Objectives

- Recognize increased cardiometabolic risks in racial/ethnic minorities and unique aspects
- Discuss advances for therapeutic lifestyle interventions, specifically for Blacks and Hispanics
- Address concerns that influence medication choices and goals, specifically for hypertension with diabetes, obesity and increased cardiometabolic risk
- Recognize evidence for benefits and risk of statins in cardiometabolic disease

Metabolic Syndrome: NCEP ATP III Definition

Positive diagnosis based on the presence of:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Men &gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td></td>
<td>Women &gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Men &lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women &lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL_fused</td>
</tr>
</tbody>
</table>


Prevalence T2DM by Race/Ethnicity

Prevalence of the NCEP Metabolic Syndrome

NHANES III by Sex and Race/Ethnicity
TG and HDL-C Axis in Population Studies

► NHANES: blacks lower TG and higher HDL-C and thus prevalence of MetS lower in blacks than whites
► Also, black vs. white Canadians and London-based Afro-Caribbeans vs. whites.
► Racial difference also true in children and more prominent in men than women.
► Considering higher stroke and MI vs. whites, favorable lipid profile of low TG and high HDL-C in blacks both surprising and paradoxical.

Yu SK et al, Metabol Synd Rel Dis 2012:10:77-82

"Race" is a crude proxy.

Correlates of Multiple CVD Risk

<table>
<thead>
<tr>
<th>Established</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Adiposity</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Socioeconomic status: income, health insurance, education</td>
</tr>
<tr>
<td>Age</td>
<td>Geographic region</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
</tr>
</tbody>
</table>


Social Determinants of Health

► The circumstances in which people are born, grow up, live, work, and age, as well as the systems put in place to deal with illness
► These circumstances in turn shaped by a wider set of forces: economics, social policies, and politics

www.cdc.gov/socialdeterminants
Treatment of the Metabolic Syndrome

- Therapeutic lifestyle interventions
- Diet
  - Increase fruits, vegetables
  - Increase omega-3 fatty acids
- Exercise
- Correct atherogenic dyslipidemia
  - Elevated triglycerides
  - Low HDL-C
  - Small, dense LDL particles
- Correct hypertension
- Aspirin for prothrombotic state

*LDL-C reduction alone does not result in full benefit

Lifestyle Management of Obesity-Related HTN

- Hypertension
- Weight loss
- Dietary Approaches to Stop Hypertension (DASH) diet
- Salt restriction
- Physical activity; exercise
- Alcohol moderation
- Behavioral modification

Journal of Clin Hypertension January 2013
Volume 15, Issue 1 | DOI: 10.1111/jch.12049

A Cheeseburger from a Five Guys Restaurant

Five Guys Cheeseburgers: Nutrition Facts & Calorie Information

- Calories-840
- Calories from Fat-500
- Total Fat (g)-55
- Saturated Fat (g)-26.5
- Cholesterol (mg)-165
- Sodium (mg)-1050
- Carbs (g)-40
- Protein (g)-47


I.O.M. - Eat Less Salt

1500 mg of sodium may further lower blood pressure and is particularly effective for middle-aged and older individuals, African Americans, and individuals with HTN

http://www.iom.edu/Reports/2010

Simple Solutions Don’t Work

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Incidence of Type 2 DM: Diabetes Prevention Program (DPP)

P<0.001 for comparison between each group

Cumulative Incidence of Diabetes (%)

Placebo
Metformin (-31%)
Intensive lifestyle modification (-58%)

Morehouse School of Medicine: e-HealthyStrides©

- Prime example of novel approach to patient-centered care
- Interactive ehealth program to improve DM self-management skills.

DM self-management integrated system to empower and engage patients, their social network, health coach and care team

Provides DM knowledge, linked to patient-driven results of blood glucose, exercise, and BP


CardioSmart’s FREE Text Messaging Services

CardioSmartTXT™ PREVENT: CVD text messaging / 2 weekly reminders about preventing CVD.

