What is New in the Management of Acute Heart Failure Syndrome?

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Declaration

• National Leader RELAX-ASIA trial
• Advisory board LCZ696
Outcome in acute HF is still poor

DOSE

Death, Rehospitalization or ER visit

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

40% at 60 days

CARRESS-HF

Death or HF Rehospitalization

HR = 1.01 (0.82, 1.64)
P = 0.9556

Courtesy Prof. Filippatos- ESC 2016
## ACC 2013 & ESC 2016 Heart Failure Guidelines

### 1974 vs. 2016 Guidelines

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Vasodilators</th>
<th>Inotropes</th>
<th>Vasopressors</th>
<th>Ultrafiltration</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACC 1974</strong></td>
<td><strong>ESC 2016</strong></td>
<td><strong>ACC 1974</strong></td>
<td><strong>ESC 2016</strong></td>
<td><strong>ACC 1974</strong></td>
<td><strong>ESC 2016</strong></td>
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<tr>
<td>Recommendations</td>
<td>Class</td>
<td>Level</td>
<td></td>
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</tr>
<tr>
<td>HF patients hospitalized with fluid overload should be treated with intravenous diuretics</td>
<td>I</td>
<td>B</td>
<td></td>
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<tr>
<td>HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then dose should be serially adjusted</td>
<td>I</td>
<td>B</td>
<td></td>
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<tr>
<td>HF patients requiring HF hospitalization on GDMT should continue GDMT except in cases of hemodynamic instability or where contraindicated</td>
<td>I</td>
<td>B</td>
<td></td>
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<tr>
<td>Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents</td>
<td>I</td>
<td>B</td>
<td></td>
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<tr>
<td>Thrombosis/thrombolysis prophylaxis is recommended for patients hospitalized with HF</td>
<td>I</td>
<td>C</td>
<td></td>
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<tr>
<td>Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medications, including diuretics</td>
<td>Ila</td>
<td>B</td>
<td></td>
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<tr>
<td>When diuresis is inadequate, it is reasonable to: a. give higher doses of intravenous loop diuretics; or b. add a second diuretic (e.g., Thiazide)</td>
<td>Ila</td>
<td>B</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis</td>
<td>Ila</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with obvious volume overload</td>
<td>Ila</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion</td>
<td>Ila</td>
<td>B</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intravenous nitrates, nitroprazide, or nesiritide may be considered as an adjunct to diuretic therapy for stable patients with HF</td>
<td>Ila</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients hospitalized with volume overload and severe hypoxemia, vasopressor antagonists may be considered</td>
<td>Ila</td>
<td>A</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Recommendations

**Diuretics**

- Intravenous loop diuretics are recommended for all patients with HF, administered with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of these diuretics.

**Vasodilators**

- **Vasodilators** should be considered for symptomatic relief in HF with SBP > 90 mmHg (and without symptomatic hypotension).
- Symptoms and blood pressure should be monitored frequently during administration of vasodilators.

**Inotropes**

- In patients with hypertensive HF, iv. inotropes should be considered as initial therapy to improve symptoms and reduce congestion.

**Vasopressors**

- **Vasopressors** should be considered for hemodynamic support (e.g., dopamine, neosynephrine, or epinephrine).

**Ultrafiltration**

- Ultrafiltration is recommended for patients with refractory congestion.

**MCS**

- Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients not already anticoagulated and with no contraindications to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.

### Other drugs

- For acute control of the ventricular rate in patients with atrial fibrillation:
  - Digoxin and/or beta-blockers should be considered as the first-line therapy.
  - Anticoagulation may be considered.
- Opiates may be considered for severe dyspnea but nausea and hypoxemia may occur.
Timeline of FDA approval and development of Acute Heart Failure Medications

Black boxes: have been approved by the FDA
Grey boxes: development suspended in U.S. (failed phase 3 studies)
White Boxes: promising phase 2 and/or phase 3 data

Hanigan J Pharm Pract 2016
Acute Heart Failure Trials of New Therapies

Negative Results in terms of Efficacy &/or Safety
AHF: Bermuda Triangle of Cardiovascular Drugs

- Lack of drug efficacy
- Patient selection
- Timing of intervention
- Endpoints

Surrogate Endpoints vs. Clinical Outcome
Pathophysiology of Acute Heart Failure

Diverse Pathophysiology
No One Therapy For All!
Heart Failure Journey: Missing Links

