Risk Stratification and Preventive Strategies for CAD: What's New?

Satish Gadi, MD FACC FSCAI
Interventional Cardiologist, Cardiovascular Institute of the South (CIS) Baton Rouge
Clinical Assistant Professor, Tulane University School of Medicine
Disclosures

• None
Heart Disease Death Rates, 2008-2010
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics
Heart Disease Death Rates, 2008-2010
Adults, Ages 65+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics
- More than a third of adults in US are obese
- Nearly 40% of adults aged 40-59 are obese
- More than 6% of adults are severely obese (BMI >/= 40)
- More than 1-in-10 children are obese from early childhood onward (2-5 year olds)
- More than 2% of young children are severely obese
- Since the 70s, adult obesity rates have more than doubled
- Childhood obesity rates have more than tripled since 1980
Leading Causes of Death for All Males and Females
United States: 2000

![Bar Chart]

Deaths in Thousands

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>440,175</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>286,082</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>63,817</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>60,004</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>31,602</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>505,661</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>267,009</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>62,005</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>37,699</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>36,655</td>
<td></td>
</tr>
</tbody>
</table>

A  Total CVD
B  Cancer
C  Accidents
D  Chronic Lower Respiratory Diseases
E  Diabetes Mellitus
F  Influenza and Pneumonia

Source: CDC/NCHS.
So what do we do?

• Know the risk factors
• Go beyond traditional risk factors
• Prediction scores
• Gene expression testing
• DIET
• DIET
• DIET
• EXERCISE
Traditional Risk Factors...

- Age
- Male sex
- BP
- Smoking
- Diabetes mellitus
- Total Cholesterol
- HDL Cholesterol
- Peripheral arterial dis.
- Ch. Kidney disease
Emerging Risk Factors

- LDL particle size and density
- Lipoprotein (a)
- Hs-CRP, Homocysteine levels, Lp(a)
- CAC score
- Ankle-Brachial Index (ABI)
- Carotid Intima-Media Thickness (CIMT)
- HBA1c
- Periodontal disease, Erectile dysfunction
Why look beyond what we have?
Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease (N = 87,869)

- 1 Risk Factor: 43.0%
- 2 Risk Factors: 27.8%
- 3 Risk Factors: 8.9%
- 4 Risk Factors (< 1%)
- No Risk Factors: 62.4%

Khot U et al, JAMA 2003;290:898-904
LDL Particle size and Density
LDL Particle Size Subclass

IDL

L3

large, buoyant

A

L2

small, dense

AB

L1

B
Significance of Small, Dense LDL

• Low cholesterol content of LDL particles
  – ↑ particle number for given LDL-C level

• Associated with ↑ levels of TG and LDL-C, and ↓ levels of HDL$_2$

• Marker for common genetic trait associated with ↑ risk of coronary disease (LDL subclass pattern B)

• Possible mechanisms of ↑ atherogenicity
  – greater arterial uptake
  – ↑ uptake by macrophages
  – ↑ oxidation susceptibility
Small dense LDL and CHD
-LDL cholesterol-

Relative risk and p level according to baseline plasma LDL cholesterol and proportion of LDL < 25.5 nm. Relative risks were adjusted for age, BMI, systolic blood pressure, type II DM, medication use at baseline, family history of IHD, and smoking habits.

Modified from St-Pierre et al. Circulation 2001;104
Lipoprotein (a)
Lipoprotein (a)

- Structurally resembles LDL
- Has a second large polypeptide, Apo(a)
- Increases cholesterol deposition in arterial wall
- Enhances O2-free radical synthesis in monocytes
- Prothrombotic – Plasminogen analogue
Hs-CRP
hs-CRP as a Risk Factor For Future CVD: Primary Prevention Cohorts

Kuller MRFIT 1996 CHD Death
Ridker PHS 1997 MI
Ridker PHS 1997 Stroke
Tracy CHS/RHPP 1997 CHD
Ridker PHS 1998,2001 PAD
Ridker WHS 1998,2000,2002 CVD
Koenig MONICA 1999 CHD
Roivainen HELSINKI 2000 CHD
Mendall CAERPHILLY 2000 CHD
Danesh BRHS 2000 CHD
Gussekloo LEIDEN 2001 Fatal Stroke
Lowe SPEEDWELL 2001 CHD
Packard WOSCOPS 2001 CV Events*
Ridker AFCAPS 2001 CV Events*
Rost FHS 2001 Stroke
Pradhan WHI 2002 MI, CVD death
Albert PHS 2002 Sudden Death
Sakkinen HHS 2002 MI

Relative Risk (upper vs lower quartile)

Ridker PM. Circulation 2003;107:363-9
Event-Free Survival With CRP, LDL-C Levels Above or Below the Median*

*Median values: CRP=1.52 mg/L, LDL-C=3.22 mmol/L.

hsCRP Adds Prognostic Information Beyond the Framingham Risk Score in ALL Major Cohorts Evaluated
Moving Toward an hs-CRP Modified Framingham Risk Score

Circulation 2004;109:2818-2925
Reynolds Risk Score
(www.reynoldsriskscore.org or www.cvdriskcheck.ca)

