Inotropes for the treatment of advanced heart failure: The role of intermittent administration

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Disclosures

- ALARM investigator received research grants and honoraria by Abbott US and Orion Pharma
- Co-PI in LEVOREP trial supported by Orion Pharma
Heart Failure Has A High Mortality Rate Similar To Aggressive Malignancies

Medical therapy alone can be a poor long-term treatment option for many in the more advanced stages of heart failure.

Many publications show the mortality risk associated with NYHA Class IV heart failure is high, with a 1-year mortality between 60 and 94 percent.¹⁻⁴

Class IV heart failure patients treated with medical therapy alone have mortality rates similar to or greater than aggressive forms of cancer.⁵

⁵ Data on file. Pleasanton, Calif: Thoratec Corp.
HF Rehospitalization risk: Timing

Post-discharge 2 months: 30%

Pre-terminal 2 months: 50%

Median Time from hospital discharge

Data by Chun et al, Circ Heart Fail 2012 and Russo et al, J Card Fail 2008
Patient profiles for inotropic therapy

- Hemodynamic impairment with low cardiac output (i.e. CI < 2.0 Lt/min/m²) and increased left and/or right ventricular filling pressures [i.e. PCWP (18–20 mmHg) and RAP (10–12 mmHg)].

- Critical patient’s conditions caused by abnormal hemodynamics and including any of the following:
  a. Severe exercise limitation
  b. Diuretic resistant fluid overload
  c. Kidney and/or liver dysfunction as shown by abnormal laboratory exams (serum creatinine, BUN, bilirubin, etc.)

Established and investigational inotropic agents

<table>
<thead>
<tr>
<th>Inotropic mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Currently used</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Beta-Adrenoceptor stimulation</td>
<td>Dobutamine, dopamine</td>
</tr>
<tr>
<td>Phosphodiesterase inhibition</td>
<td>Enoximone, milrinone</td>
</tr>
<tr>
<td>Calcium sensitization</td>
<td>Levosimendan</td>
</tr>
<tr>
<td><strong>Investigational</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Istaroxime</td>
</tr>
<tr>
<td>plus SERCA activation</td>
<td></td>
</tr>
<tr>
<td>Acto-myosin cross-bridge activation</td>
<td>Omecamtiv mecarbil</td>
</tr>
<tr>
<td>SERCA activation</td>
<td>Gene transfer</td>
</tr>
<tr>
<td>SERCA activation plus vasodilation</td>
<td>Nitroxyl donor; CXL-1020</td>
</tr>
<tr>
<td>Ryanodine receptor stabilization</td>
<td>Ryanodine receptor stabilizer; S44121</td>
</tr>
<tr>
<td>Energetic modulation</td>
<td>Etomoxir, pyruvate</td>
</tr>
</tbody>
</table>

Eur Heart J, 2011:32;1838–1845
Levosimendan

Istaroxime

Drugs used to treat AHF that are positive inotropes or vasopressors or both

<table>
<thead>
<tr>
<th></th>
<th>Bolus</th>
<th>Infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>No</td>
<td>2–20 µg/kg/min (β+)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>No</td>
<td>&lt;3 µg/kg/min; renal effect (δ+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–5 µg/kg/min; inotropic (β+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 µg/kg/min: (β+), vasopressor (α+)</td>
</tr>
<tr>
<td>Milrinone</td>
<td>25–75 µg/kg over 10–20 min</td>
<td>0.375–0.75 µg/kg/min</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0.5–1.0 mg/kg over 5–10 min</td>
<td>5–20 µg/kg/min</td>
</tr>
<tr>
<td>Levosimedan*</td>
<td>12 µg/kg over 10 min (optional)$^b$</td>
<td>0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>No</td>
<td>0.2–1.0 µg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min</td>
<td>0.05–0.5 µg/kg/min</td>
</tr>
</tbody>
</table>

*Also a vasodilator.
$^b$Bolus not recommended in hypotensive patients (systolic blood pressure <90 mmHg).

