This program has been brought to you by PharmCon

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Legal Disclaimer: The material presented here does not necessarily reflect the views of Pharmaceutical Education Consultants (PharmCon) or the companies that support educational programming. A qualified healthcare professional should always be consulted before using any therapeutic product discussed. Participants should verify all information and data before treating patients or employing any therapies described in this educational activity.

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Legal Disclaimer: The material presented here does not necessarily reflect the views of Pharmaceutical Education Consultants (PharmCon) or the companies that support educational programming. A qualified healthcare professional should always be consulted before using any therapeutic product discussed. Participants should verify all information and data before treating patients or employing any therapies described in this educational activity.

Pharmacists: 0798-0000-10-002-L01-P
Pharmacy Technicians: 0798-0000-10-002-L01-T
Nurses: N-002

Program Overview:
Cardiometabolic disease, which includes diabetes, obesity and coronary artery disease, kills well over 1 million people in our country each year. The importance of this learning activity is highlighted by the fact that it will serve as an overview to understand how obesity, insulin resistance, and diabetes type 2 relates to cardiovascular risk. Also included will be a discussion on emerging cardiovascular biomarkers and risk sensitivity. Pharmacologic and non-pharmacologic prevention and treatment strategies will be discussed in some detail as well. Lastly, patient education and counseling strategies will be addressed which will be followed up with a live 15 minute question and answer session involving all participants.

Objectives:
1. Explain glucose and lipid metabolism in a manner that will enhance the participants’ understanding of vascular inflammation and atherosclerotic plaque formation and vulnerability as it relates to cardiovascular risk. Also included will be a discussion on emerging cardiovascular biomarkers and risk sensitivity. Pharmacologic and non-pharmacologic prevention and treatment strategies will be discussed in some detail as well. Lastly, patient education and counseling strategies will be addressed which will be followed up with a live 15 minute question and answer session involving all participants.

Speaker: Dr. Ravotti has been a practicing Physician Assistant for over 20 years, with most of his experience being in primary care and orthopedics. He has also been involved with non-invasive anti-inflammatory research in an industrial rehabilitative setting. Prior to becoming a PA, Dr. Ravotti earned his BS degree at Slippery Rock University in Health Education/Athletic Training and taught in the public school systems of Western Pennsylvania. Dr. Ravotti earned his Physician-Assistant degree from Saint Francis University and graduated in 1984. He also received his Masters degree in Human Resource Management and holds a Doctorate of Health Sciences degree from Nova Southeastern. Dr. Ravotti is currently employed by Abbott Laboratories as a Cardiovascular Clinical Science Manager where he focuses most of his efforts on the management of dyslipidemia. He is also an adjunct Assistant Professor at Saint Francis University in the Department of Physician Assistant Sciences where he has taught for 22 years.

Speaker Disclosure: Dr. Ravotti has no actual or potential conflicts of interest in relation to the program.
Causes vs. Consequences of CMD

- Atherosclerosis (Coronary Artery Disease)
- Type 2 Diabetes
- Cerebrovascular Disease
- Peripheral Artery Disease
- Obesity
- Hypertension
- Insulin Resistance

Cardiometabolic Disease Prevalence

CVD REMAINS THE #1 KILLER OF AMERICANS

- Approximately 1/3 of Adult Americans are Obese
- 27 million Americans are Diabetic
- 44 million Americans have Metabolic Syndrome

Prevalence of CMD

- Cardiovascular disease accounts for 37% of all deaths in the US
- 20 million Americans have some form of CVD
- $403 Billion = cost of CVD
- Half of all US Adults have Total-C > 200 mg/dl
- 40% have LDL-C > 130 mg/dl
- 20% have HDL-C < 40 mg/dl
- 870,000 deaths annually related to CVD

CVD Burden on Healthcare

- In 2006, healthcare spending exceeded $2 Trillion ($6,700 per person)
- Healthcare is 16% of GDP
- Healthcare spending is expected to double in the next 5 years to $4 Trillion (1 out of $5)
- 75% of spending is on chronic disease (CAD, HTN, DM Type 2)
- As this trend continues, healthcare will be unaffordable
Diabetes: US Trends 2006

- 27 million Americans (6.3%)
- (Pennsylvania is 8%)
  - Diagnosed: 15.0 million
  - Undiagnosed: 6 million
  - Estimated 44 million metabolic syndrome
- 1.3 million new adult cases per year
- Rapid growth of high-risk populations
  - 30% of US adults are obese (BMI >30)
  - 16% of US children are overweight (BMI >25)


