Session 6:
Reducing Cardiovascular Risk: New Strategies for Managing Hypertension, Dyslipidemia, and Other Modifiable Factors in Patients with Diabetes

Learning Objectives

1. Re-intensify efforts to manage cardiometabolic risk factors, including hypertension and dyslipidemia, in patients with diabetes, with a particular focus on addressing racial disparities in cardiometabolic disease that may influence treatment decisions.

2. Utilize up-to-date guidelines and clinical evidence to set treatment targets for lipid levels and blood pressure in patients with diabetes, and develop rational treatment plans to mitigate cardiovascular risk.

Content Collaborator:
Session 6: Reducing Cardiovascular Risk: New Strategies for Managing Hypertension, Dyslipidemia, and Other Modifiable Factors in Patients with Diabetes

Faculty

Keith C. Ferdinand, MD FACC, FAHA
Professor of Clinical Medicine
Cardiology Division
Tulane University School of Medicine
New Orleans, Louisiana

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.

In 2004, Dr Ferdinand received the Louis B. Russell, Jr. Memorial Award of the American Heart Association and the Walter M. Booker Community Service Award of the Association of Black Cardiologists. In 2010, he was recognized by the Congressional Black Caucus Health Trust with an award for journalism and the Charles Drew award for medical excellence in conjunction with the National Minority Quality Foundation.

Faculty Financial Disclosure Statement

The presenting faculty reports the following:

Dr Ferdinand receives speaking honoraria from AstraZeneca and Takeda, and receives consulting fees from Merck & Co., Inc., Sanofi, and Daiichi Sankyo.
SESSION 6
3:45–5:15pm

Reducing Cardiovascular Risk: New Strategies for Managing Hypertension, Dyslipidemia, and Other Modifiable Factors in Patients with Diabetes

SPEAKERS
Keith C. Ferdinand, MD FACC, FAHA

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Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

• Re-intensify efforts to manage cardiometabolic risk factors, including hypertension and dyslipidemia, in patients with diabetes, with a particular focus on addressing racial disparities in cardiometabolic disease that may influence treatment decisions.

• Utilize up-to-date guidelines and clinical evidence to set treatment targets for lipid levels and blood pressure in patients with diabetes, and develop rational treatment plans to mitigate cardiovascular risk.

Case: Jill, 53-year-old African-American Female

Annual Exam
T2DM x 7 yrs; HTN x 12 yrs; Dyslipidemia x 5 yrs
- 5’3”; 214 lb BMI: 37.9 BP: 150/96 mm Hg
Current Labs
- HbA1C: 7.6% 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 88%
  (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

Diabetes, CVD, and Death


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

<table>
<thead>
<tr>
<th>Vascular Outcome</th>
<th>Number of Cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>26,505</td>
<td>2.10 (1.83–2.40)</td>
<td>64 (54–71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,566</td>
<td>2.31 (2.05–2.60)</td>
<td>41 (24–54)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</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 (1.90–2.68)</td>
<td>1 (0–20)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19–2.05)</td>
<td>0 (0–26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.49–2.25)</td>
<td>33 (12–46)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.35–2.18)</td>
<td>0 (0–26)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.
Diabetes Is Both a Metabolic and a Vascular Disease

Features of Metabolic Syndrome*

- Hyperinsulinemia
- IGT
- Obesity
- Upper body (abdominal) fat distribution
- Hypertension
- Hypertriglyceridemia/low HDL
- Small, dense LDL
- Positive family history
- Dysfibrinolysis (high PAI-1)
- Vascular reactivity/endothelial dysfunction
- Inflammation
- Microalbuminuria
- Polycystic ovary syndrome
- NASH/NAFLD

*Also sometimes known as Insulin Resistance Syndrome or Syndrome X.

PAI-1 = plasminogen activator inhibitor-1; NASH/NAFLD = nonalcoholic steatohepatitis/nonalcoholic fatty liver disease.

Harmonizing the Metabolic Syndrome: Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Trait</th>
<th>Categorical Cut Point</th>
</tr>
</thead>
<tbody>
<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) &lt; 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.


