Treating the patient with acute heart failure. What do we really know?

Principles of acute heart failure treatment

Marco Metra, MD, FESC
Cardiology
University of Brescia, Italy

Disclosures: Co-chairman of the RELAX-AHF trial, received honoraria from Abbott vascular, Bayer, Corthera, Novartis.
Cardiac dysfunction

- Systolic
- Diastolic

Renal changes / renal dysfunction

Na-H₂O retention

Congestion

End-organ hypoperfusion

End-organ hypoperfusion

↑ venous pressure

Myocardial ischemia

Coronary perfusion pressure

↓ CO / ↑ LVEDP

Neurohormonal activation

RAA – SNS - ADH

Inflammatory activation

Fluid redistribution to the lungs

Lung congestion

↑ LV afterload

↑ LV preload

↑ LV wall stress

MVO₂

tachycardia

Pathophysiologic mechanisms in acute heart failure

Metra, Brutsaert, Dei Cas, Gheorghiade. ESC Intensive Acute Cardiac Care textbook
Factors which influence clinical presentations & prognosis of AHF

• **Fluid status**

• Blood pressure (*afterload mismatch, LV function?*)

• Myocardial ischemia

• Kidney dysfunction

• Other pathogenic mechanisms
  – Neurohormonal activation
  – Endothelial dysfunction
  – Inflammatory activation

• Time of treatment
# Symptoms in patients with acute HF in major registries

<table>
<thead>
<tr>
<th>Study, year</th>
<th>No of patients</th>
<th>dyspnea, %</th>
<th>Orthopnea, %</th>
<th>Pulm. Rales, %</th>
<th>Peripheral edema, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudiger et al. 2005&lt;sup&gt;1&lt;/sup&gt;</td>
<td>312</td>
<td>94</td>
<td>72</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADHERE, 2005&lt;sup&gt;2&lt;/sup&gt;</td>
<td>187,565</td>
<td>89</td>
<td>34</td>
<td>67</td>
<td>66</td>
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<tr>
<td>IMPACT-HF, 2005&lt;sup&gt;3&lt;/sup&gt;</td>
<td>567</td>
<td>77</td>
<td>41</td>
<td>65</td>
<td>59</td>
</tr>
<tr>
<td>OPTIMIZE-HF, 2006&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,612</td>
<td>90</td>
<td>44</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Goldberg et al. 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2604</td>
<td>97</td>
<td>36</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>Tavazzi et al. 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2807</td>
<td>100</td>
<td>-</td>
<td>87</td>
<td>59</td>
</tr>
<tr>
<td>ALARM-HF, 2010&lt;sup&gt;7&lt;/sup&gt;</td>
<td>4953</td>
<td>75</td>
<td>51/ 66*</td>
<td>55/ 72*</td>
<td>50/ 39*</td>
</tr>
</tbody>
</table>

Transition From Chronic Compensated to Acute Decompensated Heart Failure
Pathophysiological Insights Obtained From Continuous Monitoring of Intracardiac Pressures

Michael R. Zile, MD; Tom D. Bennett, PhD; Martin St. John Sutton, MD; Yong K. Cho, PhD; Philip B. Adamson, MD; Mark F. Aaron, MD; Juan M. Aranda, Jr, MD; William T. Abraham, MD; Frank W. Smart, MD; Lynne Warner Stevenson, MD; Fred J. Kueffer, MS, MD; Robert C. Bourge, MD

B  HF Hospitalizations only

Systolic heart failure
Diastolic heart failure

Circulation 2008;118:1433-1441
Initial treatment in the patients hospitalized for HF: ADHERE registry

Costanzo et al. Am Heart J 2007;154:267277
Association between patient-assessed dyspnoea status and body weight change at inpatient Day 1.

