Session 6: Managing Hypertension and Dyslipidemia in the Cardiometabolic Patient

Learning Objectives

1. Evaluate the cardiometabolic profiles of various antihyperglycemic agents to increase effective management of hypertension and dyslipidemias in patients with type 2 diabetes, with special attention to patients with impaired renal function.

2. Critically evaluate evidence-based strategies to mitigate CV risk in patients, including the risks and benefits of pharmacologic therapies for patients with prediabetes and mixed dyslipidemia.
Session 6

Managing Hypertension and Dyslipidemia in the Cardiometabolic Patient

Faculty

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Tulane University School of Medicine
New Orleans

Keith C. Ferdinand, MD, FACC, FAHA, FASH, FNLA, is a professor of clinical medicine in the cardiology division, Tulane Heart and Vascular Institute, Tulane University School of Medicine, and the chair of the National Forum for Heart Disease and Stroke Prevention.

Dr Ferdinand was the principal investigator, and is a present board member, of the Healthy Heart Community Prevention Project, a cardiovascular risk program targeting African-American and other high-risk populations.

Dr Ferdinand received his medical degree from Howard University College of Medicine and completed internal medicine at the Louisiana State University (LSU) Health Sciences Center and cardiology at LSU and Howard University. He is board certified in internal medicine and cardiovascular disease, a diplomate certified in the subspecialty of nuclear cardiology, an American Society of Hypertension certified specialist in clinical hypertension, and a fellow of the American College of Cardiology, American Heart Association, the National Lipid Association, and the American Society of Hypertension.

Dr Ferdinand is widely published and has written chapters for Cardiology Clinics, Annual of Drug Therapy, AHA Hypertension Primer, and Cardiovascular Diseases in Blacks. Dr Ferdinand was editor-in-chief of the 2009 Educational Review Manual in Cardiovascular Disease (Castle Connolly). He is co-author of Overcoming Katrina: African American Voices from the Crescent City and Beyond (Palgrave McMillan 2009), a collection of 27 oral histories. He also was co-editor of Cardiovascular Disease in Racial & Ethnic Minorities (Humana Press 2009).

He is the present chair of the National Forum for Heart Disease and Stroke Prevention, a coalition that provides the leadership and encouragement for collaboration among over 60 organizations.

Faculty Financial Disclosure Statement

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Suggested Reading List


Learning Objectives

• Employ a personalized approach to the evaluation and management of hypertension and dyslipidemias in patients with type 2 diabetes, with special attention to patients with impaired renal function.

• Critically evaluate emerging strategies to mitigate CV risk in patients at highest risk, including the risks and benefits of pharmacologic therapies for patients with pre-diabetes and mixed dyslipidemia.

Pre-Test Question #1:

Metabolic differences between African Americans and European Americans include all the following EXCEPT:

1. Higher BP
2. Higher TG and lower HDL
3. Higher insulin secretion
4. Insulin resistance
5. Less visceral adipose tissue

Pre-Test Question #2:

Niacin and fibrates are useful as adjunctive therapy in which of the following scenarios?

1. High LDL
2. High TG
3. Low HDL
4. None of the above
5. 2 and 3

Pre-Test Question #3

Specific to managing hypertension in African Americans, which of the following guidelines should be followed? (Select all that apply)

1. Use thiazides or calcium channel blockers (CCBs) as first-line therapy because they have greater BP-lowering effects compared to other anti-hypertensive medication classes
2. Avoid use of beta-blockers (BBs) and renin-angiotensin system blockers (RAS-block) because they always produce less BP-lowering effects compared to other anti-hypertensive medication classes
3. Most individuals will require combination therapy
4. Control of glycemia, blood pressure and dyslipidemia is critical in reducing global cardiovascular risk
Clinical Pearls: Hypertension

• Specific to African-Americans
  - Up to 80% of patients may require combination therapies
  - Thiazides & CCBs may have greater BP-lowering effects than other classes in blacks
  - As monotherapy, conventional BBs and RAS-block may produce less BP-lowering effect in blacks than in whites
  - however, this depends on the dose used
  - Consider RAS blockers for target organ protection because of high prevalence of early target organ damage in African Americans with hypertension
  - Use caution when combining CCBs with BBs

Case: Althea, 56-year-old African-American Female

Annual Exam
T2DM x 7 yrs; HTN x 12 yrs; Dyslipidemia x 5 yrs
- 5’5”; 234 lb BMI: 39 BP: 148/96 mm Hg

Current Labs
- A1C: 7.8% Random BG: 132 mg/dL
- SCr: 0.9 mg/dL Urine dipstick: 2+ protein
- LDL-C: 116 mg/dL; TG: 190 mg/dL; HDL: 40 mg/dL; TC:194 mg/dL

