Ο ρόλος των αγγειοδιασταλτικών και των διουρητικών, υπό το φως των πρόσφατων μελετών

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Speaker: Gregory Giamouzis, MD, PhD

I have the following potential conflicts of interest to report:

**Lecture fees:** Astra-Zeneca, Bayer, Boehringer-Ingelheim, Menarini, MSD, Novartis, Pfizer, Servier.

**Advisory Boards:** Boehringer-Ingelheim, Menarini, MSD, Novartis, Servier.
Disclosures

I have the following potential conflicts of interest to report:

I am a friend of the Guru in Acute Heart Failure ....

...who -by the way- happens to be the chairman...
One step forward, two steps back

Mihai Gheorghiade and Andrew Ambrosy

Patients with heart failure (HF) fall into two categories—those who are stable and ambulatory with a relatively low event rate, and patients requiring hospitalization who are characterized by high post-discharge mortality and rates of rehospitalization. HF trials in 2010 contributed to the advancement of outpatient management, whereas the development of novel therapies with a survival benefit remains an unmet need in acute HF syndromes.

Why is Acute Heart Failure Important?

- The fastest growing disease in the world – leading cause of hospital admissions all over the planet – developed and developing.

- One of the leading medical related expenses to society.

- Huge short term morbidity and mortality (post-discharge re-hospitalization 20-30% and mortality 10-20% within 3-6 months.)
Influence of History of HF Hospitalization on Outcome

Prior HF hosp | Hazard Ratio and 95% CI
---|---
Yes | 1.95 (1.59 – 2.39)
No | 1.00

Number at risk

Prior HF hospitalization | No | Yes
<table>
<thead>
<tr>
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<tr>
<td>0</td>
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<td>42</td>
<td>135</td>
<td>300</td>
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</tbody>
</table>

Lancet 2003; 362: 777-81
Natural History of AHF patients

Acute Exacerbations May Contribute to the Progression of the Disease

Outcome in AHF is still poor

40% at 60 days

**DOSE-AHF**
Death, rehospitalisation or ER visit

- Low dose
- High dose

Hazard ratio with high dose strategy, 0.83 (95% CI, 0.60–1.16)
p = 0.28

**CARRESS-HF**
Death or HF rehospitalisation

- Pharmacological care
- Ultrafiltration

HR = 1.01 (0.62–1.64)
p = 0.9556

AHF = acute heart failure; CI = confidence interval; ER = emergency room; HF = heart failure; HR = hazard ratio

Goals of Treatment in Acute Heart Failure
Θεραπευτική προσέγγιση της οξείας καρδιακής ανεπάρκειας

Λεπτά

Υπεροξεία Φάση
Επείγουσα αντιμετώπιση (BLS-ALS)
Αιμοδυναμική - Συμπτώματα

Τμήμα Επειγόντων

Υποξεία Φάση
1-2 μέρες
Ενδεικνυόμενη ενδοφλέβεια αγωγής
Βελτιστοποίηση κατανομής όγκου

Μονάδα Εντατικής Θεραπείας

“Χρόνια” Φάση
2-7 μέρες
Διακοπή ενδοφλέβειας αγωγής
Τιτλοποίηση ευεργετικών φαρμάκων
Επιμόρφωση ασθενούς-περιβάλλοντος

Κλινική

Προγραμματισμός επανέλεγχου εντός 7 ημερών

Ε.Ι.
‘Time-to-treatment’ concept in AHF

**Table 12.6 - Goals of treatment in acute heart failure**

### Immediate (ED/ICU/CCU)
- Improve haemodynamics and organ perfusion.
- Restore oxygenation.
- Alleviate symptoms.
- Limit cardiac and renal damage.
- Prevent thromboembolism.
- Minimize ICU length of stay.

### Intermediate (in hospital)
- Identify aetiology and relevant co-morbidities.
- Titrate therapy to control symptoms and congestion and optimize blood pressure.
- Initiate up-titrate disease-modifying pharmacological therapy.
- Consider device therapy in appropriate patients.

### Pre-discharge and long-term management
- Develop a care plan that provides:
  - A schedule for up-titration and monitoring of pharmacological therapy.
  - Need and timing for review for device therapy.
  - Who will see the patient for follow-up and when.
- Enrol in disease management programme, educate, and initiate appropriate lifestyle adjustments.
- Prevent early readmission.
- Improve symptoms, quality of life, and survival.

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Ponikowski P, et al. 
*Eur Heart J* 2016;37:2129–2200
Conventional Treatment of Acute HF

**Diuretics**
- Reduce fluid volume

**Vasodilators**
- Decrease preload and/or afterload

**Inotropes**
- Augment contractility

Fonarow G. Rev Cardiovasc Med 2001
Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion

## Acute heart failure:
recommendations and levels of evidence

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McMurray et al. Eur Heart J 2012;33:1787-1846
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O’Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*
DOSE-AHF

- 308 patients with acute decompensated heart failure randomized to:
  - bolus every 12 hours or continuous infusion
  - at either a low dose (equivalent to the patient’s previous oral dose) or a high dose (2.5 times the previous oral dose).

