Bridging Emerging Science and Clinical Care in Cardiometabolic Disease: Are We Meeting the Challenge?

Educational Partner

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Houston, TX

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Advancing Healthcare Practice Through Education
Session 4: Bridging Emerging Science and Clinical Care in Cardiometabolic Disease: Are We Meeting the Challenge?

Learning Objectives
1. Understand the progressive nature of cardiometabolic disease and the dangers of suboptimal management.
2. Outline screening and assessment tools to identify patients with cardiometabolic risk.
3. Identify strategies that reduce the risk and pathophysiologic burden of cardiometabolic disease.

Faculty

Juan P. Frías, MD
Assistant Clinical Professor
Department of Medicine
University of California San Diego
San Diego, California

Juan P. Frías, MD, is assistant clinical professor of medicine at the University of California, San Diego, and director of research at TeamType 1, a not-for-profit organization comprised of competitive cycling, triathlon, and running teams, with a mission of inspiring and educating people with diabetes. Dr Frías was previously the chief medical officer of Johnson and Johnson, Diabetes Care. He received his medical degree from Vanderbilt University and completed his training in endocrinology, diabetes and metabolism at the University of California, San Diego. He has held academic positions at the University of Colorado Health Sciences Center (Barbara Davis Center for Childhood Diabetes) and the University of California, San Diego, where he is currently on the voluntary clinical staff. Dr Frías has been involved in diabetes-related research for over a decade and has authored numerous publications in this field.

Frank Lavernia, MD
Faculty, National Diabetes Education Initiative (NDEI)
Adjunct Faculty, Vascular Biology Working Group (VBWG)
Adjunct Faculty, Coalition for the Advancement of Cardiovascular Health
Coconut Creek, Florida

Frank Lavernia, MD, has been a practicing diabetologist for more than 30 years in South Florida. He founded the North Broward Diabetes Center at the North Broward Medical Center in Pompano Beach, Florida. His most recent project has been the development of Dr. Frank’s Diabetes Workshops to teach and empower people with diabetes. The American Diabetes Association has accredited Dr. Lavernia’s private practice with the certificate of recognition for Diabetes Care for the past 13 years.

Dr Lavernia serves on various national faculties, including the Vascular Biology Working Group, the Coalition for the Advancement of Cardiovascular Health, and the National Diabetes Education Initiative, a think tank for type 2 diabetes and insulin resistance. As a member of numerous national speakers’ bureaus, he lectures about many diverse aspects of diabetes care around the country for the American Diabetes Association, the American College of Physicians, and Pri-Med.

Anthony L. McCall, MD, PhD, FACP
James M. Moss Professor of Diabetes
Diabetes & Hormone Center of Excellence
University of Virginia Health System
Charlottesville, Virginia

Dr McCall received his medical degree from the Medical College of Wisconsin and his PhD in neural and endocrine regulation from the Massachusetts Institute of Technology. His clinical training was at the Boston University Medical Center, where he did his residency in internal medicine and his endocrinology fellowship and where he served as chief medical resident. His current positions at the University of Virginia are as the James M. Moss Professor of Diabetes in Internal Medicine, the director of the Diabetes Clinical Services at UVA Health System, the medical director of the Virginia Center for Diabetes Professional Education, and the medical director of the Diabetes Education & Management Program. He has also been medical director of the UVA Islet Cell Transplant program.

Much of his research has focused on how diabetes and hypoglycemia affect the central nervous system. He is working with UVA colleagues on a computer-controlled insulin infusion for insulin pumps. Areas in basic research include glucose transporter physiology and regulation in the brain as well as vascular metabolism and factors affecting hypoglycemia defenses. A recent focus is with Dr Leon Farhy on pancreatic network control of glucagon regulation. His clinical research deals with insulin therapies, patterns of glycemia with different therapies, and the influence of these patterns on symptoms and complications. He has been a co-investigator on clinical studies of glycemic control in ischemic stroke. He is funded by the National Institutes of Health to study the genetics of
cardiovascular risk in patients with type 2 diabetes and to understand and reverse defective glucagon counterregulation in type 1 diabetes. His clinical work focuses on diabetes complications and their prevention. He works collaboratively in a Diabetes Cardiovascular Clinic and Cardiometabolic Risk center for women’s health that he initiated with others at the UVA. He is a section editor for Current Diabetes Reports for Pharmacologic Treatment of Type 2 Diabetes Mellitus and Obesity and for the online journal Diabetic Hypoglycemia.

