Current Pharmacological Treatment in Chronic Heart Failure

ESC HF Guidelines 2012
The Principal Changes from the 2008 Guidelines

Stamatis Adamopoulos, MD, PhD (Imperial College)

Heart Failure-Transplant Unit
Onassis Cardiac Surgery Center
The Principal Pharmacological Changes from the 2008 Guidelines Relate to:

- an expansion of the indication for mineralocorticoid (aldosterone) receptor antagonists (MRAs)
- a new indication for the sinus node inhibitor ivabradine

ESC HF Guidelines 2012
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

**EMPHASIS-HF Trial**

F Zannad et al,
Pharmacological Treatments Indicated in Potentially All Patients with Symptomatic (NYHA Functional Class II–IV) Systolic HF

<table>
<thead>
<tr>
<th>MRA’s</th>
<th><strong>ESC HF Guidelines 2012</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Class</td>
</tr>
<tr>
<td>An <strong>MRA</strong> is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤ 35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death</td>
<td>I</td>
</tr>
</tbody>
</table>
Ivabradine and Outcomes in Chronic Heart Failure: a Randomised Placebo-Controlled Study

SHIFT Trial

K Swedberg et al, LANCET 2010, September 11
# Other Treatments with Less-Certain Benefits in Patients with Symptomatic (NYHA class II–IV) HF and Reduced LVEF (≤40%)

<table>
<thead>
<tr>
<th>Ivabradine</th>
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<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Class</strong></td>
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<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF≤35%, a heart rate remaining ≥70 b.p.m. and persisting symptoms (NYHA class II–IV) despite an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB) and an MRA (or ARB)</td>
<td>IIa</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF≤35%, a heart rate remaining ≥70 b.p.m., who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB)</td>
<td>IIb</td>
</tr>
</tbody>
</table>
Pharmacological Treatment Options for Patients with Chronic Symptomatic Systolic Heart Failure (NYHA Class II-IV)

The Task Force in collaboration with HFA of the ESC, Eur Heart J 2012, June 26

**Diuretics to relieve symptoms/signs of congestion**

+ **ACE inhibitor (or ARB if not tolerated)**

   ADD a beta-blocker

   Still NYHA class II-IV?

   Yes

   ADD a MR antagonist

   Still NYHA class II-IV?

   Yes

   LVEF ≤ 35%?

   Yes

   Sinus rhythm and HR ≥ 70 beats/min?

   Yes

   ADD ivs bradine

   No

   No

No

HF Guidelines 2012: principal changes
Effect of Oral Digoxin in High-Risk Heart Failure Patients: a Pre-Specified Subgroup Analysis of the DIG Trial

M Gheorghiade et al, Eur Heart J 2013, May

NYHA class III–IV symptoms, LVEF < 25%, cardiothoracic ratio (CTR) > 55%
New Perspectives for New Guidelines

Heart Failure and Cardiomyopathies

ESC Congress Barcelona 2014
Angiotensin Receptor Neprilysin Inhibition

LCZ696

Angiotensin receptor blocker + Inhibition of neprilysin
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides that Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites

Neprilysin inhibition

Neurohormonal activation

Vascular tone

Cardiac fibrosis, hypertrophy

Sodium retention

ESC Congress Barcelona 2014

Congress Highlights
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>At 180</td>
<td>3922</td>
<td>3883</td>
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<tr>
<td>At 360</td>
<td>3663</td>
<td>3579</td>
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<tr>
<td>At 540</td>
<td>3018</td>
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<td>At 720</td>
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<td>At 900</td>
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<td>1488</td>
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<tr>
<td>At 1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>At 1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

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, September 11
PARADIGM-HF: All-Cause Mortality

HR = 0.84 (0.76-0.93)  
P<0.0001

Enalapril (n=4212)  
LCZ696 (n=4187)

Patients at Risk

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<tr>
<td>180</td>
<td>4056</td>
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<td>360</td>
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<td>540</td>
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<td>1080</td>
<td>1005</td>
<td>994</td>
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<tr>
<td>1260</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

JJV McMurray et al, NEJM 2014, September 11
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril the LCZ696 was:

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

The magnitude of the beneficial effect of LCZ696, as compared with enalapril, on cardiovascular mortality was at least as large as that of long-term treatment with enalapril, as compared with placebo.
Effect of Ferric Carboxymaltose on Functional Capacity in Patients with Heart Failure and Iron Deficiency (CONFIRM-HF)

**Primary endpoint:** change in 6-minutes walking test distance at Week 24

- **FCM vs placebo:** $33 \pm 11$ m (least squares mean $\pm$ SE)

P $= 0.002$

ESC Congress Barcelona 2014

P Ponikowski et al, Eur Heart J 2014, August 31
Hospitalizations in CONFIRM-HF
Secondary Endpoint: First Hospitalization Due to Worsening HF

FCM reduced the risk of recurrent hospitalisations due to worsening HF (post hoc): Hazard Ratio (95% CI) – 0.30 (0.14-0.64), p=0.0019
Efficacy of Beta-Blockers for Preventing Death in Patients with Heart Failure plus AF