- Coprimary end points:
  - patients’ global assessment of symptoms, quantified as the area under the curve (AUC) of the score on a visual-analogue scale over the course of 72 hours
  - the change in the serum creatinine level from baseline to 72 hours

- Of note: not a placebo controlled trial
DOSE-AHF: main findings

- **Bolus versus Continuous:**
  - No significant difference in symptom relief
  - No significant difference in change in creatinine

- **High versus low dose:**
  - Trend towards better dyspnea relief in high dose
  - No significant difference in change in creatinine

- **Conclusion:** no direct evidence that diuretics in AHF reduce symptoms and/or improve outcome compared with placebo
# Acute heart failure: recommendations and levels of evidence

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Rationale for the use of vasodilators in Acute Heart Failure
Weight gain is associated with HF hospitalization

However, in 50% of patients who were admitted due to AHF, no weight changes preceding hospitalization were present

Fast and slow mechanisms of circulatory congestion

Precipitant (minor)

Sympathetic activation

Mobilization of venous reservoir

↑ Effective circulatory volume

Congestion

Renal and dietary mechanisms

Sodium and water retention

Fast

Slow

mainly splanchnic vessels; can be recruited with activation of the SNS, drugs, or hormones

Fallick C et al. Circ Heart Fail. 2011;4:669-675
**Fluid redistribution or accumulation?**

**Key question (different pathophysiology with therapeutic consequences)**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac (central / systolic)</th>
<th>Vascular (peripheral / diastolic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main mechanism of onset</td>
<td>↓ contractility, Sodium and water renal retention</td>
<td>↑ afterload and/or predominant LV diastolic dysfunction</td>
</tr>
<tr>
<td>Main cause of symptoms</td>
<td>Fluid accumulation</td>
<td>Fluid redistribution to the lungs</td>
</tr>
<tr>
<td>Gain in body weight</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual (days)</td>
<td>Rapid (hours)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>Normal to low</td>
<td>Normal to high</td>
</tr>
<tr>
<td>LV filling pressure</td>
<td>May be low with low CO</td>
<td>High</td>
</tr>
<tr>
<td>LVEF &amp; Cardiac output</td>
<td>Low</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**First-line therapy**  
- **diuretics**  
- **vasodilators**
Nitrates in Acute Heart Failure

An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.

Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

Gad Cotter, Einat Metzkor, Edo Kaluski, Zwi Faigenberg, Rami Miller, Avi Simovitz, Ori Shaham, Doron Marghitay, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, Ahuva Golik

Lancet 1998
Nitrates in Acute Heart Failure

- 110 patients presenting to mobile emergency units with signs of congestive heart failure randomized to:
  - High dose Isosorbide dinitrate (3 mg bolus administered intravenously every 5 min; n=56)
  - Furosemide (80 mg bolus administered intravenously every 15 min) + low dose isosorbide dinitrate (1 mg/h, increased every 10 min by 1 mg/h; n=54).

- Main endpoints:
  - Death
  - Need for mechanical ventilation
  - Myocardial infarction
Nitrates in Acute Heart Failure: main findings

- High dose ISDN alone compared with low dose ISDN + furosemide did:
  - Not reduce mortality
  - Reduce the need for mechanical ventilation
  - Reduce the risk of myocardial infarction
  - Reduce the risk of any adverse event
Nitrates in Acute Heart Failure

- VMAC Study JAMA 2002
- 489 acute decompensated heart failure patients
- Randomized to nesiritide (n=204), nitroglycerin (n=143), or placebo (n=142) for 3 hours, followed by nesiritide (n=278) or nitroglycerin (n=216) for 24 hours
- Main outcome parameter: Change in wedge and dyspnea relief after 3 hours
- Secondary outcome parameters: difference in hemodynamic and clinical effects between nesiritide and nitroglycerin at 24 hours
Nitroglycerin in AHF: VMAC Results

- Wedge was significantly better reduced by nesiritide compared with both nitroglycerin and placebo
- No significant difference in change in wedge between nitroglycerin and placebo
- Dyspnea relief was significantly better reduced by nesiritide compared with placebo, but no effect of nitroglycerin
- At 24 hours: better reduction of PCWP by nesiritide compared with nitroglycerin, without any other differences
# Acute heart failure:
## recommendations and levels of evidence

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McMurray et al. Eur Heart J 2012;33:1787-1846
Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study.

