Managing Cardiometabolic Risk

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

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Program Goals

- Explain cardiometabolic syndrome
- Outline the cardiovascular consequences of the syndrome
- Discuss the management of cardiometabolic syndrome.
- Identify the pharmacist’s role in identifying and managing patients with cardiometabolic syndrome.
Cardiometabolic Syndrome (CMS)

WHO 2001 Working Group on Diabetes

Kylin 1923
Kaplan 1989 (deadly quartet)
Vague 1947
Crepaldi 1967
Reaven 1988 (syndrome X)
Ferrannini 1991 & Haffner 1992 (insulin resistance syndrome)
# Cardiometabolic Syndrome

If any 3 of the 5 are present

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>&gt; 40 in. (men)</td>
</tr>
<tr>
<td></td>
<td>&gt; 35 in. (women)</td>
</tr>
<tr>
<td>Elevated triglycerides*</td>
<td>≥ 150 mg/dl</td>
</tr>
<tr>
<td>Low HDL cholesterol*</td>
<td>&lt; 40 mg/dl (men)</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dl (women)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>≥ 130/ ≥ 85 mm Hg</td>
</tr>
<tr>
<td>Impaired fasting glucose*</td>
<td>≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

* Or drug treatment for the condition

Cardiometabolic Syndrome

Causes

- Acquired causes
  - Overweight and obesity
  - Physical inactivity
- Genetic causes

*Obesity is on track to overcome smoking as leading cause of death*

Healthy Lifestyle Characteristics Among Adults in the United States

- 3% of population leads a healthy lifestyle
  - nonsmoking
  - healthy weight (BMI 18.5 – 25)
  - 5 or more fruits & vegetables/day
  - regular physical activity (≥ 30 minutes for ≥ 5 times/week)

*Arch Intern Med* 2005;165:854-857

1 in 4 Adults Have Diabetes or Cardiometabolic Syndrome

Population at risk (millions)

- Undiagnosed diabetes*: 6.2
- Diagnosed diabetes*: 14.6
- Metabolic syndrome†: ~64

*2005 US data, NIDDK, NIH.
†Based on revised NCEP/ATP III definition

Prevalence, %,

0 5 10 15 20 25 30 35

White Black Hispanic Other

Metabolic syndrome

References:

JAMA. 2003;289:76-79.
Diabetes Care. 2004;27:2444-
A Major Health Issue Worldwide - Prevalence of the metabolic syndrome (ATP III)
Prevalence

- 4.2% of adolescents (12-19)
  - 50% of severely obese
  - 28.7% of overweight
  - 6.1% of borderline high weight
  - 0.1% of normal weight

- Criteria in adolescents
  - 3 or more: TG ≥ 110 mg/d, HDL-C ≤ 40 mg/dL
  - FBG ≥ 110 mg/dL, BP at or above the 90th percentile for age, sex and height, waist circumference at or above the 90th percentile for age and sex

NEJM 2004;350:2362-74
WEAPONS OF MASS EXPANSION.
Why is Cardiometabolic Syndrome a Bad Thing?
Atherogenic Consequences of Cardiometabolic Syndrome

Central Obesity

Dyslipidemia
- ↓ HDL
- Small, dense LDL
- ↑ TG

Endothelial dysfunction
- ↑ VCAM
- ↓ NO

Impaired thrombosis
- ↑ PAI-1
- ↓ tPA

Hypertension

Inflammation
- ↑ CRP
- ↑ IL-6

Insulin Resistance

Glucose Intolerance

Diabetes

Nonalcoholic steatohepatitis

Atherosclerosis

PCOS

Atherogenic Consequences of Cardiometabolic Syndrome

- glucose intolerance
- inflammation
- ↑ CRP, ↑ IL-6
- hypertension
- central obesity
- insulin resistance
- dyslipidemia
- ↓ HDL, ↑ TG, ↑ small dense LDL
- endothelial dysfunction
- ↑ VCAM, ↓ NO
- impaired thrombosis
- ↑ PAI-1, ↓ tPA
- hypertension
- inflammation
- ↑ CRP, ↑ IL-6
- atherosclerosis
- PCOS
- nonalcoholic steatohepatitis
Anatomy of Fat Deposits

