Cardiovascular Risk:
The Impact of Established Factors and Emerging Markers
Importance of Identifying Valid CAD Risk Factors

- Established risk factors are the principal determinants of CAD risk
- Emerging risk markers may modify assessments of CAD risk and can be influential in guiding treatment options
- Emerging risk markers themselves may serve as therapeutic targets
- Identified risk markers and risk factors can assist in expanding the traditional risk-factor–based treatment strategy

CAD = coronary artery disease.
Atherosclerosis

- Atherosclerosis is the leading cause of death and disability in North America
- Key processes in atherosclerosis are the intimal thickening and lipid accumulation that produce the characteristic atheromatous plaques
- Atherosclerosis is a slow and progressive disease that often begins as early as infancy
Normal Arterial Wall
Atherosclerosis and Plaque Formation (3)
Atherosclerosis and Plaque Formation (4)

HDL = high-density lipoprotein.
CVD Mortality in the US

2003 CVD Mortality in the US*

- 37.3% CVD Deaths
- All Other Causes of Death

1 of every 2.7

CVD = cardiovascular disease.
*Preliminary 2003 data.
Leading Causes of Death by Gender in the US for 2003*

Deaths in Thousands

A: Total CVD
B: Cancer
C: Accidents
D: Chronic lower respiratory diseases
E: Diabetes mellitus
F: Alzheimer's disease

*Preliminary 2003 data.
CVD Mortality Trends for US Males and Females (1979-2003*)

*Preliminary 2003 data.

Key Factors Contributing to Elevated CAD Risk

**CAD Risk**

**Established**
- Nonmodifiable
  - Age
  - Gender
  - Race
  - Family history

- Modifiable
  - High LDL-C
  - Low HDL-C
  - High TG
  - Hypertension
  - Diabetes
  - Smoking
  - Obesity or waist/hip ratio
  - Physical inactivity

**Emerging**
- CRP
- Apolipoprotein B
- Homocysteine
- LDL particle size
- Lipoprotein (a)
- Thrombogenic/hemostatic factors
- Lp-PLA$_2$

**Abbreviations:**
- LDL-C = low-density lipoprotein cholesterol
- HDL-C = high-density lipoprotein cholesterol
- TG = triglyceride
- CRP = C-reactive protein
- LDL = low-density lipoprotein
- Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$. 
Impact of Recent Clinical Trials: Revised CAD Risk Categories

CAD Risk

- Very High
  - Established CVD + 3+ Risk factors or Poorly controlled severe risk factors or Metabolic syndrome or ACS

- High
  - Established CAD or CAD risk equivalents + 2+ Risk factors 10-y risk >20%

- Moderate-High
  - 2+ Risk factors 10-y risk 10%-20%

- Moderate
  - 2+ Risk factors 10-y risk <10%

- Low
  - 0-1 Risk factor

CVD = cardiovascular disease; ACS = acute coronary syndrome.
### NCEP ATP III Guidelines: Global Risk Assessment

Cumulative point scale for estimating 10-year CAD* risk (Framingham scoring) for men/women

<table>
<thead>
<tr>
<th>Age M/W</th>
<th>TC (age 40-49 y)</th>
<th>TC (age 50-59 y)</th>
<th>Smoker (age 20-39 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34 = -9/-7</td>
<td>160 = 0/0</td>
<td>160-199 = 3/3</td>
<td>No = 0/0</td>
</tr>
<tr>
<td>35-39 = -4/-3</td>
<td>200-239 = 5/6</td>
<td>160-199 = 2/2</td>
<td>Yes = 8/9</td>
</tr>
<tr>
<td>40-44 = 0/0</td>
<td>240-279 = 6/8</td>
<td>200-239 = 3/4</td>
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<tr>
<td>45-49 = 3/3</td>
<td>≥ 280 = 8/10</td>
<td>240-279 = 4/5</td>
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<tr>
<td>50-54 = 6/6</td>
<td></td>
<td>≥ 280 = 5/7</td>
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<tr>
<td>55-59 = 8/8</td>
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<td>60-64 = 10/10</td>
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<td>65-69 = 11/12</td>
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<td>70-74 = 12/14</td>
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<td>75-79 = 13/16</td>
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<table>
<thead>
<tr>
<th>Systolic Blood Pressure</th>
<th>HDL-C</th>
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</tr>
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<tbody>
<tr>
<td>Treatment No Yes</td>
<td>≥ 60 = -1/-1</td>
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</tr>
<tr>
<td>&lt; 120 = 0/0</td>
<td>50-59 = 0/0</td>
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<tr>
<td>120-129 = 0/1</td>
<td>40-49 = 1/1</td>
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</tr>
<tr>
<td>130-139 = 1/2</td>
<td>&lt; 40 = 2/2</td>
<td></td>
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<tr>
<td>140-159 = 1/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 160 = 2/4</td>
<td>3/6</td>
<td></td>
</tr>
</tbody>
</table>