Dace Trence, MD
Associate Professor
Division of Metabolism, Endocrinology, and Nutrition
Director, Diabetes Care Center
University of Washington
Director, Endocrine Fellowship Program
University of Washington Medical Center
Seattle, Washington

Dace L. Trence, MD, FACE, is currently director of the Diabetes Care Center and associate professor of medicine at the University of Washington Medical Center in Seattle. She is also the University of Washington Endocrine Fellowship Program Director and Director of Endocrine Days. She currently serves as chair for the American Association of Clinical Endocrinology AACE) CME committee, and is a trustee of the American College of Endocrinology. She is co-editor of EmPower magazine (AACE’s journal on endocrine disorders for the general public). She has been on the editorial boards of several journals, including Clinical Diabetes. She has had articles published in JCEM, JAMA, and Diabetes Care, and is a co-author of Optimizing Diabetes Care for the Practitioner.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Frías has indicated no real or apparent conflicts.
Dr Lavernia has disclosed a financial relationship with Abbott Laboratories.
Dr McCall has disclosed receiving consulting fees and serving on an advisory board for Pfizer, Inc, as well as receiving grant support from sanofi-aventis U.S.
Dr Trence has disclosed receiving consulting fees and/or being on an advisory board for sanofi-aventis U.S.; having ownership interest (stocks/stock options) in sanofi-aventis U.S. and Medtronic, Inc.; and having a financial relationship with Halozyme Therapeutics and Novo Nordisk.

Education Partner Financial Disclosure Statement
The content collaborators at Med-IQ have no relationships to report.

Drug List

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<td>WelChol</td>
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<tr>
<td>exenatide</td>
<td>Byetta</td>
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<td>ezetimibe</td>
<td>Zetia</td>
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<td>liraglutide</td>
<td>Victoza</td>
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<table>
<thead>
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<tr>
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<td>Actos</td>
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<td>Onglyza</td>
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<td>simvastatin</td>
<td>Zocor</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
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Suggested Reading List


Learning Objectives

- Understand the progressive nature of cardiometabolic disease and the dangers of suboptimal management
- Outline screening and assessment tools to identify patients with cardiometabolic risk
- Identify strategies that reduce the risk and pathophysiologic burden of cardiometabolic disease
- Describe the role of quality improvement in improving care in patients with cardiometabolic risk

Today’s Goals

- Describe the importance of cardiometabolic risk, its prevention, and its management
  - Evidence
  - Expert debate
- Define the role of quality improvement in your practice and in cardiometabolic risk management
- Provide methods for you to directly assess your practice in cardiometabolic risk management
  - Specific performance measures that can be applied to your practice

Cardiometabolic Disease (CMD) and Cardiometabolic Risk (CMR)

Cardiometabolic Disease (CMD)

Working Definition:

- A clustering of risk factors predisposing individuals to cardiovascular and metabolic disease (type 2 diabetes)
  - CMD increases cardiovascular morbidity and mortality by 3- to 4-fold

Cardiometabolic Risk Profile

- Abnormal Lipid Metabolism
  - LDL
  - Non-HDL
  - HDL
  - Triglycerides
- Metabolic Syndrome
  - Waist Circumference
  - Insulin Resistance
- Hypertension
- Renal: CKD, Albuminuria
- Inflammation, Hypercoagulation
- Smoking, Physical Inactivity

Adapted from Barnett AH. Diabetes Vasc Dis Res. 2006;3(1):2-17.
Definition of Cardiometabolic Disease

