Acute Decompensated Heart Failure: A Case Presentation

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Demographics and past history

- C.G, a 48 y old male, married+4, until recently non-sedentary lifestyle
- **Risk factors**: Dyslipidemia treated with statins, past history of smoking (18 years ago). No significant family history for IHD or CMP
Current event

- Fatigue over recent months.
- A month before admission “common cold” w/o fever.
- Progressive symptoms of fatigue, extreme weakness, effort dyspnea, epigastric pain, vomiting and weight loss.
- Admission to another hospital. Echo demonstrated dilated left ventricle with estimated LVEF of 20% and antero-apical dyskinesis.
- Coronary angiography revealed anatomically normal coronary arteries.
- A diagnosis of **non-ischemic CMP (M/P post myocarditis)** was made and the patient was discharged under treatment of B.blockers, ACE inhibitors and diuretics.
Due to further clinical deterioration (NYHA 3) the patient was admitted to a second hospital with signs of low CO state with secondary “shock liver” and acute renal failure.
- Echo at that time: LVEDD 62 mm, EF 15%, moderate MR, mild pulmonary HTN, severe RV dysfunction
- TDI- no evidence of intraventricular disynchrony.
Right heart Catheterization

- RA A: 25.4
- RA V: 21.7
- PA: 48/34; mean 38
- PCW A: 32.6
- PCW V: 38.3
- RV 40/15

- CO 1.7
- CI 1.1
- SVR 34 wood
- PVR 5.9 wood
?What can we do
Clinical Conditions

**Acute decompensation of CHF**: Signs and symptoms are mild

- Heart rate +/-
- SBP +/-
- CI +/-
- PCWP +
- Diuresis +
- Hypoperfusion +/-

**AHF with pulmonary oedema**: Severe respiratory distress with rales over the lungs

- Heart rate +
- SBP +/-
- CI -
- PCWP ++
- Diuresis +
- Hypoperfusion +/-

*ESC Guidelines on the Diagnosis and Treatment of Acute Heart Failure*
Clinical Conditions
Cardiogenic shock

Low output syndrome: reduced BP, low urine output, tissue hypoperfusion

- Heart rate +
- SBP -
- CI -
- PCWP +
- Diuresis -
- Hypoperfusion +

Severe Cardiogenic shock: low BP, organ hypoperfusion, anuria

- Heart rate ++
- SBP --
- CI --
- PCWP ++
- Diuresis --
- Hypoperfusion ++
Forrester Classification

**Normal**
Cardiac index: 2.2 L/min/m²

**Diuretics vasodilators**

**Pulmonary oedema**

**Hypovolemic**
Fluid administration

Normal blood pressure:
Vasodilators
Reduced blood pressure:
Inotropics or vasopressors

**Pulmonary congestion**
PCWP: 18 mmHg
Treatment Approach for the Patient with Heart Failure

**Stage A**
At high risk, no structural disease

**Therapy**
- Treat Hypertension
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake
- ACE inhibition

**Stage B**
Structural heart disease, asymptomatic

**Therapy**
- All measures under stage A
- ACE inhibitors in appropriate patients
- Beta-blockers in appropriate patients

**Stage C**
Structural heart disease with prior/current symptoms of HF

**Therapy**
- All measures under stage A
- Drugs:
  - Diuretics
  - ACE inhibitors
  - Beta-blockers
  - Digitalis
  - Dietary salt restriction

**Stage D**
Refractory HF requiring specialized interventions

**Therapy**
- All measures under stages A, B, and C
- Mechanical assist devices
- Heart transplantation
- Continuous (not intermittent) IV inotropic infusions for palliation
- Hospice care

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Figure 1: Immediate goals in treatment of the patients with acute heart failure [13]

ACEI, angiotensin-converting enzyme inhibitor; BNP, brain natriuretic peptide; CPAP, continuous positive airway pressure; NTG, nitroglycerine; PDEI, phosphodiesterase inhibitors; SBP, systolic blood pressure.

