The Identification and Management of Cardiometabolic Risk
Outline

Chapter 1:
The Medical Management of Cardiometabolic Risk
  – Definition of Cardiometabolic Risk
  – Consequences of Cardiometabolic Risk
  – The Dyslipidemia of Metabolic Syndrome

Chapter 2:
Concept of “Residual Risk” of Cardiovascular Events in patients with optimal LDL-C levels
  – Definition of Residual Risk
  – Treatment of Risk Factors Beyond LDL-C
Chapter 1

The Medical Management of Cardiometabolic Risk
Obesity and Abdominal Adiposity Are Leading Drivers of Cardiometabolic Risk

Body size
Body mass index
Abdominal adiposity

Insulin resistance

Glucose metabolism
↑ PP glucose
↑ IFG
↑ IGT
↑ T2DM

Uric acid metabolism
↑ Uric acid
↑ Urinary uric acid clearance

Dyslipidemia
↑ TG
↑ PP lipemia
↓ HDL-C
↓ Small, dense LDL

Hemodynamic
↑ SNS activity
↑ Na retention
↑ Hypertension

Inflammation/Thrombosis
↑ CRP
↑ PAI-1
↑ Fibrinogen

CORONARY HEART DISEASE

CMR: Cardiometabolic Risk, PP=postprandial, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, T2DM=type 2 diabetes mellitus, TG=triglycerides, PP lipemia= Post-prandial lipemia, HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein, SNS=sympathetic nervous system, Na=sodium, CRP=chronic relapsing pancreatitis, PAI-1=plasminogen activator inhibitor

Overweight and Obesity: Basic Concepts

- Practical problem
  - Obesity can be treated, but almost always recurs

- Emerging paradigm
  - Obesity is an incurable chronic disease requiring lifelong palliation
(*Body mass index [BMI] ≥30, or about 30-lbs overweight for a 5’4” person)

Obesity and Diabetes: Twin United States Epidemics

Obesity¹

Diabetes²

Medical Complications of Obesity

- Pulmonary disease
  - Obstructive sleep apnea
  - Abnormal function
  - Hypoventilation syndrome

- Nonalcoholic fatty liver disease
  - Steatosis
  - Steatohepatitis
  - Cirrhosis

- Gall bladder disease

- Reproductive abnormalities
  - Abnormal menses
  - Infertility
  - Polycystic ovarian syndrome
  - Male hypoandrogen/hyperestrogen

- Osteoarthritis

- Gout

- Coronary heart disease (CHD)

- Diabetes

- Dyslipidemia

- Hypertension

- Severe pancreatitis

- Cancer
  - Breast, colon, prostate, uterus, cervix, esophagus, pancreas, kidney

- Stroke

- Phlebitis, deep vein thrombosis
  - Venous stasis

“Cardiometabolic” Elements Are Common and Overlapping
Kaiser Permanente database, Northern California
N = 2.1 million adults
47% had ≥1 “cardiometabolic” condition(s)

Dyslipidemia 36%
Hypertension 28%
Diabetes 8.7%

~20% of all patients had ≥2 conditions

“Cardiometabolic” condition=dyslipidemia, hypertension, or diabetes.
Prevalence based on application of age- and sex-specific prevalence estimates for each condition from the Third National Health and Nutrition Examination Survey (NHANES III) data to the Kaiser Permanente membership to simulate full ascertainment.

Clinical Identification of the Metabolic Syndrome (NCEP 2005)*

- Elevated waist circumference
  - Men \( \geq 40 \text{ in (} \geq 102 \text{ cm)} \)
  - Women \( \geq 35 \text{ in (} \geq 88 \text{ cm)} \)
- TG \( \geq 150 \text{ mg/dL} \)
- HDL-C
  - Men \( < 40 \text{ mg/dL} \)
  - Women \( < 50 \text{ mg/dL} \)
- BP \( \geq 130/\geq 85 \text{ mm Hg} \)
- Fasting glucose \( \geq 100 \text{ mg/dL} \)

*Diagnosis is established when \( \geq 3 \) of these factors are present.
†Patients must either meet the indicated criteria OR be on drug treatment for that factor.