The Spectrum of Cardiometabolic Disease

Metabolic Evolution of Type 2 Diabetes

Pathogenesis of the Metabolic Syndrome Trait Complex
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

Hypertension, High Serum Total Cholesterol, and Diabetes: Racial and Ethnic Prevalence Differences in US Adults, 1999–2006

Metabolic Differences in African Americans versus European Americans

- Relative to European Americans, African Americans have:
  - Less visceral adipose tissue
  - Higher rates of insulin resistance
  - Higher BP
  - Lower TGs/higher HDL
  - Lower resting metabolic rate
  - Higher insulin secretion
  - Decreased hepatic insulin extraction

Lipids

Lipoprotein (Sub)Classes
**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

**Alternate Measures of Plasma Atherogenicity**

- Non-HDL-Cholesterol
  - Non-HDL-C = TC – HDL-C
- Apoprotein B
- LDL particle number

**Population Equivalent Cut Points for Alternate Measures of Atherogenicity**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Population</th>
<th>Percentile Equivalent Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>Framingham1</td>
<td>50th 130 80th 160</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>Based on ATP III2</td>
<td>10th 130 50th 160</td>
</tr>
<tr>
<td>Measured apoB (mg/dL)</td>
<td>Framingham1</td>
<td>50th 80th 100 120</td>
</tr>
<tr>
<td>NMR LDL-P (mmol/L)</td>
<td>Framingham1</td>
<td>85th 1100 50th 1400</td>
</tr>
<tr>
<td></td>
<td>MESA2</td>
<td>70th 1330 80th 1600</td>
</tr>
</tbody>
</table>

3. NCEP ATP III JAMA, 2001;285:2486-2497

**Jill**

- T2DM x 7 yrs; HTN x 12 yrs; Dyslipidemia x 5 yrs
- 5’3”; 214 lb; BMI: 37.9; BP: 150/96 mm Hg
- Current Labs
  - A1C: 7.6%; 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

**ADA 2013 Recommendations:**

Lipid Goals/Emphasis on Statins

- Statin therapy should be added to lifestyle therapy regardless of baseline lipid levels for DM patients with overt CVD, or those without overt CVD, >40 years old, with one or more other CVD risk factors
  - Without overt CVD: primary goal is LDL-C <100 mg/dL
  - With overt CVD: optional goal is LDL-C <70 mg/dL, using a high dose of a statin
- If patients do not reach target on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative goal
  - TG <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women is desirable. However, LDL-targeted statin therapy remains the preferred strategy
  - Combination therapy may be considered for some patients
**AACE 2013 Recommendations: Lipid Goals**

<table>
<thead>
<tr>
<th>RISK LEVEL</th>
<th>Moderate*</th>
<th>High**</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>&lt;3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>&lt;1200</td>
<td>&lt;1000</td>
</tr>
</tbody>
</table>

*DM but no other major risk and/or age <40 years  
**DM + major CVD risk(s) (HTN, Family Hx, low LDL-C, smoking) or CVD


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**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

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

<table>
<thead>
<tr>
<th>Primary Event Rate (%)</th>
<th>Treatment</th>
<th>Control</th>
<th>Aggressive Lipid Lowering Better</th>
<th>Aggressive Lipid Lowering Worse</th>
<th>Difference in LDL-C (mg/dL)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>Diabetes, CHD</td>
<td>13.8</td>
<td>17.9</td>
<td>0.75</td>
<td>0.026</td>
<td>0.70</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Diabetes, HTN</td>
<td>9.2</td>
<td>11.9</td>
<td>2.7</td>
<td>0.036</td>
<td>0.35†</td>
</tr>
<tr>
<td>CARDS</td>
<td>Diabetes, no CVD</td>
<td>5.6</td>
<td>9.0</td>
<td>0.43</td>
<td>0.001</td>
<td>0.46†</td>
</tr>
<tr>
<td>HPS</td>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td>0.72</td>
<td>&lt;0.0001</td>
<td>0.38†</td>
</tr>
<tr>
<td></td>
<td>Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td>0.72</td>
<td>0.0003</td>
<td>0.38†</td>
</tr>
</tbody>
</table>

*Atorvastatin 10 vs 80 mg/day  
†Statin vs placebo.


