Cardiovascular Epidemiologic Studies and Lessons in Preventive Cardiology: Framingham and Beyond

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Disclosures

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Advisory board: Genzyme

Consultant: Re-Engineering Healthcare
Objectives

• Understand the evolution of and lessons in preventive cardiology learned from key epidemiologic studies from Framingham and beyond.
• Understand future needs for research collaborations among large cardiovascular epidemiologic studies
Epidemiological studies of CHD and the evolution of preventive cardiology

Nathan D. Wong

Abstract | Cardiovascular diseases (CVDs) cause nearly one-third of all deaths worldwide. Coronary heart disease (CHD) accounts for the greatest proportion of CVDs, and risk factors such as hypertension, cigarette smoking, diabetes mellitus or elevated glucose level, elevated cholesterol levels, and obesity or being overweight are the top six causes of death globally. Ecological and population-based longitudinal studies, conducted globally or within individual countries, have established the role of traditional and novel risk factors and measures of subclinical disease in the prediction of CHD. Risk assessment with short-term or long-term risk prediction algorithms can help to identify individuals who would benefit most from risk-factor interventions. Evaluation of novel risk factors and screening for subclinical atherosclerosis can also help to identify individuals at highest cardiovascular risk. Prevention of CHD focuses on identifying and managing risk factors at both the population and individual levels through primordial, primary, and secondary prevention. Epidemiological studies have provided the hypotheses for subsequent clinical trials that have documented the efficacy of risk-factor interventions, which are the basis of preventive cardiology. Future research efforts will determine the screening and intervention strategies that have the greatest effect on CHD prevention.

Wong, N. D. Nat. Rev. Cardiol. advance online publication XX Month 2014; doi:10.1038/nrcardio.2014.26
Foundations of CVD Epidemiology

• Lack of reliable data on CVD noted as early as 1880’s and in 1934 the Society of Geographic Pathology noted the frequency of atherosclerotic lesions by country, social class and occupation.

• In 1946 the first prospective study of CVD was launched by Ansel Keys in Minnesota businessmen.
<table>
<thead>
<tr>
<th>Study</th>
<th>References</th>
<th>Year</th>
<th>Location</th>
<th>Population Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minnesota Businessmen</td>
<td>6</td>
<td>1946</td>
<td>Minnesota, USA</td>
<td>281 men aged &lt;55 years</td>
</tr>
<tr>
<td>Seven Countries</td>
<td>7-10</td>
<td>1958</td>
<td>Global</td>
<td>12,763 men aged 40-59</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td>11-27</td>
<td>1948</td>
<td>Massachusetts, USA</td>
<td>5209 men and women aged 30-62 original cohort</td>
</tr>
<tr>
<td>MONICA</td>
<td>28-33</td>
<td>1979</td>
<td>Global</td>
<td>15 million men and women ages 25-64</td>
</tr>
<tr>
<td>INTERHEART</td>
<td>34-35</td>
<td>1999</td>
<td>Global</td>
<td>15,152 MI and 14,820 controls</td>
</tr>
<tr>
<td>PURE</td>
<td>36-38</td>
<td>2002</td>
<td>17 countries</td>
<td>153,996 adults aged 35-70</td>
</tr>
<tr>
<td>Ni-Hon-San</td>
<td>39-40</td>
<td>1965</td>
<td>Japan, Hawaii, San Francisco</td>
<td>20,000 Japanese men aged 45-69</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Start Year/End Year</td>
<td>Country</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
<td>---------------------</td>
<td>---------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Whitehall / Whitehall II</td>
<td>41-48</td>
<td>1967/1985</td>
<td>United Kingdom</td>
<td>18,403 male civil servants aged 40-64 / 10,314 men and women aged 35-55</td>
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<tr>
<td>Rejkavik / AGES</td>
<td>49-51</td>
<td>1968/2003</td>
<td>Iceland</td>
<td>9141 / 2499 men aged 34-79 years</td>
</tr>
<tr>
<td>PROCAM</td>
<td>52-54</td>
<td>1979</td>
<td>Germany</td>
<td>4043 men and 1333 women aged 50-65.</td>
</tr>
<tr>
<td>ARIC</td>
<td>60-64</td>
<td>1987</td>
<td>Four US communities</td>
<td>15792 African-American and white aged 45-64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Start Year</th>
<th>End Year</th>
<th>Study Population</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Heart Study</td>
<td>65-67</td>
<td></td>
<td>USA, 13 American Indian Tribes</td>
<td>4549 men and women aged 45-75</td>
</tr>
<tr>
<td>Cardiovascular Health Study (CHS)</td>
<td>68-71</td>
<td>1989</td>
<td>Four US communities</td>
<td>5888 African-American and White, aged</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65-102</td>
</tr>
<tr>
<td>JACKSON Heart Study</td>
<td>72-73</td>
<td>2000</td>
<td>Jackson, MS</td>
<td>5302 African-American adults aged</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21-94</td>
</tr>
<tr>
<td>Multiethnic Study of Atherosclerosis (MESA)</td>
<td>74-80</td>
<td>2000</td>
<td>Six US communities</td>
<td>6814 African-American, Chinese,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hispanic and White, aged 45-80</td>
</tr>
<tr>
<td>Hispanic Community Health Study / Study of Latinos</td>
<td>81-82</td>
<td>2996</td>
<td>Four US communities</td>
<td>15,079 Hispanic, aged 18-72</td>
</tr>
</tbody>
</table>
Cholesterol intake and CHD Death Rate: The Seven Countries Study (n=12763 men aged 40-59)
Cholesterol and Mortality:
WHO Monica
(n=15 million men and women aged 25-64)
Becoming the Framingham Study 1947–1950

