REVISITING the ROLE of BETA-BLOCKERS in the MANAGEMENT of HYPERTENSION:
A CLOSER LOOK AT COMPLICATED CASES

CHARLOTTE, NORTH CAROLINA • SEPTEMBER 4, 2008
Session 6: Revisiting the Role of Beta-Blockers in the Management of Hypertension: A Closer Look at Complicated Cases

Learning Objectives

- Identify/discuss clinical considerations involved in the management of patients with complicated hypertension.
- Describe at least 1 of the latest clinical trial results on beta-blockers and its effects on metabolic parameters.

Faculty

Matthew J. Sorrentino, MD, FACC
Associate Professor of Medicine
University of Chicago Pritzker School of Medicine
Department of Medicine
Section of Cardiology
Chicago, Illinois

Matthew J. Sorrentino, MD, FACC, is associate professor of medicine at the University of Chicago Pritzker School of Medicine. Dr Sorrentino is a preventive cardiologist with clinical and research interests in hyperlipidemia and hypertension. He is an American Society of Hypertension hypertension specialist.

Dr Sorrentino received his medical degree from the University of Chicago Pritzker School of Medicine. He completed his internship and residency in internal medicine and a fellowship in cardiovascular disease at the University of Chicago Hospitals.

Dr Sorrentino is an abstract reviewer for the American College of Cardiology and the American Diabetes Association. He is a host on ReachMD, a satellite radio station for medical professionals. Dr Sorrentino has written numerous book chapters and over 70 articles published in journals such as The American Journal of Medicine, Journal of the American College of Cardiology and Journal of Geriatric Cardiology.

William C. Cushman, MD, FACP
Professor of Preventive Medicine and Medicine
University of Tennessee College of Medicine
Memphis, Tennessee

Chief of Preventive Medicine Section
Veterans Affairs Medical Center
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William C. Cushman, MD, FACP, is professor of preventive medicine and medicine at the University of Tennessee College of Medicine and chief of the Preventive Medicine Section at the Veterans Affairs Medical Center, Memphis. He is lead hypertension consultant to medical service in Central Office of the Department of Veterans Affairs.

Dr Cushman graduated from the University of Mississippi School of Medicine. He completed his residency training at the University of Mississippi, Jackson, and served on the faculty for 11 years.

Dr Cushman’s research interests include drug treatment and lifestyle changes in the prevention and management of hypertension and lipid abnormalities, prevention of cardiovascular outcomes, and cardiovascular disease epidemiology. His trials include morbidity and mortality outcomes, efficacy, compliance, predictors of response, hypertension in special populations, and intermediate endpoints. Research in lifestyle changes includes exercise, weight loss and intakes of alcohol, sodium, and potassium.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:
Dr Sorrentino receives speaking honoraria from Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and Takeda Pharmaceuticals North America, Inc.
Dr Cushman serves as a consultant for Bristol-Myers Squibb; Daiichi Sankyo, Inc.; Novartis Pharmaceuticals Corporation; Sciele Pharma, Inc.; and Takeda Pharmaceuticals North America, Inc. Dr Cushman receives grant support from Novartis Pharmaceuticals Corporation.
**Education Partner Financial Disclosure Statements**

The content collaborators at The France Foundation have reported that they have nothing to disclose.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>acebutolol</td>
<td>Sectral</td>
</tr>
<tr>
<td>atenolol</td>
<td>Tenormin</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>Zebeta</td>
</tr>
<tr>
<td>carvedilol</td>
<td>Coreg</td>
</tr>
<tr>
<td>labetalol</td>
<td>Normodyne, Trandate</td>
</tr>
<tr>
<td>lisinopril</td>
<td>Prinivil, Zestril</td>
</tr>
</tbody>
</table>

**Investigational**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>bucindolol</td>
<td></td>
</tr>
<tr>
<td>celiprolol</td>
<td></td>
</tr>
<tr>
<td>dilevalol</td>
<td></td>
</tr>
</tbody>
</table>

