Acute and refractory heart failure: how to treat and what role for pharmacologic therapies?

Dr. Carlo Campana
U.O di Cardiologia
A.O. Sant’Anna Como
Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- **INOTROPIC AGENTS**: indicated in the presence of peripheral hypoperfusion with or without congestion or pulmonary oedema refractory to diuretics and vasodilators at optimal doses. Their use can be useful in the improvement of the hemodynamics

- **Class IIa recommendation, level of evidence C**

- **Their use is potentially harmful as they increase oxygen demand and calcium loading and they should be used with caution**
<table>
<thead>
<tr>
<th></th>
<th>SITE OF ACTION</th>
<th>MECHANISMS</th>
<th>HEMODYNAMIC EFFECT</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOBUTAMINE</strong></td>
<td>β1-β2 adrenergic receptors</td>
<td>↑c AMP, ↑Ca release, ↑O2 demand</td>
<td>↑contractility, ↑Stroke volume, ↑Arterial vasodilatation</td>
<td>β-blockers treatment tolerance (β-receptors down – regulation) tachycardia arrhythmias</td>
</tr>
<tr>
<td><strong>DOPAMINE</strong></td>
<td>Dopaminergic receptors, β adrenergic receptors</td>
<td>↑c AMP, ↑Ca release (↑ O2 demand)</td>
<td>↑contractility, ↑Stroke volume, Vasoconstriction (↑ afterload)</td>
<td>tachycardia arrhythmias</td>
</tr>
<tr>
<td><strong>PDE III INHIBITORS</strong></td>
<td>Inhibition of PDE III involved in breakdown of cAMP into AMP</td>
<td>↑Ca release</td>
<td>↑contractility vasodilation (↓ pre-and afterload) in pts on β-blockade</td>
<td>hypotension</td>
</tr>
<tr>
<td><strong>Ca SENSITIZERS LEVOSIMENDAN</strong></td>
<td>↑sensitivity of troponinc to intracellular ionized Ca PDE III inhibition ATP-dependent K channels action</td>
<td>No ↑c AMP, No ↑O2 demand</td>
<td>↑Stroke volume, ↓SVR, ↓PVR, ↓ filling pressures</td>
<td>hypotension</td>
</tr>
</tbody>
</table>
Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- **Dopamine**: may be used as an inotrope in AHF with hypotension, to improve renal blood flow and diuresis in decompensated HF with hypotension and low urine output
  - Class of recommendation IIb, level of evidence C

- **Dobutamine**: is currently indicated when there is peripheral hypoperfusion with or without congestion or pulmonary oedema refractory to diuretics and vasodilators at optimal doses; prolonged infusion is associated with tolerance; increased, dose-related incidence of arrhythmias
  - Class of recommendation IIa, level of evidence C

- For several years no controlled trials on DOB in AHF patients and some trials showed unfavourable effects with increased cardiovascular events
Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- **Phosphodiesterase inhibitors**: in presence of peripheral hypoperfusion with or without congestion refractory to diuretics and vasodilators at optimal doses and preserved systemic blood pressure
  - Class of recommendation IIb, level of evidence C
- PDEIs type III: should be preferred to dobutamine in patients on concomitant beta-blocker therapy, and/or with an inadequate response to dobutamine
  - Class of recommendation IIa, level of evidence C
- The PDEIs effects on outcome of pts with AHF are insufficient but raise concerns about safety in pts with ischemic HF
Vasopressor therapy in cardiogenic shock: is required when the combination of inotropic agents and fluid challenge fails to restore adequate arterial and organ perfusion despite an improvement in cardiac output.

In emergencies to sustain life and maintain perfusion in the face of life-threatening hypotension.

Epinephrine: can be used in case of dobutamine refractoriness and very low BP, with arterial and PAC monitoring.

