Beta-blockers in 2011
Current role in hypertension

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Dr. Harun A. Otieno MD FACC
Consultant Physician & Interventional Cardiologist
Aga Khan University Hospital Nairobi
Objectives

- Review current concerns regarding beta-blockers
- Highlight features of vasodilatory beta-blockers
- Role of beta-blockers in hypertension & compelling indications
JNC 7 Guidelines
Beta-blockers in Hypertension

LIFESTYLE MODIFICATIONS

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for patients with diabetes or chronic kidney disease)

INITIAL DRUG CHOICES

Without Compelling Indications

Stage 1 Hypertension (SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mmHg)
Two-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).

With Compelling Indications

Drug(s) for the compelling indications
(See table 8)
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
## Guideline basis for compelling indications for individual drug classes

<table>
<thead>
<tr>
<th>Compelling Indication*</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>Aldo AInt</th>
<th>Clinical Trial Basis‡</th>
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<tr>
<td>Heart failure</td>
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<td>Chronic kidney disease</td>
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<td>Recurrent stroke prevention</td>
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<td>PROGRESS35</td>
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</tbody>
</table>
Choosing drugs for patients newly diagnosed with hypertension

**Abbreviations:**

- **A** = ACE inhibitor (consider angiotensin-II receptor antagonist if ACE intolerant)
- **C** = calcium-channel blocker
- **D** = thiazide-type diuretic

**Black patients** are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients.

**Beta-blockers** are not a preferred initial therapy for hypertension but are an alternative to **A** in patients younger than 55 years in whom **A** is not tolerated or is contraindicated (including women of childbearing potential).

**Steps:**

**Step 1:**
- Younger than 55 years: **A**
- 55 years or older or black patients of any age: **C** or **D**

**Step 2:**
- **A + C** or **A + D**

**Step 3:**
- **A + C + D**

**Step 4:**
- Add further diuretic therapy or alpha-blocker or beta-blocker
- Consider seeking specialist advice
Atenolol in hypertension: is it a wise choice?

CV Mortality tended to be higher, HR 1.16 [1.00 - 1.34] & stroke risk was 1.30 [1.12 - 1.50]

Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of β-blocking agents?

Effects of subchronic treatment (>2 months) with β-adrenergic receptor blocker on insulin sensitivity.

Weight Gain
↓ mLPL, LCAT
Δ insulin clearance
↑ TPR

Jacob S, Rett K, Henriksen EJ. Am. J. Hypertens. 11, 1258–1265
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Pharmacology of Nebivolol

Absorbed rapidly, Peak 1h

98% protein bound, t½ 12 – 19 hr

D-isomer – selective β1 blocker

L-arginine/NO pathway
Effects of nebivolol on proliferation and apoptosis of human coronary artery smooth muscle and endothelial cells.

(A) Control cells, produced high amounts of prepro-ET-1mRNA with a cytoplasmatic localization.

(B) After 12 h of nebivolol (2×10^{-6} mol/l) incubation the cells show only weak prepro-ET-1 mRNA expression.

Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Nebivolol</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic values (seated)</td>
<td></td>
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<tr>
<td>SBP/DBP (mmHg)</td>
<td>160 ± 11/101 ± 4</td>
<td>148 ± 21***/92 ± 8***</td>
<td>147 ± 20***/91 ± 5***</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>78 ± 2</td>
<td>67 ± 7***</td>
<td>66 ± 11***†</td>
</tr>
<tr>
<td>Ambulatory monitoring</td>
<td></td>
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<tr>
<td>24 h means</td>
<td></td>
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</tr>
<tr>
<td>SBP/DBP (mmHg)</td>
<td>152 ± 11/90 ± 5</td>
<td>138 ± 16***/81 ± 8***</td>
<td>136 ± 19***/78 ± 9***†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 9</td>
<td>66 ± 7***</td>
<td>61 ± 7***†</td>
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<tr>
<td>Daytime</td>
<td></td>
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<tr>
<td>SBP/DBP (mmHg)</td>
<td>158 ± 10/94 ± 6</td>
<td>142 ± 16***/84 ± 8***</td>
<td>138 ± 17***/81 ± 9***††</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 9</td>
<td>70 ± 7***</td>
<td>63 ± 8***††</td>
</tr>
<tr>
<td>Night-time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP/DBP (mmHg)</td>
<td>144 ± 14/82 ± 7</td>
<td>131 ± 20***/75 ± 9***</td>
<td>131 ± 23***/73 ± 12***</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 9</td>
<td>60 ± 7***</td>
<td>57 ± 7***†</td>
</tr>
<tr>
<td>CLAMP</td>
<td></td>
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</tr>
<tr>
<td>Glucose disposal rate (M) (mg/kg per min)</td>
<td>4.62 ± 2.04</td>
<td>4.30 ± 2.17</td>
<td>3.89 ± 1.68*</td>
</tr>
<tr>
<td>Mean insulin concentration (Î² (pmol/l))</td>
<td>672 ± 150</td>
<td>723 ± 168</td>
<td>722 ± 152</td>
</tr>
<tr>
<td>Insulin sensitivity index (M/I)</td>
<td>0.74 ± 0.40</td>
<td>0.65 ± 0.39</td>
<td>0.58 ± 0.33**††</td>
</tr>
<tr>
<td>IVGTT</td>
<td></td>
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</tr>
<tr>
<td>Glucose disappearance rate (M) (min⁻¹)</td>
<td>1.12 ± 0.34</td>
<td>1.16 ± 0.41</td>
<td>1.00 ± 0.31**††</td>
</tr>
<tr>
<td>Peak insulin response (pmol/l)</td>
<td>322 ± 231</td>
<td>347 ± 266</td>
<td>350 ± 287</td>
</tr>
<tr>
<td>Insulin AUC (nmol/l.min) 0–120 min</td>
<td>38 ± 19</td>
<td>42 ± 27</td>
<td>46 ± 28</td>
</tr>
<tr>
<td>Glucose AUC (mmol/L.min) 0–120 min</td>
<td>1258 ± 177</td>
<td>1244 ± 229</td>
<td>1323 ± 190*††</td>
</tr>
</tbody>
</table>