Acute heart failure with systolic dysfunction

- Oxygen/CPAP
- Furosemide ± vasodilator
- Clinical evaluation (leading to mechanistic therapy)

1. SBP >100 mmHg
   - Vasodilator (NTG, nitroprusside, BNP)

2. SBP 85–100 mmHg
   - Vasodilator and/or inotropic (dobutamine, PDEI or levosimendan)

3. SBP <85 mmHg
   - Volume loading? inotrope and/or dopamine >5 μg/kg/min and/or norepinephrine

No response: reconsider mechanistic therapy, inotropic agents

Good response
- Oral therapy furosemide, ACEI
Figure 2 Algorithm for acute heart failure treatment, data from Canadian Cardiovascular Society guidelines on the management of acute decompensated heart failure [14]

AHF diagnosed, treatment initiated based on symptoms and signs

Volume overload

Mild volume overload

IV diuretics

IV furosemide bolus
  • serum creatinine <20 μmol/L 40 mg
  • serum creatinine >500 μmol/L 80 mg

IV diuretics + IV vasodilators
  • consider furosemide infusion
  • add IV nitroglycerin starting at 5–10 μg/kg/min
  • titrate to clinical status, BP or PCWP, if available

Moderate to severe volume overload

• inadequate response to IV diuretics
• increased oxygen requirement
• CPAP and BiPAP requirement
• fatigue

Volume overload + low cardiac output

Mild to moderate low output

Very low output

• consider PA line
• add vasodilator after BP stabilized

SBL >90 mmHg

• milrinone 0.275 μg/kg/min or
• dobutamine

SBP <90 mmHg

• dobutamine
  • 2–5 μg/kg/min
• may also require vasopressors

AHF, acute heart failure; BiPAP, bilevel positive airway pressure; BP, blood pressure; CPAP, continuous positive airway pressure; IV, intravenous; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure.
Medical treatment
Medical Rx

- The ideal treatment should:
  - improve symptoms and hemodynamics without increasing myocardial oxygen demand and increasing propensity for arrhythmias.
  - Improve outcome!!!
- Do current therapies meet these criteria?
### Table 1: Summary of selected treatment options for acute decompensated heart failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Setting</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>Natriuresis (preload reduction)</td>
<td>Volume overload with elevated left and right ventricular filling pressures</td>
<td>Bolus intravenous infusion (dose is often about twice the patient’s usual dose at home); adjust dose based on urine output; add thiazide (metolazone 2.5-5 mg orally daily or chlorothiazide 250-500 mg intravenously once or twice daily), or switch furosemide to a continuous infusion (5-30 mg/h), or both in severe cases with diuretic resistance</td>
<td>Foundation of treatment for acute decompensated heart failure in patients with symptoms of congestion (“wet and warm”)</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Venovenous filter to remove free water</td>
<td>Alternative to loop diuretics for treatment of volume overload</td>
<td>Ultrafiltration/hemofiltration system; fluid removal rates as dictated by clinical assessment, adequate blood pressure and system capabilities</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Venodilation (preload reduction), coronary vasodilator (anti-ischemic)</td>
<td>Volume overload with adequate blood pressure, cardiac ischemia</td>
<td>1-2 sprays of sublingual nitroglycerin (0.3-0.8 mg) every 3-5 min at first. Consider transition to continuous intravenous infusion (v. topical paste): 10-20 µg/min intravenously at first; increase by 5-20 µg/min every 3-5 min as blood pressure allows</td>
<td>Probably underused in patients presenting with acute decompensated heart failure and adequate blood pressure</td>
</tr>
<tr>
<td>Positive pressure ventilation</td>
<td>Positive intrathoracic pressure (preload reduction)</td>
<td>Volume overload with (or without) dyspnea or hypoxia</td>
<td>Continuous positive airway pressure (with or without bilevel positive airway pressure) at pressure of 5-20 cm H₂O</td>
<td>Consider short-term use (hours) in patients with acute decompensated heart failure in acute respiratory distress</td>
</tr>
<tr>
<td>Morphine</td>
<td>Venodilator (preload reduction)</td>
<td>Volume overload with adequate blood pressure after nitroglycerin</td>
<td>Bolus 2-4 mg intravenously</td>
<td>No evidence of efficacy; second-line treatment</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Indications</td>
<td>Dosage</td>
<td>Additional Information</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>-------------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Venodilator (preload reduction)</td>
<td>Volume overload with adequate blood pressure</td>
<td>Bolus 2 µg/kg; then infusion 0.01 µg/kg per min, adjusting dose up to 0.03 µg/kg per min</td>
<td>Not currently available in Canada</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Arterial vasodilator (afterload reduction)</td>
<td>Acute heart failure with severe hypertension, or mitral valve regurgitation with adequate blood pressure</td>
<td>Continuous intravenous infusion of 0.3 µg/kg per min at first; titrate rapidly to desired blood pressure; maximum dose 10 µg/kg per min</td>
<td>Use nitroglycerin instead in most patients with acute decompensated heart failure; light sensitive; toxic levels of thiocyanate may accumulate</td>
</tr>
<tr>
<td>Vasodilating inotropes (dobutamine, milrinone)</td>
<td>Inotrope, chronotrope, systemic vasodilator, pulmonary vasodilator</td>
<td>Acute heart failure unresponsive to above therapies, worsening renal function</td>
<td>Dobutamine: 2-20 µg/kg per min intravenously Milrinone: 0.125-0.75 µg/kg per min intravenously (may load 50 µg/kg intravenously over 10 min, but not necessary); renal adjustment necessary</td>
<td>For short-term use in patients with significantly impaired cardiac output; may increase arrhythmia and risk of death; milrinone has longer half-life than the β-agonists</td>
</tr>
<tr>
<td>Vasopressor inotropes (dopamine, norepinephrine)*</td>
<td>Inotrope, chronotrope, vasoconstrictor</td>
<td>Shock with inadequate blood pressure (possibly low-dose dopamine in cardiorenal syndrome)</td>
<td>Dopamine: 1-50 µg/kg per min intravenously Norepinephrine: 0.01-0.4 µg/kg per min intravenously</td>
<td>Used in critically ill patients with hypotension; typically avoided in pure heart failure with high systemic vascular resistance, but such resistance may be low in acute decompensated heart failure owing to activation of systemic inflammatory response or total circulatory collapse</td>
</tr>
</tbody>
</table>