In the epidemiological imagination, the Framingham Heart Study has attained iconic status, both as the prototype of the cohort study and as a result of its scientific success.

When the Public Health Service went in search of the ‘Framingham Heart Study,’ 7 it had to find an already created cohort of middle-aged men and women with a clear epidemiological hallmark for an infectious disease. If infectious disease had defined the original cohort, all the epidemiologists of the time knew that cardiovascular disease would define both the cohort and the public health need. [...] The disease, all the time, was being defined by the cohort. And any cohort has to be thought of as a community... Community in the sense that we understood it in America as a neighborhood, a group of individuals who were more or less voluntarily associated with one another. That idea of community has changed in the last half-century. People who have been defined as part of the Framingham Heart Study in the last thirty years are the defining members of the community... What is a cohort of people? It is a group of people who have been defined by their history. Cohort is a word that is used in medicine, and used by epidemiologists in medicine, to define the kind of community that they are trying to deal with... Cohort is a word that is used in medicine, and used by epidemiologists in medicine, to define the kind of community that they are trying to deal with. Cohort means a group of people who have been defined by their history.

Framingham ‘is the epitome of successful epidemiological research, productive of insights and applications...[and] the prototype and model of the cohort study.’

Gerald M. Oppenheimer, PhD, MPH
Framingham Heart Study

• Longest running study of cardiovascular disease in the world
• Began in 1948 with original cohort of 5,209 subjects aged 30-62 at baseline
• Biennial examinations, still ongoing, most of original cohort deceased
• Offspring cohort of 5,124 of children of original cohort enrolled in 1971, and more recently and still being enrolled to better understand genetic components of CVD risk are up to 3,500 grandchildren of the original cohort.
• Routine surveillance of cardiovascular disease events adjudicated by panel of physicians
Concept of cardiovascular “risk factors”

Age, sex, hypertension, hyperlipidemia, smoking, diabetes, (family history), (obesity)

Framingham Most Significant Milestones

- **1960** Cigarette smoking found to increase the risk of heart disease
- **1961** Cholesterol level, blood pressure, and electrocardiogram abnormalities found to increase the risk of heart disease
- **1967** Physical activity found to reduce the risk of heart disease and obesity to increase the risk of heart disease
- **1970** High blood pressure found to increase the risk of stroke
- **1976** Menopause found to increase the risk of heart disease
- **1978** Psychosocial factors found to affect heart disease
- **1988** High levels of HDL cholesterol found to reduce risk of death
- **1994** Enlarged left ventricle (one of two lower chambers of the heart) shown to increase the risk of stroke
- **1996** Progression from hypertension to heart failure described
There is a strong relationship between CVD risk and the presence of dyslipidemia: Framingham.

