Beta Blockers in Hypertension, The Final Word

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Beta – blockers still WONDER us !!!
Classification of B-Blockers

First generation (beta 1 & 2 noncardioselective)

- Propranolol

Second generation (beta 1 cardioselective)

- Atenolol
- Metoprolol
- Acebutolol
- Bisoprolol
- Betaxolol
- Celiprolol
Third generation

Vasodilatory properties
• Carvedilol (beta 1&2 alpha 1)
• Bucindolol
• Nebivolol (beta 3)

Betablockers with beta-2 intrinsic sympathomimetic activity
• Pindolol, penbutolol, celiprolol, carteolol
• acebutolol
## PROPERTIES OF $\beta$-BLOCKERS

<table>
<thead>
<tr>
<th>Name</th>
<th>$\beta$-1 Selective</th>
<th>$\alpha$-blockade</th>
<th>Lipophilic</th>
<th>Increases ISA</th>
<th>Other ancillary properties</th>
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<tbody>
<tr>
<td>Atenolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Acebutolol</td>
<td>Disputed</td>
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<td>No</td>
<td>Yes</td>
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<td>Bisoprolol</td>
<td>Yes</td>
<td>No</td>
<td>Weak</td>
<td>No</td>
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<tr>
<td>Bucindolol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Disputed</td>
<td>Vasodilator action</td>
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<tr>
<td>Carvedilol</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Antioxidant, effects on endothelial function</td>
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<tr>
<td>Celiprolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>$\beta$-2 only</td>
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<tr>
<td>Metoprolol</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>Vasodilation through nitric oxide</td>
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<tr>
<td>Propranolol</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Membrane stabilizing Effect</td>
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<td>Timolol</td>
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<td>Anti-platelet effects</td>
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LVH......

- Left ventricular hypertrophy (LVH) is a cardinal manifestation of preclinical cardiovascular disease that strongly predicts myocardial infarction, stroke, and cardiovascular death in hypertensive patients, the general population, and patients with coronary artery disease. Several studies suggest that regression of hypertensive LVH is associated with improved prognosis.
Trials with B-Blockers

The benefit of B-blockers compared with that of other antihypertensive agents has recently been questioned on the basis of the results of two large randomized trials,

LIFE study
&
ASCOT study
LIFE study

- The most important result of the study is that treatment based on once-daily administration of losartan reduced LVMI during up to 5 years of treatment significantly more than conventional atenolol-based treatment, confirming previous suggestions of superior regression of hypertensive LVH by AT1 receptor antagonism. In the Treatment of Mild Hypertension Study (TOMHS), no difference was observed between the ACE inhibitor and B-blocker arms.
ASCOT Trial – Blood Pressure Lowering Arm

- **Amlodipine/Perindopril** therapy conferred an advantage over **Atenolol/thiazide** therapy on all major CV events, all-cause mortality, fatal and nonfatal stroke, and new-onset diabetes (original study halted after 5 ½ years due to efficacy)

- Various measures of **visit-to-visit BP variability** are powerful predictors of both stroke and CHD outcomes and other measures of variability predict CVD outcomes to a lesser extent

- Adjusting for BP variability explains differences in stroke and CHD outcomes between amlodipine-based and atenolol-based treatment in the original study
• **ACCORD** Aggressive BP lowering no advantage for CVD outcome, but improved stroke outcome
• **NAVIGATOR** *neither* valsartan or nateglinide improved CVD outcomes in diabetics
• **ASCOT** Amlodipine/perindopril therapy conferred an advantage over atenolol/thiazide therapy on major CV events, all-cause mortality, fatal and nonfatal stroke
• **INVEST** Tight BP control not associated with improved CV outcomes compared with usual control
• **HYVET** Treating hypertension in the elderly reduces Stroke, mortality and HF
• **BOGALUSA** BP variability causes LVH
A recent meta-analysis shows that, when compared with placebo, b-blockers based therapy did indeed reduced stroke significantly. [J Hypertens 2006;24:2131-2141.MA]

This suggests that at least part of the inferiority of the B-blocker-thiazide combination reported in ASCOT may be due to a lesser BP reduction, particularly of central BP that occurred in this trial.
The above quoted meta-analyses of B-blockers initiated trials well illustrate the difficulties inherent in many recent trials in which combination therapy hinders the attribution of either benefits or harms to individual compounds.
Metaanalysis of 26 trials, MIAMI, ISIS, COMMIT Trials

- Death 13%
- Reinfarction 22%
- Sudden cardiac death 15%
Trials

- MAPHY, SYST- EUR, SYST –CHINA , ABCD , ALLHAT Trials
- Psaty BM et al – meta-analysis of 18 trails
- CVS mortality reduces by 39%
Nice

Avised the use of B-blockers **ONLY** as fourth line antihypertensive agents
Conditions favouring use of B-Blockers

- Angina pectoris
- Post-myocardial infarction
- Heart failure
- Tachyarrhythmias
- Glucoma
- Pregnancy
Compelling & possible contraindications of B-Blockers

- **Compelling:**
  - Asthma
  - A-V block (grade 2 or 3)
- **Possible:**
  - Peripheral arterial disease
  - Metabolic syndrome
  - Glucose intolerance
  - Athletes & physically active patients
  - Chronic obstructive pulmonary disease
2007 ESH/ESC Hypertension Guidelines
First Choice Drug Treatment

- Diuretics*
- ACE-inhibitors
- Calcium antagonists
- Angiotensin receptor antagonists
- Beta-blockers*

* not to be initially preferred in patients at high risk of developing diabetes
Choice of Combinations

- Despite trial evidence of outcome reduction, the BB / diuretic combination favours development of diabetes and should thus be avoided, unless required for other reasons, in predisposed subjects.

- Use of an ACEI / ARB combination presents a dubious potentiation of benefits with a consistent increase of serious side effects.

- Specific benefits in nephropathic patients with proteinuria (because of a superior antiproteinuric effect) expect confirmation in event based trials.
Antihypertensive Treatment in the Elderly (I)

- In the elderly antihypertensive treatment is highly beneficial (large meta-analyses)
- In patients aged ≥ 65 the proportional benefit is no less than in younger patients
- Data (large meta-analyses) do not support the claim that antihypertensive drug classes significantly differ in their ability to lower BP / exert CV protection both in younger and in elderly patients
- The choice of the drugs to employ should thus not be guided by age
- Thiazide diuretics / ACEIs / CA / ARBs / BBs can be considered for initiation / maintenance of treatment also in the elderly
Atrial Fibrillation

- In a meta-analysis on almost 12,000 patients with systolic HF BBs were found to reduce (-27%) AF
- In patients with an AF history and systolic HF BBs are a specific indication
Beta – blockers still WONDER us !!!
Blocker

ARBs
Thank You.....