From Hypertension to Heart Failure: A Renewed Look at Beta Blockade in Clinical Practice

Thursday, May 28, 2009
St. Louis, MO

The Clinical Management of Hypertension with Today’s β-Blockers
C. Venkata S. Ram, MD, MACP, FACC
Medical Director, Texas Blood Pressure Institute; Director of Medical Education and Research, Dallas Nephrology Associates; Clinical Professor of Internal Medicine, University of Texas, Southwestern Medical Center; Dallas, TX

Reviewing the Clinical Impact of β-Blockers in Heart Failure
Clive Rosendorff, MD, PhD, DScMed
Professor of Medicine
Mount Sinai School of Medicine
Department of Medicine
VA Medical Center
New York, NY
Session 1: From Hypertension to Heart Failure: 
A Renewed Look at β-Blockade in Clinical Practice

Learning Objectives

- Analyze the pharmacologic and clinical differences between older-generation and newer β-blockers, and describe how newer formulations may aid in the control of complicated hypertension and elevated cardiovascular risk in primary care practice.
- Evaluate the evidence supporting the use of β-blockers in the management of patients with heart failure, and delineate how newer β-blockers may have a particular role in this patient population.

Faculty

C. Venkata S. Ram, MD, MACP, FACC
Medical Director, Texas Blood Pressure Institute
Director of Medical Education and Research, Dallas Nephrology Associates
Clinical Professor of Internal Medicine, University of Texas, Southwestern Medical Center
Dallas, Texas

Dr C. Venkata Ram has centered his professional career on the management of hypertension, and he is one of the very few individuals who have combined clinical practice with an academic career. The author of more than 290 articles and a book on the treatment of hypertension, Dr Ram is also a renowned speaker in the field. Dr Ram has made numerous contributions to our understanding of both the physiology and the management of hypertension.

In addition to expertise in clinical research and medical practice, Dr Ram is considered a uniquely skilled communicator of scientific advances. Dr Ram was the youngest person ever to become the Master of American College of Physicians. Dr Ram is on the editorial boards of numerous national and international medical journals as well as chairman, Board of Governors and vice-president of the American Society of Hypertension.

Clive Rosendorff, MD, PhD, DScMed
Professor of Medicine
Mount Sinai School of Medicine
Department of Medicine
VA Medical Center
New York, New York

Dr Clive Rosendorff is an accomplished writer, researcher, and speaker, and serves on the editorial boards of 12 major cardiovascular journals. He has authored 3 textbooks and over 250 peer-reviewed research papers and book chapters on the subjects of hypertension, vascular biology, cardiovascular pharmacology, coronary blood flow, and cerebral circulation. He has lectured on the topics of vascular biology and atherogenesis, preventive cardiology, acute coronary syndrome and heart failure. He recently served as chair of the American Heart Association Guidelines Committee on the management of hypertension in patients with ischemic heart disease. He is also principal investigator of an international study of B-type natriuretic peptide (BNP) in heart failure.

Dr Rosendorff is certified by the American Society of Hypertension as a clinical hypertension specialist and is a fellow of the Royal College of Physicians of London, the American College of Cardiology, and the American College of Physicians. He is the recipient of numerous awards, including the International Academy of Cardiology’s Walter Bleifeld Memorial Award for Distinguished Contribution to Clinical Research.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:

Dr Ram discloses that he receives honoraria for his role as an advisory board participant in connection with Peer Group/AHM/Cogonix.

Dr Rosendorff has nothing to disclose.
Education Partner Financial Disclosure Statement
The individual content collaborators at Strategic Medical Initiatives, LLC, report that there are no conflicts which would impact the content of this activity.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
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<tr>
<td>acebutolol</td>
<td>Sectral</td>
<td>pindolol</td>
<td>Visken</td>
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<td>Tenormin</td>
<td>propranolol</td>
<td>Inderal</td>
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<td>bisoprolol</td>
<td>Zebeta</td>
<td>timolol</td>
<td>Blocadren</td>
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<td>carvedilol</td>
<td>Coreg</td>
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<td>labetalol</td>
<td>Normodyne</td>
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<td>metoprolol</td>
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<tr>
<td>metoprolol succinate</td>
<td>Toprol XL</td>
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<tr>
<td>metoprolol tartrate</td>
<td>Lopressor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nebivolol</td>
<td>Bystolic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Investigational**