- Visceral fat = intraperitoneal and extraperitoneal fat
  - Most responsible for health hazards
  - Excess is an independent risk factor for type 2 DM, dyslipidemia, hypertension, and cardiovascular disease

- Subcutaneous fat
Adipose Tissue as an Endocrine Organ

Traditional View
Fat is an inert storage depot

Emerging View
Fat is a secretory endocrine organ

Fatty Acids → Glucose → Fatty Acids → Glycerol

Leptin, fatty acids, adiponectin, TNF-α, PAI-1, cytokines

PAI-1 = plasminogen activator

*J Clin Endocrinol Metab. 2004;89:2548-2556.*
Risk of MI, Stroke, Diabetes, or Death with Cardiometabolic Syndrome

- 2-fold \( \uparrow \)’d risk of MI compared with those without the syndrome
- 1.5 to 2 fold \( \uparrow \)’d risk for stroke
- 5-fold \( \uparrow \)’d risk for developing type 2 diabetes
- Relative risk of CHD mortality = 3.77%

References:
- Stroke. 2008;39:30-35
- J Am Coll Cardiol 2004;43:475A
- JAMA 2002;288:2709-16
Metabolic Syndrome: Impact on Mortality

*P < 0.001.

The clock begins ticking for atherosclerosis years before diagnosis of diabetes

Treatment Goals

- Prevention of type 2 diabetes
- Reduce risk of clinical atherosclerotic disease
Therapeutic Objectives

- Lifestyle Modification
  - Dietary changes
  - Weight loss or control
  - Physical activity

- To treat associated lipid and non-lipid risk factors
  - Hypertension
  - Prothrombotic state
  - Atherogenic dyslipidemia
  - Diabetes or impaired glucose tolerance
  - Smoking cessation
Recommended Dietary Changes

- Reduce simple carbohydrates
- Increase complex carbohydrates
- Reduce saturated fats, trans fats, and cholesterol
- Increase fish
Weight Loss

- Reduces risk factors
- Initial goal
  - 7-10% of body weight in first year
- Continue weight loss thereafter to extent possible
- Ultimate goal
  - BMI < 25 kg/m²
# Do You Know Your Own BMI?

<table>
<thead>
<tr>
<th>Height</th>
<th>Weight (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’0”</td>
<td>23 25 27 29 31 33 35 37 39 41 43 45 47 49</td>
</tr>
<tr>
<td>5’2”</td>
<td>22 24 26 27 29 31 33 35 37 38 40 42 44 46</td>
</tr>
<tr>
<td>5’4”</td>
<td>21 22 24 26 28 29 31 33 34 36 38 40 41 43</td>
</tr>
<tr>
<td>5’6”</td>
<td>19 21 23 24 26 27 29 31 32 34 36 37 39 40</td>
</tr>
<tr>
<td>5’8”</td>
<td>18 20 21 23 24 26 27 29 30 32 34 35 37 38</td>
</tr>
<tr>
<td>5’10”</td>
<td>17 19 20 22 23 24 26 27 29 30 32 33 35 36</td>
</tr>
<tr>
<td>6’</td>
<td>16 18 19 20 22 23 24 26 27 29 30 31 33 34</td>
</tr>
<tr>
<td>6’2”</td>
<td>15 17 18 19 21 22 23 24 24 26 27 28 30 31</td>
</tr>
</tbody>
</table>
# Weight Guidelines

<table>
<thead>
<tr>
<th>Weight category</th>
<th>Obesity class</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>I</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>II</td>
<td>35.0–39.9</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Percentage of Population Obese by Self-Reported Weight/Height

- 60.5% overweight
- 23.9% obese

overweight/obese ≠ cardiometabolic syndrome
BMI - Advantages

- More accurate measure of total body fat compared with body weight alone
- Consistent with other, more precise measures of body fatness
- Predictor of disease
- Easy and inexpensive to obtain
BMI - Limitations

