The NEW Heart Failure Guidelines
HF scenario of the Case Presentations

- HF as a complex and heterogeneous syndrome
- Several proposed pathophysiological mechanisms involving the heart and the interplay with cardiac and non-cardiac comorbidities
- Applicability in clinical practice (real world) of trial’ results derived from well-selected population ? RCT generalization ?
- HF rather than a specific disease but with several distinct subtypes (clinical phenotypes)
- Differences between regions
2016 ESC Guidelines for the Diagnosis and Treatment of HF

Class I
- C-Experts opinion and/or small studies, retrospective studies or registry
- A-Multiple randomized clinical trial or meta-analysis
- B-Single randomized clinical trial or large non-randomized studies

Class IIa
- C-Experts opinion and/or small studies, retrospective studies or registry
- A-Multiple randomized clinical trial or meta-analysis
- B-Single randomized clinical trial or large non-randomized studies

Class IIb
- C-Experts opinion and/or small studies, retrospective studies or registry
- A-Multiple randomized clinical trial or meta-analysis
- B-Single randomized clinical trial or large non-randomized studies

Class III
- C-Experts opinion and/or small studies, retrospective studies or registry
- A-Multiple randomized clinical trial or meta-analysis
- B-Single randomized clinical trial or large non-randomized studies

Eur Heart J 2016;37:2129-2200
The Challenges in the decision-making Process in Selecting the Best Strategies Evidence-based or Guidelines-oriented in Clinical Practice

• Common patient with a frequent condition but not in concordance with trial inclusion and exclusion criteria (selected condition)
• Associated systemic co-morbidities or cardiac co-morbidities as anemia, angina, cancer, COPD, cachexia, depression, cardio renal syndrome, diabetes, gout, erectile dysfunction, gout, hyperlipidemia, iron deficiency, prostatic obstruction, sleep disturbance, obesity
• Specific etiology and etiopathogenesis as myocarditis, Chagas 'heart disease
• Specific etiopathogenesis and remodeling process as non-compactened cardiomyopathy
• Specific etiology in a specific pathophysiology as peripartum cardiomyopathy and pregnancy
New Classification and Diagnosis

The principal changes from the 2012 guidelines relate to:

- New term for patients with HF and a LVEF that ranges from 40 to 49% — ‘HF with midrange EF (HFmrEF)’; this may stimulate research into the underlying Characteristics, pathophysiology and treatment of this population
- Clear recommendations on the diagnostic criteria for HF with reduced EF (HFrEF), HFmrEF and HF with preserved EF (HFpEF)
- New algorithm for the diagnosis of HF in the non-acute setting based on the evaluation of HF probability
- New algorithm for a combined diagnosis and treatment of acute HF based on the presence/absence of congestion/hypoperfusion

www.escardio.org/guidelines
New Classification and Diagnosis

The principal changes from the 2012 guidelines (continue):

- Recommendations aimed at prevention or delay of the development of overt HF or the prevention of death before the onset of symptoms;
- Indications for the use of the new compound sacubitril/valsartan, the first in the class of angiotensin receptor neprilysin inhibitors (ARNIs);
- Modified indications for cardiac resynchronization therapy (CRT);
- The concept of an early initiation of appropriate therapy going along with relevant investigations in acute HF that follows the ‘time to therapy’ approach already well established in ACS;

www.escardio.org/guidelines
67 year old woman known with:

• Hypertension
• Diabetes

3 week history of dyspnoea, now unable to walk more than 50m on the flat, 3 pillow orthopnoea and intermittent PND with a nocturnal cough

She also recently noted that her legs were swelling.

