DECLARATION OF CONFLICT OF INTEREST
Third generation beta-blockers in the treatment of arterial hypertension

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Because beta-blockers .... have adverse effects on lipid metabolism and increase .... the incidence of new onset diabetes they should not be preferred in hypertensives with multiple metabolic risk factors
2007 ESC Guidelines for the management of arterial hypertension

Because beta-blockers … have adverse effects on lipid metabolism and increase … the incidence of new onset diabetes they should not be preferred in hypertensives with multiple metabolic risk factors

It may not apply, however, to vasodilator beta-blockers, such as carvedilol and nebivolol, which have less or no dysmetabolic action as well as a reduced incidence of new onset diabetes compared with classical beta-blockers
The three generations of beta-blockers

<table>
<thead>
<tr>
<th>Generation</th>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} generation</td>
<td>non-selective</td>
<td>(Propranolol, Sotalol)</td>
</tr>
<tr>
<td>2\textsuperscript{nd} generation</td>
<td>\textit{beta}_1-selective („cardioselective“)</td>
<td>(Atenolol, Metoprolol, Bisoprolol)</td>
</tr>
<tr>
<td>3\textsuperscript{rd} generation</td>
<td>additional vasodilating effects</td>
<td>(Carvedilol, Nebivolol, Labetalol)</td>
</tr>
</tbody>
</table>
Third generation beta-blockers

Carvedilol
Beta₁− + Beta₂− + Alpha-blockade
Predominantly oral administration
Third generation beta-blockers

**Carvedilol**

Beta₁– + Beta₂– + Alpha–blockade
Predominantly oral administration

**Nebivolol**

Beta₁–blockade + NO–mediated vasodilation
Predominantly oral administration
Third generation beta-blockers

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Beta₁– + Beta₂– + Alpha–blockade
Predominantly oral administration

**Nebivolol**
Beta₁–blockade + NO–mediated vasodilation
Predominantly oral administration

**Labetalol**
Beta₁– + Beta₂– + Alpha–blockade
Predominantly intravenous administration
Third generation beta-blockers

„General“ side effects of beta-blockers

- Bradycardia
- AV-block
- Heart failure
- Bronchospasm
- Peripheral vasoconstriction
- Increase of plasma glucose
- Increase of plasma lipids
- Erectile dysfunction
- Sleep disturbances (melatonin↓)
Atenolol in hypertension:
Is it a wise choice?

Our results cast doubts on atenolol as a suitable drug for hypertensive patients. Moreover, they challenge the use of atenolol as a reference drug in outcome trials in hypertension


Lancet 2004; 364: 1684-1689
Results of studies with Beta-Blockers versus other Antihypertensives

Results of studies with Beta-Blockers without Atenolol versus other Antihypertensives

Third generation beta-blockers

Carvedilol

Advantages:
Additional $\alpha$-blockade
Third generation beta-blockers

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Additional $\alpha$-blockade
$\rightarrow$ more blood pressure ↓
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→ no plasma levels ↑ of lipids and glucose
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Disadvantages:
No β₁-selectivity
Third generation beta-blockers

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Dosing twice daily
Third generation beta-blockers

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Dosing twice daily
No large outcome trials in arterial hypertension
Different effects on resting heart rate of increasing single oral doses of Carvedilol, Metoprolol und Bisoprolol (*, p < 0.05)
In patients with arterial hypertension and diabetes mellitus II the Insuline Sensitivity Index was decreased by Atenolol (-24%, p < 0.01) but increased by Carvedilol (+27%, p < 0.01); at the same time plasma concentrations of triglycerides were increased by Atenolol (+12%, p < 0.01) but decreased by Carvedilol (-20%, p < 0.01)

*Ann Intern Med* 1997; 126: 955-959
Third generation beta-blockers

Nebivolol

Advantages:
Vasodilation by an additional nitrate effect
Third generation beta-blockers

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Disadvantages:
Rather weak beta-blockade
Third generation beta-blockers

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Rather weak beta-blockade
No large outcome trials in arterial hypertension
Additional indication only in the elderly with heart failure
Third generation beta-blockers

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Disadvantages:
Rather weak beta-blockade
No large outcome trials in arterial hypertension
Additional indication only in the elderly with heart failure
Actually no indication in CAD
Effects of intra-arterial infusions of nebivolol and atenolol on forearm blood flow. Nebivolol and atenolol were infused at equimolar doses. Nebivolol increased blood flow significantly (235)
Nebivolol: $\beta_1$-blocking potency (9)

A: Percentage decrease in exercise-induced tachycardia (n=11) (Modified from fig. 2A)

- Nebivolol 5 mg, day 7
- Nebivolol 25 mg, day 7
- Atenolol 50 mg, day 7
- Atenolol 100 mg, day 7

B: Mean reduction in mean arterial pressure at rest (n=11) (Modified from fig. 2B)