Obesity Trends* Among US Adults
(*BMI >30, or about 30 lbs overweight for 5’4” person)

Causes Of Death Annually (2,443,387)

- Heart Disease = 870,000
- Cancer = 557,271
- Stroke = 162,672
- Accidents = 106,724
- Diabetes = 73,249
- Influenza/Pneumonia = 65,000
- Alzheimers = 58,000
- Nephritis/Nephrotic Syndrome= 40,000
- Septicemia = 33,000


- Heart Disease
- Stroke
- Lung Cancer
- COPD
- Breast Cancer

(Estimated that 40% to 50% of deaths have preventable causes)

Source: US Census Bureau.

*Variables that are rounded to the nearest thousand. COPD = chronic obstructive pulmonary disease.
To learn more, visit www.nhlbi.nih.gov/health/heart/hearttruth.
Challenge Conventional Wisdom

1. Think in a manner that promotes “Upstream Intervention”
2. Early Detection (Accurate CVD Risk Assessment)
3. Early Intervention (Aggressive management)
4. Prevention
5. It is no longer appropriate to wait and treat the consequences of CMD
6. Downstream interventions remain critical

Metabolic Syndrome Criteria

- Waist Circumference: > 40 inches (male) or > 35 inches (female) * Note: ethnic variances
- Triglycerides (TGs) > 150 mg/dl
- HDL-C < 40 mg/dl (male) or < 50 mg/dl (female)
- Blood Pressure > 130/80 mm/hg (either s/d)
- Fasting Plasma Glucose > 100 mg/dl

* Note: At least three criteria must be present

Grundy, S.W., Circulation 2005; 112: 2735-2752

So When Does the Problem Start?

Diabetic Trends

- For every Kg of weight gain; there is a 4.5% increased chance of developing diabetes
- 28.4% of children (12-17) have elevated CRP levels (3.8mg/L)
- 100 million American have Cholesterol-T levels above 200 mg/dl

Ford, E.S., Diabetes Care, 2005. Vol 28
Metabolic Syndrome

• Metabolic Syndrome rates have increased by 50% among our nation’s youth within the last decade

• Over 2 million US Adolescents have Metabolic Syndrome

Insulin Resistance

glucose does not go into cell

CMD: Risk Factors

• Abdominal Obesity (associated IR)
• Hyperglycemia (Met S., DM and IR)
• Dyslipidemia
• Hypertension
• Pro-thrombotic State
• Pro-inflammatory State (CRP)

Recommendations of the 2003 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

• Dx of DM2 = FPG ≥ 126 mg/dL x2
• Impaired fasting glucose (IFG): ≥100 mg/dL
• Normal fasting plasma glucose (FPG): <100 mg/dL
• FPG and 2-h plasma glucose (2-h PG) tests preferred for diagnosis of diabetes
  • 2-h PG test is more sensitive than FPG
  • FPG test is more reproducible, less costly, and more convenient than 2-h PG
Obesity

- Fat is a highly active endocrine organ
- Causation of chronic low-grade vascular inflammation
- Expresses variety of toxic cytokines (adipokines) and Free Fatty Acids (FFAs)
- Circulating FFAs cause desensitization of Insulin Receptors (Lipotoxicity)

Boden, European Journal of Clinical Investigation, 2002; 32: 14-23

Abdominal Adiposity: The Critical Adipose Depot

- Subcutaneous fat
- Abdominal muscle layer
- Intra-abdominal fat

Boden, European Journal of Clinical Investigation, 2002; 32: 14-23

Obesity

- FFAs + intracellular lipids inhibit signaling cascade decreasing the transport of glucose to tissue
- Vascular inflammatory response leads to endothelial dysfunction and increased atherogenesis
- Vascular inflammation increases plaque vulnerability
- Fat cells (size matters) adiponectin production and other adipokines
- Apoptotic adipocytes promote inflammatory response and FFA release

Boden, European Journal of Clinical Investigation, 2002; 32: 14-23

Is this correct?