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

All-cause mortality: Sinus rhythm

- Survival proportion
- HR 0.73 (95% CI 0.67-0.80); p<0.001

All-cause mortality: Atrial fibrillation

- Survival proportion
- HR 0.97 (95% CI 0.83-1.14); p=0.73

Number at risk
- Beta-blocker: 7123, 5014, 1798, 722
- Placebo: 6819, 4604, 1530, 561

D Kotecha et al, Lancet 2014, September 2
Association between Use of Beta-Blockers and Mortality in Patients with Heart Failure and Preserved Ejection Fraction: a Prospective Propensity Score-Matched Cohort Study

- β-blockers associated with reduced mortality in HFpEF
  
  Un-adjusted HR: 0.73, p < 0.001
  
  Matched HR: 0.92, p = 0.021

- But β-blockers not associated with reduced combined mortality/HF hospitalization in HFpEF

Lund LH, JAMA 2014, Nov 19 (the Swedish Registry)
ESC CONGRESS 2015 HIGHLIGHTS

HEART FAILURE

ESC Congress London 2015
ESC 2015: TRILOGY OF LV-REMODELING

Peri-infarct Zone Pacing to Prevent Adverse Left Ventricular Remodeling in Patients with Large Myocardial Infarction

Results from the PRomPT Trial

Gregg W. Stone, MD
Eugene S. Chung, Branislav Stancak, Jesper H. Svendsen, Trent M. Fischer, Fred Kueffer, Thomas Ryan, Jeroen Bax, and Angel Leon, for the Post-Myocardial Infarction Remodeling Prevention Therapy (PRomPT) Trial Investigators

GW Stone et al. Eur Heart J 2015, August 30

ALBATROSS

Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up


On behalf of the ALBATROSS investigators

G. Montalescot, ESC 2015, London

CIRCUS Trial

Cyclosporine before PCI in Patients with Acute Myocardial Infarction

Between December 2010 and October 2013, 126 patients were randomized at 27 sites in Europe, the Middle East, and the United States.

**PRomPT: ENROLLMENT**

Randomized 1:1:1

- **LV and RV pacing** (n=41)
  - 1 withdrew
  - 1 withdrawn
  - Successful implant (n=37)
    - 1 withdrew
    - **18-month FU** (n=38)  
      - As-treated (n=37)  
      - ITT (n=41)

- **LV pacing only** (n=40)
  - 1 withdrew
  - 1 withdrawn
  - Successful implant (n=38)
    - 2 lost to FU
    - **18-month FU** (n=36)  
      - As-treated (n=38)  
      - ITT (n=40)

- **No implant** (n=45)
  - 5 withdrew
  - 3 lost to FU
  - 1 missed
  - **18-month FU** (n=36)  
    - As-treated (n=45)  
    - ITT (n=45)

**GW Stone et al. Eur Heart J 2015, August 30**
**PRomPT: PRIMARY ENDPOINT – ΔLVEDV**

Paired echocardiographic results between the baseline and 18-month follow-up visits

![Graph showing paired echocardiographic results](image)

- **Control**
- **Single Site**
- **Dual Site**

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Control</th>
<th>Single Site</th>
<th>Dual Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<td>3</td>
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<td>6</td>
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<tr>
<td>12</td>
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<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
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</tr>
</tbody>
</table>

**N with data:**

- **Single-site**: 37, 32, 27, 27, 29, 31
- **Dual-site**: 37, 33, 34, 28, 25, 33
- **Control**: 44, 34, 34, 33, 31, 34

*GW Stone et al. Eur Heart J 2015, August 30*
ALBATROSS STUDY DESIGN

AMI (ST+ or ST-) in the first 72hrs

Aldosterone blockade

iv K⁺ canrenoate*  
them
spironolactone**

R  
Randomized  
Open label  
N=1600

case

control

1° End Point: death, resuscitated cardiac death, VF/VT, indication for defibrillator, heart failure  
up to 6-month FU

* Soludactone  
200mg

** Aldactone  
25mg od

G. Montalescot, ESC 2015, London
**PRIMARY END POINT**

Death, resuscitated death, VF/VT, indication for ICD or heart failure

HR = 0.97 [0.73-1.28]  
P = 0.81

**MRA Regimen**

- N at risks
  - Standard Therapy: 801
  - MRA Regimen: 802

**Follow-up (days)**

- Days: 0, 50, 100, 150, 200

**Primary end point**

- N at risks
  - Standard Therapy: 687, 669, 645, 273
  - MRA Regimen: 705, 683, 660, 183

*G. Montalescot, ESC 2015, London*

**MRA**: Mineralocorticoid Receptor Antagonist; **VF**: Ventricular Fibrillation;  
**VT**: Ventricular Tachycardia; **ICD**: Implantable Cardioverter Defibrillator
CIRCUS: Cyclosporine before PCI in Patients with Acute Anterior Myocardial Infarction

RESULTS OF ARTS-HF: FINERENONE VERSUS EPLERENONE IN PATIENTS WITH WORSENING CHRONIC HEART FAILURE AND DIABETES AND/OR CHRONIC KIDNEY DISEASE

Finerenone (BAY 94-8862) is a novel non-steroidal MRA that has greater receptor selectivity than spironolactone and better receptor affinity than eplerenone in vitro.\(^1\)

Study objective: to compare the safety and efficacy of different once-daily oral doses of finerenone with eplerenone in patients who presented in emergency departments with worsening chronic HFrEF with type 2 diabetes mellitus and/or chronic kidney disease (CKD).