CardioSmartTXT™ QUIT: Smoking cessation texting service, providing tips and inspiration before and after desired quit date.

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Seven Steps to a Healthy Heart
Presented by: Association of Black Cardiologists

7 Steps to a Healthy Heart Educational Series overview

Addresses importance of:
- Being spiritually active
- Taking charge of your blood pressure
- Controlling cholesterol
- Tracking blood glucose levels
- Healthy diet and exercise programs
- Smoking cessation
- Gaining access to better health

7 Steps to a Healthy Heart Go to Guide Program Deliverables

**Digital Go-to-Guide:**
- 46-page interactive workbook
- “7 Steps to a Healthy Heart”
- English/ Spanish versions: 7 Chapters
- Video; Animations
- Printable Tools
  - PDFs for Placement on Community Web-Sites
  - Email and Social Media Share

The 7 Steps to a Healthy Heart Go-To-Guide™ Features...
- Unique page turning format familiar and comfortable to wider audience even those less web savvy
- Audio voice over of text improves comprehension at all reading levels

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Blood Pressure Goals for Patients with Diabetes: Where are We Now and Where are We Heading?

81 y/o female HTN & T2DM now on lisinopril 10 mg qd vs. Average BP 168/94 mmHg

What would be least appropriate target BP goal for this patient?

1. < 150/80 mm Hg
2. < 130/80 mm Hg
3. < 140/85 mm Hg
4. < 145/90 mm Hg

Goals of Therapy: JNC 7

Treat to BP <140/90 mm Hg or BP <130/80 mm Hg in patients with diabetes or chronic kidney disease


Goals of Therapy: JNC 8?*

Revisions to the Standards of Medical Care in Diabetes—2013

Revised SBP goal for many people with DM and HTN should be <140 mmHg

Lower SBP targets (such as <130 mmHg) may be appropriate for certain individuals, e.g. younger patients, if it can be achieved without undue treatment burden.

Diabetes Care January 2013 vol. 36 no.Supplement 1 S3
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group

Baseline Characteristics - ACCORD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean or %</th>
<th>Characteristic</th>
<th>Mean or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62</td>
<td>Blood Pressure (mm Hg)</td>
<td>139/76</td>
</tr>
<tr>
<td>Women %</td>
<td>48</td>
<td>On Antihypertensive %</td>
<td>87</td>
</tr>
<tr>
<td>2°prevention %</td>
<td>34</td>
<td>Creatinine (mg/dL)</td>
<td>0.9</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
<td>eGFR (mL/min/1.73m²)</td>
<td>92</td>
</tr>
<tr>
<td>White %</td>
<td>61</td>
<td>DM Duration (yrs)</td>
<td>10</td>
</tr>
<tr>
<td>Black %</td>
<td>24</td>
<td>A1C (%)</td>
<td>8.3</td>
</tr>
<tr>
<td>Hispanic %</td>
<td>7</td>
<td>BMI (kg/m²)</td>
<td>32</td>
</tr>
</tbody>
</table>

Primary Outcome: Nonfatal MI, Nonfatal Stroke or CVD Death

HR = 0.88
95% CI (0.73-1.06)

Secondary Outcome

Nonfatal Stroke

HR = 0.63
95% CI (0.41-0.96)
(p=0.03)

Total Stroke

HR = 0.59
95% CI (0.39-0.89)
(p=0.01)

Original Article

Intensive Blood-Pressure Control in Hypertensive Chronic Kidney

Appel, LJ, Wright, JT, et al., for the AASK Collaborative Research Group

N Engl J Med

Volume 363(10):918-929

September 2, 2010

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Which Class of Antihypertensive Drugs to Use First with Diabetes, Obesity and Cardiometabolic Risk?

A 72 y/o obese Black man has BP 148/92 mm Hg and no other co-morbid conditions. Which antihypertensive class is least desirable for combined effects on BP and further avoiding weight gain?

