Approaches to Reduce Cardiovascular Risk in Minorities

Cardiometabolic Congress
Boston, MA
April 24, 2013

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Professor of Clinical Medicine
Tulane University School of Medicine
Chair, National Forum for Heart Disease & Stroke Prevention
Presenter Disclosure Information

The following relationships exist related to this presentation:

Consultant Fees/Honoraria
AstraZeneca; Daiichi Sankyo, Inc.; Forest; Novartis; Takeda

Research/Research Grants
Eli Lilly; Daiichi Sankyo, Inc.; Forest; Novartis
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
Prevalence of T2DM by Race/Ethnicity

2007-2009 National Survey Data
(people aged 20+)

Non Hispanic White: 7.1%
Non Hispanic Black: 12.6%
Hispanic: 11.8%
Asian American: 8.4%

Prevalence T2DM by Race/Ethnicity

care.diabetesjournals.org/content/34/Supplement_1/S11.full
Metabolic Syndrome: NCEP ATP III Definition

*Positive diagnosis based on the presence of at least one of the following:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference*)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&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†modified</td>
</tr>
</tbody>
</table>

Prevalence of the NCEP Metabolic Syndrome
NHANES III by Sex and Race/Ethnicity

Ford et al JAMA 2002;287:356-9
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
The widespread use of TG levels to predict insulin resistance, CVD and T2DM needs re-evaluation.
“Race” is a crude proxy.

- Individual
  - biology
  - genotype

- DISEASE
- Environment
  - diet, lifestyle
  - SES, exposures
Addressing Cultural Contexts in Health Care

### 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></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>Geographic region</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

NCEP ATP III. Circulation. 2002;106:3145-3421

*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
Cumulative Incidence of Diabetes (%)

Year

$P<0.001$ for comparison between each group

Placebo

Metformin (-31%)

Intensive lifestyle modification (-58%)

e-HealthyStrides©: an Interactive ehealth program to improve DM self-management skills

- Pemu PE, Quarshie AQ, Josiah-Willock R, Ojutalayo F, Alema-Mensah E, Ofili EO.
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

e-HealthyStrides©

- After 12 weeks intervention in 90 African Americans
- Both SBP/DBP significantly dropped by 6.4 (P=0.02) and 5.75 mm Hg (P<0.0001)
- Additionally, exercise significantly increased (P=0.0003)
- Overall blood glucose level dropped by 19.47 mg/dL (P=0.03).
- Generally, these results supported the self-care process model

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.

Sign up today for free CardioSmart text messages.
Seven Steps to a Healthy Heart
Presented by: Association of Black Cardiologists
7 Steps to a Healthy Heart Educational Series overview

- Easy to understand educational program provides tools to make critical lifestyle changes
- Encourages healthy behaviors which positively impact heart health
- Delivered by trusted health advocates within the community
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
Printable tools and logs help personalize material for their specific needs.

The 7 Steps to a Healthy Heart Go-To-Guide™
Features...

**STEP 3**

**Checking Triglycerides**

The lipoprotein profile that measures your cholesterol levels will also measure your triglycerides. Triglycerides are fatty substances that your liver makes from the food you eat.

People who are obese or have diabetes are likely to have high triglyceride levels. Recent studies show a strong link between high triglyceride levels and the risk of heart disease.

<table>
<thead>
<tr>
<th>Triglyceride Levels (mg/dL)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 150 mg/dL</td>
</tr>
<tr>
<td>Borderline risk</td>
<td>150-199 mg/dL</td>
</tr>
<tr>
<td>High risk</td>
<td>200-499 mg/dL</td>
</tr>
<tr>
<td>Very high risk</td>
<td>More than 500 mg/dL</td>
</tr>
</tbody>
</table>

My Triglyceride Levels (mg/dL)

Each time you have your triglycerides measured, use the table below to record the results. If your levels are above 150 mg/dL, ask your healthcare provider about ways to reduce your triglycerides. In general, you need to do the same things you would do to reduce cholesterol—stick to a healthy low-fat diet and get plenty of exercise. In addition, you need to limit sugar and other carbohydrates in your diet, and if you smoke, you need to quit now. You health care provider might also determine that you need to take medication to help control high triglyceride levels.