Current medications
- Metformin 1000 mg BID
- Atenolol 50 mg QD
- ASA 162 mg QD

Diabetes, CVD, and Death

• Diabetes is the seventh leading cause of death listed on US death certificates
• Cardiovascular disease (CVD) is the leading cause of death among people with diabetes—about 68% (2 of 3 patients) die of heart disease or stroke
• Overall risk for death among people with diabetes is about 2x that of people without diabetes

Hazard Ratios for Vascular Outcomes in People With vs Those Without Diabetes at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Number of Cases</th>
<th>HR (95% CI)</th>
<th>P (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>20,305</td>
<td>2.00 (1.83–2.19)</td>
<td>64 (54–71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.21 (2.02–2.40)</td>
<td>41 (24–56)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14,741</td>
<td>1.82 (1.64–2.02)</td>
<td>37 (19–51)</td>
</tr>
<tr>
<td>Stroke subtypes*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95–2.66)</td>
<td>1 (0–20)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1,183</td>
<td>1.96 (1.78–2.15)</td>
<td>0 (0–10)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.69–2.01)</td>
<td>33 (12–46)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51–1.98)</td>
<td>0 (0–20)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

Diabetes Is Both a Metabolic and a Vascular Disease
The Spectrum of Cardiometabolic Disease

Pre-diabetic States
1. Pre-diabetes
   i. IFG
   ii. IGT
   iii. HbA1C
2. Metabolic Syndrome

Type 2 Diabetes

Cardiovascular Disease

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; HbA1C = glycosylated hemoglobin.

Metabolic Syndrome (Syndrome X, Insulin Resistance Syndrome)

- Hyperinsulinemia
- IGT
- Obesity
- Upper body (abdominal) fat distribution
- Hypertension
- Hypertriglyceridemia/low HDL
- Small, dense LDL
- Positive family history
- Vascular reactivity/endothelial dysfunction
- Inflammation
- Microalbuminuria
- Polycystic ovary syndrome
- NASH/NAFLD

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; HbA1C = glycosylated hemoglobin.

Metabolic Evolution of Type 2 Diabetes

Late-phase Insulin Secretion
First-phase Insulin Secretion
Insulin Sensitivity
Pre-diabetes
Overt Diabetes

Harmonizing the Metabolic Syndrome: Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Trait</th>
<th>Categorical Cut Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Population/Country Specific Definitions US: males 102 cm/40 in., females 88 cm/35 in.</td>
</tr>
<tr>
<td>Elevated TG</td>
<td>150 mg/dL (1.7 mM) (or drug Tx for ↑ TG*)</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>&lt; 40 mg/dL males (1.0 mM) or 50 mg/dL females (1.3 mM) or drug Tx for ↓ HDL*</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>Systolic 130 and/or diastolic 85 mmHg or anti-HTN drug Tx or HTN Hx</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>100 mg/dL (5.6 mM) (or drug Tx for hyperglycemia)</td>
</tr>
</tbody>
</table>

*Primarily refers to fibrates, niacin, fish oil/omega-3 fatty acids.

Pathogenesis of the Metabolic Syndrome Trait Complex

Ventral Adiposity
Secreted Adipocyte Factors
Dyslipidemia
- Increased large VLDL
- Increased small LDL
- Increased LDL particles
- Decreased large HDL

Insulin Resistance
- Glucose intolerance

Endothelial Dysfunction
- Vascular reactivity
- Dysfibrinolysis
- Inflammation
- Foam cell

Lipoprotein (Sub)Classes

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Diameter (nm)</th>
<th>Density (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>5-20</td>
<td>0.95-1.02</td>
</tr>
<tr>
<td>VLDL</td>
<td>20-50</td>
<td>0.95-1.02</td>
</tr>
<tr>
<td>IDL</td>
<td>50-80</td>
<td>1.02-1.06</td>
</tr>
<tr>
<td>LDL</td>
<td>80-100</td>
<td>1.06-1.20</td>
</tr>
<tr>
<td>HDL</td>
<td>100-1500</td>
<td>1.06-1.22</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>20-1000</td>
<td>1.20-1.34</td>
</tr>
</tbody>
</table>

Chylomicrons
VLDL
IDL
Lp(a)
HDL
LDL
Chylomicron Remnants

Diameter (nm)
Density (g/mL)
0.95
1.00
1.05
1.10
1.15
1.20
5
10
20
40
60
80
100
1500

Pathophysiology of Low-density Lipoprotein Foam Cell Formation

Particle transport abnormalities
- Enhanced endothelial transport
- Increased plasma concentration

Oxidative Modifications

Scavenger Clearance

MCP-1 = monocyte chemotactic protein-1.

