Inotropes for the management of AHF- still an option?

Dr John T Parissis
Attikon University Hospital
Athens, Greece

Disclosures:
- ALARM investigator received research grants by Abbott US and Orion Pharma
- Co-PI in LEVOREP trial supported by Orion Pharma
Conventional Treatments of Acute Heart Failure

Reduce fluid volume

Decrease preload and/or afterload

Augment contractility

IV Diuretics

Reduce Volume Overload

Loop Diuretics

Vasodilators

Decrease Preload and Afterload

Nitroglycerin
Nitroprusside
Nesiritide

Inotropes

Augment Contractility

Dobutamine
Levosimendan
Milrinone

## Established and investigational inotropic agents

### Inotropic mechanism

#### Currently used
- Sodium-potassium-ATPase inhibition
- Beta-Adrenoceptor stimulation
- Phosphodiesterase inhibition
- Calcium sensitization

#### Investigational
- Sodium-potassium-ATPase inhibition plus SERCA activation
- Acto-myosin cross-bridge activation
- SERCA activation
- SERCA activation plus vasodilation
- Ryanodine receptor stabilization
- Energetic modulation

### Drugs

#### Currently used
- Digoxin
- Dobutamine, dopamine
- Enoximone, milrinone
- Levosimendan

#### Investigational
- Istaroxime
- Omecamtiv mecarbil
- Gene transfer
- Nitroxyl donor; CXL-1020
- Ryanodine receptor stabilizer; S44121
- Etomoxir, pyruvate

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

Istaroxime

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.)

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
An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.

**Recommendation: IIa  Level of Evidence : C**

An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.

**Recommendation: IIb  Level of Evidence : C**

<table>
<thead>
<tr>
<th>Edema (+)</th>
<th>Edema (±)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm extremities</td>
<td>Cool extremities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SBP &gt; 100 mmHg</th>
<th>SBP 85 - 100 mmHg</th>
<th>SBP ≤ 85 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Vasodilators (e.g., nitrates) + IV diuretics therapeutic optimization; adjust ACEI/oral vasodilator</td>
<td>Optimization of IV diuretics + adjustment of standard therapy; levosimendan (continuous 0.1 - 0.2 μg/kg/min) [If SBP &lt; 85 mmHg after the initiation of treatment, consider 0.05 μg/kg/min] or dobutamine or milrinone (in nonischemic HF) + vasopressor to maintain SBP &gt; 85 mmHg</td>
<td>Volume correction if no response: IV vasopressors (dobutamine, dopamine at vasoconstricting dosing and/or norepinephrine) If no response: mechanical support hemofiltration If necessary, addition of levosimendan (continuous 0.05 - 0.1 μg/kg/min)</td>
</tr>
</tbody>
</table>
Drug Therapy in AHF

Overall use of AHF therapies: IV diuretics, vasodilators, inotropes and levosimendan: by All AHF vs. top 3 AHF Classifications

Driven by Cardiogenic Shock sub-group

Inotropes: Dobutamine Is the Most Frequently Used Drug Across All AHF Indications (58%)
However, 26% of iv inotrope patients receive >1 agent*

![Pie chart showing distribution of inotrope use]

- 74% use 1 inotrope
- 23% use 2 inotropes
- 3% use 3 inotropes
- 0.4% use 4 inotropes

Average no. of inotropic agents:
- All AHF = 1.3
- Cardiogenic shock = 1.7

*Note: the same molecule administered on 2 separate occasions counts as ‘2 inotropes’

Sample = All inotrope patients (2010)

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) ***

Short-term Survival by Treatment Among Patients Hospitalized with Acute Heart Failure: The Global ALARM-HF Registry Using Propensity Scoring Methods

PDE Inhibitors Have Failed to Cause Sustained Improvement Without Adverse Outcomes

OPTIME-CHF: In-hospital Adverse Events

- **Treatment Failure From Adverse Event (48 h)**: 12.6% (Milrinone) vs. 2.1% (Placebo), $P < 0.001$
- **Sustained Hypotension**: 10.7% (Milrinone) vs. 3.2% (Placebo), $P < 0.001$
- **Acute MI**: 1.5% (Milrinone) vs. 0.4% (Placebo), $P = 0.18$
- **Afib**: 4.6% (Milrinone) vs. 1.5% (Placebo), $P = 0.004$
- **Mortality**: 3.8% (Milrinone) vs. 2.3% (Placebo), $P = 0.19$

Cuffe MS et al. JAMA 2002;287:1541
**Effect of Dobutamine on Survival**

**FIRST Trial: Adjusted Survival**

- **No Dobutamine**  
(n = 391)

- **Dobutamine**  
(n = 80)

\[
P = 0.0001^* \]

*For NYHA III-IV patients.*

Effects on Myocardial Oxygen Consumption

- Dobutamine: 58% increase, $P<0.05$, $n=5$
- Levosimendan: 12% increase, $P=0.06$, $n=6$

LIDO trial: Change (%) in Haemodynamic Variables at 24 Hours

SURVIVE
180-day All-Cause Mortality

Probability of Surviving

Levosimendan
Dobutamine

p=0.401

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

<table>
<thead>
<tr>
<th>Day, Group</th>
<th>Favors Levosimendan</th>
<th>Favors Dobutamine</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 β-blocker users*</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>β-blocker non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 β-blocker users*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>β-blocker non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 β-blocker users*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 β-blocker users*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 β-blocker users*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Within 24 hours of study drug infusion

SURVIVE
Mean Change from Baseline in BNP

For comparison between treatment groups at all time points ($P<0.0001$)
Due to the skewness in the data, median percent change is presented versus mean percent change from baseline

Prognostic role of liver congestion in ADHF: A SURVIVE subanalysis

Evidence for cardio-hepatic syndrome?