*Vasopressin and phenylephrine would not typically be used in acute decompensated heart failure.
Diuretics

Table 1  Systemic effects associated with acute high-dose diuretic administration

- ↑ RAAS stimulation
- ↑ AVP levels
- ↑ HR
- ↑ Norepinephrine levels
- ↓ GFR
- ↑ SVR

RAAS-renin-angiotensin-aldosterone-system; AVP-arginine vasopressin; HR-heart rate; GFR-glomerular filtration rate; SVR-systemic vascular resistance

Fig. 1  The “iatrogenic” cardio-renal syndrome of heart failure
The use of diuretics for the treatment of patients with ADHF represents an area of medicine with a paucity of rigorous clinical trials. The acceptance of diuretics into the HF treatment paradigm is largely based on clinical and anecdotal experience over the last forty years without the benefit of large, multi-center randomized trials.
There is evidence that low-dose furosemide in combination with vasodilators may enhance diuresis with less adverse effects than high-dose boluses.

Inotropes
Table 2 Classification and mechanisms of agents which improve contractility and their concomitant clinical effects

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Incr. i Ca</th>
<th>PDEi</th>
<th>SV</th>
<th>Vasodilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inotropic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Milrinone</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Enoximone</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cardiac enhancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levosimendan</td>
<td>+ –</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Pimobendan</td>
<td>+ –</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Incr. I Ca: increasing of intracellular calcium; PDEi: Phosphodiesterase inhibitors; SV: stroke volume
Short-term inotropic infusion, although frequently used to improve hemodynamics and symptoms in acute decompensated heart failure, remains controversial. When patients present with profound circulatory collapse, inotropes may be absolutely required.

For patients with acute decompensated heart failure who have evidence of end-organ hypo perfusion or diuretic resistance, but no frank hypotension, the use of inotropes is not well supported.
The ESCAPE trial published in 2007 revealed that inotropic agents such as dobutamine and milrinone in heart-failure patients with low ejection fraction and hypotension had higher 6-month mortality rates [hazard ratio (HR) 2.14, 95% CI 1.10–4.15] than patients on vasodilators such as Nesiritide when compared with placebo (HR 1.39, 95% CI 0.64–3.0). Inotropes in combination with vasodilators showed the highest mortality (HR 2.90, 95% CI 1.88–4.48)
- Indicated in the case of peripheral hypo perfusion with or without pulmonary edema

*Class IIa C*
Recommendation 12.18 (1 of 3)

Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by:

- LV dilation
- Reduced LVEF
- And diminished peripheral perfusion or end-organ dysfunction (low output syndrome)

Particularly if these patients:

- Have marginal systolic blood pressure (<90 mm Hg),
- Have symptomatic hypotension despite adequate filling pressure,
- Or are unresponsive to, or intolerant of, intravenous vasodilators.