NCEP=National Cholesterol Education Program
BP=Blood Pressure

There’s no such thing as a sudden heart attack. It requires years of preparation.

Central adiposity + Lack of physical activity + Genes = Metabolic syndrome/insulin resistance
Abdominal Adiposity: The Critical Adipose Depot

Is this where you measure?

Metabolic Syndrome: Waist Circumference Cutpoints for Special Populations

• For clinical purposes, the waist circumference cutpoints on the previous slide will continue to apply to United States populations

• European cutoffs are defined as 37 inches and 31.5 inches for males and females, respectively
  – Sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations should use European cutpoints until more specific data are available

• For people of Chinese, Japanese, or South Asian descent and for ethnic South and Central Americans, the cutpoints are 35.4 inches and 31.5 inches for males and females, respectively

# Increasing Prevalence of Abdominal Adiposity

**US National Health and Nutrition Examination Survey (NHANES)**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>29.5%</td>
<td>42.4%</td>
<td>+44%</td>
</tr>
<tr>
<td>Women</td>
<td>47.0%</td>
<td>61.3%</td>
<td>+30%</td>
</tr>
</tbody>
</table>

Abdominal adiposity defined as waist circumference: 
≥40 in (≥102 cm) in men or ≥35 in (≥88 cm) in women

Data are adjusted for age.

Abdominal Adiposity Increases the Risk of Type 2 Diabetes and Coronary Heart Disease

**Relative Risk: Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Waist Circumference (cm)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;71</td>
<td>1.6</td>
</tr>
<tr>
<td>71–75.9</td>
<td>4.6</td>
</tr>
<tr>
<td>76–81</td>
<td>8.7</td>
</tr>
<tr>
<td>81.1–86</td>
<td>12.1</td>
</tr>
<tr>
<td>86.1–91</td>
<td>16.7</td>
</tr>
<tr>
<td>91.1–96.3</td>
<td>22.4</td>
</tr>
</tbody>
</table>

*Relative Risk: CHD*

*Waist circumference was independently associated with increased age-adjusted risk of CHD, even after adjusting for BMI and other CVD risk factors.*

<table>
<thead>
<tr>
<th>Quintiles of Waist Circumference (cm)</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>&lt;69.8</td>
<td>1.27</td>
</tr>
<tr>
<td>69.8–74.1</td>
<td>2.08</td>
</tr>
<tr>
<td>74.2–79.1</td>
<td>2.31</td>
</tr>
<tr>
<td>79.2–86.2</td>
<td>2.44</td>
</tr>
</tbody>
</table>

**CVD= Cardiovascular Disease**

A Greater Number of Metabolic Syndrome Components Leads to Greater Risk for CV Events: Framingham Offspring Study 8-Year Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Metabolic Syndrome Risk Factors</th>
<th>Age-Adjusted Relative Risk (95% CI)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>0</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>1.48 (0.69–3.16)</td>
<td>3.39 (1.31–8.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>3.99 (1.89–8.41)</td>
<td>5.95 (2.20–16.11)</td>
<td></td>
</tr>
<tr>
<td>Hard CHD</td>
<td>0</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>0.98 (0.36–2.67)</td>
<td>3.77 (0.45–31.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>2.55 (0.96–6.79)</td>
<td>7.21 (0.81–64.37)</td>
<td></td>
</tr>
<tr>
<td>Total CHD</td>
<td>0</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>1.24 (0.54–2.83)</td>
<td>3.29 (0.95–11.34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>3.01 (1.33–6.83)</td>
<td>3.96 (1.02–15.38)</td>
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<tr>
<td>T2DM</td>
<td>0</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>4.16 (0.98–17.64)</td>
<td>6.10 (1.85–20.10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>23.83 (5.80–98.01)</td>
<td>29.69 (9.10–96.85)</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk of New-onset Diabetes as Correlated with the Number of Characteristics of the Metabolic Syndrome