HF as a Progressive Disease

With each AHF decompensation:
- survival rate decrease and
- patient never return to baseline

Readmission rate
Post-discharge mortality
In-hospital mortality
Congestion status (discharge)
Worsening HF in-hospital
End-organ dysfunction
The ‘continuum’ of pathophysiological changes associated with AHF
Risk of death by early changes in markers of organ function, damage, and congestion

In-Hospital Worsening Heart Failure Is an Important Event in Acute Heart Failure

In-hospital worsening heart failure

Prolonged need for IV therapy and slow conversion to outpatient treatment

Release of cardiac troponin

Prolongation of hospital stay

Increased cardiovascular mortality

Factors:

Hours

Days

Months

% Patients Experiencing Relief of Dyspnea

Time Since Randomization

\( \approx 10-20\% \) of patients develop in-hospital worsening heart failure during first 7 days

Least dyspnea

Worst dyspnea

IV intervention

J Card Fail 2009;15: 639-44
What is Our aim from A Therapy?

• Improve symptoms of dyspnea acutely?

• Prevent postdischarge cardiac death?

• Prevent organ dysfunction/damage?

• Prevent readmission?

• Reduce or prevent Worsening in patient HF?
Options for Targeting Therapy at Various Stages During Hospitalization

1. Improve signs and symptoms (e.g. dyspnoea)
2. Improve haemodynamics without adversely effecting heart rate and blood pressure
3. Improve the neurohumoral profile
4. Do not cause myocardial and/or kidney damage
5. Be effective in the context of current evidence-based therapy such as ACE-I and beta-blockers
6. Demonstrate efficacy in both the acute and chronic setting
7. Be affordable
8. Reduce both in-hospital and post-discharge morbidity and mortality.

Initiate short-term infusion earlier
Short-term infusion
Target the “vulnerable phase”
Initiate therapies during hospitalization for long-term use
Initiate infusion in-hospital and switch to either sub-cutaneous or oral formulation for post-discharge short or long-term use
Decongestion: Mainstay of Therapy

TWO-MINUTE ASSESSMENT OF HEMODYNAMIC PROFILE

<table>
<thead>
<tr>
<th>Congestion at rest?</th>
<th>Evidence for congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>Orthopnea</td>
</tr>
<tr>
<td></td>
<td>Elevated jugular venous pressure</td>
</tr>
<tr>
<td></td>
<td>Bendopnea</td>
</tr>
<tr>
<td>NO</td>
<td>Rales (rarely)</td>
</tr>
<tr>
<td></td>
<td>New S3</td>
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<tr>
<td></td>
<td>Hepatomegaly</td>
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<tr>
<td></td>
<td>Ascites</td>
</tr>
<tr>
<td></td>
<td>Edema (more common in older patients)</td>
</tr>
<tr>
<td></td>
<td>Valsalva square wave</td>
</tr>
<tr>
<td>YES</td>
<td></td>
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</tbody>
</table>

Evidence for low perfusion
- Narrow auscultated pulse pressure
- Cool extremities
- May be sleepy, obtunded
- Suspect from ACEI/ARB hypotension
- Progressive oliguria

CONGESTION

Volume overload → increased cardiac filling pressures

Volume misdistribution

IV Vasoactive Meds

Most Common IV Medications
ADHERE Registry
All-Heart Congestive Heart Failure
October 2003 - January 2004

IV Dicarba, Dobutamine, Dopamine, Milrinone, Nesiritide, Nitroglycerin, Nitroprusside

Sympathetically-driven mobilization of splanchnic circulation: contributor to HF worsening

Regulation of capacitance function:
1. PASSIVE:
   - Arterial perfusion
   - Venous return
   - Renal sodium excretion

2. ACTIVE:
   - Sympathetic stimulation
   - Venous return
   - Decreased cardiac output

ACCFMiddle East Conference 2016
Congestion Mechanism

Volume overload

Fluid redistribution: arterial system
(ventriculovascular mismatch)

Fluid redistribution: Venous system
(Vasculo-ventricular mismatch)
Decongestion Strategies: ?Volume Overload