- bucindolol
- celiprolol
- dilevalol

**Suggested Reading List**


From Hypertension to Heart Failure: A Renewed Look at β-blockade in Clinical Practice

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Meeting Agenda and Learning Objectives

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 30 minutes | The Clinical Management of Hypertension With Today’s β-blockers
C. Venkata S. Ram, MD, MACP, FACC |
| 30 minutes | Reviewing the Clinical Impact of β-blockers in Heart Failure
Olva Rosendorff, MD, PhD, DScMed |
| 15 minutes | Questions and Answers |

Learning Objectives

- Analyze the pharmacologic and clinical differences between older generation and newer β-blockers, and describe how newer formulations may aid in the control of complicated hypertension and elevated cardiovascular risk in primary care practice
- Evaluate the evidence supporting the use of β-blockers in the management of patients with heart failure, and delineate how newer β-blockers may have a particular role in this patient population

C. Venkata S. Ram, MD, MACP, FACC

Grant/Research Support Peer Group/AHM/Cogonix

Consultant None

Speakers’ Bureau None

Hypertension* Prevalence Increases With Age (NHANES 1999-2004)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>11.2</td>
<td>8.4</td>
</tr>
<tr>
<td>35-44</td>
<td>23.2</td>
<td>18.3</td>
</tr>
<tr>
<td>45-54</td>
<td>37.5</td>
<td>37.4</td>
</tr>
<tr>
<td>55-64</td>
<td>48.1</td>
<td>48.1</td>
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<tr>
<td>65-74</td>
<td>63.6</td>
<td>63.6</td>
</tr>
<tr>
<td>75+</td>
<td>83.8</td>
<td>83.8</td>
</tr>
</tbody>
</table>

*Defined as systolic/diastolic blood pressure ≥ 140/90 mm Hg.
NHANES=National Health and Nutrition Examination Survey.

Awareness, Treatment, and Control Rates by Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Awareness</th>
<th>Treatment</th>
<th>Control (all hypertensive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Whites</td>
<td>66.4</td>
<td>53.7</td>
<td>36.4</td>
</tr>
<tr>
<td>Non-Hispanic Blacks</td>
<td>66.4</td>
<td>55</td>
<td>28.9</td>
</tr>
<tr>
<td>Mexican Americans</td>
<td>63.5</td>
<td>48.3</td>
<td>26.5</td>
</tr>
</tbody>
</table>

NHANES 2003–2004

[Graphs and tables representing data]

Age-adjusted:
NHANES=National Health and Nutrition Examination Survey. hypertension=average BP ≥ 140/90 mm Hg. or patient was taking antihypertensive medications.
**Ischemic Heart Disease Rates by SBP, DBP, and Age**

- **CI=confidence interval; DBP=diastolic blood pressure; IHD=ischemic heart disease; SBP=systolic blood pressure.**

**Systolic Blood Pressure**
- 40-49 years: 256
- 50-59 years: 128
- 60-69 years: 64
- 70-79 years: 32
- 80-89 years: 16
- 90-99 years: 8
- 100-109 years: 4
- 110-119 years: 2
- 120-129 years: 1

**Diastolic Blood Pressure**
- 70-79 years: 256
- 80-89 years: 128
- 90-99 years: 64
- 100-109 years: 32
- 110-119 years: 16
- 120-129 years: 8
- 130-139 years: 4
- 140-149 years: 2
- 150-159 years: 1

**Average reduction in events (%)**
- Stroke: 35%-40%
- Myocardial infarction: 20%-25%
- Heart failure: >50%

**Long-term Antihypertensive Therapy Significantly Reduces CV Events**

**The Role of β-blockers in the JNC 7 Algorithm for Blood Pressure Control**

**JNC 7 Compelling Indications**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diuretic</th>
<th>β-blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>AA</th>
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</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>

**Current Considerations with β-blockers**

- Efficacy of β-blockers is well established in primary prevention, secondary prevention, and subpopulations<sup>1-7</sup>
- Emerging evidence has called into question the role of β-blockers<sup>3</sup>

ARS Question
When prescribing a β-blocker, what characteristics are you most likely to look for in your patients?

