<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Servier, Bayer, Roche Boehringer Ingelheim</th>
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<tr>
<td>Speaker’s bureau:</td>
<td>Servier, Bayer, Roche Boehringer Ingelheim</td>
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<td>Research grant:</td>
<td>Servier, Boehringer Ingelheim, Novartis, Roche</td>
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<td>Advisory Board:</td>
<td>Servier, Bayer, Roche Boehringer Ingelheim</td>
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</table>
Update on Heart Failure Pharmacological Treatment

Roberto Ferrari
ESC 2012 HF Guidelines (GL)

- Achievements
- Challenges
- Limitations
- Barriers
- Unmet needs
ESC 2012 HF GL: Achievements

• Well structured and clear
• Recommendations - and non - motivated
• Uncertainties highlighted
• Neutral / balanced position
Confirmation

- Diuretics
- A β-blocker and an ACE inhibitor as soon as possible for:
  - Better action on remodelling
  - More sudden death reduction
Main changes from 2008 GL

**Drugs**

- An expanded indication for mineralocorticoid receptor antagonists (MRAs).
- A new indication for the sinus node inhibitor ivabradine.
RALES: Spironolactone in severe HF (NYHA III – IV)

EPHESUS: Eplerenone in post MI and LVD or HT

EMPHASIS: Eplerenone in mild HF (NYHA II – III) on top of contemporary treatment
EMPHASIS
CV Death /HF hospitalsations

HR [95% CI] = 0.63 [ P < 0.0001

Eplerenone
Placebo

N Eng J Med 364;1 January 2011
Initial pharmacological therapy

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

No
If current in the sinus node: the determinant of HR
Objectives

To evaluate whether ivabradine improves outcomes in patients with:

1. Moderate to severe chronic HF
2. LV ejection fraction $\leq 35\%$
3. Sinus rhythm, HR $\geq 70$ bpm and
4. Recommended therapy
Primary composite endpoint

Ivabradine n=793 (14.5%PY)  Placebo n=937 (17.7%PY)

Cumulative frequency (%)

-18%

HR = 0.82 [95% CI 0.75-0.90]  p<0.0001

Months
Hospitalisation for heart failure

Ivabradine n=514 (9.4%PY)   Placebo n=672 (12.7%PY)

Cumulative frequency (%)  

HR = 0.74 [95% CI 0.66-0.83]  
p<0.0001  

- 26%
Effect of ivabradine on recurrence of hospitalizations for HF

Total-time approach

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hospitalization</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.75</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Second hospitalization</td>
<td>189 (6%)</td>
<td>283 (9%)</td>
<td>0.66</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Third hospitalization</td>
<td>90 (3%)</td>
<td>128 (4%)</td>
<td>0.71</td>
<td>p=0.012</td>
</tr>
</tbody>
</table>

Borer JS et al. Eur Heart J 2012;33(22):2813-20
Ivabradine is safe and effective in lowering the relative risk of the primary composite end point in both COPD and non-COPD patients.

Tavazzi L et al. *Eur Heart J.* 2013; 34, 652
Ivabradine can be used safely in patients with HF and LBBB.

Ivabradine did not increase major adverse effects in LBBB compared with placebo. The beneficial effect of treatment was directionally similar to that in patients without LBBB.

Effect of ivabradine on composite of CV death or HF hospitalization

![Graph showing the effect of ivabradine on composite of CV death or HF hospitalization.](image)

- **Placebo, renal dysfunction**: N at risk:
  - RD (pl): 799
  - RD (iva): 780
  - NRD (pl): 2293
  - NRD (iva): 2288

- **Ivabradine, renal dysfunction**: N at risk:
  - RD (pl): 706
  - RD (iva): 720
  - NRD (pl): 2119
  - NRD (iva): 2166

- **Placebo, no renal dysfunction**: N at risk:
  - RD (pl): 612
  - RD (iva): 612
  - NRD (pl): 1847
  - NRD (iva): 1963

- **Ivabradine, no renal dysfunction**: N at risk:
  - RD (pl): 488
  - RD (iva): 489
  - NRD (pl): 1551
  - NRD (iva): 1662

- **Statistical significance**:
  - $P = 0.023$ (Placebo, renal dysfunction vs. Ivabradine, renal dysfunction)
  - $P < 0.001$ (Ivabradine, renal dysfunction vs. Placebo, renal dysfunction)
  - $P < 0.001$ (Ivabradine, renal dysfunction vs. Ivabradine, no renal dysfunction)
Pharmacological therapy – next step

- Still NYHA class II–IV?
  - Yes
  - LVEF ≤35%?
    - Yes
        - Sinus rhythm and HR ≥70 beats/min?
          - Yes
              - ADD ivabradine®
          - No
    - No
  - No
Main changes from 2008 GL

Devices and procedures

- Expanded indication for resynchronisation (CRT)
- New role of coronary revascularisation
- Recognition of the growing use of assist devices (VADs).
MADIT – CRT Study (2009)
Multicenter Automatic Defibrillator Implantation Trial

![Graph showing survival analysis with different risk groups and probabilities of survival](image)

