Cosa c’è di nuovo nelle LLGG e nella gestione del paziente con scompenso cardiaco

Maurizio Volterrani
IRCCS San Raffaele
Rome

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Treatment options for patients with chronic symptomatic systolic heart failure (NYHA class II-IV)
Increased heart rate in CHF

CIBIS II:
baseline HR and all-cause mortality


SHIFT:
baseline HR and CV mortality and HF hospitalization


Increase in risk by 3% per 1 bpm ↑, 16% per 5 bpm ↑
Heart rate in recent HF registries

- **IMPACT RECO III**: 1407 patients
  - HR ≤70 bpm: 54.6%
  - HR >70 bpm: 31%
  - HR >80 bpm: 22.5%

- **HF OUTCOME**: 3480 patients
  - HR ≤70 bpm: 53.4%
  - HR >75 bpm: 29.7%
  - HR >80 bpm: 17.2%

- **ESC PILOT HF**: 2450 patients
  - HR ≤70 bpm: 55.6%
  - HR >75 bpm: 33.7%
  - HR >80 bpm: 20.7%

*Courtesy of Prof Tavazzi
**Courtesy of Prof Maggioni*
Proportion of patients with chronic HF and with HR <70 or ≥70 bpm

Total population (3460 pts)

- <70 bpm: 53%
- ≥70 bpm: 47%

Treated with Beta Blockers (2763 pts 80%)

- <70 bpm: 52%
- ≥70 bpm: 48%

Not treated with Beta Blockers (697 pts 20%)

- <70 bpm: 40%
- ≥70 bpm: 60%

p<.0001

HR: mean±SD:
- Total population: 71±13
- Betablocker: 70±13
- NO betablocker: 73±13  p<.0001

Courtesy of Prof Maggioni
Heart rate awareness in patients with chronic stable heart failure.
Medication classes in those achieving and not achieving target heart rates

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>HR&lt; 70 bpm</th>
<th>HR≥ 70 bpm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>549</td>
<td>100%</td>
<td>373</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Beta-blocker usage**

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>491</td>
<td>89%</td>
<td>355</td>
<td>95%</td>
<td>136</td>
<td>76%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>At target BB dose</td>
<td>121</td>
<td>25%</td>
<td>81</td>
<td>23%</td>
<td>40</td>
<td>29%</td>
<td>ns</td>
</tr>
<tr>
<td>No target BB dose</td>
<td>370</td>
<td>75%</td>
<td>274</td>
<td>77%</td>
<td>96</td>
<td>71%</td>
<td>ns</td>
</tr>
<tr>
<td>Not on BB</td>
<td>58</td>
<td>11%</td>
<td>18</td>
<td>5%</td>
<td>40</td>
<td>23%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial

BB naive or 25% of guidelines approved dosage

n=2160

Mean AGE : 72,8 (5,5)

n=1277

60%

n=833

bisoprolol 10

out n=45

n=386

carvedilol 25x2

out n=49

n=396

PEP : reaching target dose and maintained it for at least 10 days
75.7% did not reached primary endpoint

Magnitude of HR reduction and outcomes in heart failure

Meta-regression of 23 beta-blocker HF trials involving 19,209 patients

Pooled mortality hazard ratio was 0.76 for an average HR reduction of 12 bpm

**Primary composite endpoint**

- Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)
  - HR = 0.82  \( p<0.0001 \)

**Hospitalization for heart failure**

- Ivabradine n=514 (9.4%PY) Placebo n=672 (12.7%PY)
  - HR = 0.74  \( p<0.0001 \)

**Death from heart failure**

- Ivabradine n=113 (1.9% PY) Placebo n=151 (2.6% PY)
  - HR = 0.74 [95% CI=0.58;0.94]  \( p=0.014 \)

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Fox K. Et al, Lancet 2010
Ivabradine Treatment in a Chronic Heart Failure Patient Cohort: Symptom Reduction and Improvement in Quality of Life in Clinical Practice

Proportion of patients with BNP levels ≤400 or >400 pg/mL from baseline to study end

Christian Zugck, Adv Ther (2014)
Ivabradine increases diastolic time by 6 min/h

content of interstitial collagen

![Graph showing content of interstitial collagen in sham, MI, and MI + IVA groups.](chart.png)
LV end-systolic volume index and outcome in the placebo group