She is currently experiencing no chest pain nor palpitations

Current meds: SHE HAS NO MEDICATION ALLERGIES
• Hydrochlorothiazide 12.5mg po daily
• Enalapril 5mg po daily
• Metformin 1g po bd
Clinical examination

- Respiratory distress – RR 32 breaths/min, Sats (room air) 92%
- Pulse 108 beats/min and regular
- Bilateral ankle oedema
- JVP elevated to angle of jaw
- A volume loaded apex in 6th ICS, AAL
- 2/6 PSM at apex with radiation to axilla
- Bilateral crackles at lung bases
CXR, ECG, Echo

Pulmonary oedema

LBBB

Dilated LV with LVEF <35%
Making a diagnosis

Clinical syndrome with some

- Typical symptoms: breathlessness, ankle swelling, fatigue
- Typical signs: elevated JVP, pulmonary crackles, peripheral oedema

Caused by a structural and/or functional cardiac abnormality

- resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress
## Signs and symptoms typical of heart failure

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical</strong></td>
<td><strong>More specific</strong></td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Elevated jugular venous pressure</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>Hepatojugular reflux</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnoea</td>
<td>Third heart sound (gallop rhythm)</td>
</tr>
<tr>
<td>Reduced exercise tolerance</td>
<td>Laterally displaced apical impulse</td>
</tr>
<tr>
<td>Fatigue, tiredness, increased</td>
<td></td>
</tr>
<tr>
<td>time to recover after exercise</td>
<td></td>
</tr>
<tr>
<td>Ankle swelling</td>
<td></td>
</tr>
<tr>
<td><strong>Less typical</strong></td>
<td><strong>Less specific</strong></td>
</tr>
<tr>
<td>Nocturnal cough</td>
<td>Weight gain (&gt;2 kg/week)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Weight loss (in advanced HF)</td>
</tr>
<tr>
<td>Bloated feeling</td>
<td>Tissue wasting (cachexia)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Cardiac murmur</td>
</tr>
<tr>
<td>Confusion (especially in the</td>
<td>Peripheral oedema (ankle, sacral, scrotal)</td>
</tr>
<tr>
<td>elderly)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Pulmonary crepitations</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Reduced air entry and dullness to</td>
</tr>
<tr>
<td>Dizziness</td>
<td>percussion at lung bases (pleural effusion)</td>
</tr>
<tr>
<td>Syncope</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Bendopnea&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Irregular pulse</td>
</tr>
<tr>
<td></td>
<td>Tachypnoea</td>
</tr>
<tr>
<td></td>
<td>Cheyne Stokes respiration</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly</td>
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<tr>
<td></td>
<td>Ascites</td>
</tr>
<tr>
<td></td>
<td>Cold extremities</td>
</tr>
<tr>
<td></td>
<td>Oliguria</td>
</tr>
<tr>
<td></td>
<td>Narrow pulse pressure</td>
</tr>
</tbody>
</table>
Signs and symptoms

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>21</td>
<td>81</td>
</tr>
<tr>
<td>PND</td>
<td>33</td>
<td>76</td>
</tr>
<tr>
<td>History of oedema</td>
<td>23</td>
<td>80</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>Pulmonary crackles</td>
<td>13</td>
<td>91</td>
</tr>
<tr>
<td>Oedema on examination</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>3rd heart sound</td>
<td>31</td>
<td>95</td>
</tr>
<tr>
<td>Raised JVP</td>
<td>10</td>
<td>97</td>
</tr>
</tbody>
</table>

Sosin M et al, Mansion Publishing 2006
Diagnostic algorithm

If these are all normal, heart failure is unlikely
3. ECG: Any abnormality

Assessment of natriuretic peptides not routinely done in clinical practice

≥1 present

NATRIURETIC PEPTIDES
- NT-proBNP ≥ 600 pg/mL

Yes

ECHOCARDIOGRAPHY

Normal

If HF confirmed (based on all available data): determine aetiology and start appropriate treatment

Not always possible

No

HF unlikely: consider other diagnosis

All absent
# EF classification of heart failure

Table 3.1  Definition of heart failure with preserved (HFrEF), mid-range (HFrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFrEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITERIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td>3</td>
<td>1. Elevated levels of natriuretic peptides&lt;sup&gt;b&lt;/sup&gt;; 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)</td>
<td>1. Elevated levels of natriuretic peptides&lt;sup&gt;b&lt;/sup&gt;; 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)</td>
<td></td>
</tr>
</tbody>
</table>
Our patient

- Clinical symptoms and sign suggestive of heart failure
- CXR showed pulmonary oedema
- ECG showed sinus rhythm and a LBBB
- Echo: Dilated LV with EF 30% and moderate MR