LDL-C is not a Good Measure for Particle Number
- At the same level of LDL cholesterol, people with small LDL have ~25% more particles than those with large LDL

Better Measures of Plasma Atherogenicity
- Non-HDL-Cholesterol
  - Non-HDL-C = TC – HDL-C
- Apoprotein B
- LDL particle number

Racial Differences in Cardiometabolic Disease

Prevalence of Type 2 Diabetes Is Elevated in Black and Hispanic Males and Females

But Prevalence of the Metabolic Syndrome Is Not Increased in African Americans: NHANESIII

Unadjusted Percentage of US Adults Aged ≥20 Years With Dyslipidemia With a Concentration of Total Cholesterol <200 mg/dL in Patients With Hypercholesterolemia: NHANES 2006 by Ethnicity
Hypertension, High Serum Total Cholesterol, and Diabetes: Racial and Ethnic Prevalence Differences in US Adults, 1999–2006

1. is the significant difference between non-Hispanic white and non-Hispanic black persons.
2. is the significant difference between non-Hispanic white and Mexican-American persons.
3. is the significant difference between non-Hispanic black and Mexican-American persons.


Metabolic Differences in African Americans versus European Americans

- Less visceral adipose tissue
- Insulin resistant
- Higher BP
- Lower TGs/higher HDL
- Lower resting metabolic rate
- Higher insulin secretion
- Decreased hepatic insulin extraction


Lipids

Althea

- She consults a dietitian with a goal of 5-10% weight loss
- Begins simvastatin 40 mg HS

6-week follow-up: 3 lb weight loss
- LDL-C: 96 mg/dL; TG: 175 mg/dL; HDL-C: 42 mg/dL; TC 175; apoB: 108 mg/dL; LDL particle concentration: 1200 nmol/L

What is the best course of action?
1. LDL-C<100 mg/dL: no further action is necessary
2. Calculate non-HDL-C and change to a more potent statin
3. Add omega-3 fatty acids 4 g/day
4. Add ezetimibe 10 mg/day
5. Increase simvastatin to 80 mg/day

How Low for LDL-C in High-risk Patients?

- HPS: Not Supported by Pravastatin Trials; Supported by HPS
- PROVE-IT: Supported by All Major Statin Trials
- TNT: Supported by All Major Statin Trials
- IDEAL: Not Supported by Pravastatin Trials; Supported by HPS
- SEARCH: Not Supported by Pravastatin Trials; Supported by HPS
- JUPITER: Supported by All Major Statin Trials

Althea

T2DM x 7 yrs; HTN x 12 yrs; Dyslipidemia x 5 yrs
- 5'5"; 234 lb  BMI: 39  BP: 148/96 mm Hg

Current Labs
- A1C: 7.8%  Random BG: 132 mg/dL
- Scr: 0.9 mg/dL  Urine dipstick: 2+ protein
- LDL-C: 116 mg/dL; TG: 190 mg/dL; HDL: 40 mg/dL;
- TC:194 mg/dL

Current medications
- Metformin 1000 mg BID
- Atenolol 50 mg QD
- ASA 162 mg QD
**LDL-C Treatment Goals for High-risk Patients Have Become More Intensive Over Time**

- **1988 ATP I**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL.
- **1993 ATP II**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL (men) or <100 mg/dL (women).
- **2001 ATP III**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL.
- **2004 ATP III Update**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL (men) or <100 mg/dL (women).
- **2006 ADA/ACC Update**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL.
- **2008 AHA/ACC Update**: LDL-C <100 mg/dL; non-HDL-C <130 mg/dL.
- **2010 ADA Update**: LDL-C <100 mg/dL.

**Benefits of Aggressive LDL-C Lowering in Diabetes**

- **Primary Event Rate (%)**
- **Aggressive Lipid Lowering Better**
- **Aggressive Lipid Lowering Worse**
- **Difference in LDL-C (mg/dL)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Primary Event Rate (%)</th>
<th>Aggressive Lipid Lowering</th>
<th>Aggressive Lipid Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>Diabetics, CHD</td>
<td>13.8</td>
<td>17.9</td>
<td>0.75</td>
</tr>
<tr>
<td>CARDs</td>
<td>Diabetics, HTN</td>
<td>9.2</td>
<td>11.9</td>
<td>0.77</td>
</tr>
<tr>
<td>CARDS</td>
<td>Diabetics, no CVD</td>
<td>5.8</td>
<td>9.0</td>
<td>0.23</td>
</tr>
<tr>
<td>HPS</td>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td>0.12</td>
</tr>
<tr>
<td>HPS</td>
<td>Diabetics, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Atorvastatin 10 vs 80 mg/day.

**Patients With Diabetes Without Prior MI Have As High An MI Risk As Those Without Diabetes With Prior MI**

**Population Study—Incidence of CV Events During 7-year Follow-up**

- No diabetes: 0.001
- No diabetes, no prior MI: 0.0001
- Diabetes: 0.001
- Diabetes, no prior MI: 0.001
- Patients with diabetes have as high an MI risk as those without diabetes with prior MI.

