Effect on sudden death of heart failure treatment started with bisoprolol followed by enalapril, compared to the opposite order: Results of the randomized CIBIS III trial

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For the CIBIS III committees and investigators
CIBIS III – Rationale

- In patients with newly diagnosed CHF, mortality high during the early phase
- Mainly due to sudden death
- β-blockers reduce sudden death more effectively than ACEi
CIBIS III – Rationale

- The sympathetic system activated early in the disease
- The RAAS triggered at a later stage
- From the pathophysiological point of view reasonable to start treatment with a betablocker
- Important to investigate if β-blockade or ACEi should be initiated first in CHF
CIBIS III - Study design

Bisoprolol-first (o.d.)

- First up-titration
- Maintenance period
- Second up-titration
- Second maintenance period

Enalapril b.i.d.

- First up-titration
- Maintenance period
- Second up-titration
- Second maintenance period

Bisoprolol o.d.

Enalapril b.i.d

* = visits

CIBIS III – Patients

• Age \( \geq 65 \) years
• Mild to moderate CHF (NYHA class II-III)
• LVEF \( \leq 35\% \)
• Stable CHF since \( \geq 7 \) days
• Essentially without prior treatment with \( \beta \)-blockers, ACE inhibitors and angiotensin-receptor blockers
## Baseline data

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol-first (n=505) Mean / n</th>
<th>% / SD</th>
<th>Enalapril-first (n=505) Mean / n</th>
<th>% / SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Males</td>
<td>72.4 / 333</td>
<td>5.8 / 65.9</td>
<td>72.5 / 356</td>
<td>5.7 / 70.5</td>
</tr>
<tr>
<td>NYHA Class II/III</td>
<td>245 / 260</td>
<td>48.5 / 51.5</td>
<td>250 / 255</td>
<td>49.5 / 50.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>28.8 / 4.8</td>
<td>28.8 / 5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm) BP (mm Hg)</td>
<td>78.8 / 134</td>
<td>13.8 / 17 / 10</td>
<td>79.5 / 134</td>
<td>13.2 / 17 / 10</td>
</tr>
<tr>
<td>Etiology</td>
<td>CAD</td>
<td>309 / 61.2</td>
<td>321 / 63.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>197 / 39.0</td>
<td>172 / 34.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>95 / 18.8</td>
<td>113 / 22.4</td>
<td></td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>Loop diuretics</td>
<td>430 / 85.1</td>
<td>421 / 83.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aldo rec blockers</td>
<td>361 / 71.5</td>
<td>338 / 66.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac glycosides</td>
<td>166 / 32.9</td>
<td>155 / 30.7</td>
<td></td>
</tr>
</tbody>
</table>

Bisoprolol-first significantly non-inferior to enalapril-first if upper limit of 95% CI below hazard ratio (HR) 1.17, P<0.025. (=RR 1.125, AR +5%)

In the PP population, bisoprolol-first was not significantly non-inferior to enalapril-first

Mean follow-up 1.22 years

In the ITT population, bisoprolol-first was significantly non-inferior to enalapril-first

CIBIS III – sudden death

Study objective:
To compare initiation of treatment in patients with CHF with the $\beta_1$-selective $\beta$-blocker bisoprolol (to which enalapril was subsequently added) to a regimen beginning with enalapril (to which bisoprolol was subsequently added) in terms of the effect on sudden death
A sudden death was a cardiovascular death:

- Occurring within 1 hour of the occurrence of new symptoms or without symptoms.
- Occurring at night during sleep without other cause.
- Occurring in odd places without other cause.
- Occurring within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death.
- Which was unwitnessed, in the absence of pre-existing progressive circulatory failure or other causes of death.
CIBIS III – sudden death

Prespecified time points of analysis:
• End of monotherapy phase
  (157-230 days post randomization, mean 162 days)
• After the first year (minimum time of follow-up for all patients)
• Study end
Sudden death - monotherapy phase