α = alpha adrenoceptor; β = beta adrenoceptor; δ = dopamine receptor.
Limitations of traditional inotropic agents

- **Tachyarrhythmias**
  - Increased ventricular arrhythmias
  - Increased ventricular rate in atrial fibrillation

- **Myocardial ischemia**
  - Hypotension—coronary hypoperfusion
  - Increased heart rate and myocardial contractility-increased myocardial oxygen consumption

- **Direct myocyte toxicity-intracellular calcium overload**
Current IV Inotropic Therapies in HF: ESC recommendations

Dobutamine: cl IIb, Level evidence B
(preferable agent due to lower cost)

Levosimendan: cl IIb, Level of evidence B
(preferable agent for patients on beta blocker)

PDEIs: cl IIb, Level evidence B

Dopamine: cl IIb, Level evidence B

ESC Guidelines 2016
Pitfalls in the use of inotropes

- AHF with preserved LVEF - 8% of pts received inotropes (ADHERE) *

- AHF with SBP >120 mmHg - 14.2% of pts received inotropes (OPTIMIZE)
  (3.2% for pts with SBP>160) **

- Acute hypertensive HF (>180/110 mmHg) - 4% of pts received dobutamine or dopamine (EHFSII) ***

ALARM-HF: clinical characteristics of AHF patients

<table>
<thead>
<tr>
<th></th>
<th>SBP &lt; 100 mmHg, n (%)</th>
<th>SBP = 100–120 mmHg, n (%)</th>
<th>SBP = 120–160 mmHg, n (%)</th>
<th>SBP &gt; 160 mmHg, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>3.5</td>
<td>2.4</td>
<td>2.2</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>51–70</td>
<td>11.4</td>
<td>10.6</td>
<td>17.1</td>
<td>7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;71</td>
<td>8.5</td>
<td>8.2</td>
<td>18.5</td>
<td>9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &gt; 45%</td>
<td>19.8</td>
<td>22.7</td>
<td>24.9</td>
<td>31.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>In-hospital treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>71.1</td>
<td>80.5</td>
<td>84.2</td>
<td>86.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>44.5</td>
<td>55.4</td>
<td>48.0</td>
<td>47.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>i.v. nitrates</td>
<td>20.5</td>
<td>26.3</td>
<td>33.8</td>
<td>34.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>i.v. diuretics</td>
<td>96.8</td>
<td>98.8</td>
<td>98.7</td>
<td>97.2</td>
<td>NS</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>34.7</td>
<td>20.8</td>
<td>14.2</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dopamine</td>
<td>24.0</td>
<td>14.7</td>
<td>6.5</td>
<td>7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>5.3</td>
<td>3.4</td>
<td>1.0</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>6.4</td>
<td>3.7</td>
<td>2.3</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>In-hospital outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>14.1</td>
<td>8.0</td>
<td>5.4</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Parissis et al. EJHF 2010;12:1193-1202
Short-term Survival by Treatment Among Patients Hospitalized with Acute Heart Failure: The Global ALARM-HF Registry Using Propensity Scoring Methods

Levosimendan vs Dobutamine in LIDO trial: Change (%) in Hemodynamic Variables at 24 Hours

SURVIVE
180-day All-Cause Mortality

Probability of Surviving

Levosimendan
Dobutamine

Days Since Start of Study Drug Infusion

p=0.401

Hazard Ratios for Patients on β-Blockers at Baseline Appeared to Favor Levosimendan

At Risk for Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- e.g., Patients with:
  - hypertension
  - atherosclerotic disease
  - diabetes
  - metabolic syndrome
  - Or Patients:
    - using cardiotoxins
    - With FHx CM

**THERAPY**

**GOALS**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**DRUGS**
- ACEI or ARB in appropriate patients
- ACEI or ARB in appropriate patients

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- e.g., Patients with:
  - previous MI
  - LV remodeling including LVH and low EF
  - asymptomatic valvular disease

**THERAPY**

**GOALS**
- All measures under Stages A & B
- Dietary salt restriction

**DRUGS FOR ROUTINE USE**
- Diuretics for fluid retention
- ACEI
- Beta-blockers

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - known structural heart disease
  - shortness of breath and fatigue, reduced exercise tolerance

**THERAPY**

**GOALS**
- All measures under Stages A, B, C
- Decision re: appropriate level of care

**OPTIONS**
- Compassionate end-of-life care/hospice
- Extraordinary measures:
  - heart transplant
  - Chronic inotropes
  - Permanent mechanical support
  - Experimental surgery or drugs

**STAGE D**
Refractory HF requiring specialized interventions

- e.g., Patients who have marked symptoms at rest despite maximal medical therapy
  - (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**THERAPY**

**GOALS**
- All measures under Stages A, B, C
- Decision re: appropriate level of care

**OPTIONS**
- Compassionate end-of-life care/hospice
- Extraordinary measures:
  - heart transplant
Intermittent dobutamine treatment in patients with chronic refractory CHF: A randomized, double-blind, placebo-controlled study