**JUPITER**

Multinational, Randomized, Double-blind, Placebo-controlled Trial of Rosuvastatin in the Prevention of CV Events Among Individuals With Low LDL and Elevated hsCRP

- JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

**JUPITER: Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death – White vs Nonwhite Subgroups**

Incident Diabetes by Trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Rate Events</th>
<th>Rate</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>7773</td>
<td>154</td>
<td>11.9</td>
<td>1.10 (0.89–1.36)</td>
<td>13.07%</td>
</tr>
<tr>
<td>HPS</td>
<td>16973</td>
<td>335</td>
<td>9.2</td>
<td>1.98 (1.61–2.45)</td>
<td>17.50%</td>
</tr>
<tr>
<td>ARMS</td>
<td>17052</td>
<td>270</td>
<td>16.0</td>
<td>1.36 (1.06–1.75)</td>
<td>15.35%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>9510</td>
<td>52</td>
<td>5.5</td>
<td>0.70 (0.67–1.15)</td>
<td>8.60%</td>
</tr>
<tr>
<td>LIPID</td>
<td>4997</td>
<td>66</td>
<td>6.8</td>
<td>0.91 (0.71–1.17)</td>
<td>9.05%</td>
</tr>
<tr>
<td>CORONA</td>
<td>3556</td>
<td>158</td>
<td>11.8</td>
<td>1.14 (0.94–1.38)</td>
<td>8.85%</td>
</tr>
<tr>
<td>PREDIMED</td>
<td>5910</td>
<td>275</td>
<td>14.1</td>
<td>1.26 (1.07–1.50)</td>
<td>10.16%</td>
</tr>
<tr>
<td>MEGA</td>
<td>6086</td>
<td>172</td>
<td>10.1</td>
<td>1.07 (0.84–1.35)</td>
<td>8.05%</td>
</tr>
<tr>
<td>ARCADIAN/ESCAPES</td>
<td>4274</td>
<td>174</td>
<td>4.1</td>
<td>1.09 (0.95–1.28)</td>
<td>9.50%</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>4222</td>
<td>219</td>
<td>16.4</td>
<td>1.32 (1.03–1.69)</td>
<td>6.94%</td>
</tr>
<tr>
<td>OMEGA-3H4</td>
<td>3759</td>
<td>259</td>
<td>13.7</td>
<td>1.07 (0.86–1.35)</td>
<td>8.03%</td>
</tr>
<tr>
<td>GISSIPREV</td>
<td>3460</td>
<td>105</td>
<td>29.9</td>
<td>0.91 (0.71–1.17)</td>
<td>6.53%</td>
</tr>
</tbody>
</table>

Overall (I²=11.2%; 95% CI 0.0–50.2%)

OR (95% CI) Weight (%)
- 1.14 (0.89–1.46) 7.07%
- 1.15 (0.98–1.35) 13.91%
- 1.26 (1.04–1.51) 11.32%
- 0.79 (0.58–1.10) 4.24%
- 0.91 (0.71–1.71) 6.53%
- 1.14 (0.84–1.55) 4.65%
- 1.32 (1.03–1.69) 6.94%
- 1.07 (0.86–1.35) 8.03%
- 0.98 (0.70–1.38) 3.76%
- 1.03 (0.84–1.28) 8.88%
- 1.15 (0.95–1.41) 10.23%
- 1.10 (0.89–1.35) 9.50%
- 0.89 (0.67–1.20) 4.94%
- 1.09 (1.02–1.17) 100%

174 excess cases in statin vs control Rx

Statins: What Is the Risk of Diabetes vs CVD Risk Protection?
- 1 additional case of DM per 255 patients taking statin for 4 y (95% CI 150–852)
- In terms of 1000 patient-years of treatment:
  - 12.23 cases / 1000 per year with statin treatment vs.
  - 11.25 cases / 1000 per year with control therapy
  - Difference: 0.98 excess cases per 1000 py
- Benefit estimates based on CTT meta-analysis:
  - Reduction of 5.4 MCE (CHD death or nonfatal MI) per 255 patients treated for 4 y per 1 mmol/L reduction in LDL-C
  - Even greater benefit counting strokes and revascularization

Despite Benefits of Statin-induced LDL-C Lowering, Treated Patients Have Substantial Residual Risk for CAD Events

To Lessen CVD Residual Risk Beyond That Achievable With Statins, Should Other Aspects of the Dyslipidemia Be Addressed?
- High TG
- Low HDL-C
- Small LDL particle concentration / high particle number

Treatment of Dyslipidemia
- Diet – ADA/AHA diets
- Regular moderate exercise
- Statins
- Cholesterol absorption inhibitors
- Resins – bile acid sequestrants
- Fibrates
- Nicotinic acid / niacin
- Fish oil / omega-3 fatty acids

Pharmacologic Combination Approaches to the Management of Dyslipidemia

Assess adequacy and tolerance of therapies with focused repetitive follow-up
CHD Prevention Trials With Fibrates in Diabetic Subjects: Subgroup Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Dose</th>
<th>No.</th>
<th>Baseline LDL-C mg/dL (mmol/L)</th>
<th>LDL-C Lowering</th>
<th>CHD Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsinki Heart Study</td>
<td>Gemfibrozil (1200 mg/day)</td>
<td>135</td>
<td>203 (5.2)</td>
<td>6%</td>
<td>68% NS</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA-HIT</td>
<td>Gemfibrozil</td>
<td>627</td>
<td>112 (2.9)</td>
<td>—</td>
<td>24% P = 0.05</td>
</tr>
</tbody>
</table>

VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.


