The cardiac insufficiency bisoprolol study II
The CIBIS-II Trial

Study Type: POEM
Study Duration: follow-up mean 1.3 years
Patients: 1901 patients, mean age 61 years (22-80), 80/20-male/female, no race mentioned, 83%/17%-Class III/IV
Trial Design: Double-blinded, placebo-controlled, randomized, intention-to-treat, multicenter (274 hospitals, 18 countries), placebo versus bisoprolol at 1.25 mg with titration up to 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg as tolerated, there was freedom for the physician to drop doses of other drugs before reduction of study drug
Purpose: Does bisoprolol reduce all-cause mortality in patients with Class III/IV HF?
Inclusion: Heart failure, measured EF < 35% within 6 weeks, symptoms HAD to include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, with or without edema, fatigue, class III/IV NYHA, patients had to be stable, 3 months from an MI or unstable angina, no change in drug therapy within 2 weeks of randomization, patient HAD to be on ACE inhibitor, and diuretic, but they could be on other drugs as well
Exclusion: uncontrolled HTN, a MI, stroke, unstable angina within 3 months, a CABG within 6 mths, advanced heart block except those treated by pacemaker, reversible COPD, SBP < 100, HR < 60, significant renal dz, drug or alcohol abuse, patients on CCB, inotropic agents except digoxin, antiarrhythmics except amiodarone
Outcome Events: Primary endpoint: All-cause mortality
Secondary endpoints: all-cause hospitalization, cardiovascular mortality, CV hospital admissions, permanent premature treatment withdrawals

1. Are the results valid?
   * randomized? yes
   * double-blinded? yes
   * placebo run in? no
   * were groups similar? yes
   * all patients accounted for? yes

2. What were the results?

<table>
<thead>
<tr>
<th>Primary endpoint:</th>
<th>Placebo</th>
<th>bisoprolol</th>
<th>RRR</th>
<th>ARR</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>17%</td>
<td>12%</td>
<td>35%</td>
<td>5</td>
<td>&lt;.0001</td>
<td>20</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalizations</td>
<td>39%</td>
<td>33%</td>
<td>20%</td>
<td>6</td>
<td>&lt;.0006</td>
<td>17</td>
</tr>
<tr>
<td>All CV deaths</td>
<td>12%</td>
<td>9%</td>
<td>29%</td>
<td>3</td>
<td>&lt;.005</td>
<td>33</td>
</tr>
<tr>
<td>Combined endpoints</td>
<td>35%</td>
<td>29%</td>
<td>21%</td>
<td>6</td>
<td>&lt;.0004</td>
<td>17</td>
</tr>
<tr>
<td>Treatment withdrawals</td>
<td>15%</td>
<td>15%</td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>6%</td>
<td>4%</td>
<td>44%</td>
<td>2</td>
<td>&lt;.0011</td>
<td>50</td>
</tr>
<tr>
<td>Unknown cause of death</td>
<td>4%</td>
<td>2%</td>
<td>55%</td>
<td>2</td>
<td>&lt;.0012</td>
<td>50</td>
</tr>
<tr>
<td>Hospital admit for worse heart failure</td>
<td>18%</td>
<td>12%</td>
<td>36%</td>
<td>6</td>
<td>&lt;.0001</td>
<td>17</td>
</tr>
</tbody>
</table>

Not significant: pump failure, MI, Other cardiovascular, Non-cardiovascular death

3. Will the results help me?
   * trail was stopped early due to mortality effect
   * treatment effect did not differ between countries
   * more admissions to the hospital for stroke in the bisoprolol group (31 vs 16, p=0.04, ARR = 1.1, NNH = 91)
   * 63% of patients in the bisoprolol group reach the 10 mg dose, 20% stayed at 5 mg
   * benefit remains despite the kind of heart failure
   * the best effect was seen in the patients with NYHA class III HF
   * sudden death reduction reflects antiarrhythmic activity of bisoprolol
   * B1-selective agents are effective
   * bisoprolol cost: Zebeta 5 mg and 10 mg = $1.00/dose, both strengths
   * there is no Zebeta 1.25 mg dose in the USA, one strength of Ziac contains 2.5 mg bisoprolol + 6.25 mg HCTZ

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