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**JUPITER**

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

- No Prior CVD or DM  
- Men ≥50, Women ≥60  
- LDL <130 mg/dL  
- hsCRP 32 mg/L

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


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**Patients With Diabetes Without Prior MI Have Same MI Risk As Those Without Diabetes With Prior MI**

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

- No diabetes; prior MI  
- No diabetes; no prior MI  
- Diabetes; prior MI  
- Diabetes; no prior MI


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**JUPITER**

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

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

Race or Ethnic Subgroup


Statins: Incident Diabetes by Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Placebo or control</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUPITER</td>
<td>1.14 (0.89–1.46)</td>
<td>7.07%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>1.15 (0.98–1.35)</td>
<td>13.91%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>1.26 (1.04–1.51)</td>
<td>11.32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>0.79 (0.58–1.10)</td>
<td>4.24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROSPER</td>
<td>0.91 (0.71–1.71)</td>
<td>6.53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEGA</td>
<td>1.14 (0.84–1.55)</td>
<td>4.65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONA</td>
<td>1.32 (1.03–1.69)</td>
<td>6.94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>1.07 (0.86–1.35)</td>
<td>8.03%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSAPREV</td>
<td>0.98 (0.70–1.38)</td>
<td>3.76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSIPREV</td>
<td>1.03 (0.84–1.28)</td>
<td>8.88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>1.15 (0.95–1.41)</td>
<td>10.23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S CARE</td>
<td>1.09 (1.02–1.17)</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Pharmacologic Combination Approaches to the Management of Dyslipidemia

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

Lipid Abnormality

High LDL-C (or non-HDL, apoB, LDL-P)
Low HDL-C
High Triglycerides
Very High Triglycerides

Lipid-modifying Agent

Statin
Ezetimibe
Bile acid sequestrant
Niacin
Fibrates
Omega-3 fatty acid
Omega-3 fatty acid

Assess adequacy and tolerance of therapies with focused repetitive follow-up
**Fenofibrate: FIELD results**

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

- **Primary Endpoint**
  - CHD death / nonfatal MI
- **Secondary Endpoint**
  - Total CVD Events

![Graph showing proportion of patients with CHD death or nonfatal MI](image)


**Fenofibrate + Simvastatin: ACCORD-LIPID results**

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

- **Primary Endpoint**
  - Major fatal or nonfatal CV event
- **Secondary Endpoints**

![Graph showing proportion of patients with major fatal or nonfatal CV event](image)

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

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

- **Endpoints**
  - Composite of CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS
  - symptom-driven coronary hospitalization for ACS
  - Ischemic Stroke

![Graph showing cardiovascular event-free survival rate](image)


**AIM HIGH Study Design**

- **Open-Label Run-In**: Up-titrate Niacin from 500mg to 2,000mg/day 4–8 weeks
- **Follow to end of study**

![Diagram showing study design](image)


**AIM HIGH 1o and 2o Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Niacin worse</th>
<th>Niacin better</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD Death</td>
<td><img src="image" alt="Graph showing event rate" /></td>
<td><img src="image" alt="Graph showing event rate" /></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td><img src="image" alt="Graph showing event rate" /></td>
<td><img src="image" alt="Graph showing event rate" /></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td><img src="image" alt="Graph showing event rate" /></td>
<td><img src="image" alt="Graph showing event rate" /></td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td><img src="image" alt="Graph showing event rate" /></td>
<td><img src="image" alt="Graph showing event rate" /></td>
</tr>
</tbody>
</table>


**Niacin Meta-Analysis: Any CVD Event**

- Eleven eligible trials of niacin, alone or in combination with other lipid-altering therapy, including 9,959 subjects were analyzed.
- Niacin use was associated with a significant reduction in the composite endpoints of any CVD event (OR: 0.66; 95% CI: 0.49 to 0.89; p =0.007) and major CHD event (OR: 0.75; 95% CI: 0.59 to 0.96; p =0.02).