<table>
<thead>
<tr>
<th>Date</th>
<th>Triglyceride Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interactive videos and animation reinforce learning and improve understanding of material.

**What is Atherosclerosis?**

When there’s too much cholesterol in the bloodstream, it can start to build up on the inside walls of the arteries and other blood vessels. This build-up is called plaque. In time, the arteries can start to harden with the built-up plaque. This process is called atherosclerosis.

Atherosclerosis is a serious condition that can lead to heart attack, heart failure, or stroke. This is why it’s so important to control your cholesterol and take other steps to help your blood vessels remain healthy.

**Controlling Atherosclerosis**

Controlling atherosclerosis is much the same as controlling cholesterol. You want to be physically and spatially active, eat healthy, nutritious foods; avoid overeating in alcohol; and don’t smoke (or quit if you do).
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>

* Median value  
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
Composite Primary Outcome, Baseline Proteinuria Status

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

- Stable angina
- Acute coronary syndromes
- CAD
- LVH
- Atherosclerosis
- Risk factor
- HTN, LDL, DM
- LV dysfunction
- Arrhythmogenicity
- LV remodeling
- LV dilatation
- Sudden cardiac death
- Heart failure
- Progressive endstage cardiomyopathy

Vijayaraghavan K, Deedwania P. Cardiol Clin. 2005;23:165-183
ACE = Angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; CAGE = Chymase-angiotensin generating enzyme.
Adapted from Hollenberg 1998.
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

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) Hot Topics in Hypertension.
Dual ACEI and ARB therapy
ONTARGET: Risk of Primary Outcome* With Telmisartan, Ramipril, or Both

*Composite of death from cardiovascular causes, MI, stroke, or hospitalization for heart failure.
ONTARGET = Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial.
Angioedema

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

- Regimens based on RAAS inhibition associated with significantly fewer cases of new DM.
- Particular importance in obese population, a group at heightened risk for development of type 2 DM.
- ACE inhibitors and ARBs not associated with weight gain or insulin resistance and provide renal protection in DM, a highly prevalent disease among obese persons.

J Clin Hypertens (Greenwich). 2013; 15:14–33
Position Paper: Obesity-Related Hypertension

- Many experts recommend low-dose thiazides (12.5 to 25 mg HCTZ or equivalent) along with close lipid and glucose monitoring.
- If greater diuretic effect required to control BP, loop diuretics and/or addition of K+ sparing agents such as spironolactone, eplerenone, or amiloride should be considered.
- Given importance of aldosterone in obesity-related HTN

*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
Clinical Trials HTN and Cardiometabolic Disease


The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI)

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

JAMA. 2002;288:2981-2997
<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone 15,255</th>
<th>Amlodipine 9,048</th>
<th>Lisinopril 9,054</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean SBP/DBP</strong></td>
<td>146 / 84</td>
<td>146 / 84</td>
<td>146 / 84</td>
</tr>
<tr>
<td>Treated (90%)</td>
<td>145 / 83</td>
<td>145 / 83</td>
<td>145 / 84</td>
</tr>
<tr>
<td>Untreated (10%)</td>
<td>156 / 89</td>
<td>157 / 90</td>
<td>156 / 89</td>
</tr>
<tr>
<td><strong>Mean age, y</strong></td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td><strong>Black, %</strong></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><strong>Current smoking %</strong></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><strong>Type 2 DM, %</strong></td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>
ALLHAT Primary Outcome by Treatment Group

Cumulative Fatal CHD and Nonfatal MI event rate (%)

Time to event, yrs

0 1 2 3 4 5 6 7

No. at Risk
Chlorthalidone 15255 14477 13820 13102 11362 6340 2956 209
Amlodipine 9048 8576 8218 7843 6824 3870 1878 215
Lisinopril 9054 8535 8123 7711 6662 3832 1770 195

