Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration

Fabrizio Oliva a,1, Enrico Perna a,1, Marco Marini b,1, Daniele Nassiacos c,1, Antonio Cirò d,1, Gabriella Malfatto e,1, Fabrizio Morandi f,1, Ivan Caico g,1, Gianpiero Perna b,1, Sabina Meloni c,1, Antonella Vincenzi d,1, Alessandra Villani c,1, Andrea Lorenzo Vecchi f,1, Chiara Minoia g,1, Alessandro Verde a,1, Renata De Maria h,e,⁎,1, on behalf of the RELEVANT-HF study group

a Cardiothoracic and Vascular Department, ASST-Great Metropolitan Hospital Niguarda, Milan, Italy
b Department of Cardiovascular Sciences, Ospedali Riuniti, Ancona, Italy
c Cardiology Department, ASST Valle Oloono, Saronno General Hospital, Saronno, Italy
d Cardiology ASST Monza, San Gerardo Hospital, Monza, Italy
e Department of Cardiology, San Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy
f Department of Cardiovascular Diseases, Ospedale di Circolo and Macchi Foundation, University of Insubria, Varese, Italy
g Cardiology Department, ASST Valle Olona, Gallarate Hospital, Gallarate, Italy
h CNR Clinical Physiology Institute, Cardiothoracic and Vascular Department, ASST-Great Metropolitan Hospital Niguarda, Milan, Italy

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ABSTRACT

Background: Ambulatory Advanced Heart Failure (AAHF) is characterized by recurrent HF hospitalizations, escalating diuretic requirements, intolerance to neurohormonal antagonists, end-organ dysfunction, short-term reduced life expectancy despite optimal medical management (OMM). The role of intermittent inotropes in AAHF is unclear. The RELEVANT-HF registry was designed to obtain insight on the effectiveness and safety of compassionate scheduled repetitive 24-hour levosimendan infusions (LEVO) in AAHF patients.

Methods: 185 AAHF NYHA class III–IV patients, with ≥2 HF hospitalizations/emergency visits in the previous 6 months and systolic dysfunction, were treated with LEVO at tailored doses (0.05–0.2 μg/kg/min) without prior bolus every 3–4 weeks. We compared data on HF hospitalizations (percent days spent in hospital, DIH) in the 6 months before and after treatment start.

Results: Infusion-related adverse events occurred in 23 (12.4%) patients the commonest being ventricular arrhythmias (16, 8.6%). During follow-up, 37 patients (20%) required for clinical instability treatment adjustments (decreases in infusion dose, rate of infusion or interval). From the 6 months before to the 6 months after treatment start we found lower DIH (9.4 (8.2) % vs 2.8 (6.6) %, p < 0.0001) and length of HF admissions (17.4 (15.6) vs 21.6 (13.4) days, p = 0.0001). One-year survival was 86% overall and 78% free from death/LVAD/urgent transplant.

Conclusions: In AAHF patients, who remain symptomatic despite OMM, LEVO is well tolerated and associated with lower overall length of hospital stay during six months. This multicentre clinical experience underscores the need for a randomized controlled trial of LEVO impact on outcomes in AAHF patients.

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1. Introduction

Advanced refractory (stage D) Ambulant Heart Failure (AAHF) is characterized by recurrent HF hospital admissions for HF, escalating diuretic requirements, intolerance to neurohormonal antagonists, end-organ dysfunction, cardiac cachexia and arrhythmias, despite maximal optimized drug and device therapy [1,2]. AAHF patients have a short-term reduced life expectancy, severely impaired functional capacity, poor quality of life and generate high health care costs [1]. End-organ dysfunction may ultimately preclude candidacy for advanced life-saving therapies, heart transplantation (HTx) and left ventricular assist device (LVAD). Moreover, heart replacement therapies do not represent viable options for most AAHF patients, because of scarce donor supply and contra-indicating comorbidities, leaving a large unmet need for effective symptom palliation.

Intermittent or continuous iv inotropes were proposed in the 90’s as palliative treatment in AAHF patients, but were suggested to worsen...
survival, with 40%–74% 6-month mortality rates [3–5]. Modern thera-
pies have broadened the role of outpatient inotropic support beyond
palliation, to preserve organ function in patients awaiting HTx or LVAD [6–8]. A large single-centre retrospective review of dobutamine
and milrinone use in AAHF patients confirmed both improvement in
haemodynamics, renal function and congestion and neutral and
potentially detrimental effects on survival [9].

The calcium sensitizer ino-dilator levosimendan has a long half-life
active metabolite and determines during and many days after a
24-hour infusion [10] prolonged clinical and haemodynamic effects
that have generated interest in its scheduled repetitive use to avoid
frequent rehospitalization in AAHF patients. Several small trials of inter-
mittent levosimendan infusions reported improvements in functional
capacity, left ventricular ejection fraction (LVEF) and quality-of-life
[11], with no detrimental mortality effects [12].

