Cardiovascular Risk & Atherosclerosis Prevention

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Outline

• The risk scores for coronary artery disease (CAD)
  – Framingham
  – Reynold’s risk score
  – SCORE
  – PROCAM
  – INTERHEART

• Biomarkers
  – Laboratory tests
  – Vascular assessment

• Prevention
Cardiovascular risk assessment

- Framingham Risk Score (FRS)
- PROCAM
- Systemic Coronary Risk Evaluation (SCORE)
- Reynold’s risk score
- INTERHEART
<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Variables Included</th>
<th>Outcomes</th>
<th>Population Derived</th>
<th>Population Validated</th>
<th>ROC</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS (6,7)</td>
<td>Age, sex, BP, smoking, use of HTN medications, TC, and HDL</td>
<td>CHD (angina, MI, sudden death)</td>
<td>U.S. white men and women, ages 30–62 yrs</td>
<td>Men, women, blacks, Europe, Mediterranean, and Asia</td>
<td>0.7744 (w) 0.7598 (m)</td>
<td>Age &lt;30 yrs, &gt;65 yrs, Japanese-American men, Hispanic men, Native-American women, LVH, DM, and severe HTN</td>
</tr>
<tr>
<td>Global cardiovascular risk (2)</td>
<td>Age, sex, SBP, smoking, TC, HDL, DM, and use of HTN medications</td>
<td>CHD, stroke, CHF, or PVD</td>
<td>U.S. white men and women, ages 30–74 yrs</td>
<td>Framingham offspring</td>
<td>0.793 (w) 0.763 (m)</td>
<td>Mainly white</td>
</tr>
<tr>
<td>SCORE (20)</td>
<td>Age, sex, smoking, either TC or TC/HDL ratio, broken up into areas of high and low CVD risk</td>
<td>Fatal CV events</td>
<td>European men and women, ages 45–64 yrs</td>
<td>Europe</td>
<td>0.71–0.84</td>
<td>No nonfatal events, “single” risk factor measurements made, rather than “usual”</td>
</tr>
<tr>
<td>ASSIGN (23)</td>
<td>Age, sex, SBP, TC, HDL, +family history, social deprivation</td>
<td>CV death, CHD admission, CABG, or PTCA</td>
<td>Scotland men and women, ages 30–74 yrs</td>
<td>Scotland</td>
<td>0.7841 (w) 0.7644 (m)</td>
<td>Marginally better than Framingham, still overestimated risk</td>
</tr>
<tr>
<td>Reynolds (21)</td>
<td>Age, SBP, smoking, total cholesterol, HDL, hsCRP, +family history, hgbAlc if DM</td>
<td>MI, stroke, coronary revascularization, or CV death</td>
<td>U.S. women, age &gt;45 yrs</td>
<td>U.S. women</td>
<td>0.808 (w)</td>
<td>Mainly white, all women, socioeconomic status not generalizable, BP, weight, and family history, all taken by self-report</td>
</tr>
<tr>
<td>QRISK (24,25)</td>
<td>Age, sex, SBP, smoking, ratio of TC/HDL, +family history, use of HTN medications, BMI, social deprivation</td>
<td>MI, CHD, stroke, TIA</td>
<td>United Kingdom men and women, ages 35–74 yrs</td>
<td>United Kingdom</td>
<td>0.7879 (w) 0.7674 (m)</td>
<td>“Home advantage,” data validated from same population it was originally derived</td>
</tr>
<tr>
<td>Reynolds, men (22)</td>
<td>Age, sex, SBP, smoking, total cholesterol, HDL, hsCRP, +family history, hgbAlc if DM</td>
<td>MI, stroke, coronary revascularization, or CV death</td>
<td>U.S. men, ages 50–80 yrs</td>
<td>U.S. men</td>
<td>0.7–0.714 (m)</td>
<td>Mainly white, middle-aged, socioeconomic status and access to care not generalizable, self-reported with family history</td>
</tr>
</tbody>
</table>
Variation in Cardiovascular Risk