G. Filippatos et al. ESC 2015, London
The proportion of patients who had an NT-proBNP decrease of more than 30% at day 90 compared with baseline was similar in the finerenone groups and the eplerenone group in the full analysis set.

*Error bars show 90% confidence intervals NT-proBNP, N-terminal of prohormone B-type natriuretic peptide*

G. Filippatos et al. ESC 2015, London
ARTS-HF: DEATH FROM ANY CAUSE, CV HOSPITALIZATION, OR WORSENING CHF

Study period

Follow-up

Probability of survival (%)

Time (days)

Eplerenone (n = 207)

Finerenone 7.5–15 mg (n = 158)

Finerenone 2.5–5 mg (n = 162)

Finerenone 10–20 mg (n = 160)

Finerenone 5–10 mg (n = 157)

Finerenone 15–20 mg (n = 158)

G. Filippatos et al. ESC 2015, London

G. Filippatos et al. ESC 2015, London
Efficacy of Long-Term Ivabradine Therapy on Prognosis, Left and Right Heart Functional Parameters in Patients with CHF and Preserved LV Systolic Function

104 patients with HFpEF, RCT, NYHA class III

In patients with HFpEF, Ivabradine improves prognosis, by reducing inflammation and improving left and right ventricular function

Chagas disease

- Third commonest parasitic disease globally
- Most common form of non-ischemic cardiomyopathy in Latin America
- 5–7 million infected, 1.4 - 2.1 million develop cardiomyopathy <20-30 yr

*T. cruzi* low level parasitemia may be a key factor

Role of trypanocidal therapy in established Chagas cardiomyopathy is unknown

BENEFIT TRIAL: PRIMARY OUTCOME
(death, resuscitated cardiac arrest, sustained VT, pacemaker/ICD, new HF, cardiac transplant, and stroke/TIA and SE)

Log-Rank p-value=0.31

# at Risk
BNZ 1431 1312 1246 1178 936 695 484 323
Pi 1423 1316 1233 1155 881 649 459 294

50–75% of all patients with HF suffer from Sleep-Disordered Breathing

- Obstructive sleep apnoea (OSA)
- Central sleep apnoea (CSA) which may manifest as Cheyne–Stokes respiration
- Resulting in: tissue hypoxia, repetitive arousal from sleep with increased sympathetic nervous system activity

Small and/or uncontrolled studies (and meta-analyses) suggest multiple beneficial effects of Adaptive Servo-Ventilation (ASV) on surrogates in HF

Post-hoc data from CANPAP (N=258) suggest that CPAP might improve mortality when CSA was controlled (AHI < 15) in HF patients with CSA and EF < 40%

*M. Cowie et al. N Engl J Med 2015, September 17*
SERVE-HF: ADAPTIVE SERVO-VENTILATION

- Non-invasive ventilatory therapy that supports inspiration when breathing amplitude is reduced and ensures sufficient respiration when respiratory effort is absent (Variable IPAP)
- Upper airway patency is ensured by provision of end-expiratory pressure
- Although algorithms employed by different ASV devices vary slightly, the principle of treatment is the same: back-up rate ventilation with adaptive pressure support

SERVE-HF: PRIMARY ENDPOINT NEUTRAL
TIME TO FIRST EVENT OF ALL-CAUSE DEATH, LIFE-SAVING CARDIOVASCULAR INTERVENTION, OR UNPLANNED HOSPITALIZATION FOR WORSENING CHRONIC HF

Hazard ratio, 1.13 (95% CI, 0.97-1.31)

Months since Randomisation
0 12 24 36 48 60
Cumulative incidence rate (%)
0 10 20 30 40 50 60 70 80 90 100

Number at risk
Control 659 463 365 222 136 77
ASV 666 435 341 197 122 52

SERVE-HF: A RUDE AWAKENING

Death from any cause

Cardiovascular Death

OPTILINK HF STUDY DESIGN

Access arm:
- **Telemedicine** guided,
- **No audible alert** for fluid retention

Control arm:
- Standard clinical assessment,
- No alert for fluid retention

Risk stratified:
- NYHA II vs. III,
- Ischemic vs. Non-Ischemic,
- Atrial Fibrillation,
- Primary vs. Secondary Prevention (VT/VF before Implant)

M Boehm et al. ESC 2015, London
Telemonitoring depends upon multiple factors: successful transmission, subsequent intervention/medical action and patient adherence.

Composite clinical endpoints should be explored where functional status and symptoms are included.

Hazard ratio = 0.867 (0.72, 1.044)
Stratified log-rank p-value = 0.132
Angiotensin Receptor Neprilysin Inhibition

LCZ696

Angiotensin receptor blocker + Inhibition of neprilysin