Bisoprolol-first vs enalapril-first:
8 versus 16 sudden deaths;
HR 0.50; 95% CI 0.21-1.16; P=0.107
1.6% ARR

% sudden death

Enalapril-first
Bisoprolol-first

N at risk
0 1 2 3 4 5 6
0 1 2 3 4 5 6

Time (months)
Sudden death – first year

Bisoprolol-first vs enalapril-first:
16 versus 29 sudden deaths;
HR 0.54; 95% CI 0.29-1.00; P=0.049
2.6% ARR
Sudden death – entire study

Bisoprolol-first vs enalapril-first:
29 versus 34 sudden deaths;
HR 0.84; 95% CI 0.51-1.38; P=0.487
All cause mortality

Monotherapy
B-first vs E-first: 23 vs 32 pts;
HR 0.72; 95% CI 0.42-1.24; P=0.24

First year
B-first vs E-first: 42 vs 60 pts;
HR 0.69; 95% CI 0.46-1.02; P=0.06

Entire study
65 vs 73 pts; HR 0.88;
95% CI 0.63-1.22; P=0.44
## Patients with event-related hospitalizations

<table>
<thead>
<tr>
<th></th>
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<th>Enalapril-first n=505</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MONOTHERAPY PHASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>84</td>
<td>16.6</td>
</tr>
<tr>
<td>CV hospitalizations</td>
<td>58</td>
<td>11.5</td>
</tr>
<tr>
<td>Worsening of CHF hospitalizations</td>
<td>39</td>
<td>7.7</td>
</tr>
<tr>
<td>Non-CV hospitalizations</td>
<td>26</td>
<td>5.1</td>
</tr>
<tr>
<td>FIRST YEAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>117</td>
<td>23.1</td>
</tr>
<tr>
<td>CV hospitalizations</td>
<td>82</td>
<td>16.2</td>
</tr>
<tr>
<td>Worsening of CHF hospitalizations</td>
<td>49</td>
<td>9.7</td>
</tr>
<tr>
<td>Non-CV hospitalizations</td>
<td>35</td>
<td>6.9</td>
</tr>
<tr>
<td>ENTIRE STUDY DURATION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>131</td>
<td>25.9</td>
</tr>
<tr>
<td>CV hospitalizations</td>
<td>91</td>
<td>18.0</td>
</tr>
<tr>
<td>Worsening of CHF hospitalizations</td>
<td>53</td>
<td>10.5</td>
</tr>
<tr>
<td>Non-CV hospitalizations</td>
<td>40</td>
<td>7.9</td>
</tr>
</tbody>
</table>

CV, cardiovascular; CHF, chronic heart failure. All between-group differences were non-significant.
At study end, for both study drugs the dose was significantly higher if it was the first initiated drug, compared to if it was the second drug.
Limitations

• The study was not designed to primarily assess sudden death. Consequently it was not adequately powered in this respect.

• The length of the monotherapy phase may be questioned from a clinical point of view. It does not constitute a recommendation.
Summary

• In patients $\geq 65$ years of age with mildly or moderately symptomatic, stable CHF and LVEF $\leq 35\%$, initiating CHF therapy with bisoprolol was significantly superior to initiating therapy with enalapril in reducing sudden death during the first year.

• The hazard reduction was similar at the end of the monotherapy phase, although not statistically significant.

• The difference between the two treatment strategies leveled out after more than six months of combined treatment.
Summary

• The early reduction in sudden death for bisoprolol-first was accompanied by a non-significant reduction in early all-cause death of similar magnitude, indicating that this strategy does not simply alter the mode of death to death of progressive CHF or other non-sudden death.

• The early reduction of sudden death was balanced by a non-significant increase in hospitalizations for worsening of CHF.
Conclusions

• These results indicate the need for early treatment with a betablocker in patients with CHF, especially to reduce early sudden death.

• A possible increased risk of early hospitalization for worsening of CHF has to be considered in this regard.
Thank you!

Cardiac Insufficiency Bisoprolol Study III