Factors Contributing to Cardiometabolic Risk

ApoB = Apolipoprotein B

Reprinted with permission from Brunzell JD et al. JACC. 2008;51:1513.
The Evolving View of Adipose Tissue: An Endocrine Organ

Old View:
Inert Storage Depot

Fed
- Fatty acids
- Glucose

Fasted
- Fatty acids
- Glycerol

Current View:
Secretory/Endocrine Organ

Muscle
Liver
Pancreas
Vasculature

Multiple secretory products

### Properties of Key Adipokines

<table>
<thead>
<tr>
<th>Adiponectin</th>
<th>Antiatherogenic/antidiabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ in IAA</td>
<td>↓ Foam cells</td>
</tr>
<tr>
<td></td>
<td>↑ Insulin sensitivity</td>
</tr>
</tbody>
</table>

| IL-6 | Proatherogenic/pro-diabetic |
| ↑ in IAA | ↑ Vascular inflammation | ↓ Insulin signalling |

| TNFα | Pro-diabetic |
| ↑ in IAA | ↓ Insulin sensitivity in adipocytes (paracrine) |

| PAI-1 | Proatherogenic |
| ↑ in IAA | ↑ Atherothrombotic risk |

IAA=intraabdominal adiposity, IL-6=interleukin-6, TNFα=tumor necrosis factor alpha, PAI-1=plasminogen activator inhibitor 1.

Intraabdominal Adiposity Promotes Insulin Resistance and Increased CVD Risk

Change in adipokine secretion
- ↑ PAI-1
- ↑ IL-6
- ↑ TNFα
- ↑ Leptin
- ↑ Resistin
- ↓ Adiponectin

Hepatic FFA flux

Insulin resistance
Mixed dyslipidemia
↑ Atherogenesis

FFA=free fatty acid

Case Study I

Special Considerations for the Overweight/Obese Patient
Case Study
Overview

• A 57-year-old male lawyer is referred by his new law practice for an initial exam
• Patient has dyslipidemia and history of “borderline” hypertension; comorbidities include erectile dysfunction, chronic fatigue, and depression
• Family history of father with MI at age 54
• Meds; Paroxetine 10 mg qd
• Current weight of 236 pounds is his highest: Ht. 5’ 10” (BMI 34). Waist circ 40 “ BP 148/92
• Reports excessive snoring at night, per spouse
  – Experiences morning headaches and daytime somnolence
Case Study
Laboratory Results

- **Glucose**: 102 mg/dL
- **TC**: 204 mg/dL
- **HDL-C**: 36 mg/dL
- **LDL-C**: 100 mg/dL
- **TG**: 340 mg/dL
- **Non–HDL-C**: 168 mg/dL
- **EKG**: sinus bradycardia, rate 56
- **A1_c**: 6.3%
- **Creatinine**: 1.2 mg/dL
- **AST**: 27 U/L
- **ALT**: 53 U/L

TC=total cholesterol, EKG=electrocardiogram, Non-HDL-C= Non high-density lipoprotein cholesterol, A1_c=hemoglobin A1_c, AST=aspartate aminotransferase, ALT=alanine aminotransferase
Case Study
Framingham Risk Score

<table>
<thead>
<tr>
<th>Points</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age: 57 years</td>
</tr>
<tr>
<td>8</td>
<td>TC</td>
</tr>
<tr>
<td>3</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>0</td>
<td>HDL-C</td>
</tr>
<tr>
<td>2</td>
<td>SBP</td>
</tr>
<tr>
<td>1</td>
<td>Total points</td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

10-year risk=16%

SBP=systolic blood pressure

Case Study

Patient Characteristics
Meeting Metabolic Syndrome Criteria

- **Waist**: 40 inches
- **TG**: 340 mg/dL
- **HDL-C**: 36 mg/dL
- **Blood pressure**: 148/92 mm Hg
- **Glucose**: 102 mg/dL
Case Study
Additional Tests