- Very muscular people
- People who have lost muscle mass (e.g., many elderly, chronically ill)
- People with edema
- People with limited stature or the very tall
Weight Loss

- Refer patients to sensible diet programs (Weight Watchers, Jenny Craig, etc.)
- May require weight loss medications
  - orlistat (Xenical® or Alli®), sibutramine (Meridia®)
- Endocannabinoid receptor antagonists and others under investigation
Medications Associated with Components of CMS

- Olanzapine (Zyprexa) **
- Clozapine (Clozaril) **
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Sodium valproate and valproic acid (Depakote)
- Protease inhibitors (saquinavir, ritonavir, indinavir, tipranavir, darunavir, nelfinavir, fosamprenavir, aztanavir)
- Stavudine (Zerit)
Waist Circumference

- Indirect measure of central adiposity, correlated with visceral fat
Visceral Fat

Obesity Types in Men and Women

Men
Central

Women
Central
Peripheral
Waist Circumference - Determination

- Locate upper hip bone and top of right iliac crest.
- Place measuring tape in a horizontal plane around the abdomen at the level of the right iliac crest.
- Ensure tape is snug but does not compress skin and is parallel to the floor.
- Measure at the end of a normal expiration.

*Circulation* 2005;112:2735-52.
Han TS et al. Obes Res 2002;10:923-931,
Janssen et al, Arch Intern Med 2002; 162:2074-2079
Waist Circumference - Interpretation

- High risk
  - Men $\geq 40$ in
    - Use $\geq 35$ inches for Asian American men
  - Women $\geq 35$ in
    - Use $\geq 31$ inches for Asian American women
- Adds one risk category above that defined by BMI
## Ethnic-specific Cut-points for Waist Circumference

<table>
<thead>
<tr>
<th>Country/Ethnic Group</th>
<th>Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europids Male</td>
<td>≥ 37 in</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 31.5 in</td>
</tr>
<tr>
<td>South Asians/Chinese Male</td>
<td>≥ 35 in</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 31.5 cm</td>
</tr>
<tr>
<td>Japanese Male</td>
<td>≥ 33.5 cm</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 35 in</td>
</tr>
<tr>
<td>Country/Ethnic Group</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Ethnic South and Central Americans</td>
<td>Use South Asian data until more specific data are available</td>
</tr>
<tr>
<td>Sub-Saharan Africans</td>
<td>Use European data until more specific data are available</td>
</tr>
<tr>
<td>Eastern Mediterranean and Middle East</td>
<td>Use European data until more specific data are available</td>
</tr>
</tbody>
</table>
### Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Disease Risk *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>Increased</td>
<td>High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30-34.9</td>
<td>1</td>
<td>High</td>
</tr>
<tr>
<td>Obesity</td>
<td>35 – 39.9</td>
<td>2</td>
<td>Very High</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>≥ 40</td>
<td>3</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>
Physical Inactivity
Physical Inactivity, U.S. Median

- Total: 27.8
- Women: 30.8
- Men: 26
Increasing physical activity

- Reduces metabolic syndrome risk factors
- Increases HDL
- Improves cardiovascular function
- Goal
  - 30 – 60 minutes at least 5 days/week
  - 60 minutes daily is preferable
- Use pedometer and aim for 10,000 steps/day
THE ACTIVITY PYRAMID

EACH WEEK, TRY TO BALANCE YOUR PHYSICAL ACTIVITY USING THIS GUIDE.

IF YOU'RE INACTIVE
(Rarely active)
Increase daily activities at the base of the pyramid.
-Walk whenever you can.
-Make leisure time as active as possible.

3+ TIMES A WEEK
STRETCH & TAKE STRETCH BREAKS YOGA/TAI CHI
STRENGTHEN YOUR MUSCLES WEIGHT LIFTING TENSION BANDS PUSH UPS/CURL UPS

3-5 TIMES A WEEK
GIVE YOUR HEART & LUNGS A WORKOUT BIKING/HIKING RUNNING/JOGGING SWIMMING/WATER AEROBICS
BRISK WALKING BASKETBALL IN-LINE SKATING

EVERYDAY
WALK OFTEN & STAY ACTIVE WALK THE DOG DO YARDWORK PLAY GOLF GO BOWLING
PARK YOUR CAR FARTHER AWAY TAKE THE STAIRS INSTEAD OF THE ELEVATOR

IF YOU'RE SPORADIC
(Active some of the time, but not regularly)
Become more consistent with activities in the middle of the pyramid.
-Plan activity in your day.
-Set realistic goals.