Total Cholesterol Distribution: 
*CHD vs Non-CHD Population*

35% of CHD Occurs in People with TC<200 mg/dL

Framingham Heart Study—26-Year Follow-up

Low HDL-C Levels Increase CHD Risk Even When Total-C Is Normal

Risk of CHD by HDL-C and Total-C levels; aged 48–83 y
Castelli WP et al. JAMA 1986;256:2835–2838
FIGURE 1. Risk of CHD according to elevated blood pressure (BP), elevated cholesterol, and left ventricular hypertrophy: Framingham cohort 6-year follow-up. Elevated BP = ≥160/95; elevated cholesterol = ≥260 mg/dl.

Framingham Heart Study: Kannel et al., 1961
1) As early as 1976, former Framingham director Dr. William Kannel had noted risk functions provide an “economic and efficient method of identifying persons at high cardiovascular risk who need preventive treatment and persons at low risk who need not be alarmed about one moderately elevated risk characteristic” (AJC 1976).

2) The ACC Bethesda Conference noted the intensity of treatment should match a person’s risk (Califf RM, JACC 1996).

3) Studies show a physician’s estimate is only accurate 24% of the time (Pignone et al, BMC health Serv Res 2003).

4) Routine use of global risk scores leads to greater use of guideline-based therapy and modest improvements in intermediate outcomes with no harm identified (Sheridan et al. BMC Health Serv Res 2008).
<table>
<thead>
<tr>
<th>Risk Score (year)</th>
<th>Endpoint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham, 1991 (Anderson)</td>
<td>10-year all CHD</td>
<td>CHD death, MI, unstable angina, angina</td>
</tr>
<tr>
<td>Framingham, 1998 (Wilson)</td>
<td>10-year all CHD and hard CHD</td>
<td>CHD death, MI, unstable angina, angina</td>
</tr>
<tr>
<td>ATP III, 2001 (Framingham)</td>
<td>10-year hard CHD</td>
<td>CHD death, nonfatal MI</td>
</tr>
<tr>
<td>PROCAM 2002 (Germany)</td>
<td>10-year hard CHD</td>
<td>CHD death, non-fatal MI</td>
</tr>
<tr>
<td>European SCORE 2003 and after</td>
<td>10-year CVD death</td>
<td>CVD death only (country and region specific)</td>
</tr>
<tr>
<td>QRISK 2007 (England and Wales)</td>
<td>10-year global CVD</td>
<td>CVD death, MI, stroke, revascularization</td>
</tr>
<tr>
<td>Framingham Global CVD 2008</td>
<td>10-year global CVD</td>
<td>CVD death, all CHD, stroke, heart failure, claudication</td>
</tr>
<tr>
<td>Pooled Cohort Equations 2013 (USA)</td>
<td>10-year and lifetime ASCVD</td>
<td>Nonfatal/fatal MI &amp; stroke</td>
</tr>
</tbody>
</table>
### Assessing CHD Risk in Women

#### Step 1: Age

<table>
<thead>
<tr>
<th>Years</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>-7</td>
</tr>
<tr>
<td>35-39</td>
<td>-3</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>12</td>
</tr>
<tr>
<td>70-74</td>
<td>14</td>
</tr>
<tr>
<td>75-79</td>
<td>16</td>
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</tbody>
</table>

#### Step 2: Total Cholesterol

<table>
<thead>
<tr>
<th>TC at Points at</th>
<th>Points at</th>
<th>Points at</th>
<th>Points at</th>
<th>Points at</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mg/dL)</td>
<td>Age 20-39</td>
<td>Age 40-49</td>
<td>Age 50-59</td>
<td>Age 60-69</td>
</tr>
<tr>
<td>&lt;160</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160-199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>200-239</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>240-279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>≥280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Step 3: HDL-Cholesterol

<table>
<thead>
<tr>
<th>HDL-C (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>

#### Step 4: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Systolic BP (mm Hg)</th>
<th>Points if Untreated</th>
<th>Points if Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>130-139</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>140-159</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>≥160</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

#### Step 6: Adding Up the Points

- Age
- Total cholesterol
- HDL-cholesterol
- Systolic blood pressure
- Smoking status
- Point total