Nikolaou M, Parissis J,…, Mebazaa A. ESC Congress 2010, Paris, France (abstr)
Levosimendan, compared to dobutamine, reduces enzymatic markers associated with liver congestion and right heart failure: A SURVIVE subanalysis

*Nikolaou M, Parissis J,…, Mebazaa A. ESC Congress 2010, Paris, France (abstr)*
Serial Levosimendan Infusions in ADHF

N=25 pts

Combined Effects Of Levo With Dob In Refractory Heart Failure

Next Step: LEVOREP Trial

Levosimendan repetitive – Study-protocol

Screening Randomization

1 week

Treatment

6 weeks

Short term

2 weeks

Long term

18 weeks

Baseline

KCCQ
6 min. walktest
Lab values
proBNP
Weight
NYHA
Heart rate
Blood pressure

KCCQ
6 min. walktest
Lab values
proBNP
Weight
NYHA
Heart rate
Blood pressure

KCCQ
6 min. walktest
Lab values
proBNP
Weight
NYHA
Heart rate
Blood pressure

Levosimendan
0.2 mg/kg/min for 6 h

Placebo

LEVOREP - Endpoints

- **Primary objective**
  - composite end-point of functional capacity (6min-WT) and quality of life (KCCQ).

- **Secondary objectives**
  - short-term and long-term event-free survival (cardiac death or cardiac related hospitalization),
  - left ventricular function and
  - left ventricular enddiastolic diameter (LVEDD)

- **Tertiary objectives**
  - markers of inflammatory activation (IL-6, IL-10 and TNF-alpha),
  - markers of the apoptotic process (Soluble Fas, sFas Ligand),
  - markers of oxidative stress (MDA, protein carbonyls, nitrotyrosine), d) markers of disease severity (NT-pro-BNP),
  - weight,
  - dose of diuretics,
  - creatinine clearance and
  - cost effectiveness.
Cardiac myosin activators increase the number of “independent force generators” (myosin heads) interacting with the actin filament.

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

A. Heart Rate

B. LV Systolic Ejection Time

C. LV End-diastolic Pressure

D. Systolic Wall Thickening

- MI-sHF
- LVH-sHF

* p<0.05 vs baseline
Metabolic effects of Cardiac Myocin Activators on the Failing Heart

Fig 6. Effects of infusion of CK-452 on myocardial oxygen consumption calculated from coronary blood flow, arterial and coronary sinus oxygen content in dogs with CHF and LVH. There were no significant changes in all indices.
Clinical data: Phase I trial with CK-1827452

- N= 34 healthy subjects,
- Placebo controlled
- 6-hour infusion once each week for four weeks
- Max tolerated dose 0.5 mg/Kg/hour
- Dose-dependent increase of LV ejection time and LVEF (+ 6.8%, p<0.001)
- No increase of troponin or other markers of myocardial injury

J. Teerlink Heart Fail Rev 2009;14:289
The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic HF: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial

Cleland et al. Lancet 2011;378:676-683
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure

ATOMIC-AHF

Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure
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 istoroxime 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(^a) (mm Hg)</td>
<td>-3.2(^b)</td>
<td>-3.3(^c)</td>
<td>-4.7(^d)</td>
<td>0.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>+4.9</td>
<td>+8.3(^b)</td>
<td>+15.6(^d)</td>
<td>+1.3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>+2.2</td>
<td>+3.3</td>
<td>+7.5(^c)</td>
<td>+0.9</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>+2.9</td>
<td>-6.4</td>
<td>-14.1(^b)</td>
<td>+3.9</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>-25.7(^e)</td>
<td>-38.0(^e)</td>
<td>-49.2(^e)</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
Use of inotropes remains still an option for the management of AHF patients with low output state and peripheral hypoperfusion.

Traditional inotropes are over-used although they have several limitations in the real clinical practice (arrythmiogenesis, myocardial injury, interaction with the oral medications).

These drugs improve symptoms but can increase mortality rates.
Levosimendan seems to be superior than traditional inotropes in improving hemodynamics and neurohormonal response but causes hypotension and have failed to improve prognosis.

Investigational cardiac enhancers such as cardiac myocin activators and istaroxime (targeting to novel pathophysiologic concepts) are promising treatment approaches without significant adverse effects and ongoing trials will define their clinical efficacy and safety.
<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased PAP</td>
<td>levosimendan, milrinone</td>
</tr>
<tr>
<td>Need for beta-blocker</td>
<td>levosimendan, milrinone</td>
</tr>
<tr>
<td>Hypotension</td>
<td>dobutamine, dopamine, norepinephrine</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>dopamine, dobutamine, levosimendan</td>
</tr>
<tr>
<td>Ischemic disease</td>
<td>levosimendan, dobutamine</td>
</tr>
</tbody>
</table>