Betablocker Therapy for Hypertensive African Americans

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Just the facts
Is There a Need to Focus Special Attention on Cardiovascular Disease in African Americans or Other Ethnic Groups?
Special Populations (JNC-7)

- In general, treatment similar for all demographic groups.

- Socioeconomic factors and lifestyle important barriers to BP control.

- Prevalence, severity of HTN increased in African Americans.

- African Americans demonstrate somewhat reduced BP responses to monotherapy with BBs, ACEIs, or ARBs compared to diuretics or CCBs.

- These differences usually eliminated by adding adequate doses of a diuretic.
Morbidity and Mortality (cont’d)

- Mortality in African American males—30% hypertension-related
- Mortality in African American females—20% hypertension-related
- Non-fatal strokes—1.3 x greater than whites
- Fatal strokes—1.8 x greater than whites
- Heart disease deaths—1.5 x greater than whites
- End-stage renal disease—5 x greater than whites

Atenolol, Captopril, Verapamil in African American Hypertensives

Percent Achieving BP Goal with Monotherapy

- Monotherapy-A-50mg, C-50mg, V-240mg
- Increased dosing

Atenolol: 46%
Captopril: 43%
Verapamil: 68%

Efficacy of Trandolapril in Racial Subgroups


D0SE = 4 MG (B)  
2 MG (W)
Treating Hypertension in African Americans Is Perceived as More Difficult

Decrement in blood pressure among whites and blacks after administration of antihypertensive drugs. Shaded area represents white and blacks who have similar responses.

Meta-analysis of 15 studies with total of 9302 white and 2902 black subjects

Percentage whites and blacks with similar response

- CCBs: 95% (95%CI;92-98)
- Diuretics: 90% (95%CI;81-99)
- ß-Blockers: 90% (95%CI;83-97)
- ACE-Is: 81% (95%CI;76-86)

International Soc.of Htn in Blacks: General Approach to Treatment

• Encourage lifestyle changes
  – DASH diet has shown to reduce SBP and DBP significantly more than other diets, especially in African Americans

• Determine patient-specific cardiovascular risk factors

• Consider family history and other co-morbid conditions when constructing the clinical picture
ISHIB: Pharmacological Recommendations

- Thiazide diuretics and CCBs as monotherapy are more effective antihypertensives in AAs
- Combination therapy with a diuretic or CCB will provide additional decrease in BP that may not be attained with BBs, ACEIs, and ARBs alone
- BBs, ACEIs, and ARBs as monotherapy in AAs do not lower BP as effectively as in white patients; higher doses of these drugs may be more effective in AAs
Current Use of β-blockers

- First-line and Add-on Therapy for Hypertension
- Hypertension with Compelling Indications:
  - Heart Failure
  - Post-MI
  - High coronary disease risk
  - Type 2 diabetes

Concerns With Traditional β-blockers

- Efficacy in certain hypertensive populations
  - Blacks
  - Elderly patients
- Side Effects
  - Fatigue
  - Sexual dysfunction
  - Cold extremities
  - Depression
  - Hyperreactive airway disorder
  - Bradycardia
- Metabolic Change
  - Glucose abnormalities
  - Lipid abnormalities
- Hemodynamic Change
  - ↓ CO, ↑ PVR
  - ↓ Exercise tolerance

CO = cardiac output; MI = myocardial infarction; PVR = peripheral vascular resistance


Main Factors Contributing to Heterogeneity Within the β-blocker Class

- $\beta_1/\beta_2$ Selectivity
- Vasodilation Properties
- Side effects
- Efficacy
- Metabolic profile
Bystolic™ (nebivolol): Mechanism of Action

Bystolic

Selective $\beta_1$-blockade

Vasodilation

Additional properties:
- Suppression of renin activity and diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers

*Decreased heart rate, decreased myocardial contractility. In extensive metabolizers and at doses ≤10 mg, nebivolol is preferentially $\beta_1$ selective.
†Decreased peripheral vascular resistance.

**Bystolic™ (nebivolol): $\beta_1$ Receptor Selectivity**

*Human Myocardium*

$\beta_1$ Selectivity = $K_i(\beta_2) / K_i(\beta_1)$.

