Beta - adrenoblockers in the treatment of arterial hypertension and CHF

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HFA ESC Congress, Belgrade, 21 May 2012
EPOCH - CHF

Relative risk of development of CHF (by Framingham criteria)

Prevalence of CHF by Framingham criteria = 4.5% (RF)
Increased risk of CV complications due to AH (>140/90 mm Hg)

**Framingham Heart Study**

CV complications due to BP levels (n=4559) 35-64 years; 36-years of F-U

Relative Risk

<table>
<thead>
<tr>
<th>CAD / AMI</th>
<th>STROKE</th>
<th>P V D</th>
<th>C H F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>22.7</td>
<td>11.8</td>
<td>9.1</td>
<td>3.8</td>
</tr>
<tr>
<td>11.8</td>
<td>9.1</td>
<td>3.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Relative Risk**

- **Males**: 2.0
- **Females**: 2.2

**Risk**

- **Males**: 22.7
- **Females**: 11.8

**Frequency**

- **Males**: 3.3
- **Females**: 2.4

**Controls**

**Hypertensives**

Influence of antihypertensive therapy: BAB (BAB + Diuretics) on the risk of CV complications (CHF)

CHF: -52%
STROKE: -38%
CV death: -21%
AMI: -16%

All changes are significant

Hebert P., Arch Intern Med, 1993; 153:978-981
Moser M et al., J Am Coll Cardiol, 1996; 27: 1214 - 1218
Relative Risk of CHF With BB as a Function of SBP Difference Between Treatment Modalities at Study End

Bangalore, S. et al. J Am Coll Cardiol 2008;52:1062-1072
Antihypertensive efficacy (% of pts at goal <140/90 mm Hg) after treatment with different beta-blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>% of pts at goal &lt;140/90 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaxolol</td>
<td>40 mg</td>
<td>73</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>100 mg</td>
<td>59</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100 mg</td>
<td>51</td>
</tr>
<tr>
<td>Talinolol</td>
<td>100 mg</td>
<td>56</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10 mg</td>
<td>83</td>
</tr>
</tbody>
</table>

Olbinskay L.I. at al., Kardiologia, 2002;41:56
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>92–98</td>
</tr>
</tbody>
</table>
Relation between plasma norepinephrine concentration and risk of death in CHF patients

Proportion of all cause deaths

Months of follow-up

P<0.0001

NE > 900 pg/ml
NE = 600 - 900 pg/ml
NE < 600 pg/ml

J.Cohn et al., 1984
Survival of patients with DCMP and CHF

First analysis of BAB influence on mortality in CHF

Digitals + Diuretics

Digitals + Diuretics + BAB

NO ACEI!

K. Swedberg et al., Lancet, 1979

Waagstein F., Hjalmarsson A., Varnauskas E., Wallentin I.
Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy.
Br. Heart J., 1975: 37, 1022-1026
Moscow study with BAB in CHF (1990-93)

Restoration of LV pump function (via increase LVEF and CO) by the time of administration of metoprolol in CHF (no ACEI!)

Initial drop of CO due to negative inotropic effect of BAB (up to first 2 weeks)

n=60; NYHA=1,83

V.Mareev et al., ESC congress. Nice, 1993
Bisoprolol effects on myocardial viability in CHF (by equilibrium radionuclide scintigraphy)

BEFORE treatment

6 months

- Akinetic (necrosis) - Normokinetic (alive) - Hypokinet (Hybernation)

Lopatin YM et al., Serdechnaya Nedostatechnost, 2000
Bisoprolol dose titration in CIBIS - II trial to avoid CHF escalation

Start with 1,25 and stepwise increase every 2 weeks (or even 4 weeks) only in stable clinical situation and BP > 90/60 mm Hg.

B- CONVINCE trial
Possibility to keep BAB treatment even in acute worsening of CHF

![Graph showing heart rate and blood pressure changes over time for patients taking BAB or not taking BAB.]

**Table 3 Clinical events**

<table>
<thead>
<tr>
<th></th>
<th>Keep BB, n = 69</th>
<th>Stop BB, n = 78</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durations (days)</td>
<td>11.5 ± 8.3</td>
<td>10.4 ± 9.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Median, range</td>
<td>9 (1–50)</td>
<td>8 (1–62)</td>
<td></td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>1 (HF)</td>
<td>2 (HF)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine (n)</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>After 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>6 (9)</td>
<td>6 (8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Rehospit, n (%)</td>
<td>27 (40)</td>
<td>36 (47)</td>
<td>0.43</td>
</tr>
<tr>
<td>For HF</td>
<td>15 (22)</td>
<td>24 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>For arrhythmia</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>1</td>
</tr>
<tr>
<td>Receiving BB, n (%)</td>
<td>61 (90)</td>
<td>58 (76)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Rehospit, rehospitalization; HF, heart failure; BB, beta-blocker.