Who is to Blame?
Impact of Metabolic Abnormalities on CHD

- Abnormal glucose metabolism
- Leads to hyperglycemia and hyperinsulinemia
- Glucose underutilized as an energy source
- Liver overproduces TGs and packages them as VLDL (Apo B containing atherogenic lipoprotein)
- Increased Apo CIII and decreased HDL-C

Cardiometabolic Risk

- Two thirds of all diabetics die from heart disease
- There is a 4 fold increased CVD if you are diabetic
- There is a 2 fold risk associated with Metabolic Syndrome

Imaging: CVD Risk Prediction

- Carotid Intima Media Thickness (CIMT)
- Intravascular Ultrasound (IVUS)
- Coronary Angiography
- MRI
- CT Scan
- Calcium Scoring

Carotid IMT

Axial Resolution = 0.4-0.6 mm
Understanding Cardiometabolic Risk: Strategies for Prevention and Management

© 2010 Pharmaceutical Education Consultants, Inc. unless otherwise noted. All rights reserved.
Reproduction in whole or in part without permission is prohibited.

Carotid IMT

- Advantages
  - Direct coronary visualization
  - High spatial resolution
  - Widely available

- Limitations
  - Not validated for serial follow-up

CT Calcium Score

Endothelial Dysfunction

1. Vascular inflammation
2. Endothelial dysfunction
3. Type 2 diabetes
4. Insulin resistance
5. Dyslipidemia
6. Atherosclerosis
7. Oxidized LDL
8. Cytokines
9. Platelet activation
10. Inflammation

Atherosclerotic Progression

1. Monocyte attachment
2. Chemotactic factors
3. Adhesion proteins
4. Lipid laden macrophages (foam cells)
5. Atheroma formation
6. Endothelial dysfunction caused by oxidized LDL, cytokines, etc
7. Inflammatory response
8. Cytokine release
9. Thrombosis
10. Thrombi

Libby P. Am J Cardiol. 2003;91:1A-6A.
Taste Great vs. Less Filling

- Focus only on LDL-C since without LDL-C, further accumulation of plaque
- Address individual vulnerability (CRP) and endothelial dysfunction, IR and weight loss

HYBRID MODEL (combine both)

Lipoproteins 101

1.20
1.10
1.06
1.02
1.006
0.95
5 10 20 40 60 80 1000
Density (g/ml)

This is LDL

POLAR SURFACE COAT
Phospholipid
Free cholesterol

This is LDL
Cholesterol

NONPOLAR LIPID CORE
Cholesterol Ester
Triglycerides

Lipids and Lipoproteins

Apo B
Chylomicrons
VLDL
IDL
LDL
HDL
HDL Cholesterol
Triglycerides (mainly)
LDL Cholesterol
Apo B

Core containing triacylglycerols and cholesterol esters

ApoB
Phospholipids
Cholesterol

Diameter (nm)
### Understanding Cardiometabolic Risk

**Strategies for Prevention and Management**

© 2010 Pharmaceutical Education Consultants, Inc. unless otherwise noted. All rights reserved. Reproduction in whole or in part without permission is prohibited.

---

**ipoPNMR Profile**

**Non-HDL Cholesterol and CVD Risk**

- Non-HDL cholesterol calculation
  - Non-HDL-C = TC – HDL-C

- Significance of non-HDL-C
  - Encompasses all known and potential atherogenic lipid particles
  - Correlates closely with obesity and especially visceral adiposity
  - Has been shown to be a stronger predictor of cardiovascular death than LDL-C

---

**Good vs. Bad Cholesterol?**

- Lipoprotein content is either cholesterol or TG
- VLDL is 80% TG
- LDL-C is mostly Cholesterol
- CETP, LPL and Hepatic Lipase allows for ongoing dynamic exchange of cholesterol and TG between particles
- Receptor site binding (upregulation of LDL receptors and hepatic receptors for large buoyant LDL particles impact lipid panel readings
- Indirect RCT

---

**Residual Cardiovascular Risk in Major Statin Trials**

- 4S
- LIPID
- CARE
- HPS
- WOS
- AFCAPS / TexCAPS

---

Atherogenesis: LDL-C and Apo B

- All Apo B containing particles contribute to Atherogenesis (LDL, IDL and VLDL)
- LDL-C is the major therapeutic target because it contains the most cholesterol

LDL Cholesterol

- Major Predictor of CVD in diabetic and non-diabetic populations (HPS, CARDS)
- LDL-C lowering is associated with improved clinical outcomes
- Cholesterol content within each particle varies from person to person
- LDL-C content influenced by metabolic abnormalities
- LDL-C is a measurement of mass (Friedewald calculation Total Cholesterol-HDL-VLDL) (VLDL is TGS divided by 5) and does not accurately reflect atherogenic burden

Cardiometabolic Profile

- Elevated TGs
- Low HDL-C
- Moderately elevated LDL-C
- Pattern B (small dense LDL-C)
- Increased LDL-P
- IR
- Obesity