Norepinephrine: used to increase SVR in presence of shock associated with low SVR.
Executive summary of the guidelines on the diagnosis and treatment of Acute Heart Failure

Eur Heart J 2005;26:384-416

- **Levosimendan**: in presence of symptomatic low cardiac output HF secondary to cardiac systolic dysfunction without severe hypotension
- **Class of recommendation IIa, level of evidence B**
- L. infusion in AHF with LV systolic dysfunction has been associated with a dose-dependent increase in CO and SV, a decrease in PWP, SVR and PVR
- A favourable outcome was shown in randomized clinical trials comparing L. with Dobutamine
- Hemodynamic response to L. Is maintained in patients on concomitant beta-blocker therapy
Hemodynamic patterns during acute HF

Cotter et al: Eur J Heart Fail, 2003; 5: 443-51
IN-HOSPITAL IV MEDICATIONS

(2807 patients)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>51.3%</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>49.5%</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Inotropes</strong></td>
<td><strong>24.6%</strong></td>
</tr>
<tr>
<td>Dopamine</td>
<td>18.5%</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>12.9%</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0.6%</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>0.8%</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1.3%</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Italian Survey on Acute Heart Failure
ADHERE
Most Common IV Medications N=105388 for AHFS

IV Vasoactive and Diuretic Medications

- IV Diuretic: 88%
- Dobutamine: 6%
- Dopamine: 6%
- Milrinone: 10%
- Nesiritide: 3%
- Nitroglycerin: 1%
- Nitroprusside: 1%

Inotropes 15%
Vasodilators 21%

Alarm-HF Acute Heart Failure global Survey of Standard treatment Retrospective Study (8 countries)

4250 AHF pts (ADCHF 65%; de novo 35%)

- Miscellaneous: 8%
- Pulmonary edema: 5%
- Shock: 36%
- Acute decompensated HF: 12%
- Hypertension: 39%
- Inotropes: 12%

<table>
<thead>
<tr>
<th>Inotropes</th>
<th>ADCHF</th>
<th>SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>Dopamine</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Norepinephrine/Epinephrine</td>
<td>18%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Follath. Heart Failure Congress 2007; Hamburg
Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial


Figure 4: Kaplan-Meier estimates (analysis of time to first event) of risk of death during first 180 days after randomisation (based on the intention-to-treat analysis)
Esperienza multicentrica con LEVOSIMENDAN: confronto di variabili clinico strumentali

L Scelsi, C Campana, S Ghio, L Monti, C Opasich, S De Feo, F Cobelli, M Orlandi, G Di Pasquale, L Tavazzi.


<table>
<thead>
<tr>
<th></th>
<th>basale</th>
<th>Dopo 24 ore</th>
<th>Delta</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peso Kg</td>
<td>73±10</td>
<td>70±9</td>
<td>+ 2,88</td>
<td>1,22</td>
<td>4,54</td>
</tr>
<tr>
<td>PASs mmHg</td>
<td>102±8</td>
<td>99±12</td>
<td>+ 2,64</td>
<td>-2,49</td>
<td>7,77</td>
</tr>
<tr>
<td>PASd</td>
<td>64±9</td>
<td>61±10</td>
<td>+ 3,2</td>
<td>-0,9</td>
<td>7,3</td>
</tr>
<tr>
<td>Creatininemia mg%</td>
<td>1,5±0,6</td>
<td>1,4±0,6</td>
<td>+ 0,03</td>
<td>-0,13</td>
<td>0,19</td>
</tr>
<tr>
<td>Natremia mEq/L</td>
<td>135±4</td>
<td>135±4</td>
<td>+ 0,66</td>
<td>-0,95</td>
<td>2,3</td>
</tr>
<tr>
<td>Potassiemia mEq/L</td>
<td>4,2±0,6</td>
<td>4,3±0,5</td>
<td>- 0,09</td>
<td>-0,42</td>
<td>0,23</td>
</tr>
<tr>
<td>BNP pg/ml</td>
<td>434±284</td>
<td>405±344</td>
<td>+ 28,61</td>
<td>-214</td>
<td>271</td>
</tr>
<tr>
<td>Log BNP</td>
<td>5,87±0,96</td>
<td>5,60±1,0</td>
<td>+ 0,22</td>
<td>-0,83</td>
<td>1,29</td>
</tr>
<tr>
<td>DTDVsx mm</td>
<td>71±10</td>
<td>70±11</td>
<td>+ 0,9</td>
<td>0,28</td>
<td>1,47</td>
</tr>
<tr>
<td>FE%</td>
<td>23±8</td>
<td>26±7</td>
<td>- 3,36</td>
<td>-4,69</td>
<td>-2,02</td>
</tr>
<tr>
<td>Score CHF</td>
<td>5±2</td>
<td>2±2</td>
<td>+ 3,4</td>
<td>0,31</td>
<td>1,34</td>
</tr>
</tbody>
</table>
SURVIVE
Mortality Trial in ADHF

