Heart Failure: A Downward Spiral Journey

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Disclosures

• Member of Committees or PI of trials sponsored by Novartis, Cardiorentis, Bayer, Vifor, European Union
Heart Failure: emerging epidemic for 21st century

Burden of HF – recent epidemiological data

- HF is prevalent
  ESC countries > 15 mln
  US: Approximately 550,000 new cases/year
  Increased 33% between 2000 and 2007

- HF is costly
  2% of national expenditure on health
  GER (2006) – direct medical costs = 2.9 bln EUR.

- HF has poor outcome
  Despite advances in therapy QoL is very poor and the outcome is ominous.
  ½ of patients admitted to hospital with HF are dead or readmitted within 1 year
Outcome in AHF is still poor

DOSE-AHF\(^1\)

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

40% at 60 days

CARRESS-HF\(^2\)

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

Outcomes for patients with HF are poor in clinical practice

- HF mortality remains high, with ~50% of patients with HF dying within 5 years of diagnosis\(^1,2\)

**Chronic HF\(^3\)**
IN-CHF Registry
1-year follow-up (n=1,315 patients)

![Bar graph showing all-cause mortality and hospitalisation due to HF in chronic HF](image)

**AHF\(^4\)**
Survey on AHF
6-month follow-up (n=1,771 patients)*

![Bar graph showing all-cause mortality and hospitalisation in AHF](image)

*From hospital discharge
IN-CHF=Italian Network on Congestive Heart Failure

Incident Heart Failure Hospitalization and Subsequent Mortality in Chronic Heart Failure: A Propensity-Matched Study

ALI AHMED, MD, MPH, RICHARD M. ALLMAN, MD, GREGG C. FONAROW, MD, THOMAS E. LOVE, PhD, FAIEZ ZANNAD, MD, PhD, LOUIS J. DELL’ITALIA, MD, MICHEL WHITE, MD, AND MIHAI GHEORGHIADE, MD

Birmingham, Alabama; Los Angeles, California; Cleveland, Ohio; Nancy, France; Montreal, Canada; Chicago, Illinois

CI = confidence interval; HFH = heart failure hospitalization; HR = hazard ratio

HF has a detrimental effect on quality of life

- Patients with HF commonly report psychological distress, including
  - Depression and anxiety
  - Limitation in their activities of daily living
  - Disruption of work roles and social interaction with friends and family

- Patient quality of life is reduced more by HF than many other chronic diseases, including diabetes, arthritis and chronic lung disease

- Patients with advanced HF had a greater number of physical symptoms, higher depression scores and lower spiritual well-being than patients with advanced cancer

Economic burden of chronic heart failure

Hospitalization accounts for most CHF-associated costs

HF presents with a wide range of symptoms, of which dyspnoea is almost universal.


Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine
In-hospital patients: clinical status at discharge

### Pulmonary congestion
- At admission: 60.9%
- At discharge: 9.7%

### Peripheral congestion
- At admission: 64.5%
- At discharge: 18.1%

### Pulmonary and/or Peripheral congestion
- At admission: 81.6%
- At discharge: 24.1%
Acute HF: persisting congestion at discharge and all-cause mortality during the follow-up

Pulmonary congestion

Yes: 22.0%
No: 12.7%
p = 0.0007

Peripheral congestion

Yes: 21.4%
No: 11.8%
p < 0.0001

Pulmonary and/or Peripheral congestion

Yes: 20.8%
No: 11.3%
p < 0.0001

n. 1610, 90.3%
n. 173, 9.7%
n. 1459, 81.9%
n. 323, 18.1%
n. 1355, 75.9%
n. 429, 24.1%
Current therapies do not provide optimal relief from AHF signs and symptoms

Only 58% of patients hospitalised for acute HF show good symptom relief with standard therapy at 6 hours\(^1,2\)

- 24% of patients hospitalised for HF in Europe have signs of congestion at discharge\(^4\)

*Patients with New York Heart Association class IV HF (n=146) were re-assessed for signs of congestion 4–6 weeks after discharge. Criteria for congestion were orthopnoea, raised jugular venous pressure, the need to increase the dose of diuretic during the past week, and attending staff assessment of weight.