Strength of Evidence = C
Phosphodiesterase inhibitors

(Milrinone)

Increases myocardial cAMP concentrations by selective inhibition of phospho-diesterase III, which leads to an increase in intracellular calcium, causing increased myocardial contractility, myocardial toxicity secondary to calcium overload, and relaxation of the endothelium.

- Intermediate effect between pure vasodilator to pure inotropic agent
# OPTIME-CHF

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>PLACEBO</th>
<th>MILRINONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 472</td>
<td>n 477</td>
<td></td>
</tr>
<tr>
<td>1. Days of H for CV cause within 60 days (mean)</td>
<td>12.5</td>
<td>12.3</td>
</tr>
<tr>
<td>2. Days of H from infusion to discharge (mean)</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>3. Death/readmission within 60 days (%)</td>
<td>35.3</td>
<td>35.0</td>
</tr>
</tbody>
</table>

*[JAMA 2002;287:1541]*
OPTIME-CHF
ADVERSE EVENTS

placebo
milrinone

p<.01
p<.01
p<.01

treatment failure
sustained hypotension
adverse event

JAMA 2002;287:1541
It can be used simultaneously with catecholaminergic agonists or antagonists.

Class IIb C
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Drawbacks of dobutamine and milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A) <em>Dobutamine</em></td>
</tr>
<tr>
<td></td>
<td>(i) Increased myocardial oxygen consumption</td>
</tr>
<tr>
<td></td>
<td>(ii) Myocardial injury</td>
</tr>
<tr>
<td></td>
<td>(iii) Tolerance/tachyphylaxis</td>
</tr>
<tr>
<td></td>
<td>(iv) Interaction with beta-blockers</td>
</tr>
<tr>
<td></td>
<td>(v) Arrhythmogenesis</td>
</tr>
<tr>
<td></td>
<td>(vi) Increased mortality</td>
</tr>
<tr>
<td></td>
<td>(B) <em>Milrinone</em></td>
</tr>
<tr>
<td></td>
<td>(i) Hypotension</td>
</tr>
<tr>
<td></td>
<td>(ii) Arrhythmogenesis</td>
</tr>
<tr>
<td></td>
<td>(iii) Worsening prognosis in ischemic disease</td>
</tr>
</tbody>
</table>
Levosimendan

- Levosimendan differs from conventional inotropic agents due to its vasodilator properties and positive inotropic effects achieved by enhancing myocyte sensitivity to calcium that is already in the cells rather than increasing calcium in the cell.
The positive inotropic effects of levosimendan are achieved by its binding to troponin C and calcium, thereby stabilizing the tropomyosin molecule and prolonging the duration of actin-myosin overlap without a change in the net concentration of intracellular calcium.

The vasodilatory effect of levosimendan is reached through activation of ATP-dependent potassium channels.
Fig. 1 Levosimendan-induced improvement in left ventricular end-systolic wall stress and pulmonary capillary wedge pressure are correlated with the concomitant reduction of circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with acutely decompensated heart failure (modified from ref. [27]).
Two most recent trials, SURVIVE and REVIVE II, both support the symptomatic benefit of Levosimendan in comparison with placebo.

*Mortality* until 180 days did not differ between levosimendan vs either inotropes or placebo(survive), and was non-significantly increased at 90 days (Revive2)