▪ Design
  - Randomized, double-blind, double-dummy
  - Multi-center, parallel-group
  - Levosimendan versus dobutamine
  - Primary end point: 180-day all-cause mortality

▪ Assumptions
  - Overall 180-day mortality rate: 25%
  - Levosimendan relative risk reduction: 25% (α = 0.05, power = 85%)
  - 330 events required (~1300 patients)

▪ 75 Sites in 9 countries:
  Austria, Finland, France, Germany, Israel, Latvia, Poland, Russia, and UK
SURVIVE
Study Design

- Hospitalized for ADHF
- LVEF ≤ 30%
- Clinical need for inotropic therapy after IV diuretics and/or IV vasodilators:
  - Oliguria,
  - And/or dyspnea at rest

Randomization
Balanced by country and previous heart failure

Levosimendan
12 μg/kg bolus
0.1 - 0.2 μg/kg/min, 24 h

Dobutamine
≥ 5 μg/kg/min, ≥ 24 h

180 Days
## SURVIVE

### Demographics and Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levosimendan (n = 664)</th>
<th>Dobutamine (n = 663)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>74</td>
<td>70</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>67 (12)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 (18)</td>
<td>79 (16)</td>
</tr>
<tr>
<td>Previous history of HF, %</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Ischemic etiology for acute HF, %</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>NYHA Class IV, %</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Median BNP*, pg/mL (Normal BNP in non-HF subjects &lt; 135 pg/mL)</td>
<td>1178</td>
<td>1231</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84 (17)</td>
<td>83 (17)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>116 (18)</td>
<td>116 (19)</td>
</tr>
</tbody>
</table>

*AXSYM® BNP Assay
SURVIVE
180-Day All-Cause Mortality

- Red: Levosimendan
- Yellow: Dobutamine

Overall 180-d Mortality: 27%

Days Since Start of Study Drug Infusion

Probability of Surviving

JAMA 2007; 297:1883-91
SURVIVE: Pre-Specified Stratum
All-Cause Mortality in Patients With / Without Previous HF

Day, Group

5  Previous HF
   No previous HF

31 Previous HF
   No Previous HF

180 Previous HF
   No Previous HF

Favors Levosimendan
Favors Dobutamine

HR 0.58 (0.33-1.01)

Hazard Ratio (95% CI)
Hospitalized for worsening heart failure
LV ejection fraction ≤ 35%
Dyspnea at rest despite IV diuretics

Placebo  Levosimendan

49  51

REVIVE I
Pilot to evaluate endpoint

301  299

REVIVE II
Trial to evaluate drug
REVIVE II Trial: Study Endpoints

**Primary Endpoint**
- Clinical composite

**Secondary Endpoints**
- B-Type natriuretic peptide (BNP) at 24 hours
- Patient global assessment at 6 hours
- Patient dyspnea assessment at 6 hours
- Days alive and out of hospital over 14 days
- Death or worsening heart failure over 31 days
- New York Heart Association class at 5 days
- All-cause mortality over 90 days
REVIVE II: Primary Endpoint (n=600)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Levosimendan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Patients

P=0.015
Patient Global Assessment at 6 Hours

- Placebo
- Levosimendan

P = 0.081 for REVIVE II
P = 0.021 for REVIVE I+II
Patient Dyspnea Assessment at 6 Hours