**Total points:**

| <0 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | ≥25 |

**10-y CAD risk (%):**

<table>
<thead>
<tr>
<th>M</th>
<th>W</th>
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<tbody>
<tr>
<td>&lt;1</td>
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<tr>
<td>1</td>
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<td>25</td>
<td>25</td>
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<tr>
<td>≥30</td>
<td>≥30</td>
</tr>
</tbody>
</table>

*CAD = MI or coronary death.

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; M = men; W = women; TC = total cholesterol; MI = myocardial infarction.

Adapted from National Cholesterol Education Program Adult Treatment Panel III. Circulation. 2002;106:3143-3421.
10-Year Absolute Risk for Hard CAD Events, by Age and Gender

Nonmodifiable Risk Factors for CAD

• Major nonmodifiable risk factors according to NCEP ATP III¹:
  – Advancing age
  – Male gender
  – Family history of premature CAD

• Although race itself is a nonmodifiable risk factor, several major modifiable risk factors show markedly varied prevalence in different ethnic groups²

US Prevalence of CVD by Risk Factors of Age and Gender*

Adapted from American Heart Association. Heart Disease and Stroke Statistics — 2005 Update.
Family History as a CAD Risk Factor

- **Evidence statement**: A positive family history for CAD in a first-degree relative (parent, sibling, or offspring) is a major risk factor for CAD... Risk for CAD is higher the younger the age of onset in the affected family member and the greater the number of affected first-degree relatives.

- **Recommendations**: The presence and age of onset of CAD in all first-degree relatives should be assessed... Because a positive family history of premature CAD is immutable but bears information about the risk for CAD and the probability of having modifiable risk factors, it should serve as a factor in making treatment decisions...

Major Modifiable Risk Factors for CAD

- Smoking
- Hypertension
- Serum cholesterol
- DM
- Obesity
- Physical inactivity

INTERHEART Study: Relation of Cigarette Smoking and Risk for MI

CI = confidence interval.
Hypertension and the Impact of JNC 7

- In persons >50 years old, systolic BP >140 mm Hg is a more critical risk factor than elevated diastolic BP.
- Normotensive men at 55 years of age and women at 65 years have a 90% risk for developing hypertension during the remainder of their lifetime.
- For prehypertensive persons (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg), health-promoting lifestyle modifications decrease CAD incidence.

Is Total Cholesterol a Useful Measure?

- LDL-C, not TC, is the primary target of cholesterol-lowering therapy
- Serum TC levels contribute to CAD risk at various levels
- TC <200 mg/dL is desirable, with <160 mg/dL preferred
- TC is useful for initial detection, with LDL-C used for risk assessment and therapy selection
- If used alone, TC may underestimate CAD risk

Diabetes Mellitus

• DM, defined by fasting glucose ≥126 mg/dL, is a major independent risk factor for CAD\textsuperscript{1,2}
• LDL-C–lowering interventions in persons with diabetes can significantly reduce CAD risk\textsuperscript{3}
• Persons with DM are at similar risk to patients with established CAD (i.e., DM is a CAD risk equivalent)\textsuperscript{1,3}

Obesity

• In the US, obesity is commonly defined by a BMI of $\geq 30$ kg/m$^2$ (NCEP ATP III)
  – Worldwide, waist/hip ratios may offer a more reliable indicator$^{1,2}$
• Persons with obesity are at higher risk for dyslipidemia, type II DM, and hypertension$^2$
• Obesity should be a direct target for clinical intervention and not merely considered a treatment indicator$^2$

Physical Inactivity

- Major, modifiable CAD risk factor
- Associated with increased obesity
- Increased physical activity has a positive impact on LDL-C, TGs, HDL-C, insulin sensitivity, and BP
- Physician guidance regarding safe forms of physical activity should be provided for sedentary persons undergoing clinical cholesterol management
Effect of HDL-C on CAD Risk