Jondeau G et al., European Heart Journal (2009) 30, 2186–2192
Relation between decrease of HR and improving survival in 12 RCI with BAB (post MI and/or CHF)

$\downarrow$ HR by 10 beats/min $\rightarrow$$\downarrow$ risk of all-cause death by 26%

$\Delta$ HR (beats/min)

P < 0.001

BAB

CCB

Cucherat et al. ESC 2006
Absence of parallelism in HR reduction and clinical effects of BAB in the treatment of patients with CHF

Treatment with BAB is not easy, needed accurate dose titration to avoid CHF worsening, BP drop, bradicardia + conduction disturbances and clinical effects appears months after start of therapy and decrease of HR

Mareev V. et al., Cardiology, 1999
LVEF dynamics during long-term treatment of CHF patients with bisoprolol (n=54)
Double-Bind placebo control trial (Substudy of CIBIS-II)

Mareev V. et al., Cardiology, 1999
Neuro-hormonal activation in CHF and possibilities of treatment (interplay between RAAS and SNS)

LVH, ischemia, hybernation, arrhythmia, cardiac remodeling: fibrosis, apoptosis, necrosis + Sodium and water retention

Development (Progression) of CHF
Dynamics of SNS (NE level) and RAAS (aldosterone concentration) activity in patients with CHF treated by bisoprolol (n=54) Double-Bind placebo control trial (Substudy of CIBIS-II)

**NE, pg/ml**

- **ISX**: 454, 521, 634
- **6 мес**: 482, 490, 528
- **12 мес**: 220, 200, 173

**Aldosterone, pg/ml**

- **ISX**: 200, 190, 200
- **6 мес**: 220, 200, 173
- **12 мес**: 200, 190, 91

*Mareev V. et al., Cardiology, 1999*
Decreases of total mortality in BAB trials in CHF

- Carvedilol (CAPRICORN) -31
- Metoprolol (MERIT-HF) -34
- Bisoprolol (CIBIS II) -34
- Bucindolol (BEST) -18
- Carvedilol (COPERNICUS) -35
- Nebivolol (SENIORS) -12

>70 years !!!

Рекомендации
Национальные рекомендации ВНОК И ОССН по диагностике и лечению ХСН (третий пересмотр)
Утверждены конференцией ОССН 15 декабря 2009 года

Комитет по подготовке текста:
Мареев В.Ю., Агеев Ф.Т., Арutyunov G.П., Коротеев А.В., Ревишвили А.Ш.
CIBIS - II

Main end-points of the study: changes in mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>-34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV</td>
<td>-29</td>
<td>0.0049</td>
</tr>
<tr>
<td>CHF</td>
<td>-26</td>
<td>0.17</td>
</tr>
<tr>
<td>Sudden</td>
<td>-44</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

CIBIS - II
Calculations of NNT and saving life figures for treatment of clinically relevant CHF by bisoprolol

🌟 If one will treat 1000 patients (CHF II-IV, LVEF < 35%) during one year he can prevent:

- 39 deaths (20 from them sudden)
- 43 Hospitalization (40 due to worsening CHF)

🌟 To save one life you need to treat with bisoprolol during one year:

- 25 patients with CHF (NYHA = III-IV)

*CIBIS II investigators, Lancet, 1999, v.353, p. 9-13*
Meta-analysis of BAB effects on mortality in patients with CHF (23 RCT, 19,209 pts)

BAB dose have no connection with prognosis (p=0.69)

↓ of HR on every 5 beats/min

Lead to ↓ of death in CHF pts

By 18% [95 CI 6-29%]
CIBIS - II
Mortality depending on the doses of BAB used

**Bisoprolol**
- Lowest doses: 1.25-3.75 mg
- Medium dose: 5 -7.5 mg
- Highest doses: 10 mg

**Placebo**
- Lowest doses: 1.25-3.75 mg
- Medium dose: 5 -7.5 mg
- Highest doses: 10 mg

**Risk of death:**

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Medium</td>
<td>0.59 (0.32-0.74)</td>
<td>0.76 (0.54-1.09)</td>
</tr>
<tr>
<td>Highest</td>
<td>0.30 (0.19-0.46)</td>
<td>0.28 (0.20-0.40)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.009</td>
<td>0.059</td>
</tr>
</tbody>
</table>