In a meta-analysis of LIDO, CASINO and SURVIVE, mortality at 6 months was lower in the Levosimendan group (relative risk 0.76, $P^{1/4} 0.032$)
Cox Proportional Hazards  $P = .40$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time Points</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan</td>
<td>664</td>
<td>608</td>
<td>586</td>
<td>525</td>
<td>462</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>663</td>
<td>596</td>
<td>568</td>
<td>519</td>
<td>454</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial acronym</td>
<td>N</td>
<td>Treatment arms</td>
<td>Duration of therapy</td>
<td>Primary end-point</td>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUSSLAN</td>
<td>504</td>
<td>Levosimendan versus placebo in post-MI cardiac failure</td>
<td>Loading dose + 6-h infusion</td>
<td>Hypotension or myocardial ischemia</td>
<td>↓ Risk of death or worsening of heart failure at 6 and 24 h ↓ mortality at 14 days and at 180 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIDO</td>
<td>203</td>
<td>Levosimendan versus dobutamine in decompensated heart failure</td>
<td>Loading dose + 24-h infusion</td>
<td>Hemodynamic improvement</td>
<td>↓ Mortality at 180 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVIVE-1</td>
<td>100</td>
<td>Levosimendan versus placebo in decompensated heart failure</td>
<td>10-min loading dose + 50-min infusion + 23-h infusion (if well-tolerated)</td>
<td>Clinical outcome</td>
<td>↓ “Worsening” (including death) at 24 h and at 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVIVE-2</td>
<td>600</td>
<td>Levosimendan versus placebo in decompensated heart failure</td>
<td>Loading dose (6–12 mcg/kg) + 24-h infusion (0.1–0.2 mcg/kg/min)</td>
<td>A composite of clinical signs and symptoms of acute decompensated heart failure over 5 days</td>
<td>Neutral effects on mortality at 90 days (secondary end-point); improvement of primary-end-point and length of hospitalization; reduction of BNP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURVIVE</td>
<td>1,327</td>
<td>Levosimendan versus dobutamine in decompensated heart failure</td>
<td>Loading dose (12 mcg/kg) + 24-h infusion (0.1–0.2 mcg/kg/min)</td>
<td>Survival at 5, 15, 30 and 180 days</td>
<td>No significantly different effects compared with dobutamine on mortality; greater reduction of BNP than dobutamine (secondary end-point)</td>
<td></td>
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</tr>
</tbody>
</table>
acute heart failure guidelines published by the European Society of Cardiology recommend its use on patients having symptomatic, low-output heart failure secondary to systolic dysfunction which is not accompanied by severe hypotension (Delle Karth et al 2003; Lehmann et al 2004; Nieminen et al 2005). Use on patients with a systolic blood pressure below 85 mmHg is not recommended (Nieminen et al 2005).
<table>
<thead>
<tr>
<th>Agent</th>
<th>Intravenous bolus dose</th>
<th>Intravenous infusion rate</th>
<th>Recommendation class</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>–</td>
<td>2–20 μg/kg/min</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Dopamine</td>
<td>–</td>
<td>≤ 2 μg/kg/min: renal effect, 2–5 μg/kg/min: inotropic effect, &gt;5 μg/kg/min: vasoconstriction</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Milrinone</td>
<td>25–75 mg/kg</td>
<td>0.375–0.75 μg/kg/min</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0.25–0.75 mg/kg</td>
<td>1.25–7.5 μg/kg/min</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>12–24 mg/kg</td>
<td>0.05–0.2 μg/kg/min</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
Vasodilators

- **Nitroglycerin**
  
  *Class I recommendation, level of evidence B*

- **Nitropruside**
  
  *Class I recommendation, level of evidence C*

- **Nesiritide**

  In severely decompensated CHF, intravenous nitroglycerin is preferred because of questionable absorption of oral and transdermal preparations and for ease of titration.
Nesiritide

Venous, arterial, coronary VASODILATION

Cardiac Index

Preload

Afterload

PCWP

Dyspnea

DIURESIS

Fluid volume
Preload
Diuretic usage

SYMPATHETIC AND NEUROHORMONAL SYSTEMS

Not proarrhythmic
Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure
A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein, MD
Marcin Kowalski, MD
Marshall Fox, MD
Keith Aaronson, MD, MS

**Context** Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short-term safety relative to standard diuretic and vasodilator therapies is less clear.

**Objective** To investigate the safety of nesiritide relative to noninotrope-based control therapies, primarily consisting of diuretics or vasodilators.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Deaths/Total No. (% of Patients)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nesiritide Therapy</td>
<td>Control Therapy</td>
<td></td>
</tr>
<tr>
<td>NSGET</td>
<td>6/85 (7.1)</td>
<td>2/42 (4.8)</td>
<td>1.48 (0.31-7.03)</td>
</tr>
<tr>
<td>VMAC</td>
<td>24/280 (8.6)</td>
<td>12/218 (5.5)</td>
<td>1.56 (0.80-3.04)</td>
</tr>
<tr>
<td>PROACTION</td>
<td>5/120 (4.2)</td>
<td>1/117 (0.9)</td>
<td>4.88 (0.58-41.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>35/485 (7.2)</td>
<td>15/377 (4.0)</td>
<td>1.74 (0.97-3.12)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ND, not determined; NSGET, Nesiritide Study Group Efficacy Trial; PROACTION, Propective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; VMAC, Vasodilation in the Management of Acute Congestive heart failure.
VMAC investigators *JAMA* 2002 287:1531