HOW WOULD YOU TREAT?
ALL patients unless CI or not tolerated should get ACE-I, betablocker or MR antagonist for survival benefit.
ACE-Inhibitors reduce mortality

CONSENSUS
Enalapril in severe HF

253 patients in NYHA class IV
Randomized to placebo/enalapril
From first patient to end of study 20 month
118 deaths

All Cause Mortality (%)

Placebo

Relative risk reduction = 27%

p=0.003

Months

0 2 4 6 8 10 12

Enalapril

Swedberg et al NEJM 1987
SOLVD Treatment Trial
All Cause Death

Cumulative incidence (%)

- Placebo
- Enalapril

Relative risk reduction = 16%
p = 0.0036

Number at risk
- Enalapril: 1285, 1127, 1010, 697, 526
- Placebo: 1284, 1085, 939, 669, 487

SOLVD Investigators NEJM 1991
ARB Trials

CHARM - Candesartan

**CHARM-Added: Primary outcome**
CV death or CHF hospitalisation

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1276</td>
<td>1176</td>
<td>1063</td>
</tr>
</tbody>
</table>

HR 0.85 (95% CI 0.75-0.96), p=0.011
Adjusted HR 0.85, p=0.010

Candesartan: 483 (37.9%)
Placebo: 538 (42.3%)

**Val-Heft: Combined All-Cause Mortality and Morbidity**

- 13.3% Risk Reduction
- P=0.009

- Have not consistently been shown to reduce mortality
- Reserved for those who are ACE intolerant or those who can take an ACE but not an MRA
Beta-blockers

- Reduce morbidity and mortality in stable patients with heart failure despite being on an ACE-I
- Used in addition to an ACE-I
- Start at low dose and uptitrate to maximum tolerated dose
- In those with acute decompensated heart failure, initiate only once patient is stable
Aldosterone inhibition

- Spironolactone or eplerenone are recommended in all patients with HFrEF (EF<35%) who remain symptomatic despite ACE-I or beta blocker.

- Reduced mortality and hospitalization.

- Renal function and Potassium should be checked regularly, especially on initiation.

**RALES**
Randomized ALdactone Evaluation Study

1663 patients, NYHA class III-IV, LVEF ≤0.35. ACE-i 95%, digoxin 73% and beta blockers 10.5%. Mean follow-up 24 months.

Pitt et al. NEJM 1999
Our patient

She was given:

- Lasix 40mg po bd for her congestion
- Enalapril 2.5mg po bd up-titrated to 5mg po bd
- Carvedilol 6.25 mg po bd

- Spironolactone 25mg po daily was added to provide symptom relief after a week
  - K and renal function was monitored

She remains symptomatic

NOW WHAT WOULD YOU DO?
### Dose recommendations

<table>
<thead>
<tr>
<th></th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE-I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 t.i.d.</td>
<td>50 t.i.d.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 b.i.d.</td>
<td>20 b.i.d.</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5.0 o.d.</td>
<td>20–35 o.d.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 o.d.</td>
<td>10 o.d.</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5 o.d.</td>
<td>4 o.d.</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 o.d.</td>
<td>10 o.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 b.i.d.</td>
<td>25 b.i.d.</td>
</tr>
<tr>
<td>Metoprolol succinate (CR/XL)</td>
<td>12.5–25 o.d.</td>
<td>200 o.d.</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>1.25 o.d.</td>
<td>10 o.d.</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4–8 o.d.</td>
<td>32 o.d.</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 b.i.d.</td>
<td>160 b.i.d.</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 o.d.</td>
<td>150 o.d.</td>
</tr>
<tr>
<td><strong>MRAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 o.d.</td>
<td>50 o.d.</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 o.d.</td>
<td>50 o.d.</td>
</tr>
<tr>
<td><strong>ARNI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>49/51 b.i.d.</td>
<td>97/103 b.i.d.</td>
</tr>
<tr>
<td><strong>If-channel blocker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5 b.i.d.</td>
<td>7.5 b.i.d.</td>
</tr>
</tbody>
</table>

Slowly up-titrare to the maximum dose that is tolerated by the patient.
• Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality
• With each acute event, myocardial injury may contribute to progressive LV dysfunction