Weight changes after HF hospitalization are predictive of subsequent re-hospitalization: results from EVEREST
Weight changes after HF hospitalization are not predictive of mortality: results from EVEREST
Freedom from congestion predicts good survival also in patients with advanced HF

146 pts with NYHA IV
4-6 weeks after discharge re-evaluated for congestion

Criteria:
1. Orthopnoea
2. ↑ JVP
3. Oedema
4. Weight gain
5. ↑ baseline diuretics

2-year survival (%)

<table>
<thead>
<tr>
<th></th>
<th>0 crit (n=80)</th>
<th>1-2 crit (n=40)</th>
<th>≥3 crit (n=26)</th>
<th>Orth+ (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 crit</td>
<td>80%</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>1-2 crit</td>
<td>60%</td>
<td>60%</td>
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<tr>
<td>≥3 crit</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

High-risk group

Lucas et al., Am Heart J 2000;140:840
Bedside Cardiovascular Examination in Patients With Severe Heart Failure

Pulmonary rales

Jugular vein distension

Probability of an HFE for 261 patients during a 6-month period in relation to chronic daily ePAD

Wireless pulmonary artery haemodynamic monitoring improves outcomes in HF: CHAMPION trial

A

Control group (254 hospital admissions for heart failure)
Treatment group (158 hospital admissions for heart failure)

Hazard ratio 0.63 (95% CI 0.52–0.77); p<0.0001

B

Control group (138 patients with event)
Treatment group (107 patients with event)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.0146

Abraham et al. The Lancet. 2011; 377: 658
Prognostic value of NT-ProBNP at discharge in patients hospitalised for AHF

Cardiac mortality

Discharge NT-ProBNP ≤6078
Discharge NT-ProBNP >6078

P<0.0001

Patients at risk
NT-ProBNP:

≤ 6078  76  69  69  42  32
> 6078  31  29  20  11  6

Cardiac mortality or CV Hospitalizations

Discharge NT-ProBNP ≤3275
Discharge NT-ProBNP >3275

P<0.0001

Patients at risk
NT-prBNP:

≤ 3275  57  46  28  24  19
> 3275  50  25  15  11  7

Factors which might influence clinical presentations & prognosis of AHF

- Fluid overload
- **Blood pressure** *(afterload mismatch?)*
- Myocardial ischemia
- Kidney dysfunction
- Others
  - Neurohormonal activation
  - Endothelial dysfunction
  - Inflammatory activation
## Spectrum of AHFS pathophysiological mechanisms

<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</td>
<td>↑ afterload and/or predominant LV diastolic dysfunction</td>
</tr>
<tr>
<td>Sodium and water renal retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominant LV diastolic dysfunction</td>
<td></td>
<td></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>Main symptom</td>
<td>Fatigue</td>
<td>Dyspnoea</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>

Metra, Brutsaert, Gheorghiade, Dei Cas., ESC Intensive Acute Cardiac Care textbook
## Spectrum of AHFS pathophysiological mechanisms

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<td>Normal</td>
</tr>
</tbody>
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Metra, Brutsaert, Gheorghiade, Dei Cas,. ESC Intensive Acute Cardiac Care textbook
The Study of Left Ventricular Function in Man by Increasing Resistance to Ventricular Ejection with Angiotensin

JOHN ROSS, JR. and EUGENE BRAUNWALD

Circulation. 1964;29:739-749

**Figure 3**

*Relationship between stroke volume index (SVI in ml. per M.² BSA) and left ventricular systolic pressure before and during increasing rates of angiotensin infusion.*
44 patients: Echo during AHPE and >48 hours afterwards; 20 asymptomatic HBP patients (control); data as mean±SE

**Arterial impedance**

<table>
<thead>
<tr>
<th></th>
<th>AHPE</th>
<th>F-Up</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmHg/mL</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<td>1</td>
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<tr>
<td>4</td>
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</table>

*p=0.024*  

**Arterial impedance / ventricular impedance ratio**

<table>
<thead>
<tr>
<th></th>
<th>AHPE</th>
<th>F-Up</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
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<td></td>
</tr>
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<td>0.5</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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</table>

*p=0.02*  

*Am J Cardiol 2012; 109: 1472*
Initial assessment of patient with suspected acute heart failure

Suspected acute heart failure

History/examination (including blood pressure and respiratory rate)
- Chest X-ray
- Echocardiogram or NP (or both)
- Blood chemistry