(acute heart failure + RHC)

P < 0.05 nsir or nitro vs placebo // p < 0.05 nesir vs nitro
Fig. 3 Proposed mechanisms for differential renal effects mediated by natriuretic peptides [3, 68]. NPs = natriuretic peptides RAAS = renin-angiotensin-aldosterone system SNS = sympathetic nervous system
The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest.

Physicians considering the use of nesiritide should consider its efficacy in reducing dyspnea, the possible risks of the drug, and the availability of alternate therapies to relieve the symptoms of congestive heart failure.
Future targets

- **Vasopressin receptor antagonists** (*tolvaptan* and *conivaptan*) There are two types of receptor, V1a and V2 receptors. V1a receptors activate peripheral arterial and coronary vasoconstriction, therefore increasing both preload and afterload. V2 receptors are responsible for free water absorption in the renal collecting duct by increasing the amount of aquaporin-2 within the membrane.
Arginine Vasopressin (AVP)

aka Antidiuretic Hormone

- V1<sub>A</sub>
  - Vascular Smooth Muscle Cell

- V1<sub>A</sub>
  - Heart

- V2
  - Distal Tubules

- Coronary Vasoconstriction
  - Myocyte Hypertrophy

- Increased afterload and wall stress
  - LV hypertrophy
  - Ischemia
  - Increased preload, hyponatremia, edema
Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA* 2004 29:1963-

- There were no differences in worsening heart failure at 60 days between the tolvaptan and placebo groups (P = .88 for trend). In post hoc analysis, 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion.

- A phase III trial EVEREST is currently being conducted to evaluate the long-term efficacy and safety of tolvaptan in hospitalized patients with severe HF.
• Adenosine A1 receptor antagonists

Show promising diuretic properties in patients with acute decompensated heart failure, particularly diuretic-refractory patients. Renal A1-receptor blockade prevents arteriolar vasoconstriction and post glomerular vasodilation resulting in improved glomerular blood flow.

(Rolofylline- presented ACC 2008 PROTECT pilot study)
Endothelin receptor antagonists (*tezosentan* and *bosentan*)

Primary endpoint of death or worsening heart failure at 7 and 30 days

- There was no difference in death or worsening heart failure between the Tezosentan group compared to the placebo group at both 7 and 30 days.

- For the primary endpoint of dyspnea at 24 hours, there was no difference between the treatment groups in either of the VERITAS trials individually or together.

**VERITAS Trial: Primary Endpoint**

Presented at ACC 2005
Published AM Heart J 2005
New inotropes
Cardiac myosin activators

- Enhancing the efficiency of actin–myosin coupling
- Increasing contractility W/O increasing intracellular calcium or oxygen consumption
Non-pharmacological therapies

Small randomized trials have shown that continuous positive airway pressure (CPAP) and other noninvasive ventilation decreased the need for endotracheal intubation in cardiogenic shock without a significant impact in mortality.

- **Ultrafiltration** - small trials revealed its potential benefit for relief of pulmonary edema, ascites, and peripheral edema.

Mechanical assistance
IABP

- Recommended in acute decompensated states, as an urgent measure of cardiac support, to stabilize the patient and maintain organ perfusion until transplantation is done.

*Class I B*
Case presentation – cont

- Being at a state of cardiogenic shock, IABP was inserted and IV inotropes (milrinone) were given with stabilization of the blood pressure and mild improvement of CI.