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Estimated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham 10-yr CHD risk score</td>
<td>2%</td>
</tr>
<tr>
<td>Reynolds Negative FH, hsCRP 0.5 mg/l</td>
<td>2%</td>
</tr>
<tr>
<td>Reynolds Negative FH, hsCRP 3.0 mg/l</td>
<td>3%</td>
</tr>
<tr>
<td>Reynolds Negative FH, hsCRP 8.0 mg/l</td>
<td>4%</td>
</tr>
<tr>
<td>Reynolds Positive FH, hsCRP 0.5 mg/l</td>
<td>3%</td>
</tr>
<tr>
<td>Reynolds Positive FH, hsCRP 3.0 mg/l</td>
<td>5%</td>
</tr>
<tr>
<td>Reynolds Positive FH, hsCRP 8.0 mg/l</td>
<td>6%</td>
</tr>
<tr>
<td>SCORE (fatal CVD) Country of low cardiovascular risk</td>
<td>1%</td>
</tr>
<tr>
<td>SCORE (fatal CVD) Country of high cardiovascular risk</td>
<td>2%</td>
</tr>
<tr>
<td>QRISK Negative FH, BMI &lt; 23 kg/m²</td>
<td>6%</td>
</tr>
<tr>
<td>QRISK Negative FH, BMI 23-32 kg/m²</td>
<td>6%</td>
</tr>
<tr>
<td>QRISK Negative FH, BMI ≥ 33 kg/m²</td>
<td>7%</td>
</tr>
<tr>
<td>QRISK Positive FH, BMI &lt; 23 kg/m²</td>
<td>10%</td>
</tr>
<tr>
<td>QRISK Positive FH, BMI 23-32 kg/m²</td>
<td>11%</td>
</tr>
<tr>
<td>QRISK Positive FH, BMI ≥ 33 kg/m²</td>
<td>12%</td>
</tr>
<tr>
<td>ASSIGN Negative FH, SIMD &lt; 10</td>
<td>7%-8%</td>
</tr>
<tr>
<td>ASSIGN Negative FH, SIMD 10-29</td>
<td>8%-10%</td>
</tr>
<tr>
<td>ASSIGN Negative FH, SIMD ≥ 30</td>
<td>10%-15%</td>
</tr>
<tr>
<td>ASSIGN Positive HH, SIMD &lt; 10</td>
<td>12%-13%</td>
</tr>
<tr>
<td>ASSIGN Positive HH, SIMD 10-29</td>
<td>13%-15%</td>
</tr>
<tr>
<td>ASSIGN Positive FH, SIMD &lt; 10</td>
<td>15%-23%</td>
</tr>
<tr>
<td>Lifetime risk for CVD</td>
<td>39%</td>
</tr>
</tbody>
</table>
Summary of the main findings and landmarks of the Framingham Heart Study
# Estimate 10-Year Risk for Men

## 1. Age

<table>
<thead>
<tr>
<th>Age</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>

## 2. Total Cholesterol (mmol/L)

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Age 20-39</th>
<th>Age 40-49</th>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4.15-5.19</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5.2-6.19</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6.2-7.2</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;7.21</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
## Estimate 10-Year Risk for Men

### 3. Smoking

<table>
<thead>
<tr>
<th></th>
<th>Points</th>
<th>Age 20-39</th>
<th>Age 40-49</th>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Smoker</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### 4. HDL-C

<table>
<thead>
<tr>
<th>HDL-C</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.55</td>
<td>-1</td>
</tr>
<tr>
<td>1.30-1.54</td>
<td>0</td>
</tr>
<tr>
<td>1.04-1.29</td>
<td>1</td>
</tr>
<tr>
<td>&lt;1.04</td>
<td>2</td>
</tr>
</tbody>
</table>

### 5. Blood Pressure

<table>
<thead>
<tr>
<th>Sys BP</th>
<th>Untreated</th>
<th>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>&gt;160</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
6. Determine 10-Year Risk for Men

<table>
<thead>
<tr>
<th>Points</th>
<th>10-year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
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<tr>
<td>10</td>
<td>6</td>
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<tr>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>10</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>&gt;17</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