1. General Uncomplicated Hypertension
2. Hypertension with Cardiovascular Disease Risk Factors
3. Heart Failure
4. Post-Myocardial Infarction
5. Angina

ARS Question
When prescribing a β-blocker for hypertension, at what point in your treatment algorithm do you typically use this class of agents?

1. First-line therapy
2. Second-agent
3. Third-agent
4. Fourth-agent

Meta-analysis of β-blockers in Hypertension

- Meta-analysis of randomized, controlled trials of treatment of primary hypertension
  - β-blocker as first-line therapy in ≥50% of all patients in one treatment group
  - Outcome data for all-cause mortality, CV morbidity, or both
- 13 trials (n=105,951) comparing β-blockers with other antihypertensive therapies
- 7 trials (n=27,433) comparing β-blockers with placebo or no therapy
- Data analyzed for all β-blockers, non-atenolol β-blockers, mixed β-blockers and diuretics, and atenolol

Meta-analysis of β-blockers in Hypertension: Outcome Data for Atenolol vs Non-β-blocker Antihypertensive Therapy

- **Stroke**: 1.26 (1.15-1.38)
- **MI**: 1.05 (0.91-1.21)
- **All-cause mortality**: 1.08 (1.02-1.14)

Meta-analysis of β-blockers in Hypertension: Outcome Data for Non-atenolol β-blockers vs Non-β-blocker Antihypertensive Therapy

- **Stroke**: 1.20 (0.30-4.71)
- **MI**: 0.86 (0.67-1.11)
- **All-cause mortality**: 0.89 (0.70-1.12)

ARS Question
In your opinion, is the increased risk of certain cardiovascular events associated with β-blockers a class effect?

1. Yes
2. No
The Evolution of β-blockers

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity</td>
<td>Non-Selective</td>
<td>Selective</td>
<td>Non-Selective</td>
<td>Selective</td>
</tr>
<tr>
<td>Vasodilating</td>
<td>Propranolol</td>
<td>Pindolol</td>
<td>Atenolol</td>
<td>Nebivolol</td>
</tr>
<tr>
<td>Vasodilating</td>
<td>Metoprolol</td>
<td>Carvedilol</td>
<td>Labetalol</td>
<td></td>
</tr>
</tbody>
</table>


Main Factors Contributing to Heterogeneity Within the β-blocker Class

- β₁/β₂ Selectivity
- Vasodilating Properties
- Side effects
- Metabolic profile
- Efficacy


Pharmacologic Properties of β-blockers

<table>
<thead>
<tr>
<th>β-blocker</th>
<th>ISA</th>
<th>Selectivity</th>
<th>Vasodilating</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>Cardioselective</td>
<td>No</td>
<td>qbid</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>No</td>
<td>qd</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>No</td>
<td>qd</td>
</tr>
<tr>
<td>Butalbital</td>
<td>+</td>
<td>Nonselective</td>
<td>Yes</td>
<td>bid</td>
</tr>
<tr>
<td>Nebivolol*</td>
<td>-</td>
<td>Cardioselective</td>
<td>Yes</td>
<td>qd</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>-</td>
<td>Nonselective</td>
<td>Yes</td>
<td>bid</td>
</tr>
<tr>
<td>Labetalol</td>
<td>+</td>
<td>Nonselective</td>
<td>Yes</td>
<td>bid</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>-</td>
<td>Cardioselective</td>
<td>No</td>
<td>qbid</td>
</tr>
<tr>
<td>Nebivolol</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>


Various Mechanisms of Action of Vasodilating β-blockers

- α₁-receptor blockade: labetalol, carvedilol, and (likely) bucindolol
  - α₁-receptors located in smooth muscle, heart
  - when stimulated, cause contraction
- β₂-agonism: dilevalol*, ceiprolol†
  - β₂-receptors located in bronchi, blood vessels, gut
  - when stimulated, cause vasodilation
- Increase in NO bioavailability: nebivolol
  - Pathways located in blood vessel walls
  - when stimulated, increases release/activity of NO, and vasodilation

*Removed from market; †not marketed in US.