**Suggested Reading List**


Hypertension Progression with Age and Related Risk Factors

Matthew J. Sorrentino, MD, FACC
Associate Professor of Medicine
University of Chicago Pritzker School of Medicine
Section of Cardiology
Chicago, Illinois

Traditional CVD Risk Factors

- Family history
- Older age
- Male gender
- Smoking
- Physical inactivity
- Overweight/obesity
- Total-C/LDL-C/HDL-C/TG
- Hypertension
- Hyperglycemia


- Hypertension: SBP > 140, DBP > 90 mm Hg, or medicated for HT
- High cholesterol: > 240 mg/dl
- Overweight: BMI > 25 kg/m²

Source: NHIS for smoking, ages > 18 and NHANES for the other risk factors, ages 35–74.

Percentage of Adults With ≥ 2 Self-Reported CV Risk Factors

High BP, High Cholesterol, Diabetes, Obesity, Smoking, Physical Inactivity (2002)


Ischemic Heart Disease Risk Increases with SBP, DBP, and Age

Systolic Blood Pressure

Diasstolic Blood Pressure

CI, confidence interval; HD, ischemic heart disease

Lower Is Better!

Synergistic Interaction of Traditional Multiple Risk Factors on CVD Risk

INTERHEART: Risk of AMI Associated With Risk Factors in the Overall Population

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% Control</th>
<th>% Cases</th>
<th>OR (99% CI) Adj. for All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B/Apo A</td>
<td>20.0</td>
<td>33.5</td>
<td>3.25 (2.81, 3.76)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>26.8</td>
<td>45.2</td>
<td>2.87 (2.58, 3.19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.5</td>
<td>18.4</td>
<td>2.37 (2.07, 2.71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>39.0</td>
<td>1.91 (1.74, 2.10)</td>
</tr>
<tr>
<td>Abdominal obesity*</td>
<td>33.3</td>
<td>46.3</td>
<td>1.62 (1.45, 1.80)</td>
</tr>
</tbody>
</table>

**Protective Factor**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% Case</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable/fruit daily</td>
<td>42.4</td>
<td>35.8</td>
</tr>
<tr>
<td>Exercise</td>
<td>19.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>24.5</td>
<td>24.0</td>
</tr>
</tbody>
</table>

*Upper limits of waist circumference.


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Elevated BMI Increases the Risk of Cardiovascular Disease Mortality

Data are from 1 million men and women (average age, 57 years) followed for 16 years who never smoked and had no history of disease at enrollment.


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Waist Circumference Correlates With BP and Insulin Resistance

Data are from 768 men with fasting glucose ≤ 126 mg/dL (≤ 7 mmol/L)


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Hypertension Is Associated With Insulin Resistance


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Diabetes Among US Adults

Data are from 1 million men and women (average age, 57 years) followed for 16 years who never smoked and had no history of disease at enrollment.

EPIC-Norfolk Study: Every 1% Increase in HbA1c Increased CV Risk

Risk Factor Defining Level Prevalence
Abdominal obesity Waist* 39%
Men > 40 in
Women > 35 in
Triglycerides, mg/dL ≥ 150 30%
HDL-C, mg/dL 37%
Men < 40
Women < 50
BP, mm Hg ≥ 130 ≥ 85 34%
Fasting glucose, mg/dL ≥ 100 (NCEP ≥ 110) 13%

Metabolic Syndrome: Prevalence Increases With Age

Over Half of Patients Referred to Cardiologists Have Metabolic Syndrome

Inflammation in Metabolic Syndrome

Diagnose by presence of 3 or more risk factors

Diagnose by presence of 3 or more risk factors

Diagnose by presence of 3 or more risk factors

Diagnose by presence of 3 or more risk factors
Effects of Weight Loss* on Inflammatory Biomarkers

Baseline | 12 months
---|---
TNF-α | P < 0.01 | P > 0.02
IL-6 | P < 0.01 | P < 0.02
P-selectin | ICAM-1 | VCAM-1

*Mean decrease of 9.8 ± 1.5 kg.