**ATP III – 3 of 5 Risk Factors**

- Waist Circumference: > 40 in. or 102 cm (men), > 35 in. or 88 cm (women)
- Triglycerides (TG): ≥ 150 mg/dL
- High-density Lipoprotein Cholesterol (HDL-C): < 40 mg/dL (men), < 50 mg/dL (women)
- Blood Pressure (BP): ≥ 130/85 mm Hg
- Glucose: FG > 100 mg/dL

FG = Fasting glucose


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CMD – Key Points

- CMD/insulin resistance is progressive and multifactorial in nature
- Early assessment and targeted intervention are needed to treat and prevent all risk factors associated with CVD and diabetes
- Treating dyslipidemia, hypertension, impairments in glucose tolerance, and obesity in patients with insulin resistance reduces the risk of diabetes and heart disease
  - Use targeted interventions to address each patient's combined risk factors

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**Tools for Calculating CMR**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Framingham/ NCEP</th>
<th>Reynolds Risk²</th>
<th>ADA Diabetes PHD³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HDL-C</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypertension</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Smoking status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gender</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Annually
2. When there are changes in clinical parameters
3. N/A, I don't use global risk assessment tools
4. N/A, I am not familiar with global risk assessment tools

Audience Response Question

How often do you use a global risk assessment tool to estimate cardiovascular risk in your patients?

- 1. Annually
- 2. When there are changes in clinical parameters
- 3. N/A, I don't use global risk assessment tools
- 4. N/A, I am not familiar with global risk assessment tools

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Tools for Calculating CMR (cont’d)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Framingham/ NCEP</th>
<th>Reynolds Risk²</th>
<th>ADA Diabetes PHD³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height and BMI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Racial/ethnicity</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LDL-C</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activity level</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical history of diabetes, CVD, microvascular complications</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physician visit frequency</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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What Are the Dangers of Suboptimal Management of Cardiometabolic Risk?

The Relationship Between Cardiometabolic Disease, Pre-Diabetes, and Diabetes

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3. https://www.diabetes.org/phd/profile/start.jsp
Diabetes and Pre-Diabetes Are Common in the United States

Total US Population Aged ≥ 20 Years
- 203.9 million
- 18.8 million
- 104.8 million
- 79 million

Prediabetes and Diabetes Aged ≥ 20 Years
- 18.8 million
- Diagnosed Diabetes (90% to 95% T2DM)
- IFG/IGT/Prediabetes (Up to 70% will develop T2DM)


Why Is Adequate Glycemic Control Important in T2DM?

HbA1c
- 21% Deaths related to diabetes
- 37% Microvascular complications
- 14% Myocardial infarction

Beta Cell function
Insulin resistance
Insulin secretion
Postprandial glucose
Fasting glucose

Progression to Type 2 Diabetes

Years from diagnosis
-10 -5 0 5 10 15
Onset Diagnosis
β-Cell function
Insulin resistance
Insulin secretion
Postprandial glucose
Fasting glucose
Microvascular complications
Macrovascular complications

Pre-diabetes Type 2 diabetes

Early Intensive Glycemic Control UKPDS Long-Term Follow-Up

UKPDS Active
UKPDS Follow-up
UKPDS Intervention End

Median A1C (%)
Conventional
Intensive

Conventional vs. Intensive intervention:
- Relatively lower mortality
- Lower risk of major macrovascular events
- Lower risk of microvascular complications

Why Is Adequate Glycemic Control Important in T2DM?

Approximately what percentage of your patients with T2DM have an A1C level between 7.0% and 8.0%?

1. 10% to 25%
2. 26% to 50%
3. 51% to 75%
4. 76% to 100%

Audience Response Question

What A1C goal do you typically strive for in your T2DM patients?