812 men with presumed acute myocardial infarction and left ventricular filling pressure of at least 12 mm Hg

Randomized double-blind placebo-controlled trial to assess the efficacy of a 48-hour infusion of sodium nitroprusside

Overall no effect on mortality; higher mortality when started early, lower mortality when started late

Conclusion of the authors: “Nitroprusside should probably not be used routinely in patients with high left ventricular filling pressures after acute myocardial infarction.”

Cohn et al. JAMA 1982
Vasodilators for Low-Output AHF

175 pts with AHF admitted to intensive care unit; 78 treated with sodium nitroprusside (NYHA IV – 58%, SBP – 110 mmHg, Na – 137 mmol/L, PCWP – 29 mmHg, LVEF – 15%)

Haemodynamic Data

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<tr>
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<th>Nitroprusside (n = 60)</th>
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<tbody>
<tr>
<td></td>
<td>Admission</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87 ± 12</td>
</tr>
<tr>
<td>Systolic PAP (mmHg)</td>
<td>65 ± 13</td>
</tr>
<tr>
<td>Diastolic PAP (mmHg)</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>CI (L/min/m2)</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

Clinical Outcome

Mullens, W. et al. J Am Coll Cardiol 2008;52:200-207
## Acute heart failure: recommendations and levels of evidence

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McMurray et al. Eur Heart J 2012;33:1787-1846
Τομέας Αναδρομική ανάλυση της (ADHERE)

<table>
<thead>
<tr>
<th>Μορφίνη</th>
<th>20782 (14.1%) έλαβαν μορφίνη</th>
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<tr>
<td>Μηχανικός αερισμός (15.4% έναντι 2.8%)</td>
<td></td>
</tr>
<tr>
<td>Διάρκεια νοσηλείας (5.6 έναντι 4.2 μέρες)</td>
<td></td>
</tr>
<tr>
<td>Εισαγωγή σε ΜΕΘ (38.7% έναντι 14.4%)</td>
<td></td>
</tr>
<tr>
<td>Θνητότητα (13.0% έναντι 2.4%) (όλα τα p&lt;0.001)</td>
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</tbody>
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McMurray et al. Eur Heart J 2012;33:1787-1846
Gaps in Evidence

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Current Wording:

“At lower doses, dopamine may have a selective renal arterial vasodilator activity and promote natriuresis, although this is uncertain.[..]
If no response to doubling of dose of diuretic, start i.v. infusion of dopamine.”
DAD-HF Trial

Clinical Trial

Impact of Dopamine Infusion on Renal Function in Hospitalized Heart Failure Patients: Results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial

GREGORY GIAMOUZIS, MD,1 JAVED BUTLER, MD, MPH,2 RANDALL C. STARLING, MD, MPH,3 GEORGE KARAYANNIS, MD,1 JOHN NASTAS, MD,4 CHARALAMBOS PARISIS, MD,1 DIMITRIOS ROVITHIS, MD,1 DIMITRIOS ECONOMOU, MD,1 KONSTANTINOS SAVVATIS, MD,5 THEMISTOKLIS KIRLIDIS, MD,4 THEMISTOKLIS TSAKNAKIS, MD,4 JOHN SKOULARIGIS, MD,1 DIRK WESTERMANN, MD,5 CARSTEN TSCHÖPE, MD,5 AND FILIPPOS TRIPOSKIADIS, MD1

Larissa, Greece; Atlanta, Georgia; Cleveland, Ohio; Volos, Greece; Berlin, Germany
## Incidence of Worsening Renal Function at 24 Hours

<table>
<thead>
<tr>
<th>Definition of WRF</th>
<th>HDF Group (n=25)</th>
<th>LDFD Group (n=25)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in sCr &gt; 0.3 mg/dL, n (%)</td>
<td>9 (36%)</td>
<td>1 (4%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Increase in sCr &gt; 25%, n (%)</td>
<td>9 (36%)</td>
<td>1 (4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Decrease in eGFR &gt; 25%, n (%)</td>
<td>8 (32%)</td>
<td>1 (4%)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Between-group comparison

eGFR, estimated glomerular filtration rate; HDF, high-dose furosemide; LDFD, low-dose furosemide plus dopamine; sCr, serum creatinine; WRF, worsening of renal function

DAD-HF II Trial
161 Patients with ADHF were prospectively randomized to receiving an 8 hour continuous infusion of:

**Group A**
- high-dose furosemide (20 mg/h)
- **HDF**, N=50

**Group B**
- Low-dose furosemide (5 mg/h) and low-dose dopamine (5 μg kg⁻¹ min⁻¹)
- **LDFD**, N=56

**Group C**
- Low-dose furosemide (5 mg/h)
- **LDF**, N=55

Using randomization method based on random number generation in a 1:1:1 ratio.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>High dose furosemide (HDF)</th>
<th>Low dose furosemide plus dopamine (LDFD)</th>
<th>Low dose furosemide (LDF)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic arterial pressure (mmHg)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>151 (130-193)</td>
<td>161 (130-187)</td>
<td>170 (125-190)</td>
<td>0.936</td>
</tr>
<tr>
<td>4 hours ✦</td>
<td>131.5 (116.5-150.8)#</td>
<td>126.5 (117-140)#</td>
<td>138 (120-149)</td>
<td>0.356</td>
</tr>
<tr>
<td>8 hours ✦</td>
<td>129 (114.3-140)#</td>
<td>120 (114-140)#</td>
<td>132 (119-140)</td>
<td>0.174</td>
</tr>
<tr>
<td><strong>Diastolic arterial pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80 (70-93)</td>
<td>86 (72-100)</td>
<td>80 (67-100)</td>
<td>0.607</td>
</tr>
<tr>
<td>4 hours ✦</td>
<td>70 (61-78)#</td>
<td>68 (60.3-75)#</td>
<td>68 (60-77)</td>
<td>0.586</td>
</tr>
<tr>
<td>8 hours ✦</td>
<td>67.5 (60-72.8)#</td>
<td>65 (60-74)#</td>
<td>75 (64.5-90)</td>
<td>0.677</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87 (74-100)</td>
<td>94 (81 -110)</td>
<td>88 (75-100)</td>
<td>0.174</td>
</tr>
<tr>
<td>4 hours ✦</td>
<td>76 (69-85)#</td>
<td><strong>89 (78-100)</strong>*</td>
<td>78 (68-88)#</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8 hours ✦</td>
<td>76 (68-89)#</td>
<td><strong>85 (76-97)</strong>*#</td>
<td>78 (65-90)#</td>
<td>0.002</td>
</tr>
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</table>

✦: after initiation of treatment; #: p<0.05 vs. baseline; *: p<0.01 vs. HDF or LDF at 4 hours and 8 hours;
Kaplan-Meier curves for one-year mortality or heart failure hospitalization.
Low dose dobutamine in AHF?

Original Investigation

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

Chen et al. JAMA 2013
ROSE-AHF methods

- Multicenter, double-blind, placebo-controlled clinical trial
- 360 hospitalized patients with acute heart failure and renal dysfunction (estimated glomerular filtration rate of 15-60 mL/min/1.73m2)
- Randomized within 24 hours of admission to low-dose dopamine (2 μg/kg/min) or low-dose nesiritide (0.005 μg/kg/min without bolus)
- Co-primary end points
  - 72-hour cumulative urine volume (decongestion end point)
  - Change in serum cystatin C from enrollment to 72 hours (renal function end point).

Chen et al. JAMA 2013
ROSE-AHF: main results (1)

P=0.59

72 hour Urine volume

Urinary Output (L)

placebo

dopamine

Chen et al. JAMA 2013
ROSE-AHF: main results (2)

P=0.72

Change in Cystatin C

Mg/dL

placebo
dopamine

Chen et al. JAMA 2013
Safety

- No significant effect of dopamine on secondary endpoints:
  - Decongestion
  - Renal function
  - Symptom relief

<table>
<thead>
<tr>
<th>Safety Drug Tolerance</th>
<th>Dopamine (n=122)</th>
<th>Placebo (n=119)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug dose reduced of stopped because of hypotension</td>
<td>0.9%</td>
<td>10.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study drug dose reduced or stopped because of tachycardia</td>
<td>7.2%</td>
<td>0.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study drug discontinued due to any cause</td>
<td>23%</td>
<td>25%</td>
<td>0.72</td>
</tr>
</tbody>
</table>
ROSE-AHF conclusions

- In patients with AHF and underlying renal dysfunction; when added to standardized diuretic dosing, low dose dopamine did not enhance decongestion or improved renal function
- Low dose dopamine not renal specific; obvious central hemodynamic effects (BP and HR)
- Future studies are needed to further evaluate the differential response in preserved versus reduced left ventricular ejection fraction
### Acute heart failure: recommendations and levels of evidence

<table>
<thead>
<tr>
<th>Group</th>
<th>Medication</th>
<th>Class recommendation, level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Loop Diuretics</td>
<td>I, B</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Nitrates</td>
<td>IIa, B</td>
</tr>
<tr>
<td></td>
<td>Sodium nitroprusside</td>
<td>IIb, B</td>
</tr>
<tr>
<td>Opiates</td>
<td>Morphine</td>
<td>IIa, C</td>
</tr>
<tr>
<td>Inotropics</td>
<td>Dopamine</td>
<td>IIb, C</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>IIa, C</td>
</tr>
</tbody>
</table>

McMurray et al. Eur Heart J 2012;33:1787-1846
Dobutamine

FIRST Trial: Adjusted Survival

No Dobutamine  \((n = 391)\)
Dobutamine  \((n = 80)\)

\[ P=0.0001^* \]

*For NYHA III-IV patients.