Baseline

ICAM = intercellular adhesion molecule; IL-6 = interleukin 6; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule.


Association of Insulin Resistance With Cardiovascular Risk Factors and Atherosclerosis

Obesity

● Glucose intolerance
● Hypertension

Insulin resistance

● Dyslipidemia

- Low HDL
- Small, dense LDL particles
- Hypertriglyceridemia

Atherosclerosis

● Inflammation
- TNF-α
- IL-6
- P-selectin
- ICAM-1
- VCAM-1

hsCRP Adds Prognostic Information to the ATP III Definition of Metabolic Syndrome

hsCRP < 3, No Metabolic Syndrome
hsCRP ≥ 3, No Metabolic Syndrome
hsCRP < 3, Yes Metabolic Syndrome
hsCRP ≥ 3, Yes Metabolic Syndrome

N = 14,719
hsCRP = high-sensitivity CRP

Hypertension Writing Group Definition of Hypertension Compared with JNC 7

SBP (mm Hg)

Stage 1

Pre-hypertension

Stage 2

Hypertension

Stage 3

Hypertension

JNC 7

Hypertension Writing Group

Classification of Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>Normal</th>
<th>Stage 1 Hypertension</th>
<th>Stage 2 Hypertension</th>
<th>Stage 3 Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive Category</td>
<td>Normal BP or norm BP elevations AND No identifiable CVD</td>
<td>Occasional or intermittent BP elevations OR Early CVD</td>
<td>Sustained BP elevations OR Progressive CVD</td>
<td>Marked and sustained BP elevations OR Advanced CVD</td>
</tr>
<tr>
<td>Cardiovascular Risk Factors</td>
<td>None or few</td>
<td>Several</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>Early Disease Markers</td>
<td>None</td>
<td>Usually present</td>
<td>Overtly present</td>
<td>Overtly present with progression</td>
</tr>
<tr>
<td>Target-organ Disease</td>
<td>None</td>
<td>None</td>
<td>Early signs present</td>
<td>Overtly present with or without CVD events</td>
</tr>
</tbody>
</table>

Summary

- The prevalence of obesity and diabetes is increasing
- Metabolic syndrome, a precursor to CVD and diabetes, is also on the rise
- Aggressive management of diabetes and other CVD risk factors is essential
- Primary care physicians are instrumental in addressing the therapeutic challenges faced by their patients with cardiometabolic risk factors

AGE: Advanced glycosylation endproduct
CRP: C-reactive protein
E-selection: Endothelial cell selection
HDL: High density lipoprotein
IL-6: Interleukin-6
NO: Nitric oxide
PAI-1: Plasminogen activator type 1
tPA: Tissue plasminogen activator
VCAM: Vascular cell adhesion molecule

Hypertension Writing Group Definition and Classification of Hypertension


Association of Insulin Resistance With Cardiovascular Risk Factors and Atherosclerosis


Hypertension Writing Group Definition of Hypertension

Evolution of Beta-Blockade and the Management of Complicated Hypertension

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Chief of Preventive Medicine Section
Veterans Affairs Medical Center
Memphis, Tennessee

The Seventh Report of the Joint National Committee

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic.


Awareness, Treatment, and Control of Hypertension in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>Awareness</th>
<th>Treatment</th>
<th>Control (All)</th>
<th>Control (Treated, with diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2000</td>
<td>69</td>
<td>58</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>2001-2002</td>
<td>71</td>
<td>66</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>2003-2004</td>
<td>76</td>
<td>65</td>
<td>37</td>
<td>26</td>
</tr>
</tbody>
</table>

Control target for Healthy People 2000 (now 2010)


Percentage of Treated Patients With Hypertension at Goal 2003–2004

- Caucasians: 68%
- African-Americans: 52%
- Mexican-Americans: 57%
- Patients ≥ 60 years old: 44%
- Patients with diabetes: 25%