ECG
- Oxygen saturation
- Full blood count

Simultaneously assess for
- Ventilation/systemic oxygenation inadequate?
- Life-threatening arrhythmia/bradycardia?
- Blood pressure <85 mmHg or shock
- Acute coronary syndrome
- Acute mechanical cause/severe valvular disease

Urgent action if present
- Oxygen
- NIV
- ETT and invasive ventilation
- Electrical cardioversion
- Pacing
- Inotrope/vasopressor
- Mechanical circulatory support (e.g. IABP)
- Coronary reperfusion
- Antithrombotic therapy
- Echocardiography
- Surgical/percutaneous intervention

Authors/Task Force Members et al. Eur Heart J 2012;33:1787-1847
Increased symptom-improvement with the novel vasodilator, relaxin, in AHF patients with elevated BP. Results from Pre-Relax-AHF

Teerlink et al. Eur Heart J 2009; 30 (Abstract Supplement), 164
Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF

Adriaan A. Voors\(^1\), Beth A. Davison\(^2\), G. Michael Felker\(^3\), Piotr Ponikowski\(^4\), Elaine Unemori\(^5\), Gadi Cotter\(^2\), John R. Teerlink\(^6\), Barry H. Greenberg\(^7\), Gerasimos Filippatos\(^8\), Sam L. Teichman\(^5\), and Marco Metra\(^9\) on behalf of the Pre-RELAX-AHF study group
Cause of AHF According to SBP: OPTIMIZE-HF Study
48 612 patients FROM 259 US HOSPITALS

LV Systolic dysfunction

<table>
<thead>
<tr>
<th>SBP quartiles, mmhg</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>63</td>
</tr>
<tr>
<td>120-139</td>
<td>52</td>
</tr>
<tr>
<td>140-161</td>
<td>44</td>
</tr>
<tr>
<td>&gt;161</td>
<td>35</td>
</tr>
</tbody>
</table>

LV Ejection fraction

<table>
<thead>
<tr>
<th>SBP quartiles, mmhg</th>
<th>LVEF units</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>33.3</td>
</tr>
<tr>
<td>120-139</td>
<td>37.8</td>
</tr>
<tr>
<td>140-161</td>
<td>40.9</td>
</tr>
<tr>
<td>&gt;161</td>
<td>44.4</td>
</tr>
</tbody>
</table>

Gheorghiade et al., JAMA 2006; 296:2217
Cause of AHF According to SBP: OPTIMIZE-HF Study
48,612 patients FROM 259 US HOSPITALS

In-hospital mortality

<table>
<thead>
<tr>
<th>SBP quartiles, mmhg</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>7.2%</td>
</tr>
<tr>
<td>120-139</td>
<td>3.6%</td>
</tr>
<tr>
<td>140-161</td>
<td>2.5%</td>
</tr>
<tr>
<td>&gt;161</td>
<td>1.7%</td>
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</table>

Postdischarge mortality

<table>
<thead>
<tr>
<th>SBP quartiles, mmhg</th>
<th>% of patients</th>
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<tbody>
<tr>
<td>&lt; 120</td>
<td>14%</td>
</tr>
<tr>
<td>120-139</td>
<td>8.4%</td>
</tr>
<tr>
<td>140-161</td>
<td>6%</td>
</tr>
<tr>
<td>&gt;161</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

Gheorghiade et al., JAMA 2006; 296:2217
Limitations of Inotropic Agents

- **Tachyarrhythmias**
  - ↑ ventricular arrhythmias
  - ↑ ventricular rate in atrial fibrillation

- **Myocardial ischemia →**
  - progression of LV dysfunction?
    - Hypotension / coronary hypoperfusion
    - ↑ myocardial VO$_2$ (contractility & HR)

- **Mechanisms**
  - ↑ cytoplasmic Ca$^{2+}$
  - Myocardial efficiency (work/VO$_2$)?
  - Vasodilation /hypotension
Effects of inotropic stimulation on the relationship between subendocardial blood flow and infarct size in anesthetized, open-chest pigs

\[ y = -161.6 \times x + 29.8 \]
\[ n = 16, r = -0.79 \]