Study Drug Dose No. Baseline LDL-C mg/dL (mmol/L) LDL-C Lowering CHD Reduction
Primary Prevention
Helsinki Heart Study Gemfibrozil (1200 mg/day) 135 203 (5.2) 6% 68% NS
Secondary Prevention
VA-HIT Gemfibrozil (1200 mg/day) 627 112 (2.9) — 24% P = 0.05

FIELD: Results

T2DM – primary prevention of CHD in 9795 patients randomized to placebo vs 200 mg/day fenofibrate

VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

FIELD: Results

HATS: Simvastatin and Niacin

- N = 160, known CHD
- 2x2 double-blind RCT
  - Simvastatin 10–20 mg plus niacin 1000 mg bid
  - Antioxidants (vitamins E and C, selenium, beta-carotene)
- 3-year event and angiographic trial
- Lipids
  - LDL-C 132 → 75 mg/dL
  - HDL-C 31 → 40 mg/dL
  - TG 202 → 126 mg/dL

HATS = HDL-Atherosclerosis Treatment Study.

Effects of Combination Lipid Therapy* in Metabolic Syndrome (FATS, HATS, and AFREGS Trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto OR 95% CI</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER-2-HATS</td>
<td>2/187</td>
<td>9/176</td>
<td>0.25 (0.08, 0.84)</td>
<td>0.24 (0.05, 1.26)</td>
</tr>
<tr>
<td>Guppin-JR et al</td>
<td>1/272</td>
<td>2/269</td>
<td>0.14 (0.00, 6.92)</td>
<td>0.24 (0.05, 1.29)</td>
</tr>
<tr>
<td>FARTS</td>
<td>0/172</td>
<td>1/172</td>
<td>0.92 (0.13, 6.65)</td>
<td>0.75 (0.38, 1.50)</td>
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<tr>
<td>HATS</td>
<td>1/106</td>
<td>5/108</td>
<td>0.14 (0.00, 6.96)</td>
<td>0.53 (0.38, 0.73)</td>
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<tr>
<td>LUSEF_3COR</td>
<td>0/49</td>
<td>1/49</td>
<td>0.91 (0.43, 1.98)</td>
<td>0.91 (0.49, 1.76)</td>
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<tr>
<td>STOCKHOLM</td>
<td>0/364</td>
<td>1/364</td>
<td>0.35 (0.05, 2.99)</td>
<td>0.35 (0.05, 2.99)</td>
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<tr>
<td>CLAB</td>
<td>0/414</td>
<td>1/414</td>
<td>0.92 (0.13, 6.65)</td>
<td>0.75 (0.38, 1.50)</td>
</tr>
<tr>
<td>CDP</td>
<td>9/2768</td>
<td>8302769</td>
<td>0.81 (0.49, 1.36)</td>
<td>0.81 (0.49, 1.36)</td>
</tr>
</tbody>
</table>

Total Test for heterogeneity: $P > 0.05$; Test for overall effect: $P < 0.001$

Niacin Meta-Analysis: Major CHD Events


ACCORD-LIPID: Results

T2DM – primary prevention of CVD in 5518 patients randomized to placebo vs 160 mg/day fenofibrate on simvastatin background Rx

ACCORD Study Group; NEJM 2010;362;1563-1574

HATS = HDL-Atherosclerosis Treatment Study.

Niacin Meta-Analysis: Major CHD Events

Niacin Meta-Analysis: Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guyton JR et al</td>
<td>0/676</td>
<td>1/272</td>
<td>0.03 (0.00, 2.38)</td>
</tr>
<tr>
<td>AFREGS</td>
<td>0/71</td>
<td>2/72</td>
<td>0.14 (0.01, 2.18)</td>
</tr>
<tr>
<td>ARBITER-2</td>
<td>0/87</td>
<td>1/80</td>
<td>0.13 (0.01, 2.15)</td>
</tr>
<tr>
<td>HATS</td>
<td>0/36</td>
<td>2/36</td>
<td>1.19 (0.38, 3.92)</td>
</tr>
<tr>
<td>STOCKHOLM</td>
<td>6/279</td>
<td>5/276</td>
<td>0.75 (0.58, 0.94)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>0.74 (0.58, 0.94)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: P = 0.27, I^2 = 21.9%
Test for overall effect: P = 0.007

Subtotal excluding CDP

Peto OR 95% CI
0.03 (0.00, 2.33)
0.14 (0.01, 2.18)
0.13 (0.01, 2.15)
1.19 (0.38, 3.92)
0.75 (0.58, 0.94)

