined (as in the previous randomized study[10]) but was event-driven by the clinical protocol, which is used by a number of centres.[20,21]

The benefits of intermittent administration of levosimendan in patients with advanced chronic heart failure are still being debated.[17–19,21] The present study offers the perspective of a hospital-based

heart failure unit in which this drug has previously been tested in pilot randomized studies.[10,12] Despite the limitations of the present study, the results suggest that intermittent levosimendan may represent an option for patients whose disease is rapidly worsening despite optimal treatment.

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Declaration of conflicting interest

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