45% of women\(^1\) and 20% of men\(^2\) at intermediate risk by Framingham are reclassified to higher or lower-risk groups using the Reynolds Score

---

hs-CRP: Recommendations for use in Clinical Practice

- hs-CRP measurement is independent marker of CVD risk
- In men >50y and women > 60y at intermediate risk (10%–19% risk of CVD per 10 years) and LDL-C < 3.5 mmol/L:
  - hs-CRP may help further risk stratification (RRS)
  - statin therapy beneficial in those with hs-CRP > 2 mg/L (JUPITER)

hs-CRP: Recommendations for use in Clinical Practice

♦ Measurements of hs-CRP:
  ♦ should be performed twice (at least 2 weeks apart)
  ♦ should be free of acute illness
  ♦ lower of the 2 values constitutes the baseline value
  ♦ fasting or nonfasting
  ♦ if level >10 mg/L, test should be repeated, patient examined for sources of infection or inflammation

Coronary Artery Calcium Score
Coronary Artery Calcium (CAC) Score

- Atherosclerosis is a chronic inflammatory process in the arterial wall
- Atherosclerosis begets calcium accumulation
- Radiation exposure is 0.7-3.0 mSv (avg. yearly “natural” exposure in US is 3 mSv)
- Agatston score – based on area and density of the calcified plaques
Normal LAD

Calcium in LAD, LCX and RCA
Meta-analysis of CAC Score and CHD Risk


HR for CHD

0 CAC = 4%
10-Year Risk

CAC 0
CAC 1-99
CAC 100-399
CAC 400-999
CAC >1000

Human Risk

0
1
2
3
4
5
6
7
8
9
10

Circulation 2007;115:402
Relative Predictive Value of CAC and Traditional Risk Factors for CHD in 1726 Asymptomatic Subjects over 40 Months: Dichotomous Analysis

- HTN
- Smoking
- HC
- DM
- CAC >75%

HR for CHD Events
Hazard Ratio for CVD Event by CAC and CIMT (per SD) in 6698 non-CVD Subjects (MESA Trial)
## Framingham Risk Score Adjustment

### CAC

<table>
<thead>
<tr>
<th>CAC</th>
<th>Male (♂)</th>
<th>Female (♀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>1-80:</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>81-400:</td>
<td>+2</td>
<td>+4</td>
</tr>
<tr>
<td>401-600:</td>
<td>+5</td>
<td>+9</td>
</tr>
<tr>
<td>&gt;600:</td>
<td>+8</td>
<td>+12</td>
</tr>
</tbody>
</table>

Grundy S et al, Am J Cardiol

### Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>-9</td>
</tr>
<tr>
<td>35-39</td>
<td>-4</td>
</tr>
<tr>
<td>40-44</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>3</td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
</tr>
<tr>
<td>55-59</td>
<td>8</td>
</tr>
<tr>
<td>60-64</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>11</td>
</tr>
<tr>
<td>70-74</td>
<td>12</td>
</tr>
<tr>
<td>75-79</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Cholesterol, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160</td>
<td>0</td>
</tr>
<tr>
<td>160-199</td>
<td>4</td>
</tr>
<tr>
<td>200-239</td>
<td>7</td>
</tr>
<tr>
<td>240-279</td>
<td>9</td>
</tr>
<tr>
<td>≥280</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39 y</td>
<td>0</td>
</tr>
<tr>
<td>40-49 y</td>
<td>3</td>
</tr>
<tr>
<td>50-59 y</td>
<td>3</td>
</tr>
<tr>
<td>60-69 y</td>
<td>4</td>
</tr>
<tr>
<td>70-79 y</td>
<td>5</td>
</tr>
</tbody>
</table>

### Smoking Status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Smoker</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td>8</td>
</tr>
</tbody>
</table>

### HDL, mg/dL

<table>
<thead>
<tr>
<th>HDL, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>-1</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
</tr>
<tr>
<td>&lt;40</td>
<td>2</td>
</tr>
</tbody>
</table>

### Systolic BP, mm Hg

<table>
<thead>
<tr>
<th>Systolic BP, mm Hg</th>
<th>If Untreated</th>
<th>If Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>130-139</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>140-159</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>≥160</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

### Point Total

<table>
<thead>
<tr>
<th>Point Total</th>
<th>10-Year Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>≥17</td>
<td>≥30</td>
</tr>
</tbody>
</table>
Ankle-Brachial Index (ABI)
Patient survival by ABI in Cardiovascular Health Study...

Newman et al ATVB 1999;19; 538-545
Five Year Mortality Rates

- Lung Cancer
- Colon/Rectal
- PAD
- Breast Cancer

*Criqui M. Presentation: Vascular Medicine of the Lower Extremities at the American Diabetes Association’s Scientific Sessions June 1999*
Prognosis in patients with Intermittent Claudication...