OPTIME-CHF Trial: Sub-Group Survival

Survival, %

Days

Milrinone
Non-ischemic
Placebo
Non-ischemic
Placebo
Ischemic
Milrinone
Ischemic

Cuffe MS, et al. JAMA 2002
Any RCT-based evidence to support use of vasodilators in AHF?

ALARM-HF: Analysis of 4167 AHF pts; 1805 pts received iv diuretics+vasodilators

Propensity-based matching:
in-hospital mortality: 7.8% vs 11.0%
HR = 0.71 (0.51-0.98)

# Recommendations for the management of patients with acute HF: pharmacotherapy

**Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP &lt; 90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

**Vaspressors**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension. In such cases intra-arterial blood pressure measurement may be considered.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Several drugs in AHF not successful

- PDE inhibitors: milrinone: OPTIME-CHF
- Endothelin antagonists: tezosentan: VERITAS
- Calcium sensitiser: levosimendan; SURVIVE/REVIVE
- AVP antagonists: tolvaptan; EVEREST
- Adenosine A1-receptor antagonist: rololofylline; PROTECT
- Natriuretic peptides: nesiritide: ASCEND-HF

AHF=acute heart failure
AVP=arginine vasopressin
PDE=phosphodiesterase

Mebazaa et al. JAMA 2007;297:1883–91; Packer et al. JACC Heart Fail 2013;1:103–11
Levosimendan improved symptoms but did not improve clinical outcome

<table>
<thead>
<tr>
<th>Worsening clinical status requiring rescue therapy in REVIVE I and REVIVE II</th>
<th>REVIVE I</th>
<th>REVIVE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan (n=81)</td>
<td>Placebo (n=49)</td>
<td>Levosimendan (n=299)</td>
</tr>
<tr>
<td>Proportion requiring rescue therapy</td>
<td>16%</td>
<td>29%</td>
</tr>
<tr>
<td>Worsening dyspnea or tachypnea</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Increased pulmonary edema</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Cool extremities and cyanosis</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Decreased mental status</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Persistent/unresponsive symptoms</td>
<td>10%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Values are %. Patients could report multiple symptoms
Tolvaptan improved symptoms but did not improve clinical outcome

Nesiritide improved symptoms but did not improve clinical outcome

Self-assessed change in dyspnea at 6 and 24 hours

- 6 hours; p=0.03
- 24 hours; p=0.007

Death from any cause or rehospitalization for HF at 30 days

- p=0.31
- HR, 0.93 (95% CI, 0.8–1.08)

Percentage point difference (95% CI)

- Death or hospitalization for HF: -0.7 (-2.1 to 0.7)
- Death: -0.4 (-1.3 to 0.5)
- Hospitalization for HF: -0.1 (-1.2 to 1.0)

CI=confidence interval; HF=heart failure; HR=hazard ratio
O’Connor et al. NEJM 2011; 365:32–43
Effect of Ularitide on In-Hospital Heart Failure Events During First 120 Hours

M. Packer, HFA Paris 2017

“...For the hierarchical clinical composite, the favourable effect in eligible patients (nominal P=0.035) was directionally opposite to the to the unfavourable effect of the drug in ineligible patients (nominal P=0.022).”

Serelaxin fails to meet primary endpoints in phase 3 RELAX-AHF-2 trial

RELAX-AHF-2:
Multicentre trial, N=6 600 patients hospitalized for AHF.
There was no difference in cardiovascular mortality at 180 days and the trend for a reduction of worsening heart failure through day five with serelaxin was not statistically significant.

There was no beneficial effect on the secondary endpoints of

- all-cause mortality at 180 days,
- length of initial hospital stay or
- cardiovascular death or rehospitalisations due to heart/renal failure through day 180
Why do drugs for Acute Heart Failure fail?
Why do drugs for Acute Heart Failure fail?

Are we using the right terminology in Acute HF?
These are some of the terms used in the 2017 ESC-HF Congress to describe AHF

Terminology

- AHF
- ADHF
- HHF
- WHF
- WCHF
- AHFS....
Why do drugs for Acute Heart Failure fail?

Is it the heterogeneity of the syndrome?
Heterogeneity of Acute Heart Failure
Why do drugs for Acute Heart Failure fail?

Are we using the right classification in chronic HF?
**New Classification: Welcome to Hell!!!**

- Heart failure with **preserved**, **mid-range** and **reduced** EF

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
</tbody>
</table>
| 3         | | 1. Elevated levels of natriuretic peptides<sup>b</sup>;  
      2. At least one additional criterion:  
      a. relevant structural heart disease (LVH and/or LAE),  
      b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides<sup>b</sup>;  
      2. At least one additional criterion:  
      a. relevant structural heart disease (LVH and/or LAE),  
      b. diastolic dysfunction (for details see Section 4.3.2). |

---

<sup>a</sup> Symptom ± Sign

<sup>b</sup> Natriuretic Peptide

[www.escardio.org/HFA](http://www.escardio.org/HFA)
Why do drugs for Acute Heart Failure fail?