1. < 8% given history of HTN and mixed dyslipidemia
2. < 7.5%
3. < 7.0%
4. < 6.5%

Audience Response Question
**Glucose Targets: T2DM vs non-T2DM**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Target</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>70-130 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial capillary glucose</td>
<td>&lt; 180 mg/dL</td>
<td>&lt; 140 mg/dL</td>
</tr>
<tr>
<td>A1C</td>
<td>&lt; 7% (ADA)</td>
<td>4% to 6% (AACE)</td>
</tr>
</tbody>
</table>

**Intensive Lifestyle Intervention**

**LOOK AHEAD STUDY**

- Diet modification/Exercise/Behavioral training
- Group support with in-person and telephone follow-ups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lifestyle Intervention (n = 2570)</th>
<th>Support and Education (n = 2575)</th>
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</thead>
<tbody>
<tr>
<td>Weight loss, %</td>
<td>-6.5</td>
<td>-0.88*</td>
</tr>
<tr>
<td>Treadmill fitness, % METS</td>
<td>12.74</td>
<td>1.96*</td>
</tr>
<tr>
<td>A1C, %</td>
<td>-0.36</td>
<td>-0.09*</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>-5.33</td>
<td>-2.97**</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>-2.92</td>
<td>-2.48**</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>3.67</td>
<td>1.97*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-25.56</td>
<td>-19.75*</td>
</tr>
</tbody>
</table>

*P < 0.001; **P = 0.01

**Audience Response Question**

What is your next step in the management of a long-standing patient (> 4 years) with T2DM whose A1Cs fluctuate between 7.5% and 7.9% and has not achieved the therapeutic goal despite taking metformin and a sulfonylurea?

1. Add a TZD
2. Add a GLP-1 agonist
3. Add insulin
4. Add a DPP-4 inhibitor
5. Unsure

**Audience Response Question**

When deciding on a therapy for a patient with T2DM who is not at goal, which treatment algorithm do you tend to reference?

1. ADA/EASD Algorithm
2. AACE/ACE Glycemic Roadmap
3. I tend to follow my own professional experience
4. None of the above

**Therapeutic Options**

**Primary Sites of Action**

- Metformin
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 agonists
- Sulfonylureas and meglitinides

**Clinical Practice Guidelines**

**ADA and AACE**

<table>
<thead>
<tr>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C target</td>
<td>&lt; 7.0%</td>
</tr>
</tbody>
</table>

**Treatment strategy**

- Encourage early combination therapy

**Choice of blood glucose–lowering drugs**

- Uses tiered approaches (well-validated vs. less-well-validated); includes GLP-1 agonists
- Includes all approved therapies, ie, GLP-1 agonists and DPP-4 inhibitors
Clinical Inertia Results in Prolonged Exposure to Hyperglycemia

<table>
<thead>
<tr>
<th>Diet/exercise</th>
<th>Sulfonylurea or metformin monotherapy</th>
<th>Combination therapy</th>
<th>Insulin</th>
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</thead>
<tbody>
<tr>
<td>9.2%</td>
<td>8.2%</td>
<td>7.1%</td>
<td>6.3%</td>
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</table>

ADA goal < 7%

At insulin initiation, the average patient had:
- 5 years with A1C > 8%
- 10 years with A1C > 7%

β-Cell Function and Glucagon in T2DM

- Loss of β-cell function and glucagon over secretion play key roles in T2DM
- Progressive β-cell decline is coupled with inadequate insulin secretion
  - β-cell function continues to decline with conventional interventions
- Glucagon is not suppressed during the postprandial period
- Hepatic glucose production is increased during the fasting period and is not suppressed during the postprandial period

Anti-Hyperglycemic Interventions: Expected A1C Reductions as Monotherapy

GLP-1 Secretion and Inactivation

- GLP-1 active
- GLP-1 inactivated

Additive Effects of Combination Therapy*

Additive Effects of Combination Therapy*
Adverse Effects and Limitations of Antihyperglycemics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Severe Hypoglycemia</th>
<th>GI Lactic Acidosis</th>
<th>Weight Gain</th>
<th>Edema</th>
<th>CHF</th>
<th>Infection/Hypersensitivity</th>
<th>Safety (special pops*)</th>
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<tr>
<td>Sulfonylureas</td>
<td>✓</td>
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<tr>
<td>Insulin</td>
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<td>✓</td>
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</table>

*Special populations = elderly, renal-impaired, and CHF patients.