SURVIVE: Mean Change From Baseline in Hemodynamic Parameters Through 5 Days by Treatment Group

Mebazaa, Nieminen, Packer et al. JAMA 2007;297:1883-1891.
Factors which might influence clinical presentations & prognosis of AHF

- Fluid overload
- Blood pressure
- **Myocardial ischemia**
- Kidney dysfunction
- Others
  - Neurohormonal activation
  - Endothelial dysfunction
  - Inflammatory activation
AHF & myocardial ischaemia

• **Acute coronary syndromes**
  – Myocardial infarction/unstable angina with large extent of ischemia and ischemic dysfunction
  – Mechanical complication of acute myocardial infarction
  – Right ventricular infarction

• **Chronic coronary artery disease**
  – Ischaemia / necrosis precipitated by AHF

• **Non-ischaemic cardiomyopathy**
  – Ischaemia / necrosis precipitated by AHF ?
Prevalence of Detectable (>0.01 pg/ml) Troponin T in patients hospitalized for HF

Metra et al., Eur J Heart Fail. 2007;9:776-86
Prognostic role of Troponin release in patients hospitalized for acute heart failure

Factors which might influence clinical presentations & prognosis of AHF

- Fluid overload
- Blood pressure
- Myocardial ischemia
- Kidney dysfunction
- Others
  - Neurohormonal activation
  - Endothelial dysfunction
  - Inflammatory activation
The heart and other organs

The role of the kidney in heart failure

Marco Metra¹*, Gad Cotter², Mihai Gheorghiade³, Livio Dei Cas¹, and Adriaan A. Voors⁴

¹Institute of Cardiology, University of Brescia, c/o Spedali Civili di Brescia, Piazzale Spedali Civili 1, Brescia 25123, Italy; ²MOMENTUM Research, Durham, NC, USA; ³Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; and ⁴Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Received 19 August 2011; revised 31 May 2012; accepted 19 June 2012

This paper was guest edited by Prof. Roberto Ferrari, Department of Cardiology and LTVA Centre, University Hospital of Ferrara and Salvatore Maugeri Foundation, IRCCS, Lumezzane, Italy

Renal dysfunction is common in patients with heart failure and is associated with high morbidity and mortality. Cardiac and renal dysfunction may worsen each other through multiple mechanisms such as fluid overload and increased venous pressure, hypo-perfusion, neurohormonal and inflammatory activation, and concomitant treatment. The interaction between cardiac and renal dysfunction may be critical for disease progression and prognosis. Renal dysfunction is conventionally defined by a reduced glomerular filtration rate, calculated from serum creatinine levels. This definition has limitations as serum creatinine is dependent on age, gender, muscle mass, volume status, and renal haemodynamics. Changes in serum creatinine related to treatment with diuretics or angiotensin-converting enzyme inhibitors are not necessarily associated with worse outcomes. New biomarkers might be of additional value to detect an early deterioration in renal function and to improve the prognostic assessment, but they need further validation. Thus, the evaluation of renal function in patients with heart failure is important as it may reflect their haemodynamic status and provide a better prognostic assessment. The prevention of renal dysfunction with new therapies might also improve outcomes although strong evidence is still lacking.
Cardio-renal interactions in heart failure and kidney disease

The cardio-renal syndrome

Decreased cardiac performance

Neurohormonal activation, inflammation, oxidative stress, anemia

$\uparrow$ NaH$_2$O retention/diuretic resistance

$\downarrow$ Renal function adenosine release others?