- **Low Risk**
- **Medium Risk**
- **High Risk**
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Initiate treatment if:</th>
<th>Primary LDL-C</th>
<th>Primary Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Consider treatment in all patients CAD,PVD Atherosclerosis Most Pts with Diabetes FRS&gt;20% RRS&gt;20%</td>
<td>&lt;2 mmol/L Or ↓50% LDL-C ApoB&lt;0.80</td>
<td>Class I Level A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class I Level A</td>
<td>Class I Level A</td>
</tr>
<tr>
<td>Moderate</td>
<td>(strive towards ➔) FRS 10-19% LDL-C&gt;3.5 mmol/L TC/HDL &gt;5.0 hsCRP &gt;2 ➔men 50+, women 60+ Family history and hsCRP modulate risk</td>
<td>&lt;2 mmol/L Or ↓50% LDL-C ApoB&lt;0.80</td>
<td>Class IIA Level A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class IIA Level A</td>
<td>Class IIA Level A</td>
</tr>
<tr>
<td>Low</td>
<td>FRS&lt;10% LDL-C&gt;5.0mmol/L</td>
<td>↓50% LDL-C</td>
<td></td>
</tr>
</tbody>
</table>
Aims:

1. To evaluate the association (odds ratio) of risk factors for MI globally, and in each region; and among major ethnic groups in the world.

2. To quantify the impact of each risk factor alone and their combination on the population’s risk (population attributable risk, PAR) overall and in each region, ethnic group, in males and females and in young and old.
Methods

**Cases:** First MI.

**Controls:** Matched to cases by age (+/-5 yr and sex) at each site

Data collected from 262 sites in 52 countries:

- **Questionnaire:** demographics, lifestyle, health hx, psychosocial, medications
- **Physical measures:** height, weight, waist & hip circum, blood pressure, heart rate

**Blood sample:** 20 ml

**Statistical methods:** OR and PAR both presented with 99% confidence intervals. All analyses adjusted for age, sex and region.

*Coordinated by the Population Health Research Institute, McMaster University, Canada*
INTERHEART: Apolipoprotein B/A-1 and MI

Deciles: 1 2 3 4 5 6 7 8 9 10

Cont 1210 1206 1208 1207 1210 1209 1207 1208 1209

Cases 1757 435 496 610 720 790 893 1063 1196 1366
### Risk of AMI associated with Risk Factors in the Overall Population

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% Cont</th>
<th>% Cases</th>
<th>OR (99% CI) adj for age, sex, smok</th>
<th>OR (99% CI) adj for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB/ApoA-1 (5 v 1)</td>
<td>20.0</td>
<td>33.5</td>
<td>3.87 (3.39, 4.42)</td>
<td>3.25 (2.81, 3.76)</td>
</tr>
<tr>
<td>Curr smoking</td>
<td>26.8</td>
<td>45.2</td>
<td>2.95 (2.72, 3.20)</td>
<td>2.87 (2.58, 3.19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.5</td>
<td>18.4</td>
<td>3.08 (2.77, 3.42)</td>
<td>2.37 (2.07, 2.71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>39.0</td>
<td>2.48 (2.30, 2.68)</td>
<td>1.91 (1.74, 2.10)</td>
</tr>
<tr>
<td>Abd Obesity (3 v 1)</td>
<td>33.3</td>
<td>46.3</td>
<td>2.22 (2.03, 2.42)</td>
<td>1.62 (1.45, 1.80)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>-</td>
<td>-</td>
<td>2.51 (2.15, 2.93)</td>
<td>2.67 (2.21, 3.22)</td>
</tr>
<tr>
<td>Veg &amp; fruits daily</td>
<td>42.4</td>
<td>35.8</td>
<td>0.70 (0.64, 0.77)</td>
<td>0.70 (0.62, 0.79)</td>
</tr>
<tr>
<td>Exercise</td>
<td>19.3</td>
<td>14.3</td>
<td>0.72 (0.65, 0.79)</td>
<td>0.86 (0.76, 0.97)</td>
</tr>
<tr>
<td>Alcohol Intake</td>
<td>24.5</td>
<td>24.0</td>
<td>0.79 (0.73, 0.86)</td>
<td>0.91 (0.82, 1.02)</td>
</tr>
<tr>
<td>All combined</td>
<td>-</td>
<td>-</td>
<td>129.2 (90.2, 185.0)</td>
<td>129.2(90.2, 185.0)</td>
</tr>
<tr>
<td>All combined (extremes)</td>
<td></td>
<td></td>
<td>333.7 (230.2, 483.9)</td>
<td>333.7 (230.2, 483.9)</td>
</tr>
</tbody>
</table>
Summary

1. Nine risk factors (ApoB/ApoA-1, current smoking status, diabetes, hypertension, abdominal obesity, psychosocial status, daily intake of veg & fruits, exercise habits and alcohol intake) are strongly associated with AMI (acute myocardial infarction) worldwide.