Sympathetic Nervous System and HTN

Rationale for Dual α₁/β Blockade in HTN

- NE
- Postganglionic SNA
- Vasoconstriction
- Tachycardia
- Renal Na+ retention
- Vascular remodeling

HYPERTENSION


Potential Benefits of Combined α and β-Blockade

- Sympathetic Activation
- α₁ receptors
- β₁ receptors
- β₂ receptors

Cardiotoxicity

Metoprolol
Propranolol
Carvedilol

Effects of Nebivolol and Atenolol on Endothelial-Mediated Vasodilation

Percent change in FBF


Effects of Nebivolol and Atenolol on NO in White and African American Endothelium

Change in ACh-stimulated NO release (fM)


Effects of Nebivolol and Atenolol on Endothelial-Mediated Vasodilation

Change in Acetylcholine (nmol/min)


Effects of Nebivolol and Atenolol on NO in White and African American Endothelium

Change in L-NMMA (µmol/min)


Effect of β-blockers on NO Release in Endothelial Cells of Black Americans

NO release (fM)


Hemodynamic Effects of Nebivolol and Atenolol in Patients with Hypertension

*Placebo corrected.


Carvedilol And Metoprolol in Patients with Hypertension: Diastolic and Systolic BP

Change from baseline in trough BP (mm Hg)


Hypertension in African-Americans

- Increased prevalence and severity
- Increased complication rate
  - 1.8 X risk for fatal stroke
  - 1.5 X risk for CHD mortality
  - 4.2 X risk for ESRD
  - 2 X risk for HF
- Volume-dependent hypertension
- Reduced BP response to β-blockers
- Reduced bioavailability of endothelial-derived NO
Efficacy Of Carvedilol and Acebutolol in Black Patients: Diastolic and Systolic BP

-6* -5* -4

Carvedilol 25 mg qd (n=20)
Acebutolol 200 mg qd (n=20)

\*P<0.05 vs baseline; †P<0.05 vs baseline.

Nebivolol in Black Patients: Diastolic and Systolic BP

Mean Δ in BP vs baseline (mm Hg)

Placebo: DBP=baseline, SBP=baseline

Nebivolol 5 mg
Nebivolol 10 mg
Nebivolol 20 mg


Nebivolol Efficacy by Baseline Systolic BP*

Mean Δ in BP vs baseline (mm Hg)

Placebo: DBP=baseline, SBP=baseline

*Hypertensive severity as defined by baseline SBP; data for patients randomized to receive placebo or nebivolol 5 mg, 10 mg, or 20 mg are shown.

ARS Question
What are the issues with traditional β-blockers that may prevent you from using them in certain patients?
1. 24-hour BP control with QD dosing (atenolol, metoprolol tartrate, carvedilol)
2. Tolerability
   - Fatigue
   - Sexual dysfunction
   - Cold extremities
   - Orthostatic hypotension
3. Hard to treat patients
   - Black patients
   - Obese patients
4. Additional considerations
   - Effects on metabolic parameters
5. All of the above

ARS Question
If adverse events were not a concern with traditional β-blockers, in which patients would you use these agents more frequently?
1. Younger patients
2. Male patients
3. Elderly patients
4. Patients with peripheral vascular disease
5. Earlier use in treatment regimen
6. Increased use across all patient types
Classic β-blocker Side Effects

• Fatigue
• Reduced exercise capacity
• Raynaud’s phenomenon
• Cold extremities
• Erectile dysfunction
• Bronchospasm
• Sinus bradycardia
• A-V block
• Metabolic effects

### Side Effects Commonly Associated with β-Blockers

<table>
<thead>
<tr>
<th>Adverse Event %</th>
<th>Nebivolol 5 mg–40 mg (n=1597)*</th>
<th>Carvedilol</th>
<th>Metoprolol Succinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.0 to 9.0 across doses</td>
<td>11.5 to 20.0 across doses</td>
<td>7.5 to 10 across studies</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.6</td>
<td>7.5% to 16% across studies</td>
<td>5.5% to 16% across studies</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.0</td>
<td>5.5% to 7.0% across studies</td>
<td>4.7 to 7.0% across studies</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.8</td>
<td>2.0% to 2.7% across studies</td>
<td>2.0% to 3.1% across studies</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>0.6†</td>
<td>13.5% to 14.0% across studies</td>
<td>4.0% to 4.0% across studies</td>
</tr>
<tr>
<td>Depression</td>
<td>0.3</td>
<td>&gt;0.1 to 1.0% across studies</td>
<td>0.1% to 4.0% across studies</td>
</tr>
</tbody>
</table>

*Pooled data from the three monotherapy US registration trials with nebivolol.
†For erectile dysfunction n=108 for placebo and n=853 for nebivolol 5 mg to 40 mg.