Is it the changing Epidemiology in phenotypes?
Ηλικιακό Φάσμα (ανά δεκαετία)

Ποσοστό ασθενών (%)

[Diagram A]

Έπιβίωση

Εισαγωγές για καρδιακή ανεπάρκεια

[Diagram B]

HFrEF

HFpEF

[Diagram C & D]
AHF with preserved EF in relationship with Acute de novo HF

Parissis J, Farmakis D, Filippatos G. EJHF 2015
Why do drugs for Acute Heart Failure fail?

Is it the numerous etiologic or precipitating factors that alter the results with their deferring prognostic implication?
Many etiologies / precipitating factors

**Ischaemic heart disease**
- Acute coronary syndromes
- Mechanical complications of acute MI
- Right ventricular infarction

**Valvular**
- Valve stenosis
- Valvular regurgitation
- Endocarditis
- Aortic dissection

**Myopathies**
- Postpartum cardiomyopathy
- Acute myocarditis

**Hypertension/arrhythmia**
- Hypertension
- Acute arrhythmia

**Circulatory failure**
- Septicaemia
- Thyrotoxicosis
- Anaemia
- Shunts
- Tamponade
- Pulmonary embolism

** Decompensation of pre-existing chronic HF**
- Lack of adherence
- Volume overload
- Infections, especially pneumonia
- Cerebrovascular insult
- Surgery
- Renal dysfunction
- Asthma, COPD
- Drug abuse
- Alcohol abuse

...with deferring prognosis!!!

Ενδονοσοκομειακή θνητότητα με βάση τον εκλητικό παράγοντα εισαγωγής για ΚΑ

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/acute coronary syndrome</td>
<td>1.52 (1.20-1.93)</td>
<td>&lt;.001</td>
<td>1.06 (0.90-1.25)</td>
<td>.49</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.76 (0.57-1.02)</td>
<td>.06</td>
<td>0.85 (0.72-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Nonadherence to diet</td>
<td>.81 (0.51-1.29)</td>
<td>.37</td>
<td>0.94 (0.73-1.21)</td>
<td>.62</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>0.61 (0.40-0.95)</td>
<td>.03</td>
<td>0.71 (0.58-0.88)</td>
<td>.002</td>
</tr>
<tr>
<td>Nonadherence to medications</td>
<td>1.10 (0.75-1.61)</td>
<td>.63</td>
<td>1.03 (0.82-1.29)</td>
<td>.90</td>
</tr>
<tr>
<td>Pneumonia/respiratory process</td>
<td>1.25 (0.96-1.62)</td>
<td>.10</td>
<td>1.02 (0.86-1.21)</td>
<td>.90</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>1.46 (1.06-2.00)</td>
<td>.02</td>
<td>1.01 (0.79-1.30)</td>
<td>.91</td>
</tr>
</tbody>
</table>
Why do drugs for Acute Heart Failure fail?

Are we using the right patients?
Wrong diagnosis in 32.5% of patients recruited in a well designed study!!!
Why do drugs for Acute Heart Failure fail?

Are we using any protocols?
Why do drugs for Acute Heart Failure fail?

Are we using any protocols? If so....

Are we using the right protocols?
Why do drugs for Acute Heart Failure fail?

Is it the regional heterogeneity of the results?
Heterogeneity in regional outcomes

**EVEREST Trials: Continental Differences**

4133 patients admitted with AHF and reduced LVEF on standard medical therapy followed 9.9 months

<table>
<thead>
<tr>
<th></th>
<th>North America</th>
<th>South America</th>
<th>Western Europe</th>
<th>Eastern Europe</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-year Estimate, %, (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>30.4 (27.6-33.1)</td>
<td>27.2 (23.3-30.8)</td>
<td>27.1 (23.0-31.1)</td>
<td>20.5 (18.1-22.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death/HF hospitalization</td>
<td>52.5 (49.4–55.3)</td>
<td>41.6 (37.3–45.6)</td>
<td>47.3 (42.6–51.7)</td>
<td>35.3 (32.4–38.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Why do drugs for Acute Heart Failure fail?

Does the heterogeneity in regional outcomes say something to us?

(Eager for funding → Increases number of recruited patients)

Do all of these patients have AHF?

(Remember TOPCAT in chronic HF)
Heterogeneity in regional outcomes

Συμβαίνει και στις καλύτερες οικογένειες…
Heterogeneity in regional outcomes

Variation in death and re-admission

Death

HF re-admission

Proportion (%)

Scott...  Glasg...  Alberta  Turin  Denm...

Scottland  Glasgow  Alberta  Turin  Denmark
Why do drugs for Acute Heart Failure fail?