- BP monitoring shows early AM systolic as high as 160, and consistent diastolic > 90 during the day
- Sleep study shows significant number of apnea spells with critical destaturation
- $\text{Lp}(a)$: 10 mg/dL
- apo B: 110 mg/dL

$Lp(a) =$ Lipoprotein(a)
Case Study
Action Plan

- Start stain to reduce LDL-C, non HDL-C and apo B
- Recommend individual dietitian consult for weight reduction
- Follow up with obtaining CPAP machine fitting/settings
- Home BP monitoring

CPAP= Continuous positive airway pressure
Non HDL-C=non HDL cholesterol
Case Study
Month 4: Registered Dietitian Visit 3

• **Weight**: 222 lbs (14 lbs total loss)

• Patient has been doing well with breakfast meal replacements, but is bored with diet and feels he has hit a weight plateau

• Plan
  – Congratulate him on losing 14 lbs!
  – Continue low-glycemic index diet
  – Food records 3 days/week, self-monitor weight every day for next 2 weeks
  – Reinforce need for physical activity
Case Study
Month 5: MD Visit 3

Lab Results

- **Glucose**: 92 mg/dL
- **TC**: 150 mg/dL
- **HDL-C**: 38 mg/dL
- **LDL-C**: 72 mg/dL
- **TG**: 200 mg/dL
- **Non–HDL-C**: 112 mg/dL
- **Apo B**: 90 mg/dL
- **A1c**: 5.6%
- **Creatinine**: 1.2 mg/dL
- **AST**: 25 U/L
- **ALT**: 40 U/L
National Weight Control Registry: Important Behaviors of Successful Long-Term Weight Management

• Self-monitoring
  – Diet: record food intake daily, limit certain foods or food quantity
  – Weight: check body weight >1x/week
• Low-calorie, low-fat diet
  – Total energy intake: 1300–1400 kcal/day
  – Energy intake from fat: 20%–25%
• Eat breakfast daily
• Regular physical activity: 2500–3000 kcal/week (e.g., walk 4 miles/day)

Case Study
Month 8: Laboratory Results

- **Glucose**: 90 mg/dL
- **TC**: 142 mg/dL
- **HDL-C**: 40 mg/dL
- **LDL-C**: 70 mg/dL
- **TG**: 160 mg/dL
- **Non–HDL-c**: 102 mg/dL
Key Learnings: Medical

- Target mixed dyslipidemia with statin therapy first to reach LDL-C, Non HDL-C, and ApoB targets, adding fibrates or niacin if indicated
- Consider sleep apnea in hypertensive obese patients
- Assess concomitant medications for weight gain potential
- Refocus on lifestyle changes at every pharmacologic intervention
Chapter 2

Concept of “Residual Risk” of Cardiovascular Events in patients with Optimal LDL-C Levels
Residual CHD Risk in Statin vs PBO Trials

- **4S**
  - Placebo: 28.0%
  - Statin: 19.4%
  - Δ LDL: -35%
  - N: 4444

- **LIPID**
  - Placebo: 15.9%
  - Statin: 12.3%
  - Δ LDL: -25%
  - N: 9014

- **CARE**
  - Placebo: 13.2%
  - Statin: 10.2%
  - Δ LDL: -28%
  - N: 4159

- **HPS**
  - Placebo: 11.8%
  - Statin: 8.7%
  - Δ LDL: -29%
  - N: 20536

- **WOSCOPS**
  - Placebo: 7.9%
  - Statin: 5.5%
  - Δ LDL: -26%
  - N: 6595

- **AFCAPS/TexCAPS**
  - Placebo: 10.9%
  - Statin: 6.8%
  - Δ LDL: -25%
  - N: 6605

PBO=Placebo

Residual CVD Risk in Patients With Intensive Statin Therapy

Patients Experiencing Major CVD Events, %

PROVE IT-TIMI 22
- Standard statin therapy: 22.4%
- High-dose statin therapy: 12.0%