**Risk reduction in bisoprolol vs placebo:**
- Lowest doses: -36% (95% CI = 0.47 –0.89)*
- Medium doses: -68% (95% CI = 0.21- 0.50)*
- Highest doses: -39% (95% CI = 0.41- 0.91)*
CIBIS - III
Design of the study (free choice of the first medications)

Weeks

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36

**STEP 2**
Bisoprolol 1/day + Enalapril 2/day

**STEP 2**
Enalapril 2/day + Bisoprolol 1p/cut

End of the study: 3 years
CIBIS - III
Primary end-point: Death + hospitalizations

B/E vs E/B
163 vs 165 pts
OP 0.97
(95% CI 0.78-1.21)
Not worse P=0.046

3% Rsk Reduction

Willenheimer R. et al., Circulation, 2005:112; 2426-2435
CIBIS - III
Number of sudden death by the end of monotherapy phase

% sudden death

B/E vs E/B
8 vs 16 pts
OP 0.50
(95% CI 0.21-1.16)
P=0.107

50% RRR

Enalapril

Bisoprolol

Number of sudden death by the end of monotherapy phase

Число случаев

505 488 467 454 444 430 251

Willenheimer R. et al., Circulation, 2005:112; 2426-2435
### CIBIS – III: Subgroups analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroups</th>
<th>BAB first better</th>
<th>ACEI first better</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>II, III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>жен, муж</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&gt; years</td>
<td>( \leq 72 ), &gt;72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF %</td>
<td>&lt;28, ( \geq 28 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>да, нет</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperension</td>
<td>да, нет</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>&lt;80, ( \geq 80 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>( \leq 140 ), &gt;140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>( \leq 11.5 ), &gt;11.5-16, &gt;16, ( &gt;16 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (ml/min)</td>
<td>( \leq 60 ), ( \geq 80 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycosdes</td>
<td>да, нет</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ P = 0.001 \]

*Willenheimer R. et al., Circulation, 2005:112; 2426-2435*
Survival of pts with CHF (NYHA) II-IV according to treatment with neurohormonal blockers
(30 years retrospective analysis of Moscow study)

Beenkov YN & Mareev VV, Cardiologia; 2008
Independent predictors of survival in CHF pts (NYHA II-IV), n=835

Multifactorial proportional analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Beta-coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAB therapy</td>
<td>-0.6120</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low SBP</td>
<td>-0.0114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA</td>
<td>0.3614</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrates therapy</td>
<td>0.3541</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.0084</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Beenkov YN & Mareev VY, Cardiologia; 2008
Real administration of BAB in clinical trials (Russia / World)

CORONA (2007):
- 91% World; 93% RF
- 75% World; 87% RF

CORONA (2007):
91% World; 93% RF
75% World; 87% RF

IMPROV
ФАСОН
ЭПОХА
СНЕГОВИК
АРХИМЕД
ДУЭЛЬ
ТРИОЛЯ

CORONA (2007):
91% World; 93% RF
75% World; 87% RF

1998
2000
2002
2004
2006
2008
2010

n = 811
n = 1445
n = 2989
n = 813
n = 448
n = 470
n = 108

Real administration of BAB in clinical trials (Russia / World)
Real administration of BAB in CHF patients in Europe

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma / COPD</td>
<td>82.1</td>
<td>35</td>
</tr>
<tr>
<td>Age ≥ 75 years old</td>
<td>31.3</td>
<td>21</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>8.3</td>
<td>7</td>
</tr>
</tbody>
</table>

*Numbers in red circles indicate percentages.*

*Numbers in black bars indicate number of patients.*

*Values in brackets indicate confidence intervals.*

*Significance levels: <0.0001.*

Characteristic and doses of BAB in CHF

- Ate: 6,1%
- Beta: 1,5%
- Biso: 51 mg/day
- Carve: 22,1 mg/day (35,5%)
- Meto Succi: 16,8%
- Meto Tartr: 69,9 mg/day (EHS=74,9)
- Nebovolol: 1,9%
- Sotalol: 1,2%

Only 46% control of HR < 70 (!)

73,8% (43% of recommended doses)
Practical usage of optimal doses of ACEI and BAB in pts with CHF

Figure 1 Percentages of patients reaching different target dose levels (<50%, ≥50% and <100%, >100%) for blockade of the renin-angiotensin system (RAS) as well as beta-blockade (BB).
1988 - Nobel prize for inventing BAB in the treatment of CVD

«No one even the best medication will not help, if the patient will not take it»