Safety/Contraindications & Dosage Adjustments in Renal Insufficiency

<table>
<thead>
<tr>
<th>Medication</th>
<th>Labeling</th>
<th>Creatinine Level or Renal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide &amp; glimepiride</td>
<td>Start low dose/titrate to avoid hypoglycemia</td>
<td><em>Kidney disease</em></td>
</tr>
</tbody>
</table>
| Metformin        | Contraindicated            | ≥ 1.4 mg/dL, women
                      |                            | ≥ 1.5 mg/dL, men
| Sitagliptin      | Reduce dose to 50 mg      | 1.8-3.0 mg/dL, men
                      |                            | 1.6-2.5 mg/dL, women
| Saxagliptin      | Reduce dose to 25 mg      | > 3.0 mg/dL, men
                      |                            | > 2.2 mg/dL, women
| Exenatide        | Not recommended            | CrCl < 60 mL/min or ESRD/dialysis |
| Liraglutide      | Use with caution (limited experience) | No dose adjustment recommended |

Evidence-Based Performance Measures

Preventive Care

Assessing / Preventing CMR

- Waist circumference measured (ACCF/AHA)
- BMI measured (PCPI)
- Exercise plan (NCQA)
- Smoking assessed (PCPI)
- Smoking cessation plan in patients who smoke (PCPI)

Each of the above measures should be obtained/monitored at each visit & noted in patient chart

ACCF/AHA = American College of Cardiology Foundation / American Heart Association; NCQA = National Committee for Quality Assurance; PCPI = Physician Consortium for Performance Improvement

Evidence-Based Performance Measures

Glycemic Control

- One or more A1C tests per year (HEDIS)
- Patients who are at goal (A1C < 7.0%) (HEDIS)
- Poor control: Patients whose most recent A1C is > 9.0% (HEDIS)
- Patients with elevated A1C who are receiving treatment (NQF)

HEDIS = Healthcare Effectiveness Data and Information Set; NQF = National Quality Forum

PANEL DISCUSSION

- What is the appropriate approach to CMD when combining therapies to achieve therapeutic goals?
  - How does this relate to the performance measures discussed?
- What does "early aggressive intervention" mean, and in which patients is this approach appropriate?
  - How does this relate to the performance measures discussed?
- Are there patients for whom higher or lower A1C targets are appropriate?
- How best to manage polypharmacy/adherence issues with patients on dual/triple therapy?

Microvascular Screening

Nephropathy
Retinopathy
Neuropathy

Hypertension
Why Is Microvascular Screening Important?

- Microalbuminuria: independent marker of ↑ CHD risk
- Rising creatinine levels, which indicate kidney damage, can develop without a rise in albuminuria
- Diabetes-related nephropathy: leading cause of ESRD
  - ~ 20% to 40% will eventually develop diabetic nephropathy
  - Of patients with nephropathy, 20% will eventually develop ESRD


SB is a male patient with a 10-year history of hypertension. His hypertension is reliably controlled with medication, and his BP is 130/78. During his annual exam, you find that his spot urine albumin:creatinine ratio is above 30. How would you follow up on this finding?

1. Rescreen SB in 1 year
2. Repeat the microalbuminuria test once within the next 3 months
3. Repeat the microalbuminuria test twice within the next 3 to 6 months
4. Refer SB to a nephrologist

Diagnostic Criteria for Chronic Kidney Disease (CKD)

- Albumin:Creatinine Ratio
  - ≥ 30 mg albumin per g creatinine

- Estimated GFR
  - < 60 mL/min/1.73 m²

- Microalbuminuria
  - 30-299 mg albumin/g creatinine

- Macroalbuminuria
  - ≥ 300 mg albumin/g creatinine


Effects of ACE Inhibitors and ARBs

- Evidence for ARBs are clearer than for ACEs in T2DM
- Positive renal function results in patients with T2DM
  - Stable kidney function maintained in normotensive patients (ACE)
  - Slower decline in GFR in hypertensive patients with microalbuminuria after more than 3 years
  - Decline in proteinuria in normotensive and hypertensive patients
  - Prevention of proteinuria
  - May reduce risk of microalbuminuria

ACE Inhibitors = angiotensin converting enzyme inhibitors
ARB = angiotensin receptor blocker

Evidence-Based Performance Measures

Microvascular Screening

- Microalbumin testing (urine protein screening) at least once during past year (NCQA)
- Patients who had at least one creatinine screening or eGFR during past year (NQF, BMA)
- Dilated or retinal eye exam during past year (HEDIS)
- Annual comprehensive foot examination (NCQA)

BMA = British Medical Association

Why Is Blood Pressure Control Important?