Dyslipidemia in Diabetes and the Metabolic Syndrome

- High levels of triglycerides
- Low levels of HDL cholesterol
- Although absolute levels of LDL-C are commonly not significantly increased, other parameters do change significantly
  - Number of LDL particles
    - Predominantly small, dense LDL particles

LDL Particle Number vs. LDL ~ C

- Measurement with NMR costly and limited access
- Studies consistently demonstrate superiority over LDL-C, non-HDL or Apo B (MESA, VA-HIT)
- LDL-P > 1000 suggests increased CVD risk
- Each LDL particle contains one Apo B100 particle which has an affinity to VCAM on endothelium. (atherogenic)
- Apo B and non-HDL (Total-C – HDL) are excellent surrogates for LDL-P

Study	| CHD Status	| CHD Endpoint	| NMR Particle Number Associations*
---|---|---|---
Cardiovascular Health Study Arterioscler Thromb Vasc Biol. 2002. | Primary Prevention | Incident MI or Angina | Increase in Total LDL-P Increase in Small LDL-P
Women’s Health Study Circulation 2002. | Primary Prevention | Incident MI, CHD Death, Stroke | Increase in Total LDL-P Increase in Small LDL-P
Healthy Women’s Study Am J Cardiol 2002. | Primary Prevention | EBCT Coronary Calcium Score | Increase in Total LDL-P Increase in Small LDL-P Increase in Large VLDL-P
Prevention Limitation of Atherosclerosis in Coronary Arteries (PLAC-I) Am J Cardiol 2002. | Secondary Prevention | Angiographic Minimal Lumen Diameter | Increase in Total LDL-P Increase in Small LDL-P Decrease in Large HDL-P
Framingham Offspring Study Am Heart Assoc 2004. | Secondary Prevention | Incident MI, Stroke, Claudication, Angina | Increase in Total LDL-P Increase in Small LDL-P

* Significant and independent in multivariate models adjusted for lipids

Same LDL-C Levels, Different Cardiovascular Risk

Correlates with:
- TC 198 mg/dL
- LDL-C 130 mg/dL
- TG 90 mg/dL
- HDL-C 50 mg/dL
- Non-HDL-C 148 mg/dL

Correlates with:
- TC 210 mg/dL
- LDL-C 130 mg/dL
- TG 250 mg/dL
- HDL-C 30 mg/dL
- Non-HDL-C 180 mg/dL

Otvos JD, Jeyarajah EJ, Cromwell WC. Am J Cardiol. 2002;90:22i-29i.

20+ years of studies
Patients with smaller LDL size have greater CHD risk at any given level of LDL-C

Lower risk
- 130 mg/dL
- Large LDL (Pattern A)

Higher risk
- 130 mg/dL
- Small LDL (Pattern B)

20+ years of studies
Patients with smaller LDL size have greater CHD risk at any given level of LDL-C

Lower risk
- 130 mg/dL
- Large LDL (Pattern A)

Higher risk
- 130 mg/dL
- Small LDL (Pattern B)
LDL-C: Does Size Matter?

Pattern A: Large Buoyant LDL particles
1. Excellent affinity to hepatic receptors
2. Short circulatory half-life
3. Associated with low particle number

Pattern B: Small dense LDL particles
1. Poor affinity for hepatic LDL receptors
2. Prolonged circulatory half-life
3. Readily oxidized
4. Easily penetrates endothelium
5. Associated with high particle number

LDL Pattern Shift

- Any pharmacologic intervention that reduces TGs also reduces VLDL and results in a shift from Pattern B to Pattern A
- Shifting to Pattern A results in increased LDL
- Though LDL-C increases, LDL-P decreases
- LDL paradox (LDL goes up, risk goes down)
  - Fibrates (fenofibrate, fenofibric acid, gemfibrozil)
  - Nicotinic acid (immediate and extended release)
  - Omega 3s (fish oil, Rx and dietary supplements)

Acute Coronary Syndrome

- Acute MIs most often evolve from mild to moderate coronary stenosis
- Plaque vulnerability is not directly related to atheroma volume
- Angiographic findings often underestimate risk
- Endothelial inflammation promotes plaque instability
- Cardio-respiratory fitness is an independent risk factor, but rarely assessed during clinical trials

AHA, Connection, 2009 p.28
Managing Risk

Early Recognition
1. Insulin Resistance/DM
2. Metabolic Syndrome
3. Framingham Risk Scoring
4. Reynolds Risk Scoring
5. Emerging Biomarkers (CRP)