Acute exacerbations may contribute to the progression of the disease

**Hypothesis:** With each decompensation, there is myocardial and/or renal damage leading to further progression of the disease

HF leads to adverse effects on the heart, lungs, kidneys and vasculature

Inflammatory
- Inflammation
- Anaemia
- Cell death
- Fibrosis/remodelling

Risk factors
- Ageing
- Diabetes
- Hypertension
- Atherosclerosis

Neurohormonal activation

Sympathetic drive + outflow

Heart failure

- Low cardiac output (Forward failure)
- Drug therapy
- RAS inhibitors
- Diuretics
- Dilatation of Efferent arteriole

High central venous pressure (Backward failure)

High intra-abdominal pressure

High pressure on Bowman’s capsule

Low urine output

Sympathetic drive + outflow

Renal dysfunction

Mechanisms of disease progression in HF

Myocardial renal injury

Apoptosis
Necrosis

Fibrosis

Apoptosis
Necrosis

Activation of compensatory mechanisms

Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section

James L. Januzzi Jr1*, Gerasimos Filippatos2, Markku Nieminen3 and Mihai Gheorghiade4

Proteolysis or turnover of myocardial contractile proteins

Direct toxicity of circulating neurohormones, inflammation, infiltrative processes, etc.

Supply demand mismatch with subendocardial ischaemia

Selected causes of reduced oxygen supply:
- Anaemia
- Hypotension

Selected causes of increased myocardial oxygen demand:
- Increased transmural wall stress
- Dilated left ventricular chamber size
- Elevated pressures in cardiac chambers
- Left ventricular hypertrophy
- Diastolic stiffening of the myocardium
Prognostic value of a $\geq 20\%$ hs-cTnT increase from baseline and effects of serelaxin

![Graph showing the cumulative risk of patients with hs-cTnT increase over study days. The graph compares the cumulative risk for patients with $<20\%$ increase and $\geq 20\%$ increase. The number at risk is also provided for each group.]

Percent of patients with hs-cTnT increase

- Placebo
- Serelaxin

$p = 0.0001$
Filippatos et al, J Am Coll Cardiol 2014.
MMPs alter ECM Structure

- Normal
- MMP Expression
- MMP Activity
- TIMP Control
- CHF

Active MMP

MMPs alter ECM Structure
Fibrosis

Changes in collagen synthesis and degradation

Changes in collagen structure
Episodes of acute heart failure syndrome are associated with marked and transient increases in markers for extracellular matrix turnover\textsuperscript{1}

- In cross-sectional studies of patients with HF with diastolic dysfunction, alterations in circulating MMP and TIMP levels are related to the extent of LV remodeling and predict clinical outcomes\textsuperscript{2}
- These data suggest that episodes of acute HF decompensation may be associated with an acceleration of pathological myocardial remodeling

PIIINP=procollagen type III N-terminal peptide
## Diagnosis and Management of Acute Heart Failure

Mihai Gheorghiade, Gerasimos S. Filippatos, and G. Michael Felker

Comorbidities of patients hospitalised with AHF from various registries

<table>
<thead>
<tr>
<th>Condition</th>
<th>ADHERE n=105,388</th>
<th>OPTIMIZE-HF n=48,612</th>
<th>EHFS II n=3,580</th>
<th>ARGENTINA n=2,974</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>57</td>
<td>50</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73</td>
<td>71</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31</td>
<td>–</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>31</td>
<td>31</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44</td>
<td>42</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>30</td>
<td>20</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>31</td>
<td>34</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>

Event rates are even higher in patients with heart failure and type 2 diabetes mellitus or chronic kidney disease.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute change(^a)</th>
<th>Relative change(^a)</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>(&gt; \text{or} \geq 0.3 \text{mg/dL})</td>
<td>(\geq 25%)</td>
<td>(\geq 2 \text{mg/dL})</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>(&gt; \text{or} \geq 0.5 \text{mg/dL})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>(&gt; 0.3 \text{mg/dL})</td>
<td>(&gt; \text{or} \geq 25%)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>(&gt; 0.3 \text{mg/dL})</td>
<td>(\geq 1.5 \times \text{baseline})</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>(&gt; 0.3 \text{mg/dL})</td>
<td>(\geq 20%)</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>(&gt; 5 \text{mL/min/year})</td>
<td>(&gt; 25%)</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>(&gt; 0.3 \text{mg/L})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Increase for serum creatinine and cystatin C; decrease for eGFR.