Mullens et al 2015
Serelaxin

- **PRE-RELAX-AHF**
- **RELAX-AHF**
- **RELAX-REPEAT**
- **RELAX-AHF II**
- **RELAX-ASIA**

**H2 and H3 relaxin (R2, R3) inhibit high (HG) glucose-induced apoptosis in neonatal rat ventricular myocytes**

**Acute treatment with relaxin protects the kidney against ischaemia/reperfusion injury**

**Improvement of cerebral blood flow and microcirculation after serelaxin administration 30 mcg/kg in a sheep model**

- Cortical blood flow
- Perfused capillary density

References:
1e Primary Endpoint: Change in dyspnea with VAS

2e Primary Endpoint: Change in dyspnea with Likert

RELAX-AHF
PRE-RELAX-AHF & RELAX-AHF Analysis on Mortality

Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and Combined

RELAX-AHF: CV death through Day 180 (efficacy endpoint), according to ejection fraction

RELAX-AHF-2 study design

**Screening epoch**
- Screening
- Maximum 16 hr. between presentation & randomization

**Randomized treatment epoch**
- I.V. Infusion (0-48 hours)
- Randomization
- Setrelaxin 30 µg/kg
- Placebo
- Follow Up

**Standard HF therapy continued throughout the study**
- D1
- D2
- D3
- D4
- D5
- D14
- D60
- D120
- D180

*Discharge*
Ularitide

✧ SIRIUS I
✧ SIRIUS II
★ TRUE-AHF

Synthetic analogue of Urodilatin
✧ Systemic vasodilation
✧ Renal vasodilation
✧ Diuresis
✧ Natriuresis
✧ RAAS inhibition
Ularitide

диаграмма:

- **TRUE-AHF**
- **SIRIUS I**
- **SIRIUS II**
- **TRUE-AHF**

Таблица:

<table>
<thead>
<tr>
<th>Study</th>
<th>Planned Time From Admission to Start of Study Drug</th>
<th>Actual Time From Admission to Start of Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND</td>
<td>(\leq 48) hours</td>
<td>15.5 hours</td>
</tr>
<tr>
<td>EVEREST</td>
<td>(\leq 48) hours</td>
<td>----</td>
</tr>
<tr>
<td>VERITAS</td>
<td>(\leq 24) hours</td>
<td>11 hours</td>
</tr>
<tr>
<td>PROTECT</td>
<td>(\leq 24) hours</td>
<td>----</td>
</tr>
<tr>
<td>RELAX-HF</td>
<td>(\leq 16) hours</td>
<td>(&lt; 7) hours</td>
</tr>
<tr>
<td>TRUE-AHF</td>
<td>(\leq 12) hours</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

Наглядное отображение:

- Краткосрочные в-комнатные симптомы
- Длительность риска жизнеугрожающих событий
- Медицинский прогноз
- Состояние в кардиоваскулярной области
- Прогнозирование в сердечной области
## Inotropic agents under investigation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na+/K+-ATPase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Istaroxime</td>
<td>Sarcolemma Na+-K+ pump inhibition: cytosolic calcium increase, SERCA2a stimulation</td>
</tr>
<tr>
<td><strong>Myosin activators</strong></td>
<td></td>
</tr>
<tr>
<td>omecamtiv mecarbil</td>
<td>Myosin stimulation: ↑ ejection phase duration, no change in ejection rate or calcium</td>
</tr>
<tr>
<td><strong>RyR stabilizers</strong></td>
<td></td>
</tr>
<tr>
<td>JTV-519, S107</td>
<td>RyR2/calstabin 2 interaction, ↓SR calcium leakage</td>
</tr>
<tr>
<td><strong>SERCA2a activators</strong></td>
<td></td>
</tr>
<tr>
<td>SERCA2a adeno-associated viral vector,...</td>
<td>↑ uptake of cytosolic calcium into the SR during diastole: better relaxation and increased calcium release during systole</td>
</tr>
<tr>
<td><strong>Metabolic modulators</strong></td>
<td></td>
</tr>
<tr>
<td>Perhexiline, trimetazidine, GL-P1</td>
<td>Carnitine palmitoyl transferase 1 inhibition: myocardial substrate shift from FFAs to glucose; other mechanisms</td>
</tr>
<tr>
<td><strong>Urocortin 2</strong></td>
<td>Myocardial and vascular CRF2 receptors</td>
</tr>
</tbody>
</table>
Acute Heart Failure Syndrome

- Challenging Therapy
- Several Missing Links
- Decongestion is the mainstay of therapy
- Novel Therapies in the Horizon