Chlorthalidone

Amlodipine

Lisinopril
<table>
<thead>
<tr>
<th></th>
<th>Relative Risk (95% CI)</th>
<th>Favors amlodipine</th>
<th>Favors chlorthalidone</th>
<th>Relative Risk (95% CI)</th>
<th>Favors lisinopril</th>
<th>Favors chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>0.93 (0.82-1.06)</td>
<td></td>
<td></td>
<td>1.15 (1.02-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age &lt;65</strong></td>
<td>0.93 (0.73-1.19)</td>
<td></td>
<td></td>
<td>1.21 (0.97-1.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age ≥65</strong></td>
<td>0.93 (0.81-1.08)</td>
<td></td>
<td></td>
<td>1.13 (0.98-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>1.00 (0.85-1.18)</td>
<td></td>
<td></td>
<td>1.10 (0.94-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>0.84 (0.69-1.03)</td>
<td></td>
<td></td>
<td>1.22 (1.01-1.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>0.93 (0.76-1.14)</td>
<td></td>
<td></td>
<td>1.40 (1.17-1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonblack</strong></td>
<td>0.93 (0.79-1.10)</td>
<td></td>
<td></td>
<td>1.00 (0.85-1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td>0.90 (0.75-1.08)</td>
<td>0.5</td>
<td>1</td>
<td>1.07 (0.90-1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nondiabetic</strong></td>
<td>0.96 (0.81-1.14)</td>
<td>1</td>
<td>2</td>
<td>1.23 (1.05-1.44)</td>
<td>0.5</td>
<td>1 2</td>
</tr>
</tbody>
</table>

ALLHAT Stroke

DM Incidence - 4 Years
(follow-up FBS ≥ 126 mg/dL for those <126 mg/dL at baseline)

ALLHAT

Chlor, Amlod, Lisin

* p<.05 compared to chlorthalidone

JAMA 2002; 288:2981-2997
ALLHAT

CHD in Participants with a History of Diabetes Mellitus or with FG 126+ at Baseline

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>0.97 (0.86-1.10)</td>
<td>0.64</td>
</tr>
<tr>
<td>L/C</td>
<td>0.97 (0.85-1.10)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

- **Chlorthalidone**
- **Amlodipine**
- **Lisinopril**
ALLHAT

Outcomes in the Blood Pressure Component of ALLHAT

DIABETIC GROUP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amlodipine / Chlorthalidone</th>
<th>Lisinopril / Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.97 (0.86 - 1.10)</td>
<td>0.97 (0.85 - 1.10)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.95 (0.86 - 1.05)</td>
<td>0.99 (0.89 - 1.09)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1.02 (0.93 - 1.12)</td>
<td>1.03 (0.94 - 1.13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89 (0.74 - 1.06)</td>
<td>1.06 (0.89 - 1.26)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.39 (1.22 - 1.59)</td>
<td>1.15 (1.00 - 1.32)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.06 (0.98 - 1.14)</td>
<td>1.07 (0.99 - 1.15)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.27 (0.97 - 1.67)</td>
<td>1.09 (0.82 - 1.46)</td>
</tr>
</tbody>
</table>

Favors Amlodipine Chlorthalidone

Favors Lisinopril Chlorthalidone
ALLHAT

Diabetics & Nondiabetics (History)
Lisinopril/Chlorthalidone

Relative Risk and 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetics</th>
<th>Nondiabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.00 (0.87, 1.14)</td>
<td>0.99 (0.88, 1.11)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.02 (0.91, 1.13)</td>
<td>1.00 (0.91, 1.09)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07 (0.90, 1.28)</td>
<td>1.23 (1.05, 1.44)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.22 (1.05, 1.42)</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.08 (1.00, 1.17)</td>
<td>1.12 (1.04, 1.19)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.17 (0.87, 1.57)</td>
<td>1.05 (0.74, 1.48)</td>
</tr>
</tbody>
</table>

Favors Lisinopril Favors Chlorthal

JAMA 2002;288:2981-2997
ALLHAT patients with DM, impaired fasting glycemia (IFG), or normoglycemia

- No evidence for superiority of Rx regimens with CCBs or ACE inhibitors compared with chlorthalidone (CTD)
- DM ($n=13,101$), IFG ($n=1,399$), or normoglycemia (NG, $n=17,012$).
- Stroke more common in NG participants assigned to lisinopril vs. CTD
- Heart failure was more common in DM and NG participants assigned to amlodipine or lisinopril vs. CTD.
ALLHAT : DM, IFG, or normoglycemia

The ALLHAT investigators concluded that thiazides should be first-step hypertensive agents in most patients, including with DM or IFG.