eGFR, estimated glomerular filtration rate
Prognostic value of a $\geq 0.3$ mg/L Cys-C increase and effects of serelaxin

Percent of patients with $\geq 0.3$ Cys-C increase

Placebo: 23.2, p = 0.0027

Serelaxin: 16, p = 0.0027
Goals of Treatment in Acute Heart Failure

Immediate (ED/ICU/CCU)

- Treat symptoms
- Restore oxygenation
- Improve organ perfusion & haemodynamics
- Limit cardiac/renal damage
- Prevent thrombo-embolism
- Minimize ICU length of stay

Intermediate (in-hospital)

- Stabilise patient and optimise treatment strategy
- Initiate and up-titrage disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients
- Identify aetiology and relevant co-morbidities

Long-term and pre-discharge management

- Plan follow-up strategy
- Enrol in disease management programme, educate, initiate appropriate lifestyle adjustments
- Plan to up-titrage/optimize disease-modifying drugs
- Assess for appropriate device therapy
- Prevent early readmission
- Improve symptoms, quality of life and survival

Phases in the AHF management

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012

McMurray et al. Eur Heart J 2012;33:1787–1847
Unmet therapeutic need in AHF:
The evidence base for many commonly used AHF treatments is limited with no proven long-term benefits

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICATION</th>
<th>CLASS OF RECOMMENDATION (I–III)</th>
<th>LEVEL OF EVIDENCE† (A–C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Loop diuretics</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Nitrates</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Sodium nitroprusside</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Opiates</td>
<td>Morphine</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Inotropes</td>
<td>Dobutamine</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

†A=data derived from multiple randomised controlled trials (RCTs) or meta-analyses; B=data derived from a single RCT or large non-randomised studies; C=consensus of opinion of experts and/or data from small studies, retrospective studies, or registries

McMurray et al. Eur Heart J 2012;33:1787–1847
## Classes of recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Condition for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective</td>
</tr>
<tr>
<td>II</td>
<td>Condition for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment</td>
</tr>
<tr>
<td>IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy</td>
</tr>
<tr>
<td>IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>III</td>
<td>Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful</td>
</tr>
</tbody>
</table>

## Levels of Evidence

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
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<td>B</td>
<td>Data derived from a single randomized trial or large non-randomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus of opinion of experts and/or small studies, retrospective studies, registries</td>
</tr>
</tbody>
</table>
There are many treatment objectives for chronic HF

<table>
<thead>
<tr>
<th>Objectives of treatment for chronic HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prognosis</td>
</tr>
<tr>
<td>• reduce mortality</td>
</tr>
<tr>
<td>2. Morbidity</td>
</tr>
<tr>
<td>• relieve symptoms and signs</td>
</tr>
<tr>
<td>• improve quality of life</td>
</tr>
<tr>
<td>• eliminate oedema and fluid retention</td>
</tr>
<tr>
<td>• increase exercise capacity</td>
</tr>
<tr>
<td>• reduce fatigue and breathlessness</td>
</tr>
<tr>
<td>• reduce the need for hospitalisation</td>
</tr>
<tr>
<td>• provide end of life care</td>
</tr>
<tr>
<td>3. Prevention</td>
</tr>
<tr>
<td>• prevent the occurrence of myocardial damage</td>
</tr>
<tr>
<td>• prevent the progression of myocardial damage</td>
</tr>
<tr>
<td>• prevent the remodelling of the myocardium</td>
</tr>
<tr>
<td>• prevent the reoccurrence of symptoms and fluid accumulation</td>
</tr>
<tr>
<td>• prevent hospitalisation</td>
</tr>
</tbody>
</table>

The ESC/HFA recommend a symptom-based treatment algorithm for HFrEF

Diuretics to relieve symptoms/signs of congestion

ACEI (or ARB if not tolerated)

β-blocker

Yes

Still NHYA class II–IV?

No

Add a MR antagonist

Yes

Still NHYA class II–IV?

No

LVEF≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min%?

Yes

Add ivabradine

No

Still LVEF≤35% and NHYA class II–IV?

Yes

QRS duration ≥120 msec?

Yes

Consider: CRT or CRT-D

No

Consider ICD

Still NHYA class II–IV?