Managing Risk

Aggressive intervention
1. Decreasing SBP by 2 mm of mercury results in a 7% risk reduction in heart disease and a 10% reduction from stroke
2. Aggressively address all aspects of Metabolic Syndrome
3. Pharmacotherapy must address multiple components of Metabolic Syndrome
4. Lowering LDL-C remains first-line therapy, but how we lower it is important

Lewington, S. Lancet, 2002; 360:1903-1913

Non-Pharmacotherapy

• Finnish Diabetes Prevention Study
  • 522 middle-aged subjects
  • Mean BMI is 31 kg/m2
  • All subjects received dietary counseling
  • All subjects increased their physical activity

• TLC (58% reduction in the development of DM vs. placebo)
• Metformin (31% reduction in the development of DM vs. placebo)

Therapeutic Lifestyle Change

The primary objective remains Weight Loss

• Reduced blood pressure
• Improved lipid profile
• Decreased depression
• Decreased arthritis
• Improved metabolic status (T2 DM)
• Reduced vascular inflammation (CRP)
**TLC: It’s not for Everybody**

- Effective TLC is more costly than pharmacotherapy
- TLC is time consuming and tedious
- TLC is initially not pleasurable
- TLC requires discipline

---

**Metabolic Nation**

*In a typical 24 hour day we buy*

- 87,000 Slim Fast Multipack Shakes
- 500,000 Hostess Twinkies
- 536,000 Dominoes Pepperoni Pizzas
- 1,900,000 Krispy Kreme glazed donuts
- 35,000,000 12oz. Cans of Bud Light

---

**Pharmacologic Management**

- Select agents with more than one beneficial effect
- Select modalities with high degrees of success (EBM)
- Do not use medication when medication is not working (Constantly assess patient motivation and compliance)
- Utilize every member of your healthcare team

---

**Pharmacological Principles**

- Address as many metabolic abnormalities with as few medications as possible
- Do as much as you need to do
- Do as little as you need to do
- Address the patient’s individual needs
- Treat the whole patient, not just the LDL
- Integrate all metabolic parameters when managing your patient (weight, BP, glucose, HDL, TGs, CRP, Apo B, etc.)
Cardiometabolic Risk

- Constellation of metabolic abnormalities
  - Dyslipidemia
  - HTN
  - Insulin Resistance
  - Obesity
- Address modifiable risk factors
  - Smoking
  - Diet
  - HTN/Obesity
- Utilize NCEP ATP III and ADA Guidelines

NCEP ATP III Definition of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Presence of 3 or more</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, inches</td>
<td>&gt;40</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>≥150</td>
<td>≥150</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>≥130/≥85</td>
<td>≥130/≥85</td>
</tr>
<tr>
<td>FPG, mg/dL*</td>
<td>≥110</td>
<td>≥110</td>
</tr>
</tbody>
</table>

Metabolic syndrome ICD-9-CM code: 277.7


Guidelines

- Primary target: LDL-C
  - Statins are drug of choice
  - Not all statins are created equal
  - Ezetemibe remains controversial (no outcomes)
- Secondary target non-HDL-C
  (30 pts. Above LDL goal)
  - Fibrates (Safe in combination, no + outcomes)
  - Nicotinic acid Imaging trials suggests regression only outcome is CDP

Combination Therapy

- Lovastatin / Niacin ER
- Simvastatin / Niacin ER
- Simvastatin / Ezetimibe
- Fenofibric acid / Rosuvastatin

- Currently, there are no outcome trial suggesting mortality benefit for fibrates, niacin, or ezetimibe
- Omega IIs have some evidence to suggest reduction of sudden death (not a function of lipid reduction)
Lipids: The Next Generation

• Biomarkers will serve as surrogates to outcomes
• Outcome trials, which are placebo controlled, can no longer be performed
• HDL functionality remains the last frontier of lipid management and risk reduction
• ACCORD trial (fenofibrate + simvastatin vs. simvastatin) *March 2010
• AIM HIGH (niacin ER + simvastatin vs. simvastatin)

Standard of Care is Killing People

• CV disease is vascular
• Vascular disease results in Insulin Resistance, Atherogenesis, proteinuria and renal disease, microvascular complications, infection, amputation etc.
• Diabetics have vascular inflammation for 15-20 years prior to diagnosis
• Treat Early (Metabolic Syndrome)
• Treat Often
(Don’t wait for the damage to occur)