### GEMINI: Hemoglobin A1c

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n=454)</th>
<th>Metoprolol Lactate (n=657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c (%)</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>Carvedilol vs Metoprolol lactate</td>
<td>-0.13% (0.22, -0.04)</td>
</tr>
</tbody>
</table>

1111 patients (90%) were evaluable for efficacy, having both a valid baseline and at least one on-therapy HbA1c assessment.

### Effect of β-Blockers on Insulin Sensitivity in Patients with Hypertension

**Difference between vasodilating and nonvasodilating β-blockers is approximately 30% (similar to effects of insulin-sensitizers)**

### Summary

- β-blockers remain an essential component of cardiovascular pharmacotherapy
- β-blockers are highly heterogeneous
  - most notable recent advance is development of vasodilating β-blockers
- Vasodilating β-blockers may have important clinical advantages

### Case Study
Presentation

- 72-year-old Caucasian woman with fatigue and headache
- Previous medical history: hypertension (5 years duration) treated with thiazide diuretic
  - 12.5 mg/d HCTZ; reports often “forgetting” to take pill
- Denies alcohol use; ex-cigarette smoker (1 ppd; quit at age 65)
- Has been told his BP was elevated on exams over the past 5 years
- Family history: positive for hypertension and MI

Risk Considerations

- Post-menopausal woman
- Family history of hypertension and MI
- 3 metabolic syndrome risk factors: abdominal obesity, hypertension, + IFG
- ECG-LVH with strain pattern

Physical Examination and Labs

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (in)</td>
<td>6'4&quot;</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>165</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3</td>
</tr>
<tr>
<td>Abdominal circumference (in)</td>
<td>40</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>172/97</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>89 and regular</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>96</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5</td>
</tr>
<tr>
<td>eGFR</td>
<td>60</td>
</tr>
<tr>
<td>K+</td>
<td>3.8</td>
</tr>
<tr>
<td>Alb/creat (mg/g creat)</td>
<td>17</td>
</tr>
</tbody>
</table>
| Lipids:
  | Total C | 185  |
  | LDL-C   | 121  |
  | HDL-C   | 32   |
  | TG      | 218  |

- Fundus: Grade II K-W change (no hemorrhages or exudates)
- Neck: normal thyroid, carotid pulses 2+, no bruits
- Cardiac exam: regular rate, $S_4$, no murmurs, gallops, rubs
- Abdomen: centrally obese, no bruits
- ECG: increased R-wave voltage with ST flattening c/w LVH

ARS Question

What is this patient’s goal BP?

1. <140/90 mm Hg
2. <140/80 mm Hg
3. <130/85 mm Hg
4. <130/80 mm Hg
5. <120/80 mm Hg

ARS Question

What treatment do you recommend for this patient?

1. Anti-hypertension monotherapy, lifestyle changes, with follow-up appointment after 1 month
2. Anti-hypertension monotherapy, lifestyle changes, with follow-up appointment after 3 months
3. Combination anti-hypertension therapy, lifestyle changes, with follow-up appointment after 2 weeks
4. None of the above

ARS Question

Which fixed-dose combination would you begin with?

1. ACE inhibitor/diuretic
2. ARB/diuretic
3. β-blocker/diuretic
4. Dihydropyridine type CCB/ACE inhibitor
5. Non-dihydropyridine type CCB/ACE inhibitor
6. Dihydropyridine type CCB/ARB
Follow-up

• Patient treated with ACEI (lisinpril 20 mg) + HCTZ 12.5 mg
• Patient returns in 4 weeks
• BP: 150/89 mm Hg

ARS Question
What treatment adjustments would you make?

1. Initiate vasodilating β-blocker therapy
2. Initiate CCB therapy
3. Initiate α-blocker therapy
4. Initiate aldosterone antagonist therapy
5. None of the above

Clive Rosendorff, MD, PhD, DScMed

Grant/Research Support
None.

Consultant
None.

Speakers’ Bureau
None.