Perceived Barriers to Optimizing β-Blocker Treatment

<table>
<thead>
<tr>
<th>Metabolic Concerns*</th>
<th>Tolerability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative effects on lipid metabolism</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Negative effects on glucose metabolism</td>
<td>Impotence</td>
</tr>
<tr>
<td>Negative effects on renal blood flow</td>
<td>Weight increase</td>
</tr>
<tr>
<td>Masked hypoglycemia</td>
<td>Peripheral vasoconstriction (cold extremities)</td>
</tr>
</tbody>
</table>

*Primarily in patients with hypertension and diabetes.


Evolution of Beta-Blockade

First Generation
- Non-Selective: Propranolol

Second Generation
- Selective: Atenolol

Third Generation
- Vasodilating Non-Selective: Metoprolol
- Vasodilating Selective: Nebivolol

Next Generation
- Carvedilol
**β-Blockers Are Heterogeneous**

<table>
<thead>
<tr>
<th>β-Blocker</th>
<th>ISA</th>
<th>Selectivity</th>
<th>Vasodilation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>Cardioselective</td>
<td>No</td>
<td>qid/bid</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>No</td>
<td>qid/bid</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>No</td>
<td>qd/bid</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>+</td>
<td>Nonselective</td>
<td>Likely via α&lt;sub&gt;1&lt;/sub&gt; blockade</td>
<td>bid</td>
</tr>
<tr>
<td>Carvediol</td>
<td>-</td>
<td>Nonselective</td>
<td>α&lt;sub&gt;1&lt;/sub&gt; blockade</td>
<td>qid/bid</td>
</tr>
<tr>
<td>Labetalol</td>
<td>+</td>
<td>Nonselective</td>
<td>No</td>
<td>bid</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+</td>
<td>Nonselective</td>
<td>No</td>
<td>qd/bid</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>L-arginine/NO pathway</td>
<td>qd</td>
</tr>
<tr>
<td>Pindolol</td>
<td>++</td>
<td>Nonselective</td>
<td>No</td>
<td>bid</td>
</tr>
<tr>
<td>Propranolol</td>
<td>-</td>
<td>Nonselective</td>
<td>No</td>
<td>bid</td>
</tr>
<tr>
<td>Timolol</td>
<td>-</td>
<td>Nonselective</td>
<td>No</td>
<td>bid</td>
</tr>
</tbody>
</table>

ISA: intrinsic sympathomimetic activity


**Responses Mediated by β-Adrenergic Receptors in the Heart**

<table>
<thead>
<tr>
<th>Beneficial effects</th>
<th>Receptor Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive chronotropic response</td>
<td>β&lt;sub&gt;1&lt;/sub&gt; &gt; β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Positive inotropic response</td>
<td>β&lt;sub&gt;1&lt;/sub&gt; &gt; β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>β&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

**Harmful effects**

- Cardiac myocyte growth: β<sub>1</sub> > β<sub>2</sub>
- Fibroblast hyperplasia: β<sub>2</sub>
- Myocyte damage/myopathy: β<sub>1</sub> > β<sub>2</sub> > α<sub>1c</sub>
- Fetal gene induction: β<sub>1</sub>
- Myocyte apoptosis: β<sub>1</sub>
- Proarrhythmia: β<sub>1</sub> β<sub>2</sub> α<sub>1c</sub>
- Vasoconstriction: α<sub>1c</sub>


**The Vasodilating β-Blockers**

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Agent(s)</th>
<th>Site of Activity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;-receptor</td>
<td>carvedilol, acebutolol,</td>
<td>receptors located in smooth</td>
<td>antagonism causes</td>
</tr>
<tr>
<td>antagonist</td>
<td>bucindolol</td>
<td>muscle, heart</td>
<td>vasodilation</td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt;-agonism</td>
<td>dilevalol, celiprolol</td>
<td>receptors located in bronchi,</td>
<td>stimulation causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood vessels, gut</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>L-arginine/NO</td>
<td>nebivolol</td>
<td>pathways located in blood vessel</td>
<td>stimulation causes</td>
</tr>
<tr>
<td>pathways</td>
<td></td>
<td>walls</td>
<td>vasoconstriction</td>
</tr>
</tbody>
</table>