Patients with primary composite endpoint, %

HR 1.62, p=0.04

LVESVI ≥ 59 mL/m²

LVESVI < 59 mL/m²

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESVI ≥59 mL/m²</td>
<td>0</td>
</tr>
<tr>
<td>LVESVI &lt;59 mL/m²</td>
<td>131</td>
</tr>
<tr>
<td>LVESVI &lt;59 mL/m²</td>
<td>132</td>
</tr>
</tbody>
</table>
Primary endpoint: change in LVESVI from baseline to 8 months

Left ventricular end-systolic volume index

Δ -5.8, P=0.0002

Δ - 7.0 ± 16.3

Δ - 0.9 ± 17.1

mL/m²

Baseline 8 months

Ivabradine (n=208)

Baseline 8 months

Placebo (n=203)
Secondary endpoint: change in LVEF from baseline to 8 months

\[ \Delta + 2.7, \ P=0.0003 \]

**Ivabradine** (n=204)  
Baseline: 32.3 ± 9.1  
8 months: 34.7 ± 10.2

**Placebo** (n=199)  
Baseline: 31.6 ± 9.3  
8 months: 31.5 ± 10.0
# Holter sub-study

<table>
<thead>
<tr>
<th>Event</th>
<th>Ivabradine (n=254)</th>
<th>Placebo (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 episode HR &lt;30 bpm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥ 1 episode HR &lt;40 bpm</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>RR &gt; 2.5 seconds</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>RR &gt; 3 seconds</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation/Flutter</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>AV block II or high-degree block</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>AV block III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Camm J. et al. Poster session 797; HF congress 2011.
Heart failure in real life: multiple profiles

The ESC Heart Failure Long-term Registry: 21 European countries, 7401 patients with CHF (2011-2013)

- HR ≥70 bpm
- Age ≥75 years
- NYHA III/IV
- COPD
- eGFR < 60 mL/min/1.73m²
- SBP < 110 mm Hg
- Diabetes

Primary composite endpoint and different levels of blood pressure

![Graph showing endpoint primary in relation to blood pressure levels]
Heart failure in real life: multiple profiles

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- HR ≥70 bpm
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Ivabradine improves outcomes independently of HF severity

Incidence of primary composite endpoint of cardiovascular death or hospitalization for heart failure in 712 severe HF patients (LVEF ≤20% and/or NYHA class IV) and 5973 less severe HF patients

16% RRR

18% RRR

P for interaction = 0.854

In severe HF and HR ≥75 bpm (n=272) Procoralan reduced CV death by 32% (p=0.034)
Ivabradine improves symptoms in daily practice

1956 patients with chronic heart failure, treated with BBs (79%), ACEI/ARB (83%), MRA (18%)

NYHA classification

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=1921)</th>
<th>1 month (n=1887)</th>
<th>4 months (n=1873)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA IV</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Signs of decompensation

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=1917)</th>
<th>1 month (n=1858)</th>
<th>4 months (n=1843)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Zugck C et al. ESC HF congress, 2013 Lisbon.
Kansas City Cardiomyopathy Questionnaire (KCCQ)

Self reported instrument with 23 items, ranging from 0 to 100 (higher score better HQoL)
Ivabradine Treatment in a Chronic Heart Failure Patient Cohort: Symptom Reduction and Improvement in Quality of Life in Clinical Practice

Quality of life of pts evaluated by EQ-5D score index and visual analog scale
Addition of Ivabradine to bisoprolol improves exercise capacity more than uptitration of bisoprolol.

Changes in physical activity (6-min walk test, meters)

- Bisoprolol 5 mg: 388 m
- Bisoprolol 5 mg + ivabradine: 446 m
- Bisoprolol 5 mg: 386 m
- Bisoprolol 5 mg + Bisoprolol 5 mg: 400 m

*p* = 0.001

Addition of ivabradine shortens carvedilol uptitration and improves exercise capacity in patients with CHF

Addition of ivabradine to carvedilol in patients with CHF resulted in a shorter β-blocker uptitration, higher final β-blocker dose, greater HR reduction, and better exercise capacity

Bagriy AE et al. J Am Coll Cardiol. 2013;61(10_S)
Change in exercise capacity

% change versus baseline

\[ \begin{align*}
\text{MVO2 Exercise cap} & : \text{Ivabradine} & \text{Carvedilol} & \text{Combination} \\
\text{6 MWT} & : \text{Ivabradine} & \text{Carvedilol} & \text{Combination}
\end{align*} \]