1. ACE inhibitors or ARBs
2. Diuretics
3. Non-selective B-blockers
4. All agents can used with similar effects on BP and metabolism

Angiotensin II and the Sequential Progression of Cardiovascular Disease

Vijayaraghavan K, Deedwania P. Cardiol Clin. 2005;23:165-183

Angiotensin II Antagonist Losartan Study (RENAAL) - losartan vs. placebo

ARBS and Renoprotection in DM

3 large RCTs ARBS +DM effective preventing nephropathy:
Renoprotective effects of irbesartan (2 doses) vs. placebo
Irbesartan Diabetic Nephropathy Trial (IDNT) - irbesartan vs. amlodipine vs. placebo
Angiotensin II Antagonist Losartan Study (RENAAL) - losartan vs. placebo
Clinical Trials Renal Outcomes Based on Proteinuria Reduction

Increased Time to Dialysis
(30-35% proteinuria reduction)
- Captopril Trial-N EJM, 1993
- AASK Trial-JAMA, 2001
- RENAAL-N EJM, 2001
- IDNT-N EJM, 2001

No Change in Time to Dialysis
No proteinuria reduction

DHPCCB arm-IDNT
DHPCCB arm-AASK

In: Egan BM, Reid RJ, and Lackland DT (eds.) Hot Topics in Hypertension.

ONTARGET: Risk of Primary Outcome* With Telmisartan, Ramipril, or Both

Cumulative Hazard Ratio

Follow-up (y)

Telmisartan
Ramipril
Telmisartan + Ramipril

ALLHAT ANGIOEDEMA

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Blacks</th>
<th>Non-blacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>8 / 15,255 (0.1%)</td>
<td>2 / 5,369 (&lt;0.1%)</td>
<td>6 / 9,886 (0.1%)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>41 / 9,054 (0.5%)</td>
<td>23 / 3,210 (0.7%)</td>
<td>18 / 5,844 (0.3%)</td>
</tr>
</tbody>
</table>

p<.001          p<.001          p=.002

Obesity-Related Hypertension:
Pathogenesis, Cardiovascular Risk, and Treatment: A Position Paper of The Obesity Society and the American Society of Hypertension

- Lewis Landsberg, Louis J. Aronne, Lawrence J. Beilin, Valerie Burke, Leon I. Igel, Donald Lloyd-Jones, and James Sowers

Journal of Clin Hypertension January 2013

Volume 15, Issue 1 | DOI: 10.1111/jch.12049

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Use of Beta-blockers in Obesity Hypertension: Potential Role of Weight Gain

- Adverse metabolic effects on lipids or insulin sensitivity
- In trials reporting weight changes, B-blockers associated weight gain of 1.2 (range -0.4-3.5) kg.
- May be attributable to decreased metabolic rate by 10% and other negative effects on energy metabolism.
- Question B-blockers as first-line therapy for overweight or obese patients with uncomplicated hypertension.

Pischon T, Sharma A; Obes Rev. 2001 Nov; 2(4)

Position Paper: Obesity-Related Hypertension

- Angiotensin is over-expressed in obesity, directly contributing to obesity-related HTN
- Making the case to consider ACE inhibitors/ARBs as first-line agents.
- In comparison, thiazide regimens increase insulin resistance and associated with increase in new cases of DM.

J Clin Hypertens (Greenwich). 2013; 15:14–33

Position Paper: Obesity-Related Hypertension

- Although thiazide diuretics are often recommended as first-line
- Known dose-related side effects include dyslipidemia and insulin resistance, undesirable in obese populations prone to MetS and type 2 DM.
- This causes a therapeutic dilemma since obesity-related HTN is salt-sensitive and diuretics will be required to control BP in most cases.

J Clin Hypertens (Greenwich). 2013; 15:14–33

A 72 y/o obese Black man has BP 148/92 mm Hg and no other co-morbid conditions. Which antihypertensive class is least desirable for combined effects on BP and further avoiding weight gain?