- Placebo
- Levosimendan

P = 0.078 for REVIVE II
P = 0.026 for REVIVE I+II

% Patients

Marked Moderate Improved Mild No change Mild Moderate Worse Marked

0 10 20 30 40 50
Brain Natriuretic Peptide

- P < 0.001 at day 1 and day 5 for REVIVE II alone and REVIVE I + II combined

Change from baseline (pg/ml)

Days From Onset of Infusion

- Levosimendan
- Placebo

Levosimendan infusion
# Duration of Initial Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan (n=299)</th>
<th>Placebo (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days for initial hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.0 ± 4.6</td>
<td>8.9 ± 8.6</td>
</tr>
<tr>
<td><strong>Length of initial hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 5 days</td>
<td>129 (45.7%)</td>
<td>108 (37.0%)</td>
</tr>
<tr>
<td>6 to 10 days</td>
<td>109 (38.7%)</td>
<td>116 (39.7%)</td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>44 (15.6%)</td>
<td>68 (23.3%)</td>
</tr>
</tbody>
</table>

P=0.006 for REVIVE II  
P=0.003 for REVIVE I+II
Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study

Greg de Lissevovoy · Kathy Fraeman · John R. Teerlink · John Mullany · Jeff Salo · Raimund Sieritz · Amy DeRobert · Robert J. Padley
Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure


<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PLACEBO (N=42)</th>
<th>NESIRITIDE (N=43)</th>
<th>NESIRITIDE (N=42)</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary-capillary wedge pressure (mm Hg)</td>
<td>+2.0±7.2</td>
<td>-6.0±7.2†</td>
<td>-9.6±6.2†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>+0.4±4.6</td>
<td>-2.6±4.4†</td>
<td>-5.1±4.7†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·sec·cm⁻⁵)</td>
<td>+161±481</td>
<td>-247±492†</td>
<td>-347±499†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>-0.1±0.47</td>
<td>+0.2±0.49§</td>
<td>+0.4±0.69†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>+0.3±11</td>
<td>-4.4±10.2</td>
<td>-9.3±12.6†</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic pulmonary-artery pressure (mm Hg)</td>
<td>+1.7±8.2</td>
<td>-9.4±10.3†</td>
<td>-12.9±12.5†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean pulmonary-artery pressure (mm Hg)</td>
<td>+2.0±5.9</td>
<td>-7.0±6.9†</td>
<td>-7.7±7.6†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne·sec·cm⁻⁵)</td>
<td>+26±197</td>
<td>-62±100</td>
<td>-2±142</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>+1.4±7.5</td>
<td>-1.6±7.1</td>
<td>+0.0±8.8</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Plus signs denote an increase, and minus signs a decrease.
†P values are for the comparison among all three groups and were calculated with the omnibus F test.
‡P<0.001 for the pairwise comparison with placebo, by the F test.
§P<0.05 for the pairwise comparison with placebo, by the F test.
Risk of death associated with nesiritide in patients with acutely decompensated heart failure

KD Aaronson, J Sackner-Bernstein. JAMA 2006;296:1465-66

<p>| Table. Mortality Within 30 Days of Treatment Associated With Nesiritide or Control Therapy |
|---------------------------------------------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>NSGET, VMAC, and PROACTION (N = 862)</th>
<th>VMAC and PROACTION (n = 736)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths/total No. (%) of patients</td>
<td>P Value</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>37/485 (7.6)</td>
</tr>
<tr>
<td>Control</td>
<td>15/377 (4.0)</td>
</tr>
<tr>
<td>Unadjusted risks (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Crude risk ratio*</td>
<td>1.92 (1.07-3.44)</td>
</tr>
<tr>
<td>Hazard ratio†</td>
<td>1.97 (1.08-3.58)</td>
</tr>
<tr>
<td>Adjusted risks (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Relative risk‡</td>
<td>1.96 (1.05-3.52)</td>
</tr>
<tr>
<td>Hazard ratio§</td>
<td>1.93 (1.06-3.52)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NSGET, Nesiritide Study Group Efficacy Trial; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natracor; VMAC, Vasodilation in the Management of Acute Congestive heart failure.2