AIM HIGH Study Design

Open-Label Run-In:
Up-Titrate Niacin from 500mg to 2,000mg/day 4–8 weeks

ER Niacin + 40–80 mg/day simvastatin
Placebo + 40–80 mg/day simvastatin

Follow to end of study

ADA Recommendations: Lipid Goals

- Without overt CVD: primary goal is LDL <100 mg/dL. (A)
- With overt CVD: goal is LDL<70 mg/dL, using a high dose of a statin, is an option. (B)
- If treated patients do not reach these targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative therapeutic goal. (A)
- TG<150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women are desirable. However, LDL–targeted statin therapy remains the preferred strategy. (C)
- If targets not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety. (E)

ADA. Diabetes Care 2012; 35(1),:S4-S10

Approach for Management of Dyslipidemia in Patients with Cardiometabolic Disease

Step 1: Assess clinical CVD risk by exam, history, and conventional lipid panel
Step 2: Establish appropriate goals of therapy
Step 3: Initiate therapy
  - Diet and exercise
  - Statin, maximize dose
  - Consider niacin/fibrate/omega-3 fatty acids for TGs >250 mg/dL
Step 4: Assess response to therapy not only by measurement of LDL-C but also non-HDL-C, apoB or particle number
Step 5: Consider combination therapy to reach LDL-C goal AND for elevated TG, low HDL, and high concentrations of LDL-P


Effects of Statins on Cardiovascular Outcomes in CKD/ESRD Patients

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>No. CKD Pts. in Subgroup</th>
<th>Serum Creatinine (mg/dL)</th>
<th>Medication Used/Dose Change vs. Placebo</th>
<th>Outcome</th>
<th>Follow-up Period (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>1,329</td>
<td>1.5–2.2</td>
<td>Simvastatin 40 mg</td>
<td>CV relative risk reduction of 28%</td>
<td>5</td>
</tr>
<tr>
<td>CARE</td>
<td>1,711</td>
<td>Mean 1.5±1.4</td>
<td>Pravastatin 40 mg</td>
<td>Decreased incidence of CHD nonfatal MI</td>
<td>Median, 4.9</td>
</tr>
<tr>
<td>OD</td>
<td>1,256 patients in trial</td>
<td>ESRD</td>
<td>Atorvastatin 20 mg</td>
<td>No change in CV mortality (possible ↑ stroke?)</td>
<td>Median, 4</td>
</tr>
<tr>
<td>AURORA</td>
<td>2,776</td>
<td>ESRD</td>
<td>Rosuvastatin 10 mg</td>
<td>No significant effect on CV mortality, nonfatal MI, or nonfatal stroke</td>
<td>Median, 3.8</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; ESRD = end-stage renal disease; HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events; OD = Okeechobee Diabetes Study Group; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events.

SHARP (Study of Heart and Renal Protection)

Rationale
- Risk of vascular events is high among patients with CKD
- Lack of clear association between cholesterol level and vascular disease risk
- Pattern of vascular disease is atypical, with a large proportion being non-atherosclerotic
- Previous trials of LDL-lowering therapy in CKD are inconclusive


National Kidney Foundation KDOQI Dyslipidemia Guidelines

- Drug therapy should be initiated for LDL-C levels between 100 and 129 mg/dL after 3 months of being on lifestyle changes
- Initial drug therapy for high LDL-C levels should be with a statin
- Fibrates are recommended for use in patients with stage 5 CKD, for patients with TGs ≥500 mg/dL, and for patients with TG >200 mg/dL
- Gemfibrozil may be the fibrate of choice for treatment of high TGs in patients with CKD


Blood Pressure

Althea

- HTN x 12 years
- Atenolol 50 mg QD
- Creatinine: 0.9 mg/dL
- Urine dipstick: 2+ protein
- BP: 148/96 mm Hg

What is the best action for treating her HTN?
1. Double the dose of atenolol to 100 mg/day
2. Add ramipril 5 mg/day
3. Add amlodipine 5 mg/day
4. Assess BP at next 3 office visits before making decision

UKPDS: BP Control in T2DM—Effect of Intensive BP Lowering on Risk of Micro- and Macrovascular Complications

Benefits of 144/82 mmHg vs. 154/87 mmHg

Long-term BP Control is Key

10-year post-trial follow-up data from UKPDS indicate relative risk reductions seen in tight BP–control group did not persist when BP differences were no longer maintained.

Optimal BP control is of major importance in reducing of microvascular and macrovascular disease risks in T2DM but must be maintained for benefits to be sustained.