**No. at Risk (Probability of Survival)**

<table>
<thead>
<tr>
<th></th>
<th>ICD only</th>
<th>CRT–ICD</th>
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</thead>
<tbody>
<tr>
<td>731</td>
<td>621 (0.89)</td>
<td>379 (0.78)</td>
</tr>
<tr>
<td>1089</td>
<td>985 (0.92)</td>
<td>651 (0.86)</td>
</tr>
<tr>
<td>173 (0.71)</td>
<td>279 (0.80)</td>
<td>58 (0.73)</td>
</tr>
</tbody>
</table>

**P < 0.001**
RAFT

Resynchronised / Defibrillation for Ambulatory Heart Failure Trial

CRT indications in 2012

- **NYHA class III, ambulatory IV:**
  
  LBBB QRS ≥120ms, LVEF ≤35% (rec IA)
  
  non-LBBB QRS ≥150ms, LVEF ≤35% (rec IIa A)

- **NYHA class II**
  
  LBBB QRS ≥ 130ms, LVEF ≤30% (rec IA)
  
  non-LBBB ≥ 150ms, LVEF ≤30% (rec IIa A)
CABG is recommended in patients with systolic HF, angina, left main stenosis or 2/3 vessel coronary disease but not in those with angina and without viable myocardium.

PCI may be considered as an alternative when patients are unsuitable for CABG.
ESC 2012 GL: challenges inconsistencies with the real world

- non reproducibility of the trials’ context: (Ex: issues in disease definitions and patient clinical profiles)
- drug target dose (optimal dose) vs target effect (optimal therapy)
- >60% stent (FDA) and >50% ICD/CRT devices are implanted of label
## Acute HF Surveys and Registries In-hospital outcome

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients n.</th>
<th>Age ys</th>
<th>Hospital stay (days)</th>
<th>In-hospital mortality %</th>
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<tbody>
<tr>
<td>OPTIMIZE HF</td>
<td>5751</td>
<td>72</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>IMPACT-HF</td>
<td>567</td>
<td>71</td>
<td>8</td>
<td>2.8</td>
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<tr>
<td>ADHERE</td>
<td>65000</td>
<td>72</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Goldberg</td>
<td>2604</td>
<td>79</td>
<td>4</td>
<td>5.1</td>
</tr>
<tr>
<td>European HFS 2</td>
<td>3580</td>
<td>70</td>
<td>9</td>
<td>6.7</td>
</tr>
<tr>
<td>Italian AHFS</td>
<td>2807</td>
<td>73</td>
<td>9</td>
<td>7.3</td>
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<tr>
<td>FINN-AKVA</td>
<td>620</td>
<td>75</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Rudiger</td>
<td>312</td>
<td>73</td>
<td>11.5</td>
<td>8</td>
</tr>
<tr>
<td>European HFS 1</td>
<td>11327</td>
<td>71</td>
<td>11</td>
<td>8.4</td>
</tr>
<tr>
<td>EFFECT</td>
<td>4031</td>
<td>76</td>
<td>-</td>
<td>8.9</td>
</tr>
<tr>
<td>Argentina Reg</td>
<td>2974</td>
<td>65-70</td>
<td>7-9</td>
<td>4-12</td>
</tr>
<tr>
<td>EFICA</td>
<td>599</td>
<td>73</td>
<td>15</td>
<td>27/43 (4weeks)</td>
</tr>
</tbody>
</table>
Target dose vs target effect

**Target dose:**
- defined in *(dated)* trials
- different background treatment
- by selected investigators
- other doses not tested

**Target effect:**
- evaluated by a marker of *individual* efficacy and safety
ESC 2012 GL: Limitations

• Trials, and consequently the Guidelines, are single disease-oriented
• Over the age of 65 comorbidity is normal
• Lack of prognostic profiles
• Full text is a “guide”
• Pocket format, posters are “prescriptive”
2012 GL - Comorbidities: gaps in evidence

- **Anaemia**: erythropoiesis-stimulating agents, iron?
- **Depression**: selective serotonin reuptake inhibitors, cognitive therapy?
- **Diabetes**: metformin, GLP-1 agonists/analogues, DPP IV inhibitors, SGLT-2 inhibitors?
- **Sleep-disordered breathing**: positive airways pressure therapies?
- **COPD/Asthma**: Beta-blockers/Beta 2-agonists?
ESC 2012 GL: Barriers from physicians

- Uniformed
- Unconvinced
- Forgotten
- Influenced by marketing
- Unwilling to accept “compulsory recommendations”
ESC 2012 GL: **Barriers from patients**

- Unconvinced of benefit
- Inadequately informed
- Fear of adverse reactions
- Costs
- Other treatment priorities
40-80% of information is immediately forgotten. Half of the information recalled is incorrect!

Both physicians and patients elaborate personal mindlines.
ESC 2012 GL: **Barriers from industry**

- High prices of new drugs
- Consumer advertising
- Effective marketing of inferior drugs
- Direct and indirect funding of physicians, organisations, patient groups etc.
It follows that...there are still several unmet needs

• Prevention of HF
• Comorbidities
• Correct use of drugs and devices
• Value of remote monitoring
Conclusion:

HF patient and healthcare journey

- Very complex
- Long lasting
- With several relapses
- A battle to win together
END