*Unadjusted and from pooled 2 × 2 table.
†Unadjusted and from univariable Cox proportional hazards model.
‡Adjusted for study by Mantel-Haenszel method (fixed-effects model).
§Adjusted for study by multivariable Cox proportional hazards model.
ASCEND-HF
ACUTE STUDY OF CLINICAL EFFECTIVENESS OF NESiritide IN DECOMPENSATED HEART FAILURE

PRINCIPAL INVESTIGATOR
Robert M. Califf, M.D., Vice-Chancellor for Clinical Research, Director of Duke Clinical Research Institute (DCRI), Professor of Medicine, will chair the trial. DCRI, the academic clinical research organization within Duke University Medical Center, will collaborate with the Cleveland Clinic Cardiovascular Coordination Center (CC) in managing the trial, and other leading medical centers around the world will participate. Duke Clinical Research Institute (DCRI) is the independent academic research organization that will lead the ASCEND-HF Trial. The ASCEND-HF study is managed outside North America by Johnson & Johnson's Global Clinical Operations (GCO).

For more information regarding enrollment, please email the following information to WDRussell@genex.in. or call 609-730-3396 (Attention: Barry Drummond, Sr. Manager, Global Trial Manager):

- Name
- Telephone
- Fax
- Email
- Hospital Name
- Hospital Address

PROTOCOL DESIGN
As currently proposed, this randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of Nesiritide will include approximately 7,000 patients with ADHF. They will be randomized to receive Nesiritide or placebo as a bolus of 2 mcg/kg followed by continuous intravenous infusion of Nesiritide or placebo at 0.01 mcg/kg/minute for a minimum of 24 hours up to a maximum of seven days in addition to standard care. The trial will be conducted at approximately 600 sites. Patient enrollment is expected to begin in the second quarter of 2007.

KEY OBJECTIVES
The study hypothesis is that Nesiritide given in addition to standard care is superior to placebo given in addition to standard care as measured by relief of breathing difficulties at 6 hours or 24 hours after Nesiritide administration, and reduction in the symptoms of decompensation due to heart failure and death from study drug administration through Day 30.

INCLUSION/ EXCLUSION CRITERIA
Inclusion Criteria:
- Men or women 18 years of age or older
- Hospitalized for the management of ADHF or diagnosed with ADHF within 48 hours after being hospitalized for another reason
- Diagnosis of ADHF is defined as dyspnea (difficulty breathing) at rest or dyspnea with minimal activity

Exclusion Criteria:
- At high risk for hypotension
- Acute coronary syndrome as primary diagnosis
- History of cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy, or pericardial tamponade
- Previous enrollment in a neisitride study
- Persistent, uncontrolled hypertension (SBP systolic blood pressure) > 180 mmHg

CLINICAL ENDPOINTS
A number of safety and clinical outcomes endpoints are proposed, including:
- All-cause mortality through day 180
- Cardiovascular mortality through day 30
- Heart Failure readmissions
- Renal impairment
- Hypotension

ABOUT NESIRITIDE
Nesiritide is indicated for the intravenous treatment of patients with ADHF who have dyspnea at rest or with minimal activity. In this population, the use of Nesiritide reduced pulmonary capillary wedge pressure and improved patient reported dyspnea. For Full Prescribing Information, visit www.nestore.com. See Important Safety Information.

RECRUITMENT DATES
Second quarter of 2007

SOURCE OF FINANCIAL SUPPORT/SPONSOR
Scios Inc.

IMPORTANT SAFETY INFORMATION
HYPOTENSION
Nesiritide may cause hypotension and should be administered only in settings where blood pressure can be monitored closely. If hypotension occurs during administration of Nesiritide, the dose should be reduced or discontinued. At the recommended dose of Nesiritide, the incidence of symptomatic hypotension (4%) was similar to that of IV nitroglycerin (5%). Asymptomatic hypotension occurred in 9% of patients managed with other drugs. In some cases, hypotension that occurs with Nesiritide may be prolonged. The mean duration of symptomatic hypotension was longer with Nesiritide than IV nitroglycerin (2.2 versus 0.7 hours, respectively). Nesiritide should not be used in patients with systolic blood pressure < 80 mmHg or who are in primary therapy in patients with cardiogenic shock. The rate of symptomatic hypotension may be increased in patients with a baseline blood pressure < 90 mmHg, and Nesiritide should be used cautiously in these patients. In earlier trials, when Nesiritide was initiated at doses higher than the 3 mcg/kg bolus followed by a 0.05 mcg/kg/min infusion, the frequency, intensity, and duration of hypotension were increased. The hypotensive episodes were more often symptomatic and more likely to require medical intervention.