‘Time-to-treatment’ concept in AHF

- Time is myocardium in Acute Myocardial infarction.
- Therefore, early interventions save lives.
- Is it the same in Acute HF?
- Shouldn’t the “time-to-treatment” concept be validated in a large trial?
Risk of death by early changes in markers of organ function, damage, and congestion

**A** Troponin T

**B** Cystatin C

**C** AST

**D** ALT

**E** NT-proBNP

**F** Worsening of heart failure

Serelaxin may protect heart and kidney tissue

- Prevention of cardiomyocyte loss
- Alleviation of cardiac wall stress and decongestion
- Prevention of renal function loss

These changes have shown to be predictive of outcome value in AHF
Serelaxin may protect heart and kidney tissue

**So What?**

- Prevention of cardiomyocyte loss
- Alleviation of cardiac wall stress and decongestion
- Prevention of renal function loss

These changes have shown to be predictive of outcome value in AHF
Why do drugs for Acute Heart Failure fail?

Are we using the right drugs?
Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry

<table>
<thead>
<tr>
<th></th>
<th>Total (n=5039)</th>
<th>&lt;85 mmHg (n=90)</th>
<th>85-110mmHg (n=1169)</th>
<th>&gt;110 mmHg (n=3484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v. Inotropes</td>
<td>11.9%</td>
<td>73.3%</td>
<td>22.3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>i.v. Nitrates</td>
<td>20.4%</td>
<td>10.0%</td>
<td>13.3%</td>
<td>23.0%</td>
</tr>
<tr>
<td>i.v. Diuretics</td>
<td>81.5%</td>
<td>77.8%</td>
<td>82.9%</td>
<td>81.1%</td>
</tr>
</tbody>
</table>
Why do drugs for Acute Heart Failure fail?

Are we using the right type of Endpoints in AHF?

- Surrogate endpoints
- Symptomatic endpoints
- Major clinical events
So, are the new drugs useful in Acute Heart Failure?
What Does It Mean to Be Useful?

Is it useful to . . . ?

- Decrease pulmonary wedge pressures
What Does It Mean to Be Useful?

Is it useful to . . . ?

- Decrease pulmonary wedge pressures
- Decrease RV filling pressures
What Does It Mean to Be Useful?

Is it useful to . . . ?

- Decrease pulmonary wedge pressures
- Decrease RV filling pressures
- Increase cardiac output
What Does It Mean to Be Useful?

Is it useful to . . . ?

- Decrease pulmonary wedge pressures
- Decrease RV filling pressures
- Increase cardiac output
- Decrease NT-proBNP
Is it useful to . . . ?

- Decrease pulmonary wedge pressures
- Decrease RV filling pressures
- Increase cardiac output
- Decrease NT-proBNP
- Decrease serum creatinine
What Does It Mean to Be Useful?

Is it useful to . . . ?

- Decrease pulmonary wedge pressures
- Decrease RV filling pressures
- Increase cardiac output
- Decrease NT-proBNP
- Decrease serum creatinine
- Decrease cardiac and renal biomarkers
Do patients complain about their...?

- Pulmonary wedge pressures?
- RV filling pressures?
- Cardiac output?
- NT-proBNP?
- Serum creatinine?
- Cardiac and renal biomarkers?
Do patients complain about their . . .?

- Pulmonary wedge pressures?

**What about relieving dyspnea? That sounds relevant. Doesn’t it?**

- NT-proBNP?
- Serum creatinine?
- Cardiac and renal biomarkers?
Worsening creatinine with persistent congestion, not WRF alone associated with adverse outcomes.
# Large-Scale Clinical Trials in Acute Heart Failure

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion strategies</td>
<td>Diuretics, ultrafiltration</td>
<td>Modest effect with renal risks</td>
</tr>
<tr>
<td>Nitrate-type vasodilators</td>
<td>Nitroglycerin, nitroprusside</td>
<td>Effects difficult to interpret</td>
</tr>
<tr>
<td>Positive inotropic agents</td>
<td>Levosimendan milrinone, istaroxime, omecamtiv mercarbil</td>
<td>Modest effect with mortality risk</td>
</tr>
<tr>
<td>Norepinephrine and angiotensin attenuation</td>
<td>Morphine, enalaprilat aliskiren, TRV027</td>
<td>No readily demonstrable clinical benefits</td>
</tr>
<tr>
<td>Endothelin, vasopressin and adenosine antagonists</td>
<td>Tezosentan, tolvaptan, rolofylline</td>
<td>No clinical benefits</td>
</tr>
<tr>
<td>Endogenous peptide vasodilators</td>
<td>Nesiritide, serelaxin ularitide</td>
<td>Modest effect without long-term benefit</td>
</tr>
</tbody>
</table>
## Large-Scale Clinical Trials in Acute Heart Failure