2. These risk factors are even more important in the young, and their effects are consistent in men and women, across all ethnic groups and all regions.

3. Abnormal apo-B/apoA-1 ratio and smoking are the most important risk factors and account for >2/3 of the PAR (population associated risk). All 9 risk factors account for >90% of the PAR globally and in most regions.

IMPLICATIONS: Implementing preventive strategies based on our current knowledge would avert the majority of premature CHD worldwide.
Errors in risk Estimations

• **Study population**
  – Framingham: mostly blue-collar suburb of Boston, mostly middle aged white people.
  – PROCAM: working men in NW Germany

• **Age of Study**
  – Framingham mostly 1970’s (higher MI rates than today)
  – PROCAM is newer, uses also TG’s, LDL-C and family history of MI

• **Endpoints**
  – PROCAM – only MI and coronary death
  – Framingham included angina pectoris

• **Interaction between variables**
  – Framingham assigns fewer points with increasing age, PROCAM does not.
  – Conversion factors have been used for various populations (e.g. Czech Republic 1.69 for men and 1.37 for women; China 0.31 for men and 0.61 for women)
Imaging
- Angiography
  - IVUS
- 3D reconstruction IVUS
- Ultrafast CT (coronary)
- Carotid ultrasound – IMT
- MRI (carotid, PAD, aortic)
- PET
- Aortic CT
- Scintigraphy (thallium, sestimibe)
- Intracoronary endo fct (Ach)
- Brachial ultrasound
- Plethysmography
- TEE (aortic)
- Skin cholesterol
- Monoclonal antibody imaging
- Pulsatile flow visualization (aorta)
- Regional aortic distensibility
- Aortic stiffness (Doppler)
- Coronary thermography
- Coronary elastography
- Coronary NIR spectroscopy

Lipids
- lipoproteins
- lipoprotein subfractions
  - (L1-3, V1-6, H1-5)
- Apolipoproteins
  - (CIII, AI1-E, LpB…)
- Lp(a)
- Lipid ratios

Coagulation
- VWF
- tPA
- PAI-1
- PF4
- D-dimer
- Tissue factor
- Fibrinogen
- Beta thromboglobulin
- Erythrocyte sed. Rate
- RBC adhesiveness/aggregation

Adhesion molecules
- s-ICAM
- s-VCAM
- P-selectin
- E-selectin

Serum glycoproteins
- Alpha 1-antitrypsin
- Alpha 1 acid glycoprotein
- Alpha 2-macroglobulin
- Ceruloplasmin
- Haptoglobin

Inflammation and Proliferation
- hsCRP
- MCSF
- PDGF
- FDF
- FGF
- Interleukins (1,6,8,10,12,15)
- MMPs (1,2,3,9)
- MIP1 (alpha and beta)
- TNF alpha
- Proliferating cell nuclear antigen
- Hyaluronan receptors
- SR-A, SR-B1
- TGF
- SM myacin heavy chains
- CD 11, 18, 36, 40, 68
- MCP-1
- CCR2
- Pentraxin-3
- Apo binding protein
- I kappa B-alpha
- Total sialic acid
- Osteopontin

Immunology
- Anti-oxLDL IgG

Genetics
- ACE polymorphism
- methylenetetrahydrofolate reductase [MTHFR]
- apolipoprotein E [apo E]
- paraoxonase [PON]
Biomarkers in Atherosclerosis

• Biomarkers of atherosclerosis are important in understanding the disease process
  – may be used to accelerate identification of clinically important therapies
  – may be used as surrogates to clinical event outcome trials
• This is an area of increasing importance and increasing controversy.
Apo B and LDL-cholesterol