Lavigne et al. JACC. 2013;61(4):440-446.
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


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


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


Effects of Statins on Cardiovascular Outcomes in CKD/ESRD Patients

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>No. of CKD Pts. in Subgroup</th>
<th>Serum Creatinine (mg/dL)</th>
<th>Medication Used/Dosage vs. Placebo</th>
<th>Outcome</th>
<th>Follow-up Period (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>1,329</td>
<td>1.0–2.3</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 1.0–1.4</td>
<td>Pravastatin 40 mg</td>
<td>Decreased incidence of CKD nonfatal MI</td>
<td>Median, 4</td>
</tr>
<tr>
<td>ID</td>
<td>1,255 patients in trial</td>
<td>ESIRD</td>
<td>Atorvastatin 10 mg</td>
<td>No change in CV mortality possible (stroke?)</td>
<td>Median, 3</td>
</tr>
<tr>
<td>AURORA</td>
<td>2,776</td>
<td>ESIRD</td>
<td>Rosuvastatin 10 mg</td>
<td>No significant effect on CV mortality, nonfatal MI, or nonfatal stroke</td>
<td>Median, 4</td>
</tr>
</tbody>
</table>

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


Blood Pressure
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 = Action to Control Cardiovascular Risk in Diabetes.


ACCORD Blood Pressure—Benefits

<table>
<thead>
<tr>
<th>Outcomes</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>206</td>
<td>1.87</td>
<td>237</td>
<td>2.09</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>K&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:
Parving HH et al. BMJ. 1989
Vahid CC et al. JAMA. 1997
Kovesdy CP et al. JAMA. 2000
Herbert L et al. Kidney Int. 1984
Lebovitz H et al. Kidney Int. 1994

GFR = glomerular filtration rate.

UKPDS: BP vs Glycemic Treatment

*Tight BP control: <150/85 mm Hg (captopril or atenolol as main treatment)
Less Tight BP control: <180/105 mm Hg

UKPDS 38. BMJ. 1998;317(7639):703–713. *P < 0.05 compared with tight glucose control.
**Combined Effects of BP and Glucose Control in UKPDS**

- Incidence of primary composite “any diabetes-related endpoint” by intention-to-treat in the 887 patients randomized to both interventions
- Stratton IM et al.

**ADVANCE Trial**

Combined effects of routine BP control and intensive glucose control on macro- and microvascular outcomes in T2DM

- Dual approach reduced the risk of
  - new or worsening nephropathy by 33% (P=0.005)
  - new onset of macroalbuminuria by 54% (P<0.0001)
  - new onset of microalbuminuria by 25% (P<0.001)
  - 18% reduction in the risk of all-cause death (P=0.04)
- Effects were additive and independent of one another
- Zoungas S et al.

**Blood Pressure Management in T2DM: Current ADA recommendations (2013)**

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140/80 mmHg.
- Lower BP targets, such as <130/80 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.
- Patients with a BP >120/80 mmHg should be advised on lifestyle changes; those with a confirmed BP ≥140/80 mmHg should also have prompt initiation and titration of pharmacologic therapy
- ADA.
  *Diabetes Care*. 2013; 36(1),:S11-S66.

**Physical Activity Is Associated With Lower Prevalence of Hypertension Regardless of Ethnicity: NHANES – Phase III**

- Prevalence of hypertension (%)
- Anglo-American 30%
- Mexican-American 25%
- African-American 20%
- Nonparticipatory (0 bouts/week)
- Irregular activity (0.1–4.9 bouts/week)
- Regular patterned activity (≥5 bouts/week)
- Hypertension is defined as a systolic BP >140 mm Hg, a diastolic BP >90 mm Hg, or being treated with antihypertensive medication.
Sodium Intake Limits Antiproteinuric Effects of RAS Blockade

- Sodium intake above 4 g/day reduces antiproteinuric effects of RAS blockade by up to 50%
  (Heeg et al. Kidney Int. 1989;36:272)
- Use of thiazide diuretics only partially restores antiproteinuric effect
  (Buter H et al. Nephrol Dialysis Transpl. 1998;16:1682)
- Mechanism for increased sodium on proteinuria is thought to be related to increased oxidant stress (partially) and increases in BP (partially)