- Hypertension - key factor in development of macrovascular and microvascular complications
- Nearly 75% of Americans with diabetes have hypertension
- < 25% incidence in general population
- Risk of cardiovascular events
  - Doubles for every 20-mm Hg increase in systolic BP
  - Decreases 34% with 10-mm Hg decrease in systolic BP
  - Doubles for 10-mm Hg increase in diastolic BP > 115/75 mm Hg


Evidence-Based Performance Measures

Hypertension

- Most recent BP < 140/90 mm Hg (HEDIS)
  - Note: ADA goal is BP < 130/80 mm Hg
- Elevated BP treated with ARB or ACE inhibitor (NQF)

Blood Pressure Guideline Recommendations

- Target Goal for T2DM: < 130/80 mm Hg
  - Altered goals may be appropriate
  - Measure BP at every routine visit
  - Therapy for patients with diabetes and hypertension:
    - Either ACE inhibitor or ARB
    - May need thiazide diuretic or loop diuretic based on eGFR
    - Combination therapy often required

JNC 7 Guidelines

Available Agents

Recommendations for Adults With HTN and Related Comorbidity

<table>
<thead>
<tr>
<th>Compelling Indicator*</th>
<th>Diuretic</th>
<th>β-Blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on documented benefits from outcome studies or on existing clinical guidelines; each compelling indicator is managed in parallel with hypertension.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker.

Key Points

- Renal insufficiency common in CMD, particularly if risk factors are not appropriately managed
- Microvascular screening is critical
- Hypertension
  - Key risk factor for micro- and macrovascular complications and leading CKD cause
  - Normalizing BP reduces CV events risk
- Drugs that inhibit the effects of angiotensin II reduce albuminuria/proteinuria and slow CKD progression
**PANEL DISCUSSION**

- How should PCPs be screening patients with CMR?
  - How does this relate to the performance measures discussed?
- How does the presence of microalbuminuria or CKD affect the management of patients either with or without diabetes?
- Should blood pressure goals vary depending on a patient’s individual risk or other specific characteristics?

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**Lipid Management**

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**Atherosclerosis Progression**

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**Pre-Test Question 2**

IP is an overweight Hispanic woman with a history of hypertension, mixed dyslipidemia, as well as moderately reduced kidney function. What should IP’s LDL-C target goal be?

1. LDL-C < 120 mg/dL
2. LDL-C < 100 mg/dL
3. LDL-C < 70 mg/dL
4. None of the above

---

**Pre-Test Question 3**

What treatment strategy would you consider for IP if her LDL-C were not at goal after 6 months of therapy with simvastatin 40 mg?

1. Monitor her lipid profiles for 6 months
2. Increase her statin dose
3. Add a bile acid sequestrant to her regimen
4. Add a cholesterol absorption inhibitor to her regimen
5. Add niacin

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**Guideline Recommendations for Lipid Control**

<table>
<thead>
<tr>
<th>ADA Goal</th>
<th>NKF-KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>LDL</td>
</tr>
<tr>
<td>&lt; 100 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>&lt; 70 mg/dL for pts with CVD</td>
<td>&lt; 70 mg/dL may be a therapeutic option</td>
</tr>
<tr>
<td>HDL</td>
<td>LDL</td>
</tr>
<tr>
<td>&gt; 40 mg/dL men</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>&gt; 50 mg/dL women</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 150 mg/dL</td>
</tr>
</tbody>
</table>

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*NKF-KDOQI 2007.*

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.
**Key Lessons From Statin Trials (> 90,000 pts)**