Patients improving at least 1 NYHA Class

Pts

\[ \begin{align*}
\text{Ivabradine} & : 78\% \\
\text{Carvedilol} & : 10\% \\
\text{Combination} & : 50\%
\end{align*} \]

Fatigue index

\[ \text{Fatigue index} = \frac{\text{work performed last repetition}}{\text{work performed first repetition}} \times 100 \]

Quality of Life - VAS

\[ \text{Score in VAS (cm)} \]

Volterrani M et al. *Int J Cardiol* 2011
Ivabradine Versus Beta-Blockers in Pts with Conduction Abnormalities or Left Ventricular Dysfunction Undergoing Cardiac Surgery

RR of ivabradine and combined therapy with ivabradine and metoprolol versus metoprolol for early postoperative AF, complete AV block/need for pacing and postoperative HF worsening

L. Iliuta, Cardiol Ther (2014)
Ivabradine Versus Beta-Blockers in Pts with Conduction Abnormalities or Left Ventricular Dysfunction Undergoing Cardiac Surgery

composite endpoint of 30-day mortality, in-hospital AF/arrhythmias, in-hospital AVblock/need for pacing, or in hospital HF worsening
Vicious circle induced by dobutamine-induced tachycardia

Ivabradine in cardiogenic shock to prevent tachycardia induced by dobutamine
Ivabradine control undesirable tachycardia induced by dobutamine in cardiogenic shock.
Effectiveness of the combination therapy with lisinopril, ivabradine and multivitamin suppl. in anthracycline-induced severe cardiotoxicity

C. De Gregorio, International Journal of Cardiology, 2014
EF ≤ 35%

ACE-i+Diuretics

IVABRADINE

SBP < 100 mmHg

SBP > 100 mmHg

βBLOCKERS

Intoll. βblocker

HR > 70 bpm

HAEMODINAMIC INSTABILITY
Pharmacological treatment of patients with chronic symptomatic systolic heart failure

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 ivabradine

No

No

No

No

ACE inhibitors occasionally cause worsening of renal function, hyperkalaemia, symptomatic hypotension, cough, and, rarely, angioedema. An ACE inhibitor should only be used in patients with adequate renal function (creatinine ≤ 221 μmol/L or ≤ 2.5 mg/dL or eGFR ≥ 30 mL/min/1.73 m²) and a normal serum potassium level (see Web Table 11).

Cardiac output and renal blood flow may initially decrease after initiation of β-blocker therapy, leading to hypotension and worsened renal function.

Spironolactone and eplerenone can cause hyperkalaemia and worsening renal function, which were uncommon in the RCTs, but may occur more frequently in ordinary clinical practice, especially in the elderly. Both should only be used in patients with adequate renal function and a normal serum potassium concentration; if either is used, serial monitoring of serum electrolytes and renal function is mandatory.

## Secondary prevention of CVD

Number needed to treat to prevent one event per 1 year (NNT-1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Event</th>
<th>NNT-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scandinavian Simvastatin Survival Study (4S)(^1)</td>
<td>Major coronary event (coronary death and nonfatal MI)</td>
<td>63 patients</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study on effect of captopril in patients with LVD after MI (SAVE)(^2)</td>
<td>Fatal and nonfatal MI</td>
<td>105 patients</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis of 82 randomized trials of beta-blockers after MI(^3)</td>
<td>Nonfatal MI</td>
<td>107 patients</td>
</tr>
<tr>
<td><strong>Ivabradine</strong></td>
<td>SHIFT study(^4)</td>
<td>26 patients</td>
</tr>
<tr>
<td></td>
<td>Death and Hosp. for HF</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Kjekshus J. *Am J Cardiol.* 1995;76:64C-68C.  
\(^3\) Fox K et al. *Lancet.* 2010
Conclusion 1

• In patients with HF Ivabradine reduces CV mortality, mortality for HF and HF hospitalization

• This beneficial effect is present in ischemic and in non-ischemic HF
Conclusion 2

• Beta-blockers improve prognosis but are often underused in clinical practise

• Ivabradine alone or in combination with β-blockers is more effective than β-blockers alone at improving exercise tolerance and quality of life in HF