1. ACE inhibitors or ARBs
2. Diuretics
3. Non-selective B-blockers****
4. All agents can used with similar effects on BP and metabolism

J Clin Hypertens (Greenwich). 2013; 15:14–33

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Clinical Trials HTN and Cardiometabolic Disease


Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP/DBP</td>
<td>146 / 84</td>
<td>146 / 84</td>
<td>146 / 84</td>
</tr>
<tr>
<td>Black, %</td>
<td>35</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Women, %</td>
<td>47</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Current smoking</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>History of CHD, %</td>
<td>26</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Type 2 DM, %</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>

ALLHAT Stroke

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>0.92 (0.85-1.01)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.92 (0.85-1.00)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>0.92 (0.85-1.00)</td>
</tr>
<tr>
<td>Men</td>
<td>0.93 (0.88-1.00)</td>
</tr>
<tr>
<td>Women</td>
<td>1.05 (0.99-1.11)</td>
</tr>
<tr>
<td>Black</td>
<td>1.12 (1.00-1.26)</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.95 (0.89-1.02)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.99 (0.93-1.06)</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>0.99 (0.89-1.10)</td>
</tr>
</tbody>
</table>

DM Incidence - 4 Years

<table>
<thead>
<tr>
<th>DM Incidence (%)</th>
<th>Chlor</th>
<th>Amlod</th>
<th>Lisin</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>11.6</td>
<td>9.8</td>
<td>* 8.1</td>
</tr>
</tbody>
</table>

* p<.05 compared to chlorthalidone

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Diabetes and Hypertension: the Bad Companions

“In general, the positive effects of antihypertensive drugs on cardiovascular outcomes outweigh the negative effects of antihypertensive drugs on glucose metabolism.”

ACCOMPLISH: Design

- N=11,506 high CV-risk HTN,
- Age ≥55, SBP ≥160 mm Hg or on Rx
- 60% DM, 23%
- Post MI, 36% post coronary revasc, 13% post CVA
- No Hx of HF or LVEF<40%
- Multicenter, randomized, double-blind, initial anti-HTN efficacy 2 fixed-dose combinations:
  - HCTZ/benazepril (12.5-25/40 mg)
  - amlodipine/benazepril (5-10/40 mg)
- Primary endpoint: CV mortality & morbidity


ACCOMPLISH: Time to First Occurrence of Primary Endpoint*

<table>
<thead>
<tr>
<th>Months</th>
<th>Benazepril + HCTZ</th>
<th>Benazepril + amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>650 events</td>
<td>526 events</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI): 0.80 (0.72, 0.90)


ACCOMPLISH: Conclusions

The benazepril/amlodipine superior to benazepril/HCTZ combination at reducing CV events in patients with hypertension at high risk for such events in spite of virtually identical blood pressure reduction


Effects of Body Size and HTN treatments on CV event rates: ACCOMPLISH

- In most patients, especially with stage 2 HTN, combination therapy will be necessary.
- Normal weight vs. obese high-risk hypertensive patients may have paradoxically higher CV event rates with HCTZ
- Obese hypertensive individuals primary event rates similar with both benazepril and HCTZ and benazepril and amlodipine.


Progression of CKD intention-to-treat population

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Thiazide Diuretics: Summary

- Not all thiazides created equal
- Chlorthalidone-most effective w/ optimal pharmacokinetic/dynamic profile
- Thiazides not effective in everyone
- When eGFR <30-40 mL/min (serum Cr ~>2.5 mg/dL), use loop diuretic


Treatment of Resistant Hypertension

- Withdrawal or down titration interfering substances
- Use adequate long-acting thiazide, preferably chlorthalidone
- Combine different mechanisms of action
- Recommended triple regimen of
  - ACE inhibitor or ARB
  - Calcium channel blocker
  - Thiazide diuretic


Additional BP Reduction w/ Spironolactone in Resistant HTN

A 44 y/o Mexican-Am. woman, with FBS 88 mg/dL, BMI 26, is concerned with starting a new prescription of statin therapy, despite a LDL-C of 162 mg/dL on optimal diet. Regarding statin therapy and the risk of new-onset DM you suggest to her:

1. There is primary prevention evidence of major statin risk of developing DM.
2. In JUPITER, DM risk is mainly limited to persons with biochemical evidence of IPG or multiple MetS components.
3. Even without DM risk factors, the absolute statin benefit on vascular events is less than hazard of developing new onset DM.
4. There is no increased risk of new-onset DM with statin therapy.