- The patient was transferred to our ICCU without improvement in LV function under above Rx.
What can we do more

!!!Assist device★
Rationale of assist device use

- Restoration of normal hemodynamics and vital organ perfusion.
- Reduction of ventricular strain and improving remodeling
Circulatory Support Milestones

- 1982 - Begin Clinical Evaluation / Pennington, SLU
- 1984 - 1st Successful Bridge to Transplant / Hill, CPMC
- 1995 - FDA Approval for Bridge to Transplant
- 1998 - FDA Approval for Postcardiotomy Recovery
- 1998 - Smallest VAD Recipient (17 Kg)
- 2000 - Youngest VAD Recipient (6 yrs)
- 2000 - Longest Duration VAD Support (566 days)
the β2-adrenergic–receptor agonist clenbuterol in combination with LVA in pts with non ischemic CMP
### Assist devices

- A bridge to recovery or to heart transplantation
  - **Class IIa B**

<table>
<thead>
<tr>
<th>Device</th>
<th>Type</th>
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<tbody>
<tr>
<td>Oxygenator</td>
<td>Short term</td>
</tr>
<tr>
<td>Thoratec</td>
<td>LV+RV</td>
</tr>
<tr>
<td>Heartmate I/II</td>
<td>long term, destination</td>
</tr>
<tr>
<td>Total artificial heart</td>
<td></td>
</tr>
</tbody>
</table>
An external drive line provides electrical power to a motor within the device. The motor drives a pusher plate up and down repeatedly, expanding and compressing the volume-displacement chamber. The direction of blood flow is maintained by inflow and outflow valves. The inflow cannula is inserted into the left ventricular apex, and the outflow cannula is inserted into the ascending aorta.
Thoratec® Implant

Versatility

Cannulation Options
BIVAD

- support of RV and LV
Total artificial heart
-abiocor
Heartmate II
Indications

- May be indicated to patients not responding to conventional Rx, when there is a potential for recovery or as a bridge to transplant
Who should get an assist device?

1. Acute heart failure
   - Initiate therapy (a)
   - No response
   - Permanent end organ dysfunction (b)
     - No → Conservative treatment
     - Yes → Potential myocardial recovery, Potential intervention to recovery (c)

2. Potential myocardial recovery, Potential intervention to recovery (c)
   - Yes → Intra-aortic balloon pump
   - No → Conservative treatment

3. Intra-aortic balloon pump
   - No response (d)
   - Left ventricular assist device (e)
     - Eventual recovery
       - Intervention to recover ventricular function / Transplant
Major complications of assist device

- Bleeding
- Infection
- Neurologic events
Univentricular vs. Biventricular Assist Device Support

- **Indications for Biventricular Support**
  - Signs of Right Heart Failure
  - Intractable Arrhythmias
  - RV/Septal Infarction
  - Elevated PVR
  - Secondary Organ Involvement
  - Prolonged Cardiogenic Shock “Sicker Patients”
Patient’s follow-up
BIVAD- Thoratec implantation

- Implantation of BIVAD
- Myocardial Biopsy- mild perivascular and interstitial fibrosis mild hypertrophic changes

**Postoperative complications:**
- Revision due to bleeding and tamponade,
- Acute delirium and restlessness treated successfully with anti psychotics
- Sepsis d/t Klebsiella originating from surgical wound - resolved with broad-spectrum Abx
Survival with assist device in Israel

- During 2007 8 assist devices (7 BIVAD; 1 RVAD) were implanted in Rabin Medical Center and the Sheba Medical Center.
- **Survival rate: 50 %**
- Until 9/2008 3 assist devices were implanted, of them only one (destination) survived.
After BIVD implantation, he is categorized as STATUS I, waiting for heart transplantation.

During this period he is mobile and even spends some time at home with the mobile BIVAD unit.
Heart transplantation statistics during 2007/8 in Israel

- During 2007 15 patients (7 in Rabin Medical Center; 8 in Sheba Medical Center) underwent orthotrophic heart transplantation.
- During 2008 7 pts underwent transplantation (3 kids).
- Survival rate: (86%) patients transplanted in Rabin Medical Center are alive, and in excellent condition.
Heart transplantation

- 3 months after BIVAD implantation, while he is categorized as STATUS I, he underwent orthotropic heart transplantation.
- Perioperative course – difficulties in hemostasis d/t warfarin Rx.
- Treatment with RATG and steroids followed by cellcept and takrolimus.
- Postoperative course- no major complications, normal function of the transplanted heart.
There is always an option for patients with severe decompensated heart failure

- Patients with acute decompensated heart failure should receive all evidence-based treatments (medical and mechanical) in order to maintain vital organ function.

- After stabilization, patients should be transferred to tertiary centers specializing in assist device implantation and orthotropical heart transplantation.