![Graph showing survival probability over time.](image)

**Fig. 1.** Kaplan-Meier plots of probability of survival in dobutamine (solid line) and placebo (broken line) treatment groups. There was no significant difference between the two groups in the probability of survival ($p = 0.7$).
Reverse LV remodeling by intermittent dobutamine infusions and amiodarone in end-stage HF due to idiopathic dilated cardiomyopathy

Impact of short-term intermittent intravenous dobutamine therapy on endothelial function in patients with severe chronic heart failure

The percent change in endothelium-dependent brachial artery flow-mediated vasodilation (FMD) from baseline in patients who received short-term intermittent intravenous dobutamine therapy (closed circles; n = 20) and control subjects (open circles; n = 20) at baseline and after 4 months.

Bar graphs showing the beneficial effects of short-term (4 months) intermittent intravenous dobutamine therapy in the 20 study participants, before (closed bars) and after (open bars) treatment on mean SVR (A), mean CI (B), and mean SI (C) assessed non-invasively with a thoracic electrical bioimpedance device. Data are expressed as means plus or minus SD.

Need for Hospice and Palliative Care Services in Patients with End-Stage HF Treated with Intermittent Infusion of Inotropes

Clin. Cardiol. Vol. 27, January 2004
Duration of the Hemodynamic Action of a 24-h Infusion of Levosimendan in Patients with ADHF

Lilleberg et al. Eur J Heart Fail 2007
Serial Levosimendan Infusions in Advanced HF

Intermittent Levosimendan Infusions in Advanced Heart Failure: Favourable Effects on Left Ventricular Function, Neurohormonal Balance, and One-Year Survival

FIGURE 1. Outline of the protocol.
Intermittent levosimendan treatment in patients with severe congestive heart failure

Planned repetitive use of levosimendan for heart failure in cardiology and internal medicine in Sweden

Tonje Thorvaldsen, Lina Benson, Inger Hagerman, Ulf Dahlström, Magnus Edner, Lars H. Lund

International Journal of Cardiology 175 (2014) 55–61
Combined Effects Of Levo With Dob In Refractory Heart Failure

Nanas et al. Am J Cardiol 2004;95:94;1329
Nanas et al. Am J Cardiol 2005;95:768
Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure

Levosimendan vs Dobutamine, p=0.037
Levosimendan vs Levosimendan plus Dobutamine, p=0.009

LEVOREP Trial

Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial

Johann Altenberger¹, John T. Parissis², Angelika Costard-Jaeckle³, Andreas Winter⁴, Christian Ebner⁵, Apostolos Karavidas⁶, Kurt Sihorsch⁷, Ekaterini Avgeropoulou⁸, Thomas Weber⁹, Lida Dimopoulos¹⁰, Hanno Ulmer¹¹, and Gerhard Poelzli¹²*
Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study

OR 0.50 (95% CI 0.24–1.05); p = 0.034
Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced HF (LevoRep) study

European Journal of Heart Failure
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.118/full#ejhf118-fig-0004
LION-HEART – Study Results

Δ% Change of NT-proBNP

- Placebo
- Levosimendan

Mean±SEM % of change in NT-proBNP by Treatment Group

p-value <0.001
LION-HEART – Study Results - Clinical Events

**KM curves**

**HF Hospitalization**

**All-cause death or HF Hospitalization**

*Cox Proportional Hazards Models (time to first event)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=21</th>
<th>Levosimendan n=48</th>
<th>p-value</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure Hospitalization</td>
<td>14 (67%)</td>
<td>11 (23%)</td>
<td>0.002</td>
<td>0.25 (0.11-0.55)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>7 (33%)</td>
<td>14 (29%)</td>
<td>0.951</td>
<td>0.85 (0.34-2.12)</td>
</tr>
<tr>
<td>All-cause Death or Heart Failure Hospitalization</td>
<td>17 (81%)</td>
<td>23 (48%)</td>
<td>0.022</td>
<td>0.39 (0.21-0.74)</td>
</tr>
</tbody>
</table>
Meta-analysis of pulsed infusion trials

Niemininen et al. Int J Cardiol 2015
High-risk setting defining the patients who could benefit from repetitive use of levosimendan in chronic advanced HF.