In extensive metabolizers and at doses less than or equal to 10 mg, nebivolol is preferentially $\beta_1$ selective. Brixius K et al. Br J Pharmacol. 2001;133:1330-1338.
Bystolic™ (nebivolol): US Registration Trials for Hypertension

Monotherapy vs placebo
- Three trials comprising 2016 patients
  - One specifically in Black patients (N=300)

Add-on therapy vs placebo
- Bystolic added to current antihypertensive therapy

Bystolic™ (nebivolol): Design of Three Monotherapy Registration Trials for FDA Approval (N=2016)

Screening
Washout/Placebo Run-In

Entry criteria: DBP ≥95 and ≤109 mm Hg

Randomization to double-blind study medication (parallel groups)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Bystolic 1.25 mg</th>
<th>Bystolic 2.5 mg</th>
<th>Bystolic 5 mg</th>
<th>Bystolic 10 mg</th>
<th>Bystolic 20 mg</th>
<th>Bystolic 40 mg</th>
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</thead>
</table>

Primary end point:
DBP at trough at end of therapy (84 days)

DBP=sitting diastolic blood pressure.
Baseline Demographics of the Three Monotherapy US Registration Trials for FDA Approval

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial 1(^1)</th>
<th>Trial 2(^2)</th>
<th>Trial 3(^3)</th>
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<tbody>
<tr>
<td>N</td>
<td>909</td>
<td>807</td>
<td>300</td>
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<tr>
<td>Age (% ≥65 yrs)</td>
<td>21.2%</td>
<td>18.2%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>43.0%</td>
<td>46.5%</td>
<td>54.7%</td>
</tr>
<tr>
<td>Race (% Black)</td>
<td>14.5%</td>
<td>13.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Diabetes (% with diabetes)</td>
<td>9.7%</td>
<td>4.6%</td>
<td>14.3%</td>
</tr>
<tr>
<td>BMI (% of patients with ≥30 kg/m(^2))</td>
<td>43.9%</td>
<td>40.1%</td>
<td>52.0%</td>
</tr>
</tbody>
</table>

No significant differences among treatment groups in each trial.

# Pooled Analysis of the Three Monotherapy US Registration Trials: Diastolic and Systolic BP

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<th>459</th>
<th>461</th>
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<tbody>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>99.8</td>
<td>99.4</td>
<td>99.3</td>
<td>99.5</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>152.3</td>
<td>152.0</td>
<td>152.8</td>
<td>152.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>-5.0</td>
<td>*</td>
<td>-9.7</td>
<td>-11.1</td>
</tr>
<tr>
<td>SBP</td>
<td>-4.3</td>
<td>*</td>
<td>-10.3</td>
<td>-10.7</td>
</tr>
<tr>
<td>Placebo DBP</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Placebo SBP</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*Only data for patients randomized to placebo, 5 mg, 10 mg, and 20 mg are shown (n=1585). *P<0.001 vs placebo.*

BP=sitting blood pressure; DBP=sitting diastolic blood pressure; SBP=sitting systolic blood pressure.
Efficacy of Bystolic™ (nebivolol) in Black Patients: Diastolic and Systolic BP

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td></td>
<td>100.6</td>
<td>99.9</td>
<td>100.3</td>
<td>101.4</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td></td>
<td>151.4</td>
<td>151.7</td>
<td>154.2</td>
<td>156.4</td>
</tr>
</tbody>
</table>

Mean Δ in BP vs baseline (mm Hg):
- DBP: -4.4, -3.6, -5.9, -9.1, -10.3, -10.2, -10.6, -12 (†)
- SBP: -6, -8, -10, -6, -8, -6, -8, -12 (†)

*Only data for patients randomized to placebo, 5 mg, 10 mg, and 20 mg are shown (n=193). †P<0.05 vs placebo.
Effectiveness was established in Black patients but as monotherapy the magnitude of effect was somewhat less than in Caucasians.
BP=sitting blood pressure; DBP=sitting diastolic blood pressure; SBP=sitting systolic blood pressure.
Bystolic™ (nebivolol) Add-on Trial*: Diastolic and Systolic BP