RELEVANT-HF (Repetitive LEVosimendan in AdvNcd refrActory
Heart Failure) was designed as a multicentre registry to obtain insight
on the effectiveness and safety of scheduled repetitive levosimendan
infusions (LEVO) in a cohort of real world AAHF patients, who had
undergone compassionate treatment to ameliorate symptoms and prevent
end organ dysfunction and recurrent hospitalizations.

2. Methods

2.1. Study design

We report the results of a multicentre data collection of AAHF patients who had been
started on LEVO for symptom palliation or as bridge to heart replacement therapies using
common standardized eligibility and management criteria at seven high-volume HF out-
patient clinics. Participating centres were four tertiary care hospitals with cardiac surgery
programs, one of these hosting a heart transplant programme, and three secondary care
hospitals with cardiac catheterization and electrophysiology laboratories.

The study was approved by the Institutional Ethics Committee of each participating
centre. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki
[13]. According to National Data Protection Authority rules, IECs waived informed consent
to anonymous retrospective clinical data use for IEC-approved studies conducted by Na-
tional health Service professional.

Patients who were included in this study had NYHA class III–IV symptoms, depressed
LVEF and 82 hospitalizations or emergency visits for HF in the previous 6 months and
could be classified as AAHF, INTERMACS level 4–7 [14]. All patients had first been admin-
istered levosimendan during an admission for acute decompensated HF and proved to tol-
erate the drug. All were on optimal medical management (OMM) including standard HF
drug therapy based on individual tolerance. Patients with contraindications such as
previous intolerance (allergy, arrhythmias, hypotension), severe chronic kidney
disease, left ventricular ejection fraction (LVEF) and quality-of-life
capacity, left ventricular ejection fraction (LVEF) and quality-of-life

2.2. Statistical methods

The sample size calculation was based on the primary efficacy endpoint DIH%. A sample size of 97 patients achieves 50% power to detect a mean of paired differences of 8 days with an estimated standard deviation of differences of 20 days and alpha 0.01
using a two-sided paired t-test. To account for the retrospective nature of the study, the
number of enrolees could be increased to have 100 evaluable patients (i.e. DIH% prior
and during the first 6 months of LEVO available).

All eligible patients dosed with LEVO were included. Default summary statistics were
performed for demographic and clinical characteristics, background drug and device
therapy, comorbidities, laboratory and echocardiographic findings and infusion type and
doses. DIH%, number and duration of hospitalizations during the first 6 months of LEVO
vs the prior 6 months preceding LEVO start were compared by paired Student’s t-test.
Direct costs in the 6 months before LEVO start and in the 6 months on treatment were
compared by the signed rank test. In a sensitivity analysis LEVO infusions were simulated
to have occurred first all during a day hospital and then all in the fully home setting.

Kaplan-Meier death/urgent HTx/LVAD implant-free survival functions were esti-
mated using a time-to-first event approach. Patients with none of the above events
were censored at the last contact date. We used the SAS System version 9.4 (SAS Institute
Inc., Cary, NC).

3. Results

We reviewed data from 185 AAHF patients started on LEVO from
May 2005 to October 2016. Enrolment ranged from 8 to 50 patients
per centre.

The study cohort (Tables 1, 2) included mostly males on OMM
for HF with reduced LVEF and a high prevalence of device therapy.
Approximately one third had an INTERMACS 4. The indication to LEVO
was palliation in 116 (63%) patients and bridge in 69 (47%); in this latter
group, 33 patients were bridged to HTx (48%) 28 to candidacy to HTx or
LVAD (41%) and 8 to decision on further options (12%).

Table 3 details LEVO timing and dosing. Infusion-related adverse
events occurred in 23 (12.4%) patients. During follow-up, 37 patients
(20%) required adjustments for clinical instability, including decreases in
rate or infusion or in the interval between infusions.

During the first 6 months on LEVO, 4 bridged patients stopped
treatment because of investigator-judged drug ineffectiveness and
were implanted with an LVAD within weeks of drop-out. DIH%,
the primary study end-point, decreased significantly from 9.4 (8.2)%
in the 6 months before to 2.8 (6.6)% in the 6 months after treatment
start (p < 0.0001) (Fig. 1). Number and length of HF admissions
were lower on LEVO than in the previous 6 months (1.3 (0.6) vs 1.8
(0.8), p = 0.0001 and 17.4 (15.6) vs 21.6 (13.4) days, p = 0.0001,
respectively).