**Lowering LDL Reduces CV Events**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Events (%)</th>
<th>Control Events (%)</th>
<th>Relative Risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4.4)</td>
<td>2769 (6.2)</td>
<td>0.74 (0.70-0.79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3.4)</td>
<td>1960 (4.4)</td>
<td>0.81 (0.75-0.87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7.4)</td>
<td>4420 (9.8)</td>
<td>0.77 (0.74-0.80)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2620 (5.8)</td>
<td>3434 (7.6)</td>
<td>0.76 (0.73-0.80)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>105 (0.2)</td>
<td>99 (0.2)</td>
<td>1.05 (0.78-1.41)</td>
</tr>
<tr>
<td>Presumed ischemic stroke</td>
<td>1235 (2.8)</td>
<td>1518 (3.4)</td>
<td>0.81 (0.74-0.89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.0)</td>
<td>1617 (3.7)</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14.1)</td>
<td>7994 (17.8)</td>
<td>0.79 (0.77-0.81)</td>
</tr>
</tbody>
</table>

(relative risk (CI)

**Effects of Statins on Cardiovascular Outcomes in CKD/ESRD Patients**

- **4D**: Der Deutsche Diabetes Dialysis Studie
  - n = 1255 CKD patients; atorvastatin 20 mg vs. placebo; 4-year follow-up
- **AURORA**: A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
  - m = 2776 CKD patients on dialysis; rosuvastatin 10 mg vs. placebo; 3.6-year follow-up
- Primary CV composite endpoint showed no benefit with either atorvastatin or rosuvastatin therapy in these patients
- Take home: study findings left it unclear how to manage patients with severe CKD

**Evolving Concepts: SHARP Trial**

**Study of Heart and Renal Protection**

- Evaluated the CV effects of lipid-lowering therapies in patients with CKD
- Eligibility: history of CKD, not on dialysis
  - Creatinine - men: ≥ 1.7 mg/dL; women: ≥ 1.5 mg/dL
- Randomization
  - Ezetimibe 10 mg plus simvastatin 20 mg daily
  - Simvastatin 20 mg daily
  - Placebo
- Primary endpoint: major atherosclerotic events – coronary death, MI, non-hemorrhagic stroke, or any revascularization
- Secondary endpoint: end stage renal disease

**SHARP: Major Atherosclerotic Events**

- Median follow-up: 4.9 years
- % of had diabetes
- Mean GFR: 27 mL/min/1.73 m²

**Relative Risk of Vascular and Non-Vascular Outcomes in People With CKD vs. People Without CKD**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-fatal myocardial infarction</th>
<th>Ischemic stroke</th>
<th>Coronary death</th>
<th>Hemorrhagic stroke</th>
<th>Presumed ischemic stroke</th>
<th>Any stroke</th>
<th>Any major coronary event</th>
<th>Any coronary revascularization</th>
<th>All</th>
<th>All cancer deaths</th>
<th>All deaths of unknown cause</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk (CI)</td>
<td>1.47 (1.24-1.73)</td>
<td>1.21 (0.75-1.95)</td>
<td>1.21 (0.98-1.48)</td>
<td>1.02 (0.55-1.89)</td>
<td>1.21 (0.74-0.89)</td>
<td>0.83 (0.74-0.88)</td>
<td>0.77 (0.74-0.80)</td>
<td>0.76 (0.73-0.80)</td>
<td>1.11</td>
<td>1.07-1.36</td>
<td>1.13 (1.03-1.23)</td>
<td>1.13 (1.03-1.23)</td>
</tr>
</tbody>
</table>

**SHARP: Safety**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Ezet/simv (n = 4650)</th>
<th>Placebo (n = 4629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>17 (0.4%)</td>
<td>16 (0.3%)</td>
</tr>
<tr>
<td>CK &gt; 10 but ≤ 40 x ULN</td>
<td>4 (0.1%)</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td>CK &gt; 40 x ULN</td>
<td>21 (0.5%)</td>
<td>18 (0.4%)</td>
</tr>
<tr>
<td>Persistent elev LFTs</td>
<td>30 (0.6%)</td>
<td>26 (9.6%)</td>
</tr>
<tr>
<td>Gallstone complications</td>
<td>83 (1.8%)</td>
<td>76 (1.6%)</td>
</tr>
<tr>
<td>Pancreatitis without gallstones</td>
<td>12 (0.3%)</td>
<td>17 (0.4%)</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal; LFTs = liver function tests