#### Step 7: CHD Risk

<table>
<thead>
<tr>
<th>Point Total</th>
<th>10-Year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>9</td>
<td>1%</td>
</tr>
<tr>
<td>10</td>
<td>1%</td>
</tr>
<tr>
<td>11</td>
<td>1%</td>
</tr>
<tr>
<td>12</td>
<td>1%</td>
</tr>
<tr>
<td>13</td>
<td>2%</td>
</tr>
<tr>
<td>14</td>
<td>2%</td>
</tr>
<tr>
<td>15</td>
<td>3%</td>
</tr>
<tr>
<td>16</td>
<td>4%</td>
</tr>
<tr>
<td>17</td>
<td>5%</td>
</tr>
<tr>
<td>18</td>
<td>6%</td>
</tr>
</tbody>
</table>

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.

**LDL-C Treatment Targets**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD or CHD risk equivalents</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (&lt;100 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>(10-year risk &gt;20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately high risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>&lt;130 mg/dL (optimal &lt;100 mg/dL)</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (100-129 mg/dL: consider Rx)</td>
</tr>
<tr>
<td>(10-year risk 10% to 20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td><strong>Lower risk:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>


# 10-Year Framingham Total Cardiovascular Disease Risk Score (D’Agostino et al, 2008)

## TABLE 5. CVD points and risk for women

<table>
<thead>
<tr>
<th>CVD Points</th>
<th>Points</th>
<th>Age</th>
<th>HDL</th>
<th>Total Cholesterol</th>
<th>SBP Not Treated</th>
<th>SBP Treated</th>
<th>Smoker</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>−3</td>
<td>−3</td>
<td>60+</td>
<td></td>
<td></td>
<td>&lt;120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2</td>
<td>−2</td>
<td>50−59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>30−34</td>
<td>45−49</td>
<td>&lt;160</td>
<td>120−129</td>
<td>&lt;120</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>35−39</td>
<td>160−199</td>
<td>130−139</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>&lt;35</td>
<td></td>
<td></td>
<td>140−149</td>
<td>120−129</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>200−239</td>
<td></td>
<td></td>
<td>130−139</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>40−44</td>
<td>240−279</td>
<td>150−159</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>45−49</td>
<td>280+</td>
<td></td>
<td>140−149</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>50−54</td>
<td></td>
<td></td>
<td>160+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>55−59</td>
<td></td>
<td></td>
<td>160+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>60−64</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>65−69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>70−74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>75+</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Global Risk Scoring: Class 1a

ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, Circulation 2010
Recommendation to begin with a global risk assessment using the Pooled Cohort Equations to estimate 10-year ASCVD Risk
# Pooled Cohort Equations 10-year ASCVD Risk Calculator (Framingham, ARIC, CARDIA, and CHS)

## Risk Factor Table

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable range of values</th>
<th>Optimal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>M or F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>20-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans) or WH (for whites or others)</td>
<td>AA or WH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>130-320</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>20-100</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>90-200</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

## Instructions

- **Your 10-Year ASCVD Risk (%)**
  - This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age. Enter M or F for Gender, Enter VH or AA for race, Enter 130-320 for TC value, Enter 20-100 for HDL value, Enter 90-200 for SBP value, Enter Y or N for treatment for hypertension, Enter Y or N for Diabetes, Enter Y or N for Smoker.

- **10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)**
  - Enter M or F for Gender. This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age. Enter VH or AA for race.

- **Your Lifetime ASCVD Risk (%)**
  - This calculator only provides lifetime risk estimates for individuals 20 to 59 years of age. Enter M or F for Gender, Enter 130-320 for TC value, Enter 90-200 for SBP value, Enter Y or N for treatment for hypertension, Enter Y or N for
Lifetime Risks of Cardiovascular Disease Death by Number of Risk Factors and Attained Age (Berry et al., 2012)

**Men**

**Optimal risk factors:** total cholesterol <180 mg/dl, blood pressure <120/80, non-smoking, non-diabetic.

**Major risk factors:** current smoker, diabetes, treated cholesterol or untreated cholesterol >=240 mg/dl, treated hypertension or untreated systolic BP >=160 mmHg or diastolic BP>=100 mmHg.