**Indication for levosimendan use in advanced heart failure**

- Severe systolic dysfunction (LVEF <35%)
- and/or NYHA IIIb–IV and/or INTERMACS levels 4, 5, 6
- and/or Repeated hospitalisation or emergency department visits (≥2 in the past year)
- All of the above despite optimal treatment for heart failure
New inotropic agents

Hasenfuss and Teerlink Eur Heart Journal 2011; 32:1838–1845
The challenge of cardiac myosin activation

Target the force generating enzyme cardiac myosin ATPase, accelerating its activity.

- Increase fractional shortening of cardiac myocytes without altering intracellular calcium levels in experimental models.

Malic et al. AHA Scientific Sessions 2005 Dallas TX
Improvement of Cardiac Function by a Cardiac Myosin Activator in Conscious Dogs With Systolic Heart Failure

You-Tang Shen, MD; Fady I. Malik, MD, PhD, FACC; Xin Zhao, MD; Christophe Depre, MD, PhD; Sunil K. Dhar, PhD; Patricio Abarzúa, PhD; David J. Morgans, PhD; Stephen F. Vatner, MD

Circ Heart Fail 2010;3:522-527
Dyspnoea Response Rate (% Responders)

<table>
<thead>
<tr>
<th>Placebo Cohort 1</th>
<th>Placebo Cohort 2</th>
<th>Placebo Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td>41%</td>
<td>51%</td>
</tr>
<tr>
<td>47%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>51%</td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>37%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response rate ratio: ratio of response rate to Placebo within each cohort

Response Rate Ratio | 1.02 | 1.02 | 1.41
95% CI             | (0.74, 1.42) | (0.76, 1.37) | (1.02, 1.93)
Istaroxime

- inhibition of the Na-K ATPase
  - cytoplasmic calcium accumulation
  - positive inotropic response
- stimulation of SERCA2
  - rapid clearance of cytoplasmic calcium to sarcoplasmic reticulum
  - luscitropic response
  - prevention of arrhythio genesis
Istaroxime: a Na/K-ATPase inhibitor with positive lusitropic properties

Sabbah et al. Am J Cardiol 2007;99:41A
Changes in hemodynamic and other measures in the HORIZON-HF trial, three dosages of IV istaroxime vs placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.5, n=29</th>
<th>1.0, n=30</th>
<th>1.5, n=30</th>
<th>Placebo, n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP&lt;sup&gt;a&lt;/sup&gt; (mm Hg)</td>
<td>-3.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-3.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-4.7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>+4.9</td>
<td>+8.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+15.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+1.3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>+2.2</td>
<td>+3.3</td>
<td>+7.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+0.9</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>+2.9</td>
<td>-6.4</td>
<td>-14.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+3.9</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>-25.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-38.0&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-49.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

- a. Primary end point
- b. p<0.05
- c. p<0.01
- d. p<0.001
- e. p=0.0001

PCWP=pulmonary capillary wedge pressure
MAP=mean arterial pressure
LVEDV=left ventricular end-diastolic volume; QTc=corrected QT interval

Gheorghiade M et al. J Am Coll Cardiol 2008; 51:2276-2285.
Nitroxy (HNO)
A Novel Approach for the Acute Treatment of Heart Failure

Hemodynamic effects of CXL-1020 in patients with symptomatic heart failure.

**Conclusions**—These data show the functional efficacy of a novel pure HNO donor to enhance myocardial function and present first-in-man evidence for its potential usefulness in HF.

*Sabbah et al. Circ Heart Fail. 2013;6:1250-1258*
TAKE HOME MESSAGES (1)

- Use of inotropes remains still an option for the management of acute and advanced HF patients with low output state and peripheral hypoperfusion.

- These drugs improve symptoms but may increase mortality.

- Levosimendan seems to be superior than traditional inotropes (dobutamine) in improving hemodynamics and neurohormonal response.

- Investigational cardiac enhancers (targeting novel pathophysiologic concepts) may be promising treatment approaches and ongoing trials will define their clinical efficacy and safety.
TAKE HOME MESSAGES (2)

- Intermittent outpatient parenteral inotropic infusion therapy is frequently prescribed and this treatment option is an effective alternative for carefully selected patients with severely symptomatic and advanced heart failure.

- Recent studies have suggested long-lasting favorable effects of levosimendan when administered repetitively, in terms of hemodynamic parameters, neurohormonal and inflammatory markers, and clinical parameters.

- Existing data, however, require further exploration to allow for definitive conclusions regarding safety and clinical efficacy of repetitive use of levosimendan.

- Further studies are needed to focus on morbidity and mortality outcomes, dosing intervals, and patient monitoring.