Reviewing the Clinical Impact of β-blockers in Heart Failure
Clive Rosendorff, MD, PhD, DScMed

The Cardiovascular Continuum: Targeting Mechanisms and Mediators
Maladaptive Cardiovascular Remodeling

- Endothelial Dysfunction
- Tissue injury (MI, stroke)
- Pathological remodeling
- Target-organ dysfunction (HF, renal disease)
- End-stage organ failure
- Death

Adapted from Pepine CJ. Am J Cardiol. 2001;88(suppl 1):5K-9K.

Development and Progression of CVD

- Risk factors
- Age, gender, smoking, inactivity, obesity, cholesterol, BP, glucose

- Genetic factors
- Endothelial function
- Inflammatory mediators
- Plaque growth, remodeling
- Clinical sequelae
- MI, stroke
- HF death

Adapted from Dzau V, Braunwald E. Am Heart J. 1991;121:1244-1263.
Progression From Cardiovascular Risk Factors to Cardiovascular Disease

- Hypertension
- Dyslipidemia
- Diabetes
- Smoking

Compensatory responses:
- Oxidative stress
- Inflammation
- Cell migration/proliferation
- Monocyte/platelet adhesion
- Platelet aggregation

CV Disease


Hypertension
Dyslipidemia
Diabetes
Smoking

Injury to endothelium
Endothelial dysfunction

Compensatory responses:
- Oxidative stress
- Inflammation
- Cell migration/proliferation
- Monocyte/platelet adhesion
- Platelet aggregation

CV Disease

More than 50% have ≥2 CV risk factors

>80% of Hypertensive Patients Have Additional Cardiovascular Risk Factors

- Obesity
- Glucose intolerance
- Hyperinsulinemia
- Reduced HDL-C
- Elevated LDL-C
- Elevated TG
- LVH

Kannel WB. Am J Hypertens. 2000:13:3S-10S.

Correlation Between Endothelial Function and Hypertension

Acetylcholine (μg/min)

Base line

Blod flow (mL/min/100 mL forearm volume)

P=0.001

No family history of hypertension

Family history of hypertension

FBF=forearm blood flow.


Endothelial Dysfunction Predicts CV Events in Hypertensive Patients

Event-free survival

Follow-up (mo)

Patients exposed to risk: 225

Total Mortality
22% to 23% reduction in total mortality in patients with hypertension or post-MI

CV Endpoints
27% to 38% reduction in sudden CV death or fatal/nonfatal stroke

Heart Failure
32% to 65% improvement in probability of event-free survival

Diabetes
Comparable cardiovascular profile in clinical end points related to diabetes (vs ACE-I)

ARS Question
Do you believe that β-blockers are underutilized in the treatment of heart failure?

1. Yes
2. No
When prescribing a β-blocker for your heart failure patients, what is the most common form of the disease you treat with this class of agents?

1. Systolic Heart Failure
2. Diastolic Heart Failure
3. Post-Myocardial Infarction

β-blockers are of proven benefit in many patients with hypertension and concomitant conditions, including:
- post-myocardial infarction
- heart failure
- high CV risk
- diabetes


RRR 22%  
P =0.028

Years  
5 10
Cumulative number of deaths
0 20 40 60 80 100

RRR 30%  
P =0.017

Years  
5 10

Summary of Trials of β-Blocker Therapy Post-MI

<table>
<thead>
<tr>
<th>Phase of Treatment</th>
<th>Total No. Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment</td>
<td>28,970</td>
<td>0.87 (0.77-0.98)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>24,298</td>
<td>0.77 (0.70-0.84)</td>
</tr>
<tr>
<td>Overall</td>
<td>53,268</td>
<td>0.81 (0.75-0.87)</td>
</tr>
</tbody>
</table>

Relative risk (RR) of death
β-blocker better
Placebo better


BP Lowering With ACEI or β-blocker Reduces Microvascular Complications in Type 2 Diabetes Mellitus

Less tight blood pressure control
Captopril
Aranoid
Tight blood pressure control
P≤0.43

Kaplan-Meier plots of proportion of patients with any clinical endpoint, fatal or nonfatal, related to diabetes.
**BEST: Evidence for β-blockers in Patients With Diabetes**

![Graph showing event-free survival over months post-randomization for Placebo and Bucindolol groups.](image)

- **Log rank=3.14**
- **P-value=0.0017**
- **Total events=559**

**Placebo** 465 352 250 167 119 82 41 17

**Bucindolol** 499 407 311 233 176 109 64 24

**Event-free survival**


**ARS Question**

In your opinion, how strong is the evidence supporting the use of β-blockers in post-MI patients?