ACCORD Blood Pressure Study


ACCORD Blood Pressure—Benefits

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N = 2362)</th>
<th>Standard Therapy (N = 2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>208 (1.87%)</td>
<td>237 (2.09%)</td>
<td>0.88 (0.73–1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>74</td>
<td>92</td>
<td>0.79 (0.61–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>54</td>
<td>63</td>
<td>0.85 (0.61–1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CV cause</td>
<td>150</td>
<td>126</td>
<td>1.19</td>
<td>0.87 (0.61–1.36)</td>
</tr>
<tr>
<td>CV death</td>
<td>60</td>
<td>52</td>
<td>0.99</td>
<td>1.04 (0.74–1.49)</td>
</tr>
<tr>
<td>Primary outcome plus prespecified or nonfatal heart failure</td>
<td>521</td>
<td>521</td>
<td>1.00</td>
<td>0.95 (0.74–1.29)</td>
</tr>
<tr>
<td>Major coronary disease event</td>
<td>255</td>
<td>227</td>
<td>1.16</td>
<td>0.94 (0.75–1.18)</td>
</tr>
<tr>
<td>Fatal or nonfatal heart failure</td>
<td>53</td>
<td>73</td>
<td>0.73</td>
<td>0.94 (0.67–1.33)</td>
</tr>
</tbody>
</table>


ACCORD Blood Pressure—Risks

<table>
<thead>
<tr>
<th>N</th>
<th>Blood Pressure</th>
<th>†BP</th>
<th>†Pulse</th>
<th>†K</th>
<th>†&lt;3.2</th>
<th>†Creat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>2371</td>
<td>133/71</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Intensive</td>
<td>2362</td>
<td>119/64</td>
<td>17</td>
<td>12</td>
<td>9</td>
<td>49</td>
</tr>
</tbody>
</table>


Blood Pressure vs. ↓ GFR

Summary of studies on nephropathy progression used in figure:
Norman J et al. JAMA. 1999
Vignozzi L et al. JAMA. 1999
Klauk S et al. JAMA. 2000
Bakris GL et al. Hypertension. 2005
Klauk S et al. Kidney Int. 2005
Bakris GL et al. Hypertension. 2005
Herbert L et al. Kidney Int. 1994
Lebovitz H et al. Hypertension. 1998

GFR = glomerular filtration rate.

ARS Question

Blood pressure vs glycemic control in diabetes: what is most important?

1. BP control
2. Glycemic control
3. They are equally important and can have synergistic benefits for the patient
4. They are equally important and can have additive benefits for the patient
5. The importance of one over the other has not been determined

Summary of studies on nephropathy progression used in figure:
Norman J et al. JAMA. 1999
Vignozzi L et al. JAMA. 1999
Klauk S et al. JAMA. 2000
Bakris GL et al. Hypertension. 2005
Klauk S et al. Kidney Int. 2005
Bakris GL et al. Hypertension. 2005
Herbert L et al. Kidney Int. 1994
Lebovitz H et al. Hypertension. 1998

*Nondiabetic; other studies are in diabetic patients.

Blood Pressure vs. MAP

Summary of studies on nephropathy progression used in figure:
Norman J et al. JAMA. 1999
Vignozzi L et al. JAMA. 1999
Klauk S et al. JAMA. 2000
Bakris GL et al. Kidney Int. 2005
Bakris GL et al. Hypertension. 2005
Herbert L et al. Kidney Int. 1994
Lebovitz H et al. Hypertension. 1998

*Non-diabetic; other studies are in diabetic patients.

=r = 0.69; P < 0.05

GFR = glomerular filtration rate.
UKPDS: BP vs Glycemic Treatment

Combined Effects of BP and Glucose Control in UKPDS

Blood Pressure Management in T2DM

Sodium Intake Limits Antiproteinuric Effects of RAS Blockade
Number of Medicines Needed for BP Lowering

- UKPDS (<85 mm Hg—Diastolic)
- ABCD (<75 mm Hg—Diastolic)
- MDRD (<92 mm Hg MAP)
- HPT (<80 mm Hg—Diastolic)
- AASK (<92 mm Hg MAP)

Benazepril With Amlodipine vs HCTZ for 1 Year

- Mean Change in GFR (m/min) Benazepril Amlodipine (N = 143) Benazepril HCTZ (N = 143)
- Mean % Change in Ualb:/Cr Ratio (mg/g) Benazepril Amlodipine (N = 145) Benazepril HCTZ (N = 145)

Perindopril/Amlodipine vs Atenolol/Thiazide in 5137 Diabetic Persons (ASCOT Subset)

- ACEI + CCB resulted in lower BP (3 mm Hg systolic and 2 mm Hg diastolic), glucose, creatinine, and TG, and higher HDL-C
- Total CV events plus procedures ↓ 14%
- Stroke ↓ 25%
- PAD ↓ 48%
- Among 14,120 nondiabetic persons, new diabetes ↓ 34% (Diabetes Care. 2008;31:982)

Aliskiren 300 mg, Irbesartan 300 mg, or Combination in Diabetic Renal Disease

- 24-h BP ↓ 3 systolic/4 diastolic mm Hg by aliskiren (NS/ P = 0.009), 12/5 mm Hg by irbesartan (P < 0.001/P = 0.002), 10/6 mm Hg by combination (P < 0.001/P < 0.001)
- GFR ↓ 4.6, 8.0, and 11.7 mL/min/1.73 m²