No significant difference in cancer – risk ratio 0.99 (0.87-1.13); log rank 2P = 0.89
Take-Home Points From SHARP

• There is a clear benefit to LDL-lowering with a statin plus ezetimibe in people who are not on dialysis
  - Patients with GFR between 45 and 15 ml/min/1.73m²
• Lipid-lowering therapy reduced the risk of first cardiovascular event (non-fatal MI, stroke, cardiac death, or revascularization) by 16.1% (P = 0.001)
  - Consider LDL goal of 70 mg/dL in patients with CKD

Lipid-Altering Therapies for the CKD Patient

LDL-C Reduction

• Statins are first-line therapy
  - Statins are safe to use in CKD as long as appropriate dosage adjustments are made based on renal function
  - Use caution with highest doses of statins, as side effects increase with statin dose
  - “Rule of 6” – doubling statin dose generally achieves a reduction in LDL-C of ~ 6% over starting dose reduction
• Add: ezetimibe or colesvelem for further LDL reduction
  - Ezetimibe – no dose adjustment needed in CKD
  - Colesvelem – increases TG; contraindicated TG > 400
Key point: Beneficial to use multiple low doses of drugs rather than a high dose of a single drug in CKD patients

Evidence-Based Performance Measures

Lipid Control

• One or more lipid profiles within the last year (HEDIS)
• Patients with T2DM with most recent LDL-C < 100 mg/dL (HEDIS)
• Lifestyle modification and lipid-lowering agent if LDL-C > 100 mg/dL (NQF)

PANEL DISCUSSION

• How should PCPs treat dyslipidemia in renally compromised patients with or without diabetes? Are statins still appropriate?
• How should statin dosages be maximized/optimized?
  - In a patient who is at the maximum dose of their statin and LDL is still high (15% to 20% above goal), what should you do?
• When should combination lipid-lowering therapy be used?
• What are the clinical considerations in managing mixed dyslipidemia?
SB is a male patient with a 10-year history of hypertension. His hypertension is reliably controlled with medication, and his BP is 130/78. During his annual exam, you find that his spot urine albumin:creatinine ratio is above 30. How would you follow up on this finding?

1. Rescreen SB in 1 year
2. Repeat the microalbuminuria test once within the next 3 months
3. Repeat the microalbuminuria test twice within the next 3 to 6 months
4. Refer SB to a nephrologist

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The Role of QI-CME in Patient Care

Have you participated in quality improvement continuing medical education or performance improvement (PI-CME)?

1. Yes
2. No, but considering it
3. No, haven’t considered it
4. What is PI-CME?

AMA, AOA, and AAFP Perspective
• Focus on disease management in the context of clinicians’ individual practice
• Move education closer to the point-of-care
• Build a framework for life-long learning
• Place more responsibility on the clinician

Clinician Perspective
• Insight to actual patient population
• Comparison with peer practices and national standards
• Maintenance of Certification (MOC), Pay for Performance (P4P), Maintenance of Licensure (MOL)

Why Quality Improvement?

AMA = American Medical Association; American Osteopathic Association; American Academy of Family Physicians.
**What Is Quality Improvement CME?**

- Performance Improvement CME (PI-CME)
  - Individual QI
  - Standardized format – retrospective assessment of patient chart data, application of improvement measures, re-assessment
  - Measures change in clinician performance related to specific measures between two time points
  - Practice is assessed on nationally standardized performance measures
  - 20 credits (*AMA PRA Category 1 Credit™*)

**Performance Measures Support Adherence to Guidelines**

**Performance Measures**

- **Common Sources**
  - National Quality Forum (NQF)
  - National Committee for Quality Assurance (NCQA) – HEDIS measures
  - Physician Consortium for Performance Improvement (PCPI)

- **Examples – process or outcome related**
  - Diet and exercise plan discussed and noted in chart (process)
  - Patients with T2DM with most recent LDL-C < 100 mg/dL (outcomes)