<table>
<thead>
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<th>168</th>
<th>166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DBP</td>
<td>mm Hg</td>
<td>96.4</td>
<td>96.4</td>
<td>95.8</td>
<td>96.5</td>
</tr>
<tr>
<td>Baseline SBP</td>
<td>mm Hg</td>
<td>146.5</td>
<td>147.4</td>
<td>145.3</td>
<td>144.8</td>
</tr>
<tr>
<td>Dose</td>
<td>Placebo</td>
<td>5 mg</td>
<td>10 mg</td>
<td>20 mg</td>
<td></td>
</tr>
</tbody>
</table>

*Add-on to no more than two other antihypertensive medications (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or diuretic).
BP=sitting blood pressure; DBP=sitting diastolic blood pressure; SBP=sitting systolic blood pressure.
Nitric Oxide Release and Vasodilatation: A Clinical Goal in Ethnic Minorities with Hypertension and Cardiovascular Disease
Physiological Features of Hypertension in African American Patients

- Black patients with hypertension have suppressed plasma renin activity and angiotensin II levels, consistent with sodium retention and "corrected" volume expansion.
- Black patients excrete a sodium load more slowly and less completely than white patients.
- In the majority, blood pressure is more salt sensitive.
- *Nitric oxide may be less bioavailable in AA*

Nitric Oxide in Hypertension

NO is involved in the regulation of arterial pressure. A lack of NO results in arterial hypertension. Any medication that stimulates NO production by the endothelium reduces arterial pressure.
Vascular Effects of Nitric Oxide

- Vasodilation
- Anti-inflammatory Actions
- Platelet Inhibition
- Inhibit SMC Proliferation
- Tissue Perfusion
- Oxygen/ROS Consumption

ROS=reactive oxygen species; SMC=smooth muscle cell.
Adapted from Vita JA. J Card Fail. 2003;9:S200.
Reduced Endothelial Vasomotor Function in Black Patients With Hypertension

- Self-defined black and white subjects with HTN
- Matched for age, gender, BP, other risk factors
- More diuretic use in blacks
- Forearm blood flow by venous occlusion plethysmography

CTR=control; FBF=forearm blood flow; HTN=hypertension.
Racial Differences in NO-Mediated Vasodilator Response to Mental Stress in Forearm Circulation

Forearm Blood Flow (mL/min/dL)

- Whites (14)
- AAs (12)

P = .02

NO-dependent vasodilator response reduced in AAs.
Nebivolol Pharmacology
Overview

- Highly selective $B_1$ receptor antagonist with $B_1/B_2$ of approximately 300 and $B_1/\alpha_1 \geq 60$
- No intrinsic sympathomimetic activity
- Highly lipophilic compound which is hepatically metabolized. Crosses into the brain, which may have benefits relating to sudden death via modulation of overall sympathetic tone
- Nitric oxide potentiating effect
- Administered using once-per-day dosing
Release of Nitric Oxide from Human Endothelium: White and African Americans

Calcium ionophore

30 mM

300 mM

0 3 6 9 12 15

Time (s)

30 mM

Calcium ionophore

Mason RP et al. Circulation 2005;112:3795-3801
Nebivolol has demonstrated remarkable acute effects on human endothelial nitric oxide stimulation that correlate with clinical findings.

Nebivolol is a potent stimulator of nitric oxide from isolated human endothelial cells.

Nebivolol compares very favorably with and is quite distinct from other β-blockers: metoprolol, atenolol, bucindolol, and carvedilol.
Summary of Treatment of Hypertension in African Americans

- Populations at high risk (diabetics, renal disease, African Americans, etc) require ACE inhibitors (ARBs), which often are inadequate alone in achieving low blood pressure goals, but offer target-organ protection.

- Nitric oxide-enhancing drugs may be useful where NO bioavailability is low.

- Such high-risk populations can only achieve low blood pressures goals with the use of combination therapies, which will include diuretics, calcium antagonists, alpha and/or beta blockers, aldosterone antagonists, centrally-acting agents (i.e. clonidine) occasionally direct-acting vasodilators (hydralazine, minoxidil).