Data are means ± SD. SBP/DBP, systolic/diastolic blood pressure; AUC, area under the curve; IVGTT, intravenous glucose tolerance test. * P < 0.05, ** P < 0.01, *** P < 0.001 versus placebo; † P < 0.05, †† P < 0.01, ††† P < 0.001 versus nebivolol.

Pharmacokinetics of the effect of nebivolol 5mg on airway patency in patients with mild to moderate bronchial asthma and arterial hypertension: a randomized, placebo-controlled study.

MR NOED Study

Nitric oxide, erectile dysfunction and β-blocker treatment: benefit of nebivolol

Randomized trial to determine the effect of nebivolol on mortality & cardiovascular hospital admission in elderly patients with heart failure (SENIORS)

Equivalence to other Beta-blockers

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial type</th>
<th>Regimen (duration in weeks)</th>
<th>Patients (n)</th>
<th>Mean sitting baseline BP (mmHg)</th>
<th>Mean sitting BP at study end point* (mmHg)</th>
<th>Response rate† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Nuten et al.</td>
<td>Double-blind, randomized, parallel-group</td>
<td>Nebivolol 5 mg q.d. (4) Atenolol 50 mg q.d. (4) Placebo</td>
<td>119 121 124</td>
<td>167/101 169/101 169/102</td>
<td>151/89 152/90.5 163/97.5</td>
<td>59⁵ 59⁶ 29</td>
</tr>
<tr>
<td>Czuriga et al.</td>
<td>Single-blind, randomized, parallel-group</td>
<td>Nebivolol 5 mg q.d. (12) Bisoprolol 5 mg q.d. (12)</td>
<td>138 135</td>
<td>153/99 153/100</td>
<td>132.5/83.3 133/84</td>
<td>90.6 87.4</td>
</tr>
<tr>
<td>Uhlig et al.</td>
<td>Double-blind, randomized, parallel-group</td>
<td>Nebivolol 5 mg q.d. (12) Metoprolol 100 mg b.i.d. (12)</td>
<td>73 67</td>
<td>160/106 157/107</td>
<td>140/89 142/91</td>
<td>79.5 65.6</td>
</tr>
</tbody>
</table>

All trials had a 4-week placebo run-in period and were multicentered.

*Decrease in baseline BP to study end point was statistically significant in active treatment groups (p < 0.05).
†Defined as achieving diastolic BP ≤ 90 mmHg.
‡Decrease in baseline BP to study end point in active treatment groups compared with placebo was statistically significant (p < 0.001).

BP: Blood pressure; q.d.: Daily; b.i.d.: Twice daily.
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Cardiovascular Mortality & Heart Rate

![Graph showing the relationship between heart rate and cardiovascular mortality. The graph includes data points for trials such as ASCOT, LIFE, INVEST, IPPPSH, and Yurenev, with a regression line and equation: \( r = -0.6133, p = 0.00001 \), \( y = 3.5913 - 0.0375x \).]
Non-Selective vs. Selective Beta-blockers & the risk of Thrombo-embolic events in HF

B-CONVINCED
Continuation vs. Discontinuation of Beta-blockers in ADHF

Question

- A 49 year old male with Type 2 Diabetes and hypertension, dyslipidemia has been started on Perindopril/Indapamide but still has elevated BP of 145/91 mmHg. HbA1C 7.2% on Metformin 1000mg BD. He has used Amlodipine in the past but reported an episode of headaches, severe rash and leg swelling. You advise which one of the following:

A. Atenolol 50mg OD
B. Nebivolol 5mg OD
C. Carvedilol 6.25mg BD
D. Metoprolol succinate 50mg OD
GEMINI
Glycemic Effects in Diabetes Mellitus: Carvedilol – Metoprolol comparison in Hypertetensives

Conclusion & Summary

- Wait for JNC
- Traditional beta-blockers adverse side-effect and metabolic profiles
- Vasodilatory beta-blockers, Nebivolol and Carvedilol may offer favorable options in hypertension
- Discontinuation in acute decompensated not advised