Yes

No further specific treatment Continue in disease management programme

No

Consider digoxin and/or H-ISDN If end-stage, consider LVAD and/or transplantation

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CRT=cardiac resynchronization therapy; CRT-D=CRT-defibrillator; ESC=European Society of Cardiology; HFrEF=heart failure with reduced ejection fraction; H-ISDN=hydralazine-isosorbide dinitrate; HR=heart rate; ICD=implantable cardioverter defibrillator; LVAD=left ventricular assist device; LVEF=left ventricular ejection fraction; NHYA=New York Heart Association

McMurray et al. Eur Heart J 2012;33:1787–1847
Are ambulatory patients with heart failure treated in accordance with ESC guidelines?

Rate of use

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate of use</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I / ARB</td>
<td>1.9%</td>
<td>92 pts</td>
<td>372 pts</td>
</tr>
<tr>
<td>ARB</td>
<td>21.6%</td>
<td>1033 pts</td>
<td></td>
</tr>
<tr>
<td>ACE-I</td>
<td>68.8%</td>
<td>3295 pts</td>
<td></td>
</tr>
<tr>
<td>Betablockers</td>
<td>92.7%</td>
<td>4439 pts</td>
<td>353 pts</td>
</tr>
<tr>
<td>MRAs</td>
<td>67.0%</td>
<td>3209 pts</td>
<td>1583 pts</td>
</tr>
</tbody>
</table>

Rate of patients at target dosage of recommended pharmacological treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I (4710 pts)</td>
<td>1380 (29.3)</td>
<td></td>
</tr>
<tr>
<td>ARBs (1500 pts)</td>
<td>362 (24.1)</td>
<td></td>
</tr>
<tr>
<td>B-blockers (6468 pts)</td>
<td>1130 (17.5)</td>
<td></td>
</tr>
<tr>
<td>MRAs (4226 pts)</td>
<td>1290 (30.5)</td>
<td></td>
</tr>
</tbody>
</table>

Maggioni et al Eur J Heart Fail 2013;15:1173–84
Chronic HF survival rates have improved over time with the advent of new therapies

Temporal trends in 5-year mortality after the diagnosis of HF by gender show improvements in survival ...

... nevertheless, the 5-year mortality rate remains high

Population-based cohort study analysing data from the Rochester Epidemiology Project, Minnesota, USA. 4,537 patients with a diagnosis of HF between 1979 and 2000 were included. Framingham criteria and clinical criteria were used to validate the diagnosis.

Roger et al. JAMA 2004;292:344–50
Chronic HF remains “malignant”

HF mortality rate is twice that of

- Breast cancer
- Bladder cancer

Greater than that of

- Prostate cancer

And similar to that of

- Colon cancer
Chronic HF: hospitalizations during the follow-up*

No 68.1%
Yes 31.9%

Causes of hospitalization:
- Non CV causes: 24.8%
- CV causes non HF: 33.5%
- HF: 41.7%

*median follow-up 364 days [336-367]
Efficacy of beta-blockers for preventing death

Unadjusted Kaplan-Meier survival (includes all reported deaths). Hazard ratios (HR) derived from the adjusted one-stage Cox model.

Kotecha D et al, Lancet 2014 on line
Angiotensin Receptor Neprilysin Inhibition

LCZ696

Angiotensin receptor blocker + Inhibition of neprilysin
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

Days After Randomization

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)

P = 0.0000002

Number needed to treat = 21

JJV McMurray et al NEJM 2014 online
To date, no therapy has been proven to reduce morbidity and mortality in patients with HFpEF.

CV=cardiovascular; HFpEF=heart failure with preserved ejection fraction; HR=hazard ratio; I-PRESERVE=Irbesartan In Patients With Heart Failure And Preserved Ejection Fraction; MI=myocardial infarction


*Primary composite endpoint of death from any cause or hospitalisation for a CV cause (HF, MI, unstable angina, arrhythmia, or stroke) in HF patients with LVEF ≥45%

†Primary composite outcome of CV death or admission to hospital for chronic HF in HF patients with LVEF >40%
HEART FAILURE

- There is an unmet need to identify safe and effective therapies for patients with AHF given the high post-discharge morbidity and mortality experienced by this group.
- The majority of AHF patients hospitalized with HF are patients with worsening chronic heart failure.