**Women**

**Optimal risk factors:** total cholesterol <180 mg/dl, blood pressure <120/80, non-smoking, non-diabetic.

**Major risk factors:** current smoker, diabetes, treated cholesterol or untreated cholesterol >=240 mg/dl, treated hypertension or untreated systolic BP >=160 mmHg or diastolic BP>=100 mmHg.
Lifetime Risk of CHD Increases with Serum Cholesterol

Framingham Study: Subjects age 40 years

Relation of Non-Hypertensive Blood Pressure to Cardiovascular Disease

Framingham Study: Subjects Ages 35-90 yrs.
## Risk of Cardiovascular Events in Diabetics

**Framingham Study**

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Men</th>
<th>Women</th>
<th>Biennial Rate Per 1000</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Disease</td>
<td>39</td>
<td>21</td>
<td>1.5**</td>
<td>2.2***</td>
</tr>
<tr>
<td>Stroke</td>
<td>15</td>
<td>6</td>
<td>2.9***</td>
<td>2.6***</td>
</tr>
<tr>
<td>Peripheral Artery Dis.</td>
<td>18</td>
<td>18</td>
<td>3.4***</td>
<td>6.4***</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>23</td>
<td>21</td>
<td>4.4***</td>
<td>7.8***</td>
</tr>
<tr>
<td>All CVD Events</td>
<td>76</td>
<td>65</td>
<td>2.2***</td>
<td>3.7***</td>
</tr>
</tbody>
</table>

Subjects 35-64 36-year Follow-up  **P<.001,** ***P<.0001
TEN-YEAR INCIDENCE OF CORONARY HEART DISEASE AMONG MEN AGE 45 TO 64 YEARS BY WIFE'S EMPLOYMENT STATUS AND EDUCATIONAL LEVEL

<table>
<thead>
<tr>
<th>Wife's Education</th>
<th>Working Outside</th>
<th>At Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 yr</td>
<td>(24) 4.2</td>
<td>(24) 12.5</td>
</tr>
<tr>
<td>9-12 yr</td>
<td>(65) 13.8</td>
<td>(83) 16.9</td>
</tr>
<tr>
<td>≥13 yr</td>
<td>(22) 31.8</td>
<td>(47) 17</td>
</tr>
</tbody>
</table>

Incidence of CHD (%)
Screening for Atherosclerosis
Risk Factors vs Disease

Numerous Risk Factors
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress

? Over 200 risk factors have been reported.

Examples of Arterial Structure Tests
- Carotid IMT and Plaque Measured by Ultrasound
- Aortic and Carotid Plaque Detected by MRI
- Coronary Calcium Score Measured by CT
- Ankle Brachial Index
- Brachial Vasoreactivity Measured by Ultrasound
- Vascular Compliance Measured by Radial Tonometry
- Microvascular Reactivity Measured by Fingertip Tonometry

Examples of Arterial Function Tests
hs-CRP Adds to Predictive Value of TC:HDL Ratio in Determining Risk of First MI

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

Ridker PM. Circulation 2003;107:363-9
Risk Factors for Future Cardiovascular Events: WHS

Lipoprotein(a)  Homocysteine  IL-6  TC  LDLC  sICAM-1  SAA  Apo B  TC: HDLC  hs-CRP  hs-CRP + TC: HDLC

Relative Risk of Future Cardiovascular Events

Cardiovascular Health Study

- 5,201 Medicare eligible individuals aged 65-102 at baseline enrolled beginning 1992 at six field centers.
- Assessment of newer and older risk factors.
- Ongoing follow-up of cardiovascular events and mortality
- Subclinical disease measures included:
  - carotid B-mode ultrasound for carotid IMT at Year 2, Year 7, and Year 11
  - m-mode echocardiographic measures of left ventricular mass and dimensions, left atrial dimension done at baseline (Year 2) (at UC Irvine) and follow-up (Year 7) examinations.
  - Ankle brachial index (ABI) for measurement of PAD
  - Pulmonary function (FVC and FEV1)
Cardiovascular Health Study (CHS) (aged 65+): MI or stroke rate 25% over 7 years in those at highest quintile of combined IMT (O’Leary et al. 1999)
Ankle Brachial Index as a Predictor of Cardiovascular Mortality in the CHS Study