Direct costs based on infusion setting as reported in Table 1
were on average lower by 1157 (8676) € in the 6 months on LEVO
vs the 6 months preceding LEVO start (5616 [4128–8215] € vs 7290
[2551–11,164] €, p = 0.053). In the sensitivity analysis, both day
hospital or fully home setting alternatives suggested potentially
greater savings with projected cost decreases during treatment
of 3959 (8773) € (p < 0.0001) and 1612 (8713) € (p < 0.002), respectively.

One year after LEVO start, 141 patients were alive and 128 still on
repeated scheduled infusion, 12 had stopped treatment, 15 had been
implanted a LVAD, six had received HTx, one was lost to follow-up
and 26 had died (three after LVAD implant). Using a time-to-first
event approach, overall 44 patients (24%) met the combined end point

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of death/urgent HTx/LVAD. One-year overall survival was 86%, while event-free survival was 76%.

Patients who needed treatment adjustments for loss of benefit during the first 6 months had worse event-free survival at one year than those in whom treatment schedule was unchanged (62% vs 80%, p = 0.032).

4. Discussion

4.1. Care of patients with Ambulatory Advanced Heart Failure

Patients with AAHF represent 0.5 to 5% of the HF population, an estimated 500,000 subjects in Europe [1]. They have a dire prognosis: one-year mortality exceeds 25% in ambulatory class III–IV and 50% in class IV patients; with decreasing sudden death rates in the current era [15] most deaths are due to progressive pump failure.

Care for AAHF patients is difficult to standardize and often remains suboptimal. Effective approaches should focus on symptom relief, while attempting to keep patients out of hospital as long as possible, since each urgent HF admission marks a further step in the downhill course of AAHF. An increased mortality risk linked to inotropes might be considered an acceptable trade-off at this stage. One-year survival in a contemporary single-centre series of AAHF patients on intermittent outpatient iv inotropes was below 50% and was better on milrinone than dobutamine [16]. Lack of interference with beta-adrenergic receptors is likely an important asset in contemporary series with high background beta-blockade rates.

Table 1

Baseline clinical characteristics of the RELEVANT-HF cohort.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>148 (80)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>81 (44)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>77 (42)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>113 (60)</td>
</tr>
<tr>
<td>Idiopathic dilated</td>
<td>46 (25)</td>
</tr>
<tr>
<td>Valvular</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Exotoxic - post chemotherapy</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>63 (34)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>57 (30)</td>
</tr>
<tr>
<td>Obesity</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>38 (20)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>31 (17)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Device therapy</td>
<td></td>
</tr>
<tr>
<td>Implantable cardioreader defibrillator</td>
<td>158 (85)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>85 (46)</td>
</tr>
<tr>
<td>Home monitoring</td>
<td>45 (26)</td>
</tr>
<tr>
<td>Heart failure medications</td>
<td></td>
</tr>
<tr>
<td>High-dose diuretics (≥125 mg/day)</td>
<td>120 (65)</td>
</tr>
<tr>
<td>Angiotensin-Converting-Enzyme- inhibitors or angiotensin receptor blockers</td>
<td>183 (99)</td>
</tr>
<tr>
<td>Betablockers</td>
<td>163 (88)</td>
</tr>
<tr>
<td>Mineralocorticoid Receptor Antagonists</td>
<td>140 (76)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>65 (35)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>74 (40)</td>
</tr>
<tr>
<td>INTERMACS level</td>
<td></td>
</tr>
<tr>
<td>4 Resting symptoms “frequent flyer”</td>
<td>53 (29)</td>
</tr>
<tr>
<td>5 Exertion intolerant “housebound”</td>
<td>51 (28)</td>
</tr>
<tr>
<td>6 Exertion limited “walking wounded”</td>
<td>52 (28)</td>
</tr>
<tr>
<td>7 “Placeholder”</td>
<td>29 (16)</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean (standard deviation) or median [interquartile range].

Categorical variables are expressed as number (percentage).

4.2. Previous experience with repetitive levosimendan in advanced heart failure

Previous studies have addressed the value of planned repeated levosimendan in AAHF [16–18]. The LEVO-REP study [16] found no advantage of levosimendan on a combined end point of exercise tolerance or improved quality of life among 120 AAHF patients randomized to fully ambulatory scheduled intermittent 6-h infusions of levosimendan at the dose of 0.2 μg/kg/min or placebo every 2 weeks for 6 weeks at 11 centres. The low-dosing schedule has been suggested as cause for lack of benefit in this study. Six-month survival free from HTx/LVAD or acute HF on levosimendan was 82.3%.