IDEAL
- Standard statin therapy: 13.7%
- High-dose statin therapy: 8.7%

TNT
- Standard statin therapy: 12.0%
- High-dose statin therapy: 8.7%

LDL-C,* mg/dL
- PROVE IT-TIMI 22: 95, 62
- IDEAL: 104, 81
- TNT: 101, 77

*Mean or median LDL-C after treatment

TNT Post-Hoc Analysis:
HDL-C Predicts CV Risk at LDL-C <70 mg/dL

Hazard ratio (95% CI) versus Q1
Q2  0.85 (0.57–1.25)
Q3  0.57 (0.36–0.88)
Q4  0.55 (0.35–0.86)
Q5  0.61 (0.38–0.97)

TNT POPULATION
Stable CHD
Age 35-75 y
N = 9,770 with HDL-C

TNT TREATMENT
Atorvastatin 10 mg
Vs.
Atorvastatin 80 mg

TNT= Treating to New Targets

On-Treatment TG >150 mg/dL Predicts CHD Events\textsuperscript{a} in Patients with ACS\textsuperscript{b} 

PROVE IT-TIMI 22 trial

LDL-C

- HR: 0.81 (0.68, 0.96) \hspace{1cm} LDL-C ≥70
- P=0.015
- LDL-C <70

TG

- HR: 0.73 (0.62, 0.87) \hspace{1cm} TG ≥150
- P<0.001
- TG <150

\textsuperscript{a}Death, MI, and recurrent ACS, \textsuperscript{b}Atorvastatin 80 mg or pravastatin 40 mg, Lipid values are in mg/dL

ACS= acute coronary syndrome  
MI= Myocardial Infarction  
PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction  

“Residual Risk”

Components

• Disease burden / extent of end-organ damage
• “Non-lipid” risk factors
  – Age / gender / ethnicity
  – Smoking / Alcohol
  – Diet / Physical Activity
  – Obesity
  – Hypertension (HTN)
  – Diabetes (DM)
  – Psychosocial factors
• Lipids and lipoproteins

What Can We “Measure”?

• Age / gender / ethnicity
• Family History
• Diseases
  – Dichotomous
• Lipids and lipoproteins
  – Apo B, Lp(a)
• Non-lipid Biomarkers
  – Serum markers
  – Imaging
• Genetic testing
Take Home Point:

Atherosclerosis is a multi-factorial disease.

Even if we create the “perfect” lipid / lipoprotein profile, there will be “residual risk”.
ADA/ACCF 2008 Consensus Statement
A Need for Better Lipoprotein Management

- Lipoprotein abnormalities (high TG, low HDL-C) are common in patients with CMR. Measurement of LDL-C may not accurately reflect the true burden of LDL particles (LDL-P).

- Even with adequate LDL-C lowering, many patients on statin therapy have significant residual CVD risk. Treatment targets and the best approach for CVD risk reduction in this population need to be better defined.

- Some have advocated that assessment of other lipoprotein parameters might be more helpful than assessment limited to LDL-C or non-HDL-C in these populations.

Brunzell et.al. JACC.2008;51:1512-1524.
ADA/ACCF Consensus Statement

- “A more accurate way to capture the risk may be to measure the number of LDL particles directly using nuclear magnetic resonance (NMR).”
- “Many cross-sectional and prospective studies show that LDL-P is a better discriminator of risk than is LDL-C.”
- “Measurements of apoB or LDL-P may more closely quantitate the atherogenic lipoprotein load. Some studies suggest that both are better indices of CVD risk than LDL-C or non-HDL cholesterol and more reliable indexes of on-treatment residual CVD risk.”
- “ApoB and LDL-P also appear to be more discriminating measures of the adequacy of LDL lowering than are LDL-C or non-HDL cholesterol.”
- “ApoB and LDL-P concentration also appear to be more closely associated with obesity, diabetes, insulin resistance, and other markers of CMR than LDL-C or non-HDL-C.”