Ankle–brachial pressure index:

- <0.8
- 0.8 to <0.9
- 0.9 to <1.0
- 1.0 to <1.5

% Surviving

Years
Does Inflammation Attenuate the Protective Association of HDL with CHD?
(Tehrani and Wong et al., Atherosclerosis 2013)

Cardiovascular Health Study Adults Aged 65+
Inflammation index consisting of hs-CRP, IL-6, and LpPla2
Multiethnic Study of Atherosclerosis

- 6,814 adults aged 45-80 enrolled at 6 field centers, including Caucasians, African-Americans, Hispanics, and Chinese beginning 2000.
- Extensive assessment of standard and novel risk factors, unique blood cohort among 1000 subjects.
- Multiple evaluations of carotid IMT, ABI, and coronary calcium. Ancillary studies of LV size and extracoronary measures of calcification (Harbor-UCLA) and abdominal aortic calcium (UC San Diego) in full or partial cohorts.
MESA Study Design Features

Four examinations approximately two years apart, exam 5 just completed
Major risk factors measured at each exam
Coronary calcium measured in entire cohort at Exam 1, ½ cohort at Exam 2, ½ cohort at Exam 3, and in about 1000 pts in Exam 4.
Carotid IMT measured at Exam 1 and 2-3.
Cardiac MRI measured at Exam 1 and 2-3
Ankle Brachial Index
Pulse wave analysis
Endothelial function measures
Follow-up for CVD events and incident DM, mortality
Cumulative Incidence of Any Coronary Event: MESA Study
(Detrano et al., NEJM 2008)
The addition of CAC to models with age, gender, ethnicity and risk factors alone resulted in net reclassification of 0.25 (p<0.001); 23% of those with events were reclassified as high risk and 13% without events were reclassified as low risk.
Can Screening for Atherosclerosis Identify Those Most Likely to Benefit from Lipid-Lowering Therapy?

Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study


Michela J Blohra, Matthew J Budoff, Andrew P DeFilippi, Ron Blankstein, Juan J Rivers, Arthur Agatston, Daniel H O'Leary, Joao Lima, Roger S Blumenthal, Khurram Nasir

[Graphs and charts showing event rates for CHD and CVD events by CAC levels and hsCRP levels, with conclusions that 75% of events occurred in 25% with CAC > 100 and the number needed to treat for different CAC levels.]
Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals

Intermediate Risk MESA Subjects (n=1330)

C-statistics:

- FRS alone 0.623
- FRS+CAC 0.784 (p<0.001)
- FRS+CIMT 0.652 (p=0.01)
- FRS+FMD 0.639 (p=0.06)
- FRS+CRP 0.640 (p=0.03)
- FRS+FamHx 0.675 (p=0.001)
- FRS+ABI 0.650 (p=0.01)

Yeboah J et al, JAMA 2012
HDL-Particle Concentration Predicts CHD Better than HDL-Cholesterol

MESA STUDY

- 5998 men and women aged 45-84 with comparison of association of HDL-C and NMR-measured HDL-P with carotid IMT and incident CHD
- HDL-P (per SD) remained independently associated with: CIMT (-22.2 um, 95% CI -33.8 to -10.6) and CHD (HR=0.75, 95% CI=0.61-0.93).
- Adjusting for each other and LDL-P attenuated associations of HDL-C but not HDL-P with CIMT and CHD (Mackey R, JACC 2012)
Coronary Artery Risk Development in Young Adults (CARDIA) – 5,115 adults (half African-American) aged 18-30 at baseline in 1985 enrolled at 4 field centers.

- Ongoing evaluation (Year 20 exam recently completed).