Althea

- You recommend a low-salt diet and provide a handout listing foods and their sodium content
- You add ramipril 5 mg/day to the atenolol, start exenatide 5 mcg SC BID, and refer her to a CDE

6 weeks follow-up, Althea reports that she has cut way down on adding salt to food. You review her typical meals and she mentions replacing potato chips with low-carb cracklins
- Sitting BP = 138/88 mm Hg

What is the best course of action?
1. Add an ARB
2. Nothing since BP is now at target
3. Add a renin inhibitor
4.Refer Althea for culturally competent dietary instruction
5. Add a diuretic
6. 4 and 5
BP Goals and Approaches in Diabetes

• More aggressive BP reduction may lead to more side effects
• But more aggressive BP reduction also may reduce CV and renal endpoints
• Are combinations of ACEI/ARB/renin/aldosterone antagonists beneficial? Evidence is at best imperfect

Cultural/Ethnic Considerations in Hypertension Management

Effective Approaches in Selected Populations: The Role of RAS Blockers

• Clinical research indicates that as monotherapy, ACEIs, ARBs, and conventional beta-blockers are not as effective in black patients compared with whites
• However, ACEIs and ARBs should be used in black populations where there is compelling evidence for their effectiveness in whites

Clinical Pearls: Hypertension

• Specific to African-Americans
  - Up to 80% of patients may require combination therapies
  - Thiazides & CCBs may have greater BP-lowering effects than other classes in blacks
  - As monotherapy, conventional BBs and RAS-block may produce less BP-lowering effect in blacks than in whites
    • however, this depends on the dose used
  - Consider RAS blockers for target organ protection because of high prevalence of early target organ damage in African Americans with hypertension
  - Use caution when combining CCBs with BBs
Althea

- Atenolol 50 mg QD, ramipril 5 mg QD
- Creatinine: 1.0 mg/dL
- Urine dipstick: 2+ protein
- BP: 148/96 mm Hg
- MDRD GFR = 83 mL/min/1.73 m²

What is her renal status?
1. Normal
2. Mild CKD
3. Moderate CKD
4. Not enough information

Global Risk Reduction

<table>
<thead>
<tr>
<th>Potential Target</th>
<th>Potential Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP reduction</td>
<td>25%–40% (ACEI/ARB/thiazide)</td>
</tr>
<tr>
<td>LDL-C reduction</td>
<td>20%–37% (statin)</td>
</tr>
<tr>
<td>HDL-C and TG</td>
<td>10%–20% (fibrate, niacin)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>20%–30% (ASA in 2º prevention)</td>
</tr>
<tr>
<td>Glucose lowering</td>
<td>Neutral—up to 10%–15%</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>25%–35%</td>
</tr>
</tbody>
</table>

Steno-2 Study

160 T2DM Subjects With Microalbuminuria
Steno-2 Study: Reduction in CVD and Microvascular Disease

Reductions After 7.8 Years of Intensive vs Conventional Rx


CVD Nephropathy Retinopathy Autonomic Dysfunction


---

Althea

She has T2DM, HTN, dyslipidemia, microalbuminuria, and mild CKD

MEDS
- atenolol 50 mg QD
- ramipril 5 mg QD
- simvastatin 40 mg QD
- ezetimibe 10 mg QD
- metformin 1000 mg BID (will d/c if SCr rises to 1.4 mg/dL)
- exenatide 10 mcg SC BID
- ASA 162 mg QD

---

Summary

- Type 2 diabetes is both a metabolic and a vascular disease
- There are racial and ethnic differences with respect to prevalence of components of cardiometabolic disease
- Control of glycemia, blood pressure and dyslipidemia is critical in reducing global cardiovascular risk
- The presence of renal impairment impacts treatment options
- Therapy should be tailored to patient-specific goals to slow disease progression and prevent complications

---

Post-Test Question #1:

Metabolic differences between African Americans and European Americans include all the following EXCEPT:

1. Higher BP
2. Higher TG and lower HDL
3. Higher insulin secretion
4. Insulin resistance
5. Lower visceral adipose tissue

---

Post-Test Question #2:

Niacin and fibrates are useful as adjunctive therapy in which of the following scenarios?

1. High LDL
2. High TG
3. Low HDL
4. None of the above
5. 2 and 3
Post-Test Question #3
Specific to managing hypertension in African Americans, which of the following guidelines should be followed (Select all that apply)?

1. Use thiazides or calcium channel blockers (CCBs) as first-line therapy because they have greater BP-lowering effects compared to other anti-hypertensive medication classes
2. Avoid use of beta-blockers (BBs) and renin-angiotensin system blockers (RAS-block) because they always produce less BP-lowering effects compared to other anti-hypertensive medication classes
3. Most individuals will require combination therapy
4. Control of glycemia, blood pressure and dyslipidemia is critical in reducing global cardiovascular risk

Questions?