Brunzell et.al. JACC.2008;51:1512-1524.
**ADA/ACCF 2008 Consensus Statement:**
Treatment Goals in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities

### Goals

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest-Risk Patient</strong></td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>Known CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes plus ≥1 additional major CVD risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High-Risk Patients</strong></td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;90 mg/dL</td>
</tr>
<tr>
<td>No diabetes or known CVD but ≥2 major CVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes but no other major CVD risk factors</td>
<td></td>
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</tr>
</tbody>
</table>

“In individuals on statin therapy who continue to have low HDL-C or elevated non–HDL-C, especially if Apo B levels remain elevated, combination therapy is recommended. The preferred agent to use in combination with a statin is nicotinic acid…”

Brunzell JD et al., *Diabetes Care.* 2008;31:811-822.
Elevated Triglycerides Are Metabolically Related to Small LDL and HDL-P

CETP=cholesteryl ester transfer protein
HDL-P= HDL particles

Same LDL-C Levels, Different Cardiovascular Risk

- **Fewer Particles**
  - LDL-C = 130 mg/dL
  - Apo B
  - Cholesterol Ester
  - 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

- **More Particles**
  - More Apo B
  - 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

What Is Non–HDL-C?

All atherogenic lipoproteins

HDL

LDL

IDL

VLDL

Chylomicron remnant

APO A-1

APO B

APO B

APO B

APO B 48

non-HDL

non–HDL-C = Total cholesterol – HDL-C
Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

The Framingham Study

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C

Relationship of LDL-P and LDL-C to Levels of HDL-C and Triglycerides

Framingham Offspring Study (n=3,473)

ApoB

• Measurement of the total number of atherogenic particles in plasma

• Apo B correlates more closely with non-HDL-C than with LDL-C:

CHD Event Associations of LDL-P versus LDL-C
Framingham Offspring Study (n=3,066)

LDL-C, LDL-P and ApoB in Metabolic Syndrome: Framingham Heart Study

Fruchart JC et al., *Am J Cardiol* 2008:102(suppl); 1K-34K.
Approaches to Therapy for the Metabolic Syndrome

I. Behavioral therapy (weight loss and increased activity)

II. Treat existing risk factors
   a) BP control, smoking cessation
   b) LDL-C < 70 mg/dl (non HDL-C < 100) reasonable in CHD patients; LDL-C < 100 mg/dL reasonable for high risk primary prevention patients

III. Insulin sensitizing therapies (metformin, TZD) in nondiabetic subjects with MS
   a) Reasonable if IGT
   b) May be reasonable if A1C 6 – 6.5%

TZD = Thiazolidinediones
Additional Agents in Combination with a Statin for Mixed Hyperlipidemia

- Statin + fenofibrate/fenofibric acid
- Statin + niacin ER (1000 mg)
- Statin + omega-3 fatty acids (3 – 4 gm EPA + DHA)
- Statin + fibrate + niacin ± omega 3
- Statin + ezetimibe + fibrate, niacin and/or omega 3

DHA= Docosahexaenoic acid
Treatments that Alter Cholesterol Content of LDL Change LDL-C and LDL-P Differentially

Cholesterol per particle decreases with:
- Statins
- Statin + Ezetimibe or Bile Acid Sequestrates
- Estrogen Replacement Therapy
- Anti-retrovirals (some)
- Low fat, High carb diet

Therapy ↓ LDL-C More Than LDL-P

Cholesterol per particle increases with:
- Fibrates
- Niacin
- Pioglitazone
- Omega 3 FAs
- Exercise
- Mediterranean and low carb diet

Therapy ↓ LDL-P More Than LDL-C

Little Change in Cholesterol per Particle with:
- Bile Acid Sequestrate or Ezetimibe Monotherapy

Similar Change in LDL-C and LDL-P

Treatment Algorithm for Patients with the Metabolic Syndrome or Diabetes

Statin therapy to achieve LDL-C <100 mg/dL (<70 mg/dL with CHD)

- **TG >150**
  - HDL >40*
    - Fibrate
    - Add Niacin
  - If Goals Not Reached

- **TG >150**
  - HDL <40*
    - Fibrate or Niacin
    - Triple Therapy
  - If Goals Not Reached