1. Very strong
2. Strong
3. Not so strong
4. Weak

**ARS Question**

In your opinion, how strong is the evidence supporting the use of β-blockers in heart failure patients with diabetes?

1. Very strong
2. Strong
3. Not so strong
4. Weak

**Neurohormonal Activation in Heart Failure**

- **Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)**
- **Morbidity and mortality**
- **Arrhythmias**
- **Pump failure**
- **Peripheral vasoconstriction**
- **Sodium retention**
- **Hemodynamic alterations**
- **Remodeling and progressive worsening of L.V. function**
- **Fibrosis, apoptosis, hypertrophy, cellular/molecular alterations, myotoxicity**
- **Activation of RAS and SNS**
- **HF symptoms: Fatigue, Activity altered, Chest congestion, Edema, Shortness of breath**

**Evidence for β-blockers in Secondary Prevention**

![Graph showing survival and risk reduction for US Carvedilol Heart Failure Study Group, CIBIS-II, COPERNICUS, MERIT-HF, and Carvedilol Heart Failure Study Group.](image)

- **US Carvedilol Heart Failure Study Group**
  - **Risk reduction=55%**
  - **P<0.0001**

- **CIBIS-II**
  - **Risk reduction=34%**
  - **P=0.0033**

- **COPERNICUS**
  - **Risk reduction=30%**
  - **P<0.0001**

- **MERIT-HF**
  - **Risk reduction=34%**
  - **P=0.0004**

**β-blocker Use on Discharge is Associated with Improved Survival**

![Graph showing survival time in days since discharge for OPTIMIZE-HF study.](image)

- **HR=0.47**
- **95% CI (0.32-0.71)**
- **P<0.0004**

**Carvedilol** vs **No β-blocker**

- **Absolute mortality rates: carvedilol 8%, no β-blocker 16%**

**Patients at risk:**
- **Carvedilol:** 1182
- **No β-blocker:** 262

**Fonarow GC et al. Am Heart J. 2007;153:9-11.**
**COPERNICUS Study**

**All Randomized Patients**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Nebivolol</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>0.79 (0.54-1.18)</td>
<td>1.00 (0.74-1.36)</td>
<td></td>
</tr>
</tbody>
</table>

**High-Risk Patients**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Nebivolol</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>0.26 (0.16-0.41)</td>
<td>1.00 (0.64-1.55)</td>
<td></td>
</tr>
</tbody>
</table>

**SENIORS Primary Endpoint: All-cause Mortality and CV Hospitalizations**

**Nebivolol**

RRR: -14%

ARR: - 4.2%

% patients with events

P = 0.039

**Placebo**


**β-blocker Heart Failure Trials and the Population Typically Treated**

<table>
<thead>
<tr>
<th>Trial</th>
<th>SENIORS</th>
<th>MERIT-HF</th>
<th>CIBIS-II</th>
<th>COPERNICUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>76.2 ± 11</td>
<td>64 ± 10</td>
<td>61 ± 11</td>
<td>63 ± 11.7</td>
</tr>
<tr>
<td>LVEF (mean ± SD)</td>
<td>≤ 35%: 65%</td>
<td>≤ 40%: 45%</td>
<td>&gt;40%: 55%</td>
<td>≤ 35%: 65%</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>I</td>
<td>III</td>
<td>IV</td>
<td>I</td>
</tr>
<tr>
<td>%</td>
<td>3%</td>
<td>36%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**ARS Question**

Are you concerned about potential metabolic side effects when treating you heart failure patients with β-blockers?

1. Yes
2. No

**Effect of β-Blockers on Insulin Sensitivity in Patients with Hypertension**

Difference between vasodilating and nonvasodilating β-blockers is approximately 30% (similar to effects of insulin-sensitizers)

SENIORS: Development of New Onset Diabetes

**Summary**

- Blockade of $\beta_1$-receptors remains an essential component of cardiovascular pharmacotherapy.
- $\beta$-blockers are of proven benefit in patients with hypertension and concomitant conditions, including post MI, high CV risk, diabetes, and heart failure.
- It is a reasonable hypothesis that vasodilating $\beta$-blockers may have endpoint advantages.