LV: left ventricular
Add MR antagonist\textsuperscript{d,e} (up-titrate to maximum tolerated evidence-based dose)

- **Yes**
  - Still symptomatic and LVEF \(\leq 35\%\)
    - **Yes**
      - Able to tolerate ACEI (or ARB)\textsuperscript{f,g}
        - ARNI to replace ACE-I
      - Sinus rhythm, QRS duration \(\geq 130\) msec
        - Evaluate need for CRT\textsuperscript{i,j}
      - Sinus rhythm, \(HR \geq 70\) bpm
        - Ivabradine
    - **No**
      - These above treatments may be combined if indicated

- **No**
  - Resistant symptoms
    - **Yes**
      - Consider digoxin or H-ISDN or LVAD, or heart transplantation
    - **No**
      - No further action required

GET HELP
# Cardiac Resynchronization Therapy Indications

**Recommendations for cardiac resynchronization therapy implantation in patients with heart failure**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>CRT is contra-indicated in patients with a QRS duration &lt; 130 msec.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
Ivabradine

- Slows heart rate by inhibiting the $I_f$ channel in sinus node

- Reduced endpoint of mortality and hospitalization in those with LVEF <35%, in SR, on OMT including a betablocker with a HR still >70

SHIFT Trial
**Figure 3.** Kaplan–Meier curves for primary end point (A) and expanded composite (B), according to treatment group. (HR and corresponding P value are from the Cox model adjusted for region). CI indicates confidence interval; and HR, hazard ratio.

| ARNI | PARADIGM-HF<sup>167</sup> | Sacubitril/valsartan (<i>n</i> = 4187) vs enalapril (<i>n</i> = 4212). | NYHA II–IV, LVEF ≤40% (amended to LVEF ≤35%), BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or if HF hospitalization within recent 12 months BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL. | 2.3 y | Composite of death from cardiovascular causes or a first HF hospitalization reduced by 20% (22% vs 27%, <i>P</i> < 0.001). | Reduction in all-cause mortality by 16% (<i>P</i> < 0.001) and cardiovascular mortality by 20% (<i>P</i> < 0.001). Reduction in HF hospitalization rate by 21% (<i>P</i> < 0.001). |

Add MR antagonist\textsuperscript{d,e} (up-titrate to maximum tolerated evidence-based dose)

- **Yes**
  - Still symptomatic and LVEF ≤35%
    - **Yes**
      - Able to tolerate ACEI (or ARB)\textsuperscript{f,g}
        - ARNI to replace ACE-I
      - Sinus rhythm, QRS duration ≥130 msec
        - Evaluate need for CRT\textsuperscript{i,j}
      - Sinus rhythm, HR ≥70 bpm
        - Ivabradine
    - **No**
      - No further action required

- **No**
  - GET HELP

**These above treatments may be combined if indicated**

- **Yes**
  - Resistant symptoms
    - Consider digoxin or H-ISDN or LVAD, or heart transplantation

- **No**
  - No further action required

Consider reducing diuretic dose
# EF classification of heart failure

Table 3.1  Definition of heart failure with preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
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<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Symptoms ± Signs³</td>
<td>Symptoms ± Signs³</td>
<td>Symptoms ± Signs³</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>1. Elevated levels of natriuretic peptides⁵; 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).</td>
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</tr>
</tbody>
</table>
Iron deficiency is common in heart failure. It is associated with a worse prognosis. Two randomized controlled trials (RCTs) showed improvement in exercise capacity and reduced heart failure hospitalizations. Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life.
• HF is a life threatening disease!

• Prognosis is guarded with therapy

Adherence to guideline therapy recommendations improves outcomes – includes up-titrating to target dosage of therapy
Take home messages

- The diagnosis of heart failure remains a clinical diagnosis
  - Natriuretic biomarker testing is a useful rule-out test if unsure of diagnosis

- ACE-inhibitors, beta-blockers and mineralocorticoid antagonists remain the mainstay of treatment

- Remember to up-titrate to maximum doses

- Do refer if no improvement on these for evaluation for more specialized therapies including newer drugs and device therapy
The End