**Atenolol Increases the Risk of Stroke and All-Cause Mortality**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.26 (1.15-1.38)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.05 (0.91-1.21)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.08 (1.02-1.14)</td>
</tr>
</tbody>
</table>


**Non-Atenolol β-Blockers Do Not Increase Stroke, MI, or Mortality**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.20 (0.30-4.71)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.86 (0.67-1.11)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.89 (0.70-1.12)</td>
</tr>
</tbody>
</table>

**β-Blockers vs Diuretics: Elderly HTN**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Active treatment events</th>
<th>Control events</th>
<th>Odds ratio and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular events</td>
<td>222/3576</td>
<td>52/1026</td>
<td>1.9 (1.5 to 2.3)</td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>99/1828</td>
<td>34/521</td>
<td>1.3 (1.0 to 1.7)</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>58/3976</td>
<td>25/1621</td>
<td>1.9 (1.5 to 2.3)</td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>123/1861</td>
<td>78/2978</td>
<td>1.2 (0.98 to 1.4)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>365/5876</td>
<td>531/6661</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>115/1521</td>
<td>197/2678</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>320/636</td>
<td>510/6618</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>130/1521</td>
<td>230/2678</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>661/5876</td>
<td>551/6661</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>227/1521</td>
<td>366/2678</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(β-Blockers)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Outcomes With β-Blocker Therapy in Diabetes: UKPDS Study**

**Relative Risk and 95% CI**

- Any diabetes-related endpoint: RR 1.10, 95% CI 0.5 to 2.3
- Diabetes-related deaths: RR 1.27, 95% CI 0.6 to 2.6
- All-cause mortality: RR 1.14, 95% CI 0.6 to 2.2
- Myocardial infarction: RR 1.12, 95% CI 0.6 to 2.2
- Stroke: RR 1.12, 95% CI 0.6 to 2.2
- Microvascular disease: RR 1.12, 95% CI 0.6 to 2.2

**GEMINI: Effect on Blood Pressure and Heart Rate**

- Carvedilol (n = 541)
- Metoprolol (n = 636)

- Metoprolol group had higher rate of bradycardia (4.1% vs 1.4%, \( P = 0.007 \))

- Baseline Month 5 Baseline Month 5

- Heart rate, minute

**Change in Hemoglobin A<sub>1c</sub>**

- GEMINI

- Mean HbA<sub>1c</sub> (%)

- Treatment Difference
  - Carvedilol vs Metoprolol: 0.8% (0.2%, 1.4%, \( P = 0.004 \))

**Change in Insulin Resistance by Homeostasis Model Assessment (HOMA)**

- GEMINI

- Treatment Difference
  - Carvedilol vs Metoprolol: 0.8% (0.2%, 1.4%, \( P = 0.004 \))

**Change in Glucose and Lipids in Patients With Diabetes**

- Glucose: -16%
- Cholesterol: -9%
- Triglycerides: -18%
Change in Insulin Sensitivity in Hypertensive Patients With Glucose Intolerance

N = 25. Crossover; 16-week treatments. Nebivolol 2.5-5 mg and atenolol 50-100 mg daily.

*P < 0.05 vs placebo.
EH, euglycemic-hyperinsulinemic; IVGTT, intravenous glucose tolerance test.


Effect of β-Blockade on Insulin Level and Sensitivity in Hypertensive Patients

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
Placebo Nebivolol Atenolol

Glucose disappearance rate
K (min⁻¹)

Glucose disposal rate
M (mg/kg per min)

Insulin sensitivity

EH clamp
IVGTT
≈ 20% reduction

Placebo Nebivolol Atenolol
≈ 10% reduction

*P < 0.01

Effect of β-Blockade on Forearm Blood Flow

N = 16 healthy men.


