Effects of heart rate reduction with ivabradine on left ventricular remodeling and function: results of the SHIFT echocardiography substudy

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Disclosures

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- The study was supported by Servier, France.
Cardiac remodeling is central to the pathophysiology of heart failure (HF) and is a prognostic factor in patients with HF.

Left ventricular (LV) enlargement and reduced ejection fraction are powerful predictors of outcomes in heart failure.

Therapeutic effects of drugs and devices on LV remodeling are associated with their longer-term effects on mortality.
SHIFT is a randomised, double-blind, placebo-controlled, multinational trial in 6505 pts with chronic HF, LVEF \( \leq 35\% \), sinus rhythm and heart rate \( \geq 70 \) bpm aiming to determine the effect of HR lowering with ivabradine on outcomes.

Patients were randomly allocated to ivabradine 5 mg bid or placebo and the dosage could be adjusted to 7.5 mg or 2.5 mg bid depending on heart rate (HR) and tolerability.

HR lowering with ivabradine led to an 18% reduction in the primary endpoint of CV death/HF hospitalization (P<0.0001).

Swedberg K et al. *Lancet*. 2010;376:875-885
Objective of the pre-specified echocardiography sub-study

To evaluate the effects of the $I_f$ inhibitor ivabradine on LV remodeling and function:

- **Primary endpoint**: the change in the LV end-systolic volume index (LVESVI) from baseline to 8 months

- **Secondary endpoints**: changes during the same interval in
  - LV end-diastolic volume index (LVEDVI)
  - LV end-systolic, end-diastolic volumes (LVESV, LVEDV)
  - LV ejection fraction (LVEF)
611 patients included from 89 centers in 21 countries

304 patients Ivabradine
- Excluded (N=96)
  - 52: Poor quality of echo recording
  - 19: No baseline and/or 8-month recording
  - 8: Non-matching biplane or 4-chamber views
  - 13: Withdrawn due to death
  - 4: Consent withdrawn

307 patients Placebo
- Excluded (N=104)
  - 52: Poor quality of echo recording
  - 15: No baseline and/or 8-month recording
  - 1: Non-matching biplane or 4-chamber views
  - 23: Withdrawn due to death
  - 13: Consent withdrawn

208 patients Ivabradine

203 patients Placebo

Median follow-up after 8-month echocardiogram: 16.1 months
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=304</th>
<th>Placebo N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Male, %</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Mean HF duration, years</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HF ischaemic cause, %</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>NYHA class II, %</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>121</td>
<td>119</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ivabradine N=304</td>
<td>Placebo N=307</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>ARB, %</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Diuretic (excludes antialdo), %</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Digitalis, %</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Devices, %</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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

Number of patients at risk:

- LVESVI ≥59 mL/m²: 131
- LVESVI <59 mL/m²: 132

Months: 0 6 12 18 24 30

- 0: 131
- 6: 104
- 12: 93
- 18: 84
- 24: 38
- 30: 13

- 0: 132
- 6: 118
- 12: 107
- 18: 100
- 24: 49
- 30: 19
Primary endpoint: change in LVESVI from baseline to 8 months

Left ventricular end-systolic volume index

Δ - 7.0 ± 16.3

Δ - 0.9 ± 17.1

Ivabradine (n=208)

Baseline 8 months

Placebo (n=203)

Baseline 8 months

Δ - 5.8, P=0.0002

65.2±29.1 58.2±28.3

63.6 ±30.1 62.8 ±28.7

D - 7.0 ± 16.3

D - 0.9 ± 17.1
Relative change in LVESVI from baseline to 8 months

- Ivabradine: 38%, 49%, 27%
- Placebo: 25%, 48%, 13%

P = 0.005

≤-15%  >-15% to <+15%  ≥+15%
Secondary endpoint: change in LVEDVI from baseline to 8 months

Left ventricular end-diastolic volume index

\[ \Delta -5.5, \ P=0.0019 \]

Ivabradine (n=204)

Baseline: 93.9 ± 32.8 mL/m^2

8 months: 85.9 ± 30.9 mL/m^2

\[ \Delta -7.9 \pm 18.9 \]

Placebo (n=199)

Baseline: 90.8 ± 33.1 mL/m^2

8 months: 89.0 ± 31.6 mL/m^2

\[ \Delta -1.8 \pm 19.0 \]
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>M8 - baseline</th>
<th>Δ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVESV, mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine (N=208)</td>
<td>123.8 ± 55.6</td>
<td>-13.0 ± 31.6</td>
<td>-11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (N=203)</td>
<td>122.2 ± 59.8</td>
<td>-1.3 ± 32.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LVEDV, mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine (N=204)</td>
<td>178.4 ± 63.4</td>
<td>-14.7 ± 36.4</td>
<td>-10.9</td>
<td>0.0014</td>
</tr>
<tr>
<td>Placebo (N=199)</td>
<td>174.7 ± 67.6</td>
<td>-2.9 ± 36.8</td>
<td></td>
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</tr>
</tbody>
</table>
**Secondary endpoint: change in LVEF from baseline to 8 months**

Left ventricular ejection fraction

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 months</th>
<th>Δ (Ivabradine)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivabradine</strong> (n=204)</td>
<td>32.3±9.1</td>
<td>34.7±10.2</td>
<td>2.4±7.7</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Placebo</strong> (n=199)</td>
<td>31.6±9.3</td>
<td>31.5±10.0</td>
<td>-0.1±8.0</td>
<td></td>
</tr>
</tbody>
</table>
Absolute change in LVEF from baseline to 8 months

<table>
<thead>
<tr>
<th>Category</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤-5%</td>
<td>18%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>&gt;-5% to &lt;+5%</td>
<td>46%</td>
<td>51%</td>
<td>0.003</td>
</tr>
<tr>
<td>≥+5%</td>
<td>36%</td>
<td>23%</td>
<td></td>
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</tbody>
</table>
### Summary of changes in HR, LV end-systolic/end-diastolic volume indexes

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=304</th>
<th>Placebo N=307</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in resting HR at 8 months, bpm</td>
<td>-14.7</td>
<td>-5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LVESVI at 8 month, mL/m²</td>
<td>-7.0</td>
<td>-0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in LVEDVI at 8 month, mL/m²</td>
<td>-7.9</td>
<td>-1.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Limitations

- Analysis not designed to clarify the time-course of treatment effects and could not evaluate the acute effect of ivabradine.
- The beta-blocker dosage was similar to other recently published data but higher doses can affect LVEF.
- Data recorded in patients with HR ≥ 70 bpm, in sinus rhythm and predominantly in men, which may limit generalisation.
- One third of patients were excluded from the analysis, usually for reasons related to the quality or collection of recordings.
Conclusions

- Heart rate reduction with ivabradine reverses left ventricular remodeling in patients with heart failure and LV systolic dysfunction:
  - Marked reductions of LV volumes
  - Significant improvement of LV ejection fraction

- These results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy
Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Jean-Claude Tardif¹*, Eileen O’Meara¹, Michel Komajda², Michael Böhm³, Jeffrey S. Borer⁴, Ian Ford⁵, Luigi Tavazzi⁶, and Karl Swedberg⁷, on behalf of the SHIFT Investigators