TNT: Aggressive Statin Therapy Reduces Major CV Events

Deedwania et al. Lancet. 2006;368:919-28
Randomised, placebo-controlled
JUPITER trial of rosuvastatin 20 mg
- Primary prevention - small risk of developing DM limited to biochemical evidence of IPG or multiple components of MetS — groups already at high DM.
- Both with and without DM risk factors, the absolute statin benefit on vascular events was greater than hazard of new onset DM.


JUPITER trial and New-onset DM
- For those with DM risk factors, total of 134 vascular events or deaths were avoided for every 54 new cases of DM diagnosed.
- For participants with no major DM risk factors, statin was associated with a 52% reduction in primary endpoint (HR 0.48, 95% CI 0.33–0.68, p=0.0001)


Randomised, placebo-controlled
JUPITER trial of rosuvastatin 20 mg
- Reassurance about lipid lowering as an adjunct to diet, exercise, and smoking cessation in the primary prevention of MI, stroke, and CV death.


Regarding statins and CHD in Blacks
1. Clinical outcomes in most landmark trials prove efficacy of statins to decrease CVD in Blacks
2. Overall, no difference in any major trial for Blacks vs. whites
3. Blacks in statin ALLHAT-LLT significantly reduced CHD events vs. non-blacks
4. Statin move favorable stroke effect in AA’s

Blacks in Statin Clinical-Event Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin</th>
<th>Total Patients, n</th>
<th>African Americans, n or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simvastatin</td>
<td>4444</td>
<td>N/A</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>6595</td>
<td>N/A</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin</td>
<td>4159</td>
<td>Others, 7-8%</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>9014</td>
<td>N/A</td>
</tr>
<tr>
<td>AFCAPS/TECAPS</td>
<td>Lovastatin</td>
<td>6665</td>
<td>206</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>20536</td>
<td>N/A</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Pravastatin</td>
<td>10355</td>
<td>3491</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Atorvastatin</td>
<td>10345</td>
<td>Others, 5-5.5%</td>
</tr>
</tbody>
</table>

CHD in African Americans ALLHAT-LLT
- First clinical outcome trial of efficacy of statin (pravastatin) with large AA population (n=10,000+)
- Overall, no difference in all-cause mortality or CHD events
- Blacks in statin group significantly reduced CHD events vs. non-blacks
- Statin less favorable stroke effect in AA


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CLINICAL RESEARCH STUDY
Relationship of Ethnic Origin, Gender, and Age to Blood Creatine Kinase Levels
Ryan C. Neal, MB, BS, Wee C. Johnson, MB, BS, Joseph Yim, PhD, Gloria Migea, MD
University College of Medical Sciences, London, UK. Demonstration of Blood Constituents, etc. Society: "The American Journal of Medicine" (2009) 122, 73-78

It is known that baseline creatine kinase (CK) levels are higher in African Americans than in whites and that they are higher in men than in women.


Summary
- Culturally-sensitive lifestyle modification needed
- Diuretics may be particularly useful for CVD outcomes even with patients with MetS/DM
- Adequate thiazide-type diuretics for most as first step agent, with chlorthalidone for resistant or high risk patients

Multiple classes, in combination, effective for high risk HTN with MetS/DM
- B-blockers troublesome adverse effects with obesity
- ACE-I /ARBs useful for cardiorenal protection

Summary
- JNC 8 may raise goals for DM, CKD and very old patients
- Blacks under-represented in most landmark statin trials
- Statin therapy CVD benefits > statin new-onset DM risk

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Thank You!