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.”

Ferrannini, E; Cushman, W.; The Lancet, Volume 380, Issue 9841, Pages 601 - 610, 11 August 2012
Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

ABSTRACT

BACKGROUND
The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting–enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic.

From the University of Michigan Health System, Ann Arbor (K.J., B.P.); the State University of New York Downstate Medical College, Brooklyn (M.A.W.); the University of Chicago Pritzker School of Medicine, Chicago (G.L.B.); Sahlgrenska University Hospital, Gothenburg, Sweden (B.D.); Novartis Pharmaceuticals, East Hanover, N.J. (V.S., A.H., I.G., M.G.); and
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*

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

Log-rank p<0.0001

Bakris GL et al. Lancet 2010;375:1173
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

Fig. 6 - Blood pressure reduction effect of spironolactone in patients with resistant hypertension.

Pimenta, Calhoun, Oparil. Arq Bras Cardiol 2007; 88(6): 604-613
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

n = 5584 with CHD and MetS

Meta-analysis clinical trials evaluating effects of statins on DM risk.

Rajpathak S N et al. Dia Care 2009;32:1924-1929
Randomised, placebo-controlled JUPITER trial of rosvuvastatin 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/TEXCAPS</td>
<td>Lovastatin</td>
<td>6605</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>10305</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. nonblacks
- Statin less favorable stroke effect in AA

Race, ethnicity, and the efficacy of rosuvastatin in primary prevention: The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial

Michelle A Albert, MD, MPH a,b, Robert J Glynn, ScD, PhD b, Francisco A.H Fonseca, MD, c
Alberto J Lorenzatti, MD d, Keith C. Ferdinand, MD, c, Jean G. MacFadyen, BA b, and Paul M Ridker, MD, MPH a,b
Boston, MA; Sao Paulo, Brazil; Cordoba, Argentina; and Atlanta, GA

Objectives The aim of this study was to evaluate the effect of statin treatment in primary prevention of cardiovascular events in different race/ethnic groups.

Background Clinical trial evidence about the efficacy of statins in the primary prevention of cardiovascular events among nonwhites is uncertain.

Methods JUPITER trial, a randomized, double-blind, placebo-controlled evaluation of rosuvastatin 20 mg in the primary prevention of myocardial infarction (MI), stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death included 12,683 whites and 5,117 nonwhites with low-density lipoprotein levels <130 mg/dL and high-sensitivity C-reactive protein levels ≥2.0 mg/L.

Results Random allocation to rosuvastatin resulted in a 45% reduction in the primary end point among whites (hazard ratio [HR] 0.55, 95% CI 0.43-0.69) and a 37% reduction among nonwhites (HR 0.63, 95% CI 0.41-0.99). Blacks (HR 0.65, 95% CI 0.35-1.22) and Hispanics (HR 0.58, 95% CI 0.25-1.39) had similar risk reductions. Among nonwhites in the placebo group, the stroke rate exceeded the MI rate (0.44 vs 0.20 per 100 person-years); an opposite pattern was observed among whites (0.31 vs 0.42 per 100 person-years). Nonwhites had higher death rates than whites (2.25 vs 0.93 per 100 person-years); however, all-cause mortality was similar at 20% with rosuvastatin treatment in both participant groups.

Conclusions When used in primary prevention among individuals with low-density lipoprotein <130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/L, rosuvastatin significantly reduced first MI, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death among whites and nonwhites. (Am Heart J 2011;0:1-9.e2.)
Primary Endpoint: MI, Stroke, UA/Revascularization, CV Death.
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
Summary

• Multiple classes, in combination, effective for high risk HTN with MetS/DM
• B-blockers troublesome adverse effects with obesity
• ACE-I /ARBs useful for cardioirenal 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
Thank You!