- HDL plays a major role in reverse cholesterol transport
- Overweight and obesity, physical inactivity, and smoking are major acquired causes of low HDL-C\(^1\)
- Increased physical exercise and subsequent HDL-C elevation may reduce CAD risk\(^2,3\)

Evidence-Based Recommendations

Four TLC Goals
1. Reduced intake of saturated fat and cholesterol (macronutrient changes)
2. Dietary and therapeutic options for enhancing LDL-C lowering
3. Weight reduction
   - BMI 18.5-24.9 kg/m²
   - Waist circumference (≤35" women / ≤40" men)
4. Increased regular physical activity

LDL-C = low-density lipoprotein cholesterol; BMI = body mass index.
NCEP ATP III: Model of Steps in TLC

Visit 1
- Begin lifestyle therapies

Visit 2
- Evaluate LDL-C response
- If LDL-C goal not achieved, intensify LDL-C-lowering Tx

Visit 3
- Evaluate LDL-C response
- If LDL-C goal not achieved, consider adding drug Tx

Visit N
- Monitor adherence to TLC

6 wks

6 wks

Q 4-6 mos

- Emphasize reduction in saturated fat and cholesterol
- Encourage moderate physical activity
- Consider referral to a dietician

- Reinforce reduction in saturated fat and cholesterol
- Consider adding plant stanols/sterols
- Increase fiber intake
- Consider referral to a dietician

- Intensify weight management and physical activity
- Consider referral to a dietician

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; Tx = treatment.
TLC: Macronutrient Recommendations

Percentage of Total Calories

- Carbohydrate: 55%
- Protein: 15%
- Saturated fat: 7%
- Polyunsaturated fat: 10%
- Monounsaturated fat: 13%
Evidence-Based Recommendations
TLC Component IV: Exercise

- Exercise lowers TG and raises HDL-C
- Limited data show resistance exercise may reduce LDL-C
- Exercise can be intimidating and its terminology confusing
- It is imperative to simplify goals
- Goal:
  - Regular exercise for at least 30 minutes on most and preferably all days of the week*

*For sedentary patients, patients over 50 years, or patients with established CAD, a physician should be consulted before an exercise regimen is initiated.

Summary (Cont’d)

- The patient and clinician educator can work together to try to achieve the following TLC goals for reducing CAD risk:
  - Reduced intake of saturated fat and cholesterol (macronutrient changes)
  - Dietary and therapeutic options for enhancing LDL-C lowering
  - Weight reduction
    - BMI 18.5-24.9 kg/m²
    - Waist circumference ≤35" women / ≤40" men
  - Increased regular physical activity
Summary: Usefulness of Established CAD Risk Factors

- Long-established risk factors are still useful for evaluating CAD risk
- Several modifiable risk factors can be significantly improved, including:
  - Smoking, hypercholesterolemia/hyperlipidemia, hypertension, DM, obesity, physical inactivity
- LDL-C is the primary target of lipid-lowering treatment, but TC can be useful in initial risk detection
- Reducing TG and raising HDL-C may also contribute to the benefit of lipid-modifying therapy
- DM should be viewed as a separate high-risk category for CAD
- Metabolic syndrome is associated with an increase in all-cause mortality and, most markedly, cardiovascular mortality
Inflammation, Atherosclerosis, and CRP

CDC and AHA consensus statement:

- Inflammation is a key component of the atherosclerotic process
- Among the many inflammatory markers, CRP is the strongest independent clinical predictor of cardiovascular events
- CRP screening can be a valuable adjunct to lipid risk evaluations

CV Risk Assessment: Incorporating CRP With LDL-C: The Women’s Health Study

CRP
Low = <1.52 mg/L
High = >1.52 mg/L

LDL-C
Low = <124 mg/dL
High = >124 mg/dL

Summary: Emerging Markers for CAD Risk Prediction

- Risk markers should be:
  - Predictive, consistent, independent, modifiable, cost-effective
- CRP is a strong predictor of CAD
  - Statin therapy has been shown to reduce CRP levels
- Apo B/Apo A-1 is a strong predictor of CAD
- Elevated homocysteine is a risk marker for CAD, but its importance as a predictor in healthy populations is unclear
  - May be a useful predictor of CAD risk in patients with type 2 DM
- Elevated Lp (a) levels appear to be associated with increased CAD
- Lp-PLA2 may complement CRP as a risk predictor in people with low LDL-C levels