Nitric Oxide Is Vasoprotective and Anti-atherogenic

Endothelium

NO

Inhibits

Oxidation of LDL cholesterol
Smooth muscle proliferation
Expression of adhesion molecules
Endothelin production
Platelet aggregation
Smooth muscle contraction
Monocyte and platelet adhesion

Nitric oxide (NO) inhibits these processes, which are involved in atherogenesis.

Endothelial Dysfunction Predicts CV Events in Hypertensive Patients

Key Findings From Recent Lipid-Lowering Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT-LT</td>
<td>2002</td>
<td>Neutral effect in HTN with mid lipid lowering</td>
</tr>
<tr>
<td>ASCOT-LA</td>
<td>2003</td>
<td>Benefit in high-risk HTN regardless of baseline LDL-C</td>
</tr>
<tr>
<td>CAROS</td>
<td>2004</td>
<td>Benefit in DM</td>
</tr>
<tr>
<td>PROVE-IT-TIMI 22</td>
<td>2004</td>
<td>Early and late benefit of intensive vs moderate lipid lowering in ACS</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>Benefit of intensive vs moderate lipid lowering in stable CAD</td>
</tr>
</tbody>
</table>

Key Findings From Recent BP-Lowering Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>2002</td>
<td>Similar CHD outcomes for diuretic, CCB, and ACEI; diuretic superior in preventing HF (and stroke &amp; CVD vs ACEI)</td>
</tr>
<tr>
<td>INVEST</td>
<td>2003</td>
<td>CCB + ACEI equivalent to β-blocker + diuretic in hypertension + CAD</td>
</tr>
<tr>
<td>VALUE</td>
<td>2004</td>
<td>ARB and CCB similar in composite 1 EP, CCB lower MI rate</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>2005</td>
<td>Benefit of CCB + ACEI vs β-blocker + diuretic in hypertension without CCB</td>
</tr>
</tbody>
</table>

Multiple Antihypertensive Agents Are Needed to Achieve Target BP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence of Sexual Dysfunction (% of pts)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCBs</td>
<td>18.3</td>
<td>Fogari et al. Am J Hypertens. 2004;17:77</td>
</tr>
</tbody>
</table>

β-Blockers Associated with Sexual Dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence of Sexual Dysfunction (% of pts)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol*</td>
<td>Desire (-18%)/Fantasies (-23%)</td>
<td>Fogari et al. Am J Hypertens. 2004;17:77</td>
</tr>
</tbody>
</table>

The Seventh Report of the Joint National Committee

<table>
<thead>
<tr>
<th>Compelling Indications</th>
<th>Diuretic</th>
<th>βB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Post-MI</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Diabetes</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>✔</td>
<td></td>
<td>⊗</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>✔</td>
<td></td>
<td>⊗</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary

- Some HTN studies and meta-analyses have shown inferior CV outcomes with β-blockers.
- The β-blockers are of critical importance in the management of patients with cardiovascular disease in general, and are useful in HTN.
- Vasodilating β-blockers (carvedilol, nebivolol) are associated with improved tolerability (metabolic symptoms) and have a better hemodynamic profile.
- Future trials of newer β-blockers may clarify their role in HTN.

Case Review for Complicated Hypertension

Case: 55-Year-Old Woman With Multiple CVD Risk Factors

New patient
- 55-year-old woman; smoker
- Previously diagnosed with slightly elevated BP, cholesterol, and glucose levels
  - Refused suggested medications
- States she is “a little overweight”
  - Asks to be prescribed weight loss pills
- Father died at age 62 of a heart attack
- Mother, age 74, developed diabetes in her mid-50s

Case: 55-Year-Old Woman With Multiple CVD Risk Factors

Physical exam
- Height: 5'5"
- Weight: 196 lb
- BMI: 32.6 kg/m²
- Waist: 44" (central obesity)
- BP: 160/96 mm Hg
- Pulse: 72 bpm
- Heart: RRR without murmur

Labs
- Total cholesterol: 238 mg/dL
- LDL-C: 105 mg/dL
- HDL-C: 32 mg/dL
- Triglycerides: 350 mg/dL
- Fasting glucose: 112 mg/dL
- HbA1C: 7.0
- Creatinine: 1.3 mg/dL
- Estimated GFR (MDRD): 62 mL/min/1.73 m²

ARS Question 1

Assuming lifestyle intervention has been implemented, which of the following CV risk factors need pharmacological treatment?