**NOTE:** apo B level does not correlate with serum triglyceride level
## LDL-C Particle Size and CVD Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford Coronary Risk Intervention Project (SCRIP)</td>
<td>Small, dense LDL-C levels at baseline were the best predictor for progression of coronary stenosis</td>
</tr>
<tr>
<td>Pravastatin Limitation of Atherosclerosis in the Coronary arteries trial (PLAC-I)</td>
<td>Small LDL-C was associated with a 5-fold greater risk of angiographic progression</td>
</tr>
<tr>
<td>Familial Atherosclerosis Treatment Study (FATS)</td>
<td>Increased LDL-C buoyancy with therapy was the most powerful predictor of coronary stenosis regression</td>
</tr>
<tr>
<td>Diabetes Atherosclerosis Intervention Study (DAIS)</td>
<td>Increased LDL-C size and decreased apoB–containing lipoproteins with treatment were associated with decreased coronary stenosis progression</td>
</tr>
</tbody>
</table>

Small, Dense Low-Density Lipoprotein Particles as a Predictor of the Risk of Ischemic Heart Disease in Men

Prospective Results From the Quebec Cardiovascular Study

Lamarche Circulation 1997;95:69-75
Lipids vs apo B “on treatment”

- Lipid profile parameters predict risk before treatment
- apo B, apo AI (and B/AI ratio) also predict outcome on treatment
Lp(a)
High Lp(a)

• If over 400 I.U./L consider lowering LDL-C to <2.0 mmol/L particularly if other risk factors present or if TC/HDL >5
Myeloperoxidase

- Myeloperoxidase mediates chlorination and nitration-dependent oxidation of proteins and is present and active in lesions\(^1\)

- LDL and HDL isolated from lesions contain MPO-specific oxidation markers

- Blood and leucocyte MPO levels are higher in CAD patients than in controls\(^2\)

- However, MPO-deficient mice get more atherosclerosis\(^3\), and some forms of HDL oxidation by MPO may be protective against atherosclerosis\(^4\)

Myeloperoxidase and C-Reactive Protein Have Combined Utility for Long-Term Prediction of Cardiovascular Mortality After Coronary Angiography

Claire L. Heslop, BMSc, Jiri J. Frohlich, MD, John S. Hill, PhD

Vancouver, British Columbia, Canada
Figure 2: Survival Curves for Cardiovascular Mortality by Elevations of MPO and CRP

Cumulative survival curves for cardiovascular mortality according to elevations of myeloperoxidase (MPO) and C-reactive protein (CRP). Patients with lowest tertile MPO and CRP (blue line) are compared with patients with highest tertile levels of either marker (green line), and patients with highest tertile measurements of both markers (red line). Log-rank test p < 0.001 for trend.

Heslop et al.
JACC 2010; 55:1102-9
Summary

- CAD patients had higher levels of MPO.
- Elevated baseline levels of MPO were predictive of mortality and cardiovascular mortality after adjustment of traditional independent risk factors.
- ROC curve analysis indicates that MPO adds significantly to risk prediction.
CRP: Atherogenic Factor

CRP localized in atherosclerotic but normal intima

CRP induced complement activation

CRP induced production of cell adhesion molecules, MCP-1, ET-1

CRP dependent monocyte recruitment into arterial wall

CRP attenuates NO production, decreases eNOS expression

CRP induced production of tissue factor in monocytes

CRP induced PAI-1 expression stabilizes PAI-1 mRNA

CRP based blunting of endothelial vasoreactivity

CRP triggered oxidation of LDL cholesterol

CRP mediated LDL uptake by macrophages

hsCRP adds prognostic information beyond traditional risk factors in all major cohorts evaluated.
JUPITER: Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

Rosuvastatin 20 mg (N=8901)

No Prior CVD or DM
Men >50, Women >60
LDL <130 mg/dL
hsCRP ≥2 mg/L

Placebo (N=8901)

4-week run-in

MI
Stroke
Unstable Angina
CVD Death
CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

JUPITER: Dual Target Analysis: LDLC<70 mg/dL, hsCRP<2 mg/L

LDL > 70 mg/dL and/or hsCRP > 2 mg/L
HR 0.64 (0.49-0.84)

LDL < 70 mg/dL and hsCRP < 2 mg/L
HR 0.35 (0.23-0.54)