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<td>Diuretics, ultrafiltration</td>
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</tr>
<tr>
<td>Nitrate-type</td>
<td>Nitroglycerin,</td>
<td>Effects difficult to define</td>
</tr>
<tr>
<td>Potassium depletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalization of sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous peptide vasodilators</td>
<td>Nesiritide, serelaxin ularitide</td>
<td>Modest effect without long-term benefit</td>
</tr>
</tbody>
</table>

The two definitive trials of vasodilators (TRUE-AHF and RELAX-AHF2) found no benefit on dyspnea, duration of hospital admission, risk of rehospitalization for heart failure or mortality.
Reasons for Inability to Discern Benefit of Acute Interventions

Favorable effect on biomarker

Pharmacological effect

Little correlation with dyspnea, length of stay, rehospitalization, or death
Reasons for Inability to Discern Benefit of Acute Interventions

- Favorable effect on biomarker
- Pharmacological effect
- Intensification of background therapy (diuretics)
- Little correlation with dyspnea, length of stay, rehospitalization, or death
Worsening Heart Failure Begins Days Before the Patient’s Hospitalization

Cardiac filling pressures

Days

Admission
Worsening Heart Failure Begins Days Before the Patient’s Hospitalization

- Cardiac filling pressures
- Days
- Dyspnea
- Admission
Worsening Heart Failure Begins Days Before the Patient’s Hospitalization

Cardiac filling pressures

Dyspnea

Admission

Discharge

Diuresis
Worsening Heart Failure Begins Days Before the Patient’s Hospitalization

Cardiac filling pressures

Dyspnea

Vasodilator

Admission
Discharge

Days
Increased Risk of Heart Failure Rehospitalization Early Post-Discharge

- Active
- Placebo

Both in RELAX-AHF and TRUE-AHF

Days After Hospital Discharge
So What Is Wrong With Treating Acute Heart Failure With Vasodilators?

- They are the wrong treatment
So What Is Wrong With Treating Acute Heart Failure With Vasodilators?

- They are the wrong treatment
- They are given at the wrong time (too late)
So What Is Wrong With Treating Acute Heart Failure With Vasodilators?

- They are the wrong treatment
- They are given at the wrong time (too late)
- They are given for too short a time
So What Is Wrong With Treating Acute Heart Failure With Vasodilators?

- They are the wrong treatment
- They are given at the wrong time (too late)
- They are given for too short a time
- They allow patients to go home too early
So What Is Wrong With Treating Acute Heart Failure With Vasodilators?

- They are the wrong treatment
- They are given at the wrong time (too late)
- They are given for too short a time
- They allow patients to go home too early
- They have dangerous adverse effects (hypotension, renal insufficiency)
Why Do Drugs for Acute Heart Failure Fail?

Adriaan A. Voors* and Dirk J. van Veldhuisen

Can we expect a drug that was given for 24–72 hours during a hospital admission for acute decompensated heart failure to both improve symptoms and reduce (cardiovascular) mortality up to 6 months after hospital admission?
This Patient Is Hospitalized for Worsening Heart Failure. What Do You Do?

The best way to treat their “acute heart failure” is to prevent it by treating their underlying chronic heart failure.
2016 ESC Guideline

Treatment Algorithm

Patients with symptomatica HFrEFb

Therapy with ACE-Ic and beta-blocker
(up-titrate to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

Add MR antagonistd,e
(up-titrate to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

Able to tolerate ACEI (or ARB)f,g

ARNI to replace ACE-I

Sinus rhythm, QRS duration ≥130msec

Evaluate need for CRTj

Sinus rhythmh, HR ≥70 beats/min

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No

No further action required. Consider reducing diuretic dose

Green indicates a class I recommendation; Yellow indicates a class IIa recommendation.
Pre-discharge management and criteria for discharge

Initiate and up-titrate disease-modifying pharmacological therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class (a)</th>
<th>Level (b)</th>
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<tbody>
<tr>
<td>In case of worsening of chronic HFrEF, every attempt should be made to continue evidence-based, disease-modifying therapies, in the absence of haemodynamic instability or contraindications.</td>
<td>I</td>
<td>C</td>
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<tr>
<td>In the case of de novo HFrEF, every attempt should be made to initiate these therapies after haemodynamic stabilization.</td>
<td>I</td>
<td>C</td>
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“in the case of haemodynamic instability/contraindications the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilized. In particular, β-blockers can be safely continued during AHF presentations except in cardiogenic shock.”

Conclusions

• AHF is a complex clinical syndrome with a very high morbidity and mortality, but evidence based therapies are lacking

• Current recommendations: loop diuretics and nitrates; however very limited evidence;

• Investigational therapies for AHF improved dyspnoea, but had no effect on (CV) mortality

• Few novel therapies are under investigation
Conclusions

To improve outcomes in AHF we need:

• Better Diagnosis
• Better Classification
• Study the Epidemiology
• Understand better the pathophysiology
Thank you

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