IF YOU'RE CONSISTENT
(Active most days of the week)
Choose activities from all levels of the pyramid.
-Change your routine if you start to get bored.
-Explore new activities.

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“To prevent a heart attack, take one aspirin every day. Take it out for a jog, then take it to the gym, then take it for a bike ride…”
Metabolic Syndrome
Meeting Goals for Concomitant Conditions
## JNC-7 Classification of Blood Pressure

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm HG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

*JAMA 2003; 289: 2560-72.*  
*JNC8 expected in 2009*
Blood Pressure Goals

\( \leq 140/80 \text{ mm HG} \)

\( \leq 130/80 \text{ mm HG in patients with diabetes/impaired glucose tolerance} \)
Effects of ARBs/ACEIs on DM Development

- Studies not designed for diabetes prevention
  - HOPE, PEACE, EUROPA – ACEIs decreased risk ~27%
  - LIFE - ARBs decreased risk 23%

- Prospectively designed for diabetes prevention
  - DREAM (N Engl J Med 9/15/06)
    - 18.1% with ramipril vs 19.5% with placebo
    - Different patient group than studies above
      - No heart disease or hypertension, IGT or IFG
Lifestyle Modifications for Hypertension Prevention and Management

- Weight loss
- Smoking cessation
- Increased physical activity
- Limit alcohol
  - 1 oz/day for men, ½ oz/day for women/lighter weight men
- Limit sodium intake to no more than 2.4 gm sodium or 6 gm sodium chloride per day
- Meet recommended daily intake of magnesium, potassium, and calcium
  - Emphasize increased consumption of fresh fruits, vegetables, and low-fat dairy products

*JAMA* 2003:289:2560-2572
Glucose Goals

- A1C < 7.0%
- Fasting and preprandial glucose 90-130 mg/dl
- Peak postprandial < 180 mg/dl

*Diabetes Care* 2008;31:S12-54.
Interventions To Delay Overt Type 2 Diabetes

- Intensive lifestyle changes
  - 58% ↓ risk in NIH Diabetes Prevention Program
    - Lost 7% of body wt
    - Walked 30 mins 3x/wk
Interventions To Delay Overt Type 2 Diabetes

Medications

- Metformin (Glucophage)
  - ↓ risk 31% in Diabetes Prevention Program
- Thiazolidinediones (Glitazones)
  - Troglitazone ↓ risk 49% in TRIPOD (high risk Hispanic women)
  - Rosiglitazone (Avandia) ↓ risk ~50% in DREAM [↑CV risk]
  - Pioglitazone (Actos) increases HDL and decreases TG more than rosiglitazone

Pharmacotherapy 2004;224(3):362-7
Lancet 2006;368:1096-105
Interventions To Delay Overt Type 2 Diabetes

Medications (continued)

- Acarbose (Precose)
  - ↓ risk 25% in STOP-NIDDM
- ACE-I
  - Ramipril (Altace) ↓ risk 34% in HOPE
- ARB
  - Losartan (Cozaar) ↓ risk 25% in LIFE
- Orlistat (Xenical)
  - ↓ risk 34% in Xendos

Pharmacotherapy 2004;224(3):362-7
Prevention with Medication

- In addition to lifestyle counseling, metformin may be considered in those who are at very high risk (combined impaired fasting glucose and impaired glucose tolerance plus other risk factors) and who are obese and under 60 years of age. [ADA]

- Metformin or acarbose in addition to lifestyle in high risk patients. [AACE]