Placebo
HR 1.0 (referent)

P < 0.0001
Intima Media Thickness (IMT)

• Marker for early atherosclerosis, predictor of events

• Lipid lowering is associated with reduced progression
Carotid Intima Media Thickness Methodology

Segment 5
Segment 3
Segment 1

Skin
External carotid
Internal carotid

1.0 cm
1.0 cm

Segment 6
Segment 4
Segment 2

CCA

Bifurcation

Intimal-media thickness (IMT)
Carotid IMT Predicts Coronary Events

The Kuopio Ischemic Heart Study

- 1227 middle-aged Finnish men
- Average follow-up: 1 year

For each 1 mm increase in carotid IMT the risk of MI increased 2.14 fold

Conclusions

- Carotid IMT is a validated surrogate measure of atherosclerosis
  - Simple, safe, noninvasive and relatively inexpensive
  - Represents a composite of the life-long effect of various risk factors on the arterial wall
  - Independent predictor of coronary heart disease events and stroke
  - Requires further standardization
Endothelial Mediators

Endothelial Dysfunction
Angiotensin II
Endothelin-1
Free radicals
TxA₂

Endothelial Health
Nitric Oxide
PGI₂
EDHF

Vasoconstriction
Inflammatory
Platelet aggregation
Procoagulant
Leaky membranes
Proliferative

Vasodilation
Anti-inflammatory
Antiplatelet
Fibrinolysis
Gap junction intact
Antiproliferative
Prognostic Value of Endothelial Function

Multivariate predictors
24 h BP: 1st vs 3rd tertile

Event-free survival

Follow-up (months)

N at risk

P = 0.0012 (log-rank test)

Perticone F et al. Circulation 2001; 104:191
10 points to remember about screening for CAD risk
1. The lifetime risk of CAD at age 50 averages 52% for men and 39% for women
2. Algorithms have been developed; 3-4 risk levels assigned based on individual’s risk factors
3. The most popular algorithm, the Framingham Risk Score has its limitation
4. Reynolds’s risk score adds CRP and family history
5. European algorithms ASSIGN and QRISK add an index of social status
6. Direct CV testing (intima media thickness, Ankle brachial pressure index etc.) may be of value in some patients (medium risk category)
7. Areas of uncertainty: 10y vs. lifetime; age at which to start treatment; can the population risk score guide therapy for individual patients?
8. Younger adults (<50) with (a) a low 10y risk and (b) high lifetime risk (>30%) at least one risk factor that could be treated: group b) develops greater subclinical disease. this should influence treatment strategies
9. Test for CV risk factors and reassess a CVD risk every 5 years
10. Provision of the risk score to the patient should promote discussion about lifestyle changes, or medications, can be a motivating tool
Prevention

0, 5 & 30
• Therapeutic lifestyle changes:
  – Exercise
  – Diet
    • Portfolio diet
    • Low salt diet (DASH)
  – Smoking cessation
  – Decrease stress

Use the 0, 5, 30 slogan

0 = No smoking
5 = servings of vegetables/fruits daily
30 = 30 min of exercise daily
Dietary Portfolio

Study Foods: available in supermarkets.

Nuts: ~30 g/d
    almonds

Viscous Fiber: ~20 g/d
    oats, barley, psyllium, legumes, eggplant, okra

Vegetable Protein: ~80 g/d (50% soy)
    soy, beans, chick peas, lentils

Plant Sterols: ~2 g/d
    plant sterol containing products

Jenkins DJ, Kendall CW et al. Metabolism 2002
Dietary Portfolio Changes in LDL-C

Jenkins DJ, Kendall CW et al. JAMA 2003
Effects of a Low-Sodium DASH Diet on Systolic Blood Pressure with Increasing Age
INTERHEART: Decreased Risk of AMI with Avoidance of Smoking; Daily Fruits/Veg, Reg Phys Activity & Alcohol

OR (99% CI)
• Medications
  – Lipid lowering medications
  – Antihypertensives
    • ACE inhibitors
    • Beta blockers
    • CCB
  – Anticoagulants
  – Medications helpful for weight reduction and quitting smoking
Questions about prevention

• Number needed to treat/cost
• Risk vs. benefit
• Women vs. men
• Young vs. elderly