1. Blood Pressure
2. Triglycerides
3. Glucose
4. 1 & 3
5. All of the Above

AHA/NHLBI-Modified ATP III Criteria for Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 40 in</td>
<td>44</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 35 in</td>
<td>350</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>≥ 150</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>Men &lt; 40</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Women &lt; 50</td>
<td></td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>≥ 130 or 85</td>
<td>160/96</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>≥ 100</td>
<td>112</td>
</tr>
</tbody>
</table>

Patient has all 5 risk factors

Case: 55-Year-Old Woman With Multiple CVD Risk Factors

Diagnosis:
- Hypertension with metabolic syndrome
- Dyslipidemia
- Smoker

Patient is identified as being at moderate risk for a CV event by Framingham risk score (17% 10-year risk)

ARS Question 2

In addition to low dose aspirin, she agrees to take a “couple” of pills; which of these would be most useful?

1. RAS blocker/calcium antagonist
2. Calcium antagonist with a statin plus fixed dose of a RAS blocker/diuretic
3. RAS blocker/β-Blocker plus fenofibrate
4. RAS blocker/calcium antagonist plus fenofibrate
5. RAS blocker/calcium antagonist plus niacin

Case: 50-Year-Old Man With T2DM and CAD

- 50-year-old man
- Being seen for increased triglycerides refractory to fibrates
- Past medical history:
  - Diagnosed with T2DM at age 42
  - 5 vessel CAD with CABG at age 47
- Family history:
  - Father died at age 62 with CAD
  - Paternal grandfather died at age 65 with CAD
  - Mother and maternal grandmother with T2DM

Medications
- ASA/Warfarin
- Metformin 1000 BID
- Glyburide 2.5 BID
- Fenofibrate 145 mg/day
- Metoprolol 100 mg/day
- HCTZ/triamterene 25/100 mg/d
- Niacin (intermittent/noncompliant)
- Fish oil x 2 grams/day
- Multivitamin x 1 daily

Case: 50-Year-Old Man With T2DM and CAD

- Physical exam
  - 220 lbs and 71 in = BMI 30.7 kg/m²
  - Central obesity
  - CABG scars
  - BP: 138/86 mm Hg
  - P: 56 regular

Case: 50-Year-Old Man With Type 2 DM and CAD

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>146 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.8%</td>
<td>5% (T2DM goal &lt; 7%)</td>
</tr>
<tr>
<td>ALT</td>
<td>66 IU/L</td>
<td>≤ 60</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1.6 mg/L</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Insulin</td>
<td>28.1 uU/mL</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Trig</td>
<td>289 mg/dL</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>LDL-C</td>
<td>117 mg/dL</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>HDL-C</td>
<td>29.9 mg/dL</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>
ARS Question 3

How should the meds/lifestyle be adjusted?

1. Taper the metoprolol and diuretics and substitute a vasodilating beta blocker and ACE inhibitor for BP
2. Stop fenofibrate and start (titrate) sustained-release niacin 2.5 g at bedtime
3. Low carbohydrate diet/increase exercise
4. Increase glyburide to 5 mg BID
5. All of the above

Case: 50-Year-Old Man With T2DM and CAD: Teaching Points

Multiple cardiovascular risk factors

– s/p CABG (secondary prevention)
– Dyslipidemia (Trig/HDL-C)
– Obesity (BMI > 27 with comorbidities)
– Diabetes