- Atenolol 50 mg, day 7
- Atenolol 100 mg, day 7

($^*p<0.05$ $^{**}p<0.01$)
No influence of Nebivolol on FEV

Increase of forearm blood flow (FBF) by iv administration of 0.4 mg/min Nitroglycerine following one week of daily intake of Placebo or 5mg Nebivolol: FBF increased significantly with Nebivolol (+96%) and more effectively (p < 0.05) than with Placebo (+54%) → **No nitrate tolerance with Nebivolol**
Effects of exercise on plasma concentrations of beta-blockers
Effects of exercise on plasma concentrations of beta-blockers
Influence of Bisoprolol, Carvedilol and Nebivolol on nocturnal melatonin release:
Compared to Placebo, Bisoprolol decreased nocturnal melatonin release by 36 % (* p < 0.05) whereas Carvedilol und Nebivolol showed no effects (n.s.)
Third generation beta-blockers

Labetalol

Beta_1^- + Beta_2^- + Alpha-blockade
Third generation beta-blockers

Labetalol

$\text{Beta}_1 -$ + $\text{Beta}_2 -$ + Alpha-blockade

$\rightarrow$ predominantly intravenous administration
Third generation beta-blockers

**Labetalol**

\[ \text{Beta}_1 - + \text{Beta}_2 - + \text{Alpha}-\text{blockade} \]

→ predominantly intravenous administration
→ hypertensive emergencies, particularly in
Third generation beta-blockers

Labetalol

Beta$_1$ – + Beta$_2$ – + Alpha–blockade
→ predominantly intravenous administration
→ hypertensive emergencies, particularly in
→ phaeochromocytoma
Third generation beta-blockers

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Beta_1^- + Beta_2^- + Alpha-blockade
→ predominantly intravenous administration
→ hypertensive emergencies, particularly in
  → phaeochromocytoma
  → pre-eclampsia
Third generation beta-blockers

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Beta₁– + Beta₂– + Alpha–blockade
→ predominantly intravenous administration
→ hypertensive emergencies, particularly in
  → phaeochromocytoma
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→ 20mg – 3mg/kgBW
Third generation beta-blockers

Labetalol

Advantages:

Additional α-blockade
Third generation beta-blockers

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Additional α-blockade
„The most effective beta-blocker in hypertensive emergencies“
Third generation beta-blockers

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$\rightarrow$ bronchospasms ↑
Third generation beta-blockers

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→ more blood pressure ↓

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**Disadvantages:**

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No large outcome trials in arterial hypertension
Conclusions

The three generations of beta-blockers are not equal
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*Third generation beta-blockers* show
→ more decrease of blood pressure
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*Third generation beta-blockers* show
- more decrease of blood pressure
- less/no increase of plasma glucose
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→ less/no decrease of nocturnal melatonin
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*Third generation beta-blockers* show
- more decrease of blood pressure
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- less/no decrease of nocturnal melatonin
- no increase of plasma concentrations by exercise
Conclusions

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→ more decrease of blood pressure
→ less/no increase of plasma glucose
→ less/no increase of plasma lipids
→ less/no decrease of nocturnal melatonin
→ no increase of plasma concentrations by exercise

Large clinical studies showing effects on morbidity and mortality are missing
Thank you very much for your attention!
Haemodynamic effects of beta-blockers

| 1. & 2. Generation |  
|---|---|---|---|
| **Blood pressure** | ↓ | | | |
| **Cardiac output** | ↓ | ↑ | | |
| **Peripheral resistance** | | ↑ | | |
| **Heart rate** | | | ↓ | |

| 3. Generation |  
|---|---|---|---|
| **Blood pressure** | ↓ | | | |
| **Cardiac output** | | ↑ | | |
| **Peripheral resistance** | | | ↓ | |
| **Heart rate** | | | | ↓ |
Beta-blockers and erectile dysfunction

Eur Heart J 2003; 24: 1928-1932

96 males (age 52 ± 7 years) with CAD (60 %) or arterial hypertension (40 %) with no contraindications for beta-blockers and without erectile dysfunction (ED) received 50 mg Atenolol once daily over three months.

They were divided in 3 groups (32 patients each) as follows:

- **Groupe 1**
  - was „blinded“ , i.e., patients *did not know* what they received

- **Groupe 2**
  - was informed about the *substance* but *not* about ED as a potential side effect

- **Groupe 3**
  - was informed about the *substance and* about ED as a potential side effect
Beta-blockers and erectile dysfunction

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Patients who reported ED as a side effect received in a 2nd phase

50 mg Sildenafil (Viagra®) or Placebo

according to a double-blind, cross-over, placebo-controlled protocol with ongoing treatment with 50 mg Atenolol once daily in order to use it at least three times
Beta-blockers and erectile dysfunction

Effect of Sildenafil Citrate and Placebo in Patients Reporting ED

% of patients reporting improvement of ED

Sildenafil Citrate     Placebo

Blinded  Knew drug  Knew SE

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