Table 2

Baseline clinical characteristics at treatment start.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 (13)</td>
</tr>
<tr>
<td>N. HF admissions (prior 6 months)</td>
<td>1.78 (0.83)</td>
</tr>
<tr>
<td>Days HF admissions (prior 6 months)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>3.2 (1.7)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.8 (4)</td>
</tr>
<tr>
<td>Systolic blood pressure mm Hg</td>
<td>106 (13)</td>
</tr>
<tr>
<td>Diastolic blood pressure mm Hg</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Serum creatinine mg/dl</td>
<td>1.43 (0.47)</td>
</tr>
<tr>
<td>eGFR ml/min/1.73 m²</td>
<td>54 (20)</td>
</tr>
<tr>
<td>Moderate kidney dysfunction (eGFR &lt; 60 ml/min/1.73 m²)</td>
<td>96 (52)</td>
</tr>
<tr>
<td>Severe kidney dysfunction (eGFR &lt; 30 ml/min/1.73 m²)</td>
<td>14 (8)</td>
</tr>
</tbody>
</table>

Natriuretic peptides

| NT-proBNP (n = 82) ng/L                     | 3804 (2110–6146) |
| BNP (n = 77) ng/L                          | 760 (383–1393) |

Echocardiography

| LV end diastolic diameter mm                | 65 (9) |
| LV end diastolic volume ml                 | 202 (73) |
| LV ejection fraction %                     | 27 (8) |
| LV ejection fraction ≤25%                  | 98 (53) |
| Mitral regurgitation grade 3–4 (n,%)       | 93 (53) |
| Pulmonary artery pressure, mm Hg          | 49 (13) |
| Tricuspid Anular Plane Systolic Excursion, mm | 15 (4) |

Continuous variables are expressed as mean (standard deviation) or median [interquartile range].

Categorical variables are expressed as number (percentage).
LVAD is now a standard of care and survival on LVAD has improved significantly over the last decade; however post-implant readmission rates remain quite high and range in different studies from 1.3 to 2.6 hospitalizations per patient-year [21]. Among ROADMAP patients the overall incidence of adverse events during one patient-year was more than double on LVAD than on OMM (relative risk 0.44) [19]. The most frequent complications and death causes are typically LVAD-related and include, beyond device malfunction, neurologic events and major infections, which were distinctly uncommon in our cohort.

4.4. Limitations

Randomized double-blind controlled clinical trials are the most accurate and reliable means to assess the efficacy of a drug for a given indication and rank highest in the hierarchy of evidence. Observational study designs carry inherent limitations and biases, yet they may have value to offer complementary insights in real world effectiveness of a treatment and pave the way to appropriately designed intervention trials. Our cohort study was a large multicentre clinical experience, with standardized and consistent criteria across a small number of homogenous specialized HF centres and focused on a pragmatic end-point that suggested a potential impact on outcomes relevant to patients in a disease area with few available, high-cost and high-risk alternatives. Nonetheless, our findings remain exploratory and await confirmation in a randomized controlled trial.

We tailored LEVO schedule to individual patient characteristics and clinical setting. Frequent clinical visits, strict monitoring and constant therapy adjustments might per se have translated into prognostic benefit. The lack of a control arm does not allow to rule out the assignment of patients in better clinical status to intermittent treatment. However, the clinical characteristics of our cohort depict a population with truly advanced HF, comparable or even clinically worse than in previous LEVO trials [16,17], in the ROADMAP [20] or REVIVAL studies [22]. The proportion of women was low, as in similar cardiology series, therefore the results cannot be fully extrapolated to female HF patients.

Although treatment was administered in an outpatient or day-hospital basis in 44% of patients, still over one half underwent an overnight hospital stay to deliver the 24 infusion, and this regimen probably reduced potential costs savings.

5. Clinical implications and conclusions

AAHF patients have a dire prognosis and limited treatment options beyond OMM and devices. LVAD may offer chances for prolongation of survival and improved quality of life. However, current LVAD technology is available in few tertiary referral centres, requires a complex and expensive organization, incurs a high rate of adverse events and may have emotional and practical drawbacks [23]. The heavy psychological burden that living with an LVAD imposes is expressed by patients’ reasons for refusal to undergo LVAD in the ROADMAP study [20]. LEVO, with its favourable medium-term effects on functional status and out-of-hospital survival and low adverse event rates, might represent a window of opportunity for AAHF patients and secondary care HF centres, before resorting to the costlier and more demanding mechanical support option. Outpatient or day-hospital delivery might also render LEVO cost-effective.

The frequent chance to see and reassess patients during LEVO mandates careful monitoring for red-flags of deterioration that might prompt switch to LVAD, if feasible, whenever drug effects start to weaken. Our multicentre clinical experience underscores the need for a randomized controlled trial on outcomes associated with repetitive use of levosimendan in AAHF patients.
Sources of funding

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Disclosures

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Drs Caico, Cirò, Marini, Meloni, Minoa, Nasciaco, Perna E., Perna GP., Vecchi, Villani, Vincenzi have nothing to disclose.

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