- **TG <150**
  - HDL <40*
    - Niacin
    - Add Fibrate

*50 mg/dL in women

Units are mg/dL

*www.lipid.org*
Case Study II

Mixed Dyslipidemia in the Patient with Cardiometabolic Risk
Case Study
Overview

• 62-year-old white female presents for new patient examination
  – Family history of heart disease (mother, age 57-years) and diabetes
  – Does not smoke and is not on hormone-replacement therapy
• Current medications: none
• On examination
  – BP: 138/84 mm Hg, BMI: 29.6, height: 65 inches, weight: 178 lbs, waist: 37 inches
  – No peripheral bruits, normal heart exam, and normal peripheral pulses
Case Study
Laboratory Results

- **TC**: 210 mg/dL
- **TG**: 240 mg/dL
- **HDL-C**: 43 mg/dL
- **LDL-C**: 110 mg/dL
- **Non–HDL-C**: 177 mg/dL
- **FPG**: 105 mg/dL
- **TSH**: within normal limits
- **ALT**: 68 U/L
- **AST**: 46 U/L

FPG = fasting plasma glucose
Case Study
Framingham Risk Score

<table>
<thead>
<tr>
<th>Points</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 62-years</td>
<td>10</td>
</tr>
<tr>
<td>TC</td>
<td>2</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1</td>
</tr>
<tr>
<td>SBP</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total points</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

**10-year risk = 3%**

Case Study
Patient Characteristics
Meeting Metabolic Syndrome Criteria

- Waist: 37 inches
- TG: 240 mg/dL
- HDL-C: 43 mg/dL
- Blood pressure: 138/84 mm Hg
- Glucose: 105 mg/dL
Case Study
Additional Laboratory Tests

• **hs-CRP**: 6.5 mg/L (high risk: >3 mg/L)
• **Hb A1C**: 6.4%
• **Lp(a)**: 30 mg/dL
• **apo B**: 115 mg/dL
• **LDL-P**: 1818

hs-CRP=high-sensitivity C-reactive protein
Diabetes Prevention Program: Greater Weight-Loss Further Reduces the Incidence of New-Onset Diabetes

*In the lifestyle intervention group over an average 3.2 years of follow-up

JUPITER: Primary Endpoint (MI, Stroke, UA/Revascularization, CV Death)

Although a little younger than the JUPITER population, this patient would most likely see similar benefits.

UA=unstable angina

Case Study
6 Month: Laboratory Data

- **TC**: 145 mg/dL
- **TG**: 170 mg/dL
- **HDL-C**: 46 mg/dL
- **LDL-C**: 65 mg/dL
- **Non–HDL-C**: 99 mg/dL
- **Apo B**: 71 mg/dL
- **LDL-P**: 1078
- **Glucose**: 101 mg/dL
- **Hb A1C**: 6.0%
Key Learnings: Medical

- The Framingham score may underestimate risk in women, especially those with the metabolic syndrome.
- The risk for CHD and diabetes may be very different in a patient with the metabolic syndrome.
  - Avoidance of diabetes is a strong motivator for patients to lose weight.
- Patients with metabolic syndrome but without diabetes or CVD, and ≥2 major CV risk-factors need to be treated to goal.
  - LDL-C: <100 mg/dL, non–HDL-C: <130 mg/dL, apo B: <90 mg/dL.
- 5%–10% weight-loss can greatly improve lipid profile, BP and markedly reduce the risk of diabetes in a patient with IFG.
- Statin treatment in women > 60 yr with hs-CRP > 2 mg/L can significantly reduce CVD risk.
Key Learnings: Metabolic Risk

- CMR represents a constellation of clinical findings associated with increased risk for diabetes and CHD.
- Increasing obesity, physical inactivity and insulin resistance are associated with increased triglycerides.
- Patients with CMR often have normal LDL-C values but elevated levels of apoB containing lipoproteins.
- Mixed dyslipidemia (low HDL-C, high TG and increased numbers of small LDL-P) is common in the metabolic syndrome and diabetes.
- Understanding the pathophysiology of CMR helps us to identify treatment targets for the prevention of CVD.