Population >55 yr

→ Intermittent Claudication

Peripheral Vascular Outcomes

- Worsening Claudication 16%
- Lower Extremity Bypass Surgery 7%
- Major Amputation 4%

Other Cardiovascular Morbidity/Total Mortality

- Nonfatal Cardiovascular Event (MI/Stroke, 5-year Rate) 20%
- 5-yr Mortality 30%
- Cardiovascular Cause 75%

Adapted from Weitz JI et al. Circulation. 1996;94:3026-3049.
CAD Imaging
64-slice CT
Quantification of Obstructive and Nonobstructive Coronary Lesions by 64-Slice Computed Tomography

- 59 patients with stable angina subjected to CTA before catheter-based angio
- Diagnostic image quality in 55 of 59
- Sensitivity for detection of stenosis <50%, >50%, and >75%: (79%, 73%, and 80%, respectively)
- Excellent accuracy with proximal lesions

Nuclear MPI
What do your genes tell you?
Genetic Prediction of CHD Risk

- 85 reported genetic variants prospectively evaluated in 811 ACS subjects and 650 controls: only 1 (β-fibrinogen promoter) marginally significant (p=0.03)

- Genome-wide analysis (SNPs) of WTCCC (1926 CHD subjects and 1644 controls) and German MI Family Study (875 MI subjects and 1644 controls)
  - 9p21.3 locus (P = 0.000003)
  - 15% ↑CHD Risk in heterozygotes
  - 40% ↑CHD Risk in homozygotes
Better Diagnostic Methods are Needed to Stratify Patients for Elective Invasive Angiography

Patient population:
- 397,954 stable patients with clinical risk factors and/or symptoms of CAD (but no prior history of CAD) undergoing cardiac catheterization for evaluation

Study found:
- 62% of patients who underwent elective cardiac catheterization did not have significant CAD
- 40% of patients had minimal to no CAD

Majority of patients (83.9%) received noninvasive diagnostic tests prior to referral to catheterization

The Challenge of Assessing CAD

Cardiac Imaging Procedures Deliver Significant Amounts of Ionizing Radiation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Effective Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial perfusion imaging study with ejection fraction</td>
<td>15.6</td>
</tr>
<tr>
<td>Diagnostic coronary angiography</td>
<td>7.0</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>15.0</td>
</tr>
<tr>
<td>Cardiac blood pool imaging, gated equilibrium; planar, single study at rest or stress</td>
<td>7.8</td>
</tr>
<tr>
<td>Cardiac computed tomography (without contrast, for assessment of coronary calcium)</td>
<td>3.0</td>
</tr>
<tr>
<td>Cardiac computed tomography (with contrast, for assessment of coronary arteries, without assessment for coronary calcium)</td>
<td>16.0</td>
</tr>
<tr>
<td>Pacemaker insertion</td>
<td>1.5</td>
</tr>
<tr>
<td>Comprehensive electrophysiological evaluation</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**MPI** procedures contributed to 74.2% of cumulative effective radiation dose from overall cardiac imaging procedures

CORUS - CAD

• The first clinically validated gene expression test for assessing obstructive CAD in non-diabetics
• Expression levels (mRNA) in blood detected of 23 genes known to indicate CAD
• Sex-specific
CASP5/IL18RAP/TNFAIP6
Apoptosis and inflammatory signaling response

CD3/TMC8
Adaptive immune response to atherosclerosis

CD79B/SPIB
Adaptive immune response to atherosclerosis

S100A12/S100A8/CLEC4E
Oxidative damage and cellular necrosis

SLAMF7/KLRC4
Innate immune response to atherosclerosis
Prospective, multi-center, blinded* study

1,343 nondiabetic patients enrolled to develop and validate Corus™ CAD

39 U.S. sites participated

Study PI: Eric Topol, MD, Scripps Research Institute

QCA Core Lab: Alexandra Lansky, MD, Columbia University/CRF

Enrolling sites and investigators included:
Correlation Between Test Score and Disease Burden

- Test Score
- Maximum Percent Stenosis by QCA

- 0%: Non-Obstructive Coronary Artery Disease
- 1-24%: Non-Obstructive Coronary Artery Disease
- 25-49%: Non-Obstructive Coronary Artery Disease
- ≥50%: Obstructive Coronary Artery Disease
  - 1 vessel
  - 2+ vessels

p<0.001
Bars indicate 95% CI
COMPASS Study


_Circulation: Cardiovascular Genetics_
April 2013;6(2):154-162

![Diagram showing the COMPASS Study workflow](image-url)
<table>
<thead>
<tr>
<th></th>
<th>Corus CAD</th>
<th>Site-read MPI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>89%</td>
<td>27%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>NPV</td>
<td>96%</td>
<td>88%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

In the COMPASS trial, Corus CAD outperformed MPI in sensitivity (89% vs. 27%, p<0.001) and negative predictive value (96% vs. 88%, p<0.001) for ruling out obstructive coronary artery disease.
<table>
<thead>
<tr>
<th>Measure</th>
<th>CORUS CAD PERFORMANCE at threshold score of 15</th>
<th>COMPASS (total N=431)</th>
<th>PREDICT-CTA* (total N=216)</th>
<th>PREDICT (total N=526)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>89%</td>
<td>83%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>52%</td>
<td>45%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>96%</td>
<td>93%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>15%</td>
<td>16%</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!!!