$\downarrow$ Renal perfusion, $\uparrow$ Renal venous pressure

Type of mechanism: Haemodynamic Neuroendocrine, humoral, local (renal)

Metra M et al. Eur Heart J 2012;eurheartj.ehs205
Kidney dysfunction in heart failure

- Heart failure
  - ↓ cardiac output
    - Hypotension
  - ↑ central venous pressure
  - Fluid overload
    - Furosemide treatment
  - Neurohormonal activation
    - Adenosine release
      - Interstitial fibrosis, tubular damage, nephron loss
      - Long-term changes in renal function
  - ↓ renal perfusion
  - ↑ renal vein pressure
  - Short-term changes in renal function
Death or urgent treatment in patients subdivided on the basis of volume status and WRF

WRF = worsening renal function

Effect of an increase in cystatin C on mortality in patients with a small rise in creatinine during HF hospitalization

Multimarker Testing with ST2 and BNP and Rates of Death After Acute Heart Failure

Rehman et al. J Am Coll Cardiol 2008;52:1458–1465
One-year outcomes in patients with HF: 
Italian IN-HF Registry (n=5610)

Mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chronic HF</th>
<th>New onset HF</th>
<th>Worsening HF</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>2.1</td>
<td>14.5</td>
<td>19.9</td>
</tr>
<tr>
<td>Non CV</td>
<td>3.8</td>
<td>4.7</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Hospitalizations

<table>
<thead>
<tr>
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<th>New onset HF</th>
<th>Worsening HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>5.5</td>
<td>17.2</td>
<td>29.5</td>
</tr>
<tr>
<td>Non CV</td>
<td>5.8</td>
<td>16.3</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Courtesy of L. Tavazzi and A. Maggioni
Frontiers in cardiovascular medicine

The current and future management of acute heart failure syndromes

Peter S. Pang\textsuperscript{1,3}, Michel Komajda\textsuperscript{2}, and Mihai Gheorghiade\textsuperscript{3*}

\textsuperscript{1}Department of Emergency Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; \textsuperscript{2}Department of Cardiology, Hopital Pitie-Salpetriere and University Pierre et Marie Curie, Paris, France; and \textsuperscript{3}Center for Cardiovascular Quality and Outcomes, Department of Medicine, Northwestern University, Feinberg School of Medicine, 645 N Michigan Ave, Suite 1006, Chicago, IL 60611, USA

Received 12 January 2010; accepted 2 February 2010; online publish-ahead-of-print 5 March 2010
Comprehensive assessment and cardiac reconstruction

**Comprehensive assessment**

<table>
<thead>
<tr>
<th>Potential targets</th>
<th>Method of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestion</td>
<td>JVP, body weight, peripheral oedema</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Blood pressure measurement</td>
</tr>
<tr>
<td>LV function, valvular disease, wall motion abnormalities, aneurysm</td>
<td>ECHO Doppler, MRI, nuclear imaging</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>Pharmacological or exercise testing with imaging</td>
</tr>
<tr>
<td>CAD</td>
<td>Cardiac catheterization and angiography</td>
</tr>
<tr>
<td>Ventricular dyssynchrony (wide QRS)</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Viable but dysfunctional myocardium</td>
<td>Low-dose dobutamine ECHO, MRI</td>
</tr>
</tbody>
</table>

**Cardiac reconstruction**

(five overarching thematic targets—myocardium, coronary arteries, electrical system, pericardium, valves)

- **Myocardium**
  - LV dysfunction:
    - ACE-I or ARB
    - Beta-blockers
    - Aldosterone antagonist
    - Hydral/ISDN
    - Digoxin
    - Macronutrients
    - Micronutrients
    - Metabolic modulators

- **Coronary arteries**
  - CAD
    - Anti-platelet
    - Statins
    - Revascularization
    - Other ESC guideline recommended therapy for secondary prevention

- **Electrical system**
  - Sudden cardiac death
    - ICD
    - Beta-blockers
    - Aldosterone antagonists
  - Ventricular dyssynchrony
    - CRT +/- ICD

- **Valves**
  - Surgery
  - Procedural
  - Statins
  - Per ESC guidelines

- **Pericardium**
  - Atrial fibrillation
    - Rate control
      - Digoxin
      - Beta-blocker
      - Non-dihydropyridine calcium channel blockers
    - Warfarin
    - Rhythm control
    - MAZE procedure

Congestion – (salt restriction, diuretics, ultrafiltration, vasopressin antagonists)

Hypertension (ACE-I or ARB, beta-blockers, diuretics, others per ESC guidelines)

Enhance Adherence (education, disease management, performance improvement systems)

Pang P S et al. Eur Heart J 2010;31:784-793