Nesiritide is not recommended for patients who are vasodilating agents are not appropriate and should be avoided in patients with low cardiac filling pressures.

RENAL
Nesiritide may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with Nesiritide may be associated with anuria. In the VALIANT trial, during 30 days, the incidence of anuria in control was 0.5 mcg/kg/min, the incidence of grade 3 renal impairment (creatinine > 1.5 mg/dL) was 2.3% in the Nesiritide and nitroglycerin groups, respectively. When Nesiritide was initiated at doses higher than the 3 mcg/kg bolus followed by a 0.05 mcg/kg/min infusion, there was an increased rate of elevated serum creatinine over baseline compared with standard therapy, although the rate of acute renal failure was not increased.

MORTALITY
In seven Nesiritide clinical trials, through 30 days, 5.5% in the Nesiritide treatment group died as compared with 4.9% in the group treated with other standard medications. In five clinical trials, through 180 days, 21.9% in the Nesiritide treatment group died as compared with 20.7% in the group treated with other medications. There is not enough information to know about the effect of Nesiritide on mortality.

BAY 58-2667 is a nitric-oxide and heme-independent activator of soluble guanylate cyclase

Figure 4-5: The hemodynamic effects of intravenous administration of 2 doses of BAY 58-2667 were assessed in experimental heart failure in dogs. Heart failure was induced in 7 dogs by rapid ventricular pacing for 10 days.
Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure.

McMurray JJV et al JAMA 2007;298:2009-19
Favorable Effects of Heart Rate Reduction with Intravenous Administration of Ivabradine in Patients with Advanced Heart Failure.

G M. De Ferrari, A Mazzuero, L Agnesina, A Bertoletti, M Lettino, C Campana, P J. Schwartz, L Tavazzi. JACC Submitted

Figure 2. Mean cardiac index throughout the study.

**p<0.001

Cardiac index (l/min*m²)

Stroke volume (ml)

***p<0.000001

Cardiac Index

Stroke Volume
**Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure**

The EVEREST Clinical Status Trials


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**Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline**

*P* value represents between-group comparison by van Elteren test.
Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial


[Graphs showing all-cause mortality and cardiovascular mortality or heart failure hospitalization with survival curves for Tolvaptan and Placebo groups.]

No. at Risk
Tolvaptan: 2072, 1812, 1446, 1112, 859, 569, 404, 239, 97
Placebo: 2051, 1781, 1440, 1109, 840, 560, 400, 233, 95

Log-Rank Test: P = .76
Peto-Peto-Wilcoxon Test: P = .63
Stratified Peto-Peto-Wilcoxon Test: P = .68

Log-Rank Test: P = .42
Peto-Peto-Wilcoxon Test: P = .55
Stratified Peto-Peto-Wilcoxon Test: P = .66
KW-3902: Adenosine A1-Receptor Antagonist

Selective affinity for A1 vs. A2A receptors

1) Inhibits reabsorption of sodium and water in the proximal tubule → enhances diuresis

2) Blocks tubuloglomerular feedback (TGF) → reverses afferent arteriole vasoconstriction → maintains GFR
The PROTECT pilot study: a randomized placebo-controlled dose-finding Study of the Adenosine A1 receptor antagonist rolofylline in patients with Acute heart failure and renal impairment

Fig. 4. Proportion of patients dying of any cause or rehospitalized for cardiovascular or renal causes during the 60-day follow-up period. (Bars represent standard errors of the proportions.)
Feeling better, dying earlier

- Acute decompensated HF patients desperately ill

- Need new therapies, but the new agents must be viewed as cautiously as the positive inotropic strategy