Blood Pressure Management in T2DM: AACE 2013 Risk Factor Algorithm

- Goal: systolic ~130, diastolic ~80 mmHg
- Initial BP <150/100 mmHg: ACEI or ARB monotherapy
- Initial BP >150/100 mmHg: Dual therapy = (ACEI or ARB) + (thiazide or CCB or beta-blocker)
- If not at goal in 2-3 months, add thiazide or CCB or beta-blocker
- If still not at goal after additional 2-3 months, add third agent (thiazide or CCB or beta-blocker)
- If still not at goal, consider alpha-blockers, central agents, vasodilators, or spironolactone

Preferences for Antihypertensive Therapies by Comorbidity

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACEI</th>
<th>ARB</th>
<th>Diuretic</th>
<th>CCB</th>
<th>BB</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>
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<tr>
<td>CHF/diastolic</td>
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<td>✓</td>
<td>⬤</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes/prediabetes</td>
<td>✓</td>
<td>✓</td>
<td>⬤</td>
<td>⬤</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</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>

*Proven benefit; †Likely benefit or safety proven. 1. Contraindicated in HFrEF; 2. If eGFR <50 mL/min per 1.73m2, eplerenone only; use spironolactone with caution, check serum K.

BB = beta-blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; AA = aldosterone antagonist; MI = myocardial infarction; CKD = chronic kidney disease; CHD = coronary artery disease

Number of Medicines Needed for BP Lowering

<table>
<thead>
<tr>
<th>Study</th>
<th>UKPDS (&lt;85 mm Hg—Diastolic)</th>
<th>ABCD (&lt;75 mm Hg—Diastolic)</th>
<th>MDRD (&lt;92 mm Hg MAP)</th>
<th>HDT (&lt;80 mm Hg—Diastolic)</th>
<th>AASK (&lt;92 mm Hg MAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Medicines Needed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

11

Benazepril With Amlodipine vs HCTZ for 1 Year in T2DM Patients

- Mean change in eGFR (mg/min): 0 to -2.03
- Median % change in Ualb/Cr: from baseline, 0 to -42.12
- P < 0.001 vs. baseline.
- P < 0.001 vs. benazepril/amlodipine.

11

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)

11
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

UAER = urinary albumin excretion rate.


Most Frequently Used Antihypertensive Combinations—Diabetic Patients

- 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 African American patients compared with Caucasians
  - However, ACEIs and ARBs should be used in African Americans where there is compelling evidence for their effectiveness in Caucasians
  - Populations Who May Benefit From ACEIs and/or ARBs
    - Patients with renal disease
    - Patients with left ventricular hypertrophy (LVH) without diabetes
    - Patients with LVH with diabetes
    - Patients with diastolic nephropathy
    - Patients with heart failure
    - Patients with diabetes without nephropathy (based on clinical practice)
  - Additionally, the ACEI ramipril reduces the risk of fatal/nonfatal serious arrhythmic events in high-risk patients without clinical heart failure or overt left 
    ventricular systolic dysfunction

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 African Americans
  - As monotherapy, conventional BBs and RAS-block may 
    produce less BP-lowering effect in African Americans than in 
    Caucasians
    - 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

Supporting Adherence in Hypertensive African-American Women

- Patient education
  - On managing hypertension
  - On managing medication side effects
  - Early screening for depression in hypertensive African Americans
  - Development of culturally sensitive hypertension 
    educational material
  - Formation of support groups for promoting adherence

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Global Approach: CVD Risk in Diabetes

<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%–35% (ASA in 2° 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>

Does It Work?

Steno-2 Study: Reduction in CVD and Microvascular Disease

Steno-2 Study

160 T2DM Subjects With Microalbuminuria

Steno-2: Effects of Multifactorial Intervention on CV Outcomes

N = 160 with type 2 diabetes and microalbuminuria

Jill

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
Stay tuned:
New NHLBI guidelines for hypertension (JNC-8) and lipids (ATP-4) are expected by the end of 2013

Questions?