*Diabetes Care* 2008;31:S12-54.
## Lipid Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CRE (10-year risk &gt; 20%)</td>
<td>&lt; 100 mg/dl (&lt;70 is option)</td>
</tr>
<tr>
<td>2+ Risk Factors (10 year risk &lt; 20 %)</td>
<td>&lt; 130 mg/dl (&lt;100 is option)</td>
</tr>
<tr>
<td>0 – 1 Risk Factor</td>
<td>&lt; 160 mg/dl</td>
</tr>
</tbody>
</table>

CRE = cardiovascular risk equivalent
RF = risk factor

*JAMA* 2001;285:2486-2497
*Circulation* 2005;110:227-239
# Lipid Goals

<table>
<thead>
<tr>
<th>Category</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL*</td>
<td>&gt; 40 mg/dl (men)</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 mg/dl (women)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dl</td>
</tr>
</tbody>
</table>

*American Diabetes Association

NCEP ATP III – HDL > 40 for both genders

AHA – HDL > 40 for men, > 45 for women

*Diabetes Care 2008;31:S12-54
JAMA 2001;285:2486-2497
Circulation 2005;110:227-239*
Should Patient’s with CMS Take Antioxidant Vitamins?

- Observational studies – people with high intake of carotene, ascorbic acid, and tocopherol (diet and/or supplements) have ↓ risk of MI and stroke

- Randomized trials – No consistent benefit as single vitamin or combination in primary or secondary prevention


*Annals of Intern Med* 2003;139:56-70
**Getting Patients to Their Lipid Goal**

- **LDL-C lowering**
  - First choice: statin
  - Second choice: ezetimibe, niacin, fibrate
  - May require combination therapy
  - Statins and fibrates have been shown to reduce CHD risk in patients with CMS
Getting Patients to Their Lipid Goal

- **HDL-C raising**
  - Behavior interventions (wt loss, increased physical activity, smoking cessation)
  - Glycemic control
  - Niacin or fibrate

- **Triglyceride lowering**
  - Glycemic control first priority
  - Fibrate or niacin
Prothrombogenic State - Aspirin

- 75-325 mg if CHD or CRE or 10 yr risk for CHD ≥ 10% (women and men)
- 81 mg in men for primary prevention if 10-year risk for CHD ≥ 10% (AHA)
- 81 mg in women for primary prevention if ≥ 65 & maybe if < 65 (AHA)
- 75-162 mg for patents with diabetes > 40 or >20 with any other CVD risk factors (ADA + AHA)
- 81 mg if > 50 with at least 1 risk factor for CVD (Guidelines for Antithrombotic Therapy for the Prevention and Treatment of Thrombosis)
- For all persons with prediabetes who are not at increased risk for bleeding. (AACE)
No specific therapies beyond lifestyle changes are recommended

Weight loss & lipid lowering agents (statins, fibrates, niacin) will reduce hs-CRP and other markers of inflammation

*Circulation* 2005;112:2735-52.
Pharmacist’s Role

- Identify and screen patients who potentially have CMS
- Refer for appropriate diagnosis and treatment
- Reinforce treatment plan and enhance adherence
- Offer lifestyle modification program
Case Study

- 35 year old male on no medications
- BMI 33, Waist 45 inches
- BP 136/86
- Family history
  - Father died of MI at 59, had DM and HTN
  - Mother, 64, has HTN and high cholesterol
- Fasting laboratory values
  - TC = 187 mg/dl
  - TG = 155 mg/dl
  - LDL = 127 mg/dl
  - HDL = 35 mg/dl
  - Glucose = 110 mg/dl
Case Study

- What should be his goals?
- What therapies should he be started on?
Case Study
The Future

- Targeting individual risk factors
  - Intense LDL reduction
  - HDL raising strategies
  - Anti-platelet therapy beyond ASA alone
  - Novel anti-glycemic approaches

- Targeting abdominal obesity
  - More public health efforts to reduce obesity
  - Better antiobesity medications
Cardiometabolic Syndrome
Conclusion

- These patients are at grave risk for heart disease and diabetes
- Weight loss and physical activity are KEY to treatment
- Each condition present should be treated to accepted goals
- Pharmacotherapy to treat conditions and prevent development of type 2 diabetes may include an ACE-I or ARB, statin ± other lipid lowering agents, metformin or TZD, and aspirin