- Echocardiographic M-mode and 2D measures available at Year 5 and Year 10 exams (UC Irvine Echo Reading Center)

- CT Coronary Calcium at Years 15 (Harbor-UCLA) and 20 (Wake Forest University)
CIMT w/w/o Plaque and CHD Incidence: ARIC Study (Nambi et al., JACC 2010)

Figure 1: Adjusted Coronary Heart Disease Incidence Rate per 1,000 Person-Years Adjusted by CIMT Categories With and Without Plaque

For every carotid intima-media thickness (CIMT) category (i.e., <25th percentile, 25th to 75th percentile, and >75th percentile), for the overall group (green bars), men (yellow bars), or women (orange bars), having carotid artery plaque is associated with a higher incidence of coronary heart disease.
NHANES Cross-Sectional and Mortality Follow-up Studies

- NHES, NHANES 2,3 Mortality Follow-up
Risk for CHD Increases with the Number of Risk Factors: NHANES/NHEFS

Risk Factors (RFs)
- SBP >140 mm Hg or DBP >80 mm Hg
- TC >240 mg/dL
- BMI >27.3 kg/m² (women) >27.8 kg/m² (men)
- Current smoker
- Diabetes

*N = 12,932

0 1 2 3 4-5
# of RFs (any combination)

6.3 15.3 22.3 29.7 35.0

Events/100 Patients*

Risk for CHD Increases with the Number of Risk Factors: NHANES/NHEFS


Distribution of HTN Subtypes in the untreated Hypertensive Population in NHANES III by Age

- ISH (SBP ≥140 mm Hg and DBP <90 mm Hg)
- SDH (SBP ≥140 mm Hg and DBP ≥90 mm Hg)
- IDH (SBP <140 mm Hg and DBP ≥90 mm Hg)

Frequency of hypertension subtypes in all untreated hypertensives (%)

- Age (y): <40, 40-49, 50-59, 60-69, 70-79, 80+

Numbers at top of bars represent the overall percentage distribution of untreated hypertension by age.

Does DM Carry a CVD or Mortality Risk Equivalent? US Men and Women Ages 30-74 (age, gender, and risk-factor adjusted Cox regression) NHANES II Follow-Up (n=6255) (Malik and Wong, et al., Circulation 2004; 110: 1245-1250)

<table>
<thead>
<tr>
<th>None</th>
<th>MetS</th>
<th>Diabetes</th>
<th>CVD</th>
<th>CVD+Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

* p<.05, ** p<.01, *** p<.0001 compared to none
Overall Half of CHD Events in DM Could be Prevented from Aggressive Control of Risk Factors: Application of UKPDS Risk Engine to NHANES 2001-2010 (Wong ND et al., Am J Cardiol 2014, in press)
Get your My Life Check Assessment

In just a few minutes with My Life Check, you can learn the state of your heart and what you can do to live a better life.
Age-standardized prevalence estimates for poor, intermediate and ideal cardiovascular health for each of the seven metrics of cardiovascular health in the AHA 2020 goals, among US adults >20 years of age, NHANES 2005-2006 (baseline available data as of January 1, 2010).

Fewer than 1% of US adults are at ideal levels for all 7 measures of cardiovascular health!
Ideal Cardiovascular Health and CVD Incidence: ARIC Study
(Folsom et al, JACC 2011)
Risk Factor Consortia

• The **Emerging Risk Factors Collaboration** incorporating over 1.3 million person years at risk demonstrate
  – the independent predictive value of C-reactive protein with CHD and stroke among 54 prospective studies (Lancet 2010)
  – the clinical utility of C-reactive protein and fibrinogen (NEJM 2012)
  – the limited role of adding the novel lipid markers apolipoprotein B, apolipoprotein A1, lipoprotein (a) and lipoprotein-associated phospholipase A2 to traditional lipid measures (JAMA 2012).

• The group also showed in 97 prospective studies the strong relation of diabetes with deaths from vascular disease and other causes (NEJM 2011).
Multinational Registries of CAD Patients

- **Euroaspirer I, II, III, IV (just completed 2013)** – compares adherence to recommended lifestyle and therapies in secondary prevention across European countries.

- **Prospective Urban Rural Epidemiology (PURE)** – 139,506 subjects enrolled among 600 communities in 17 low, middle and high income countries.
Big Gap in use of Evidence Based Drugs for Secondary Prevention in China
PURE study

For Antiplatelets:
- North America/Europe: 55.4%
- South America: 32.8%
- Middle East: 15.5%
- South Asia: 14.9%
- China: 3.4%
- Malaysia: 11.6%
- Africa: 4.9%

For Beta-blockers:
- North America/Europe: 45.4%
- South America: 37.0%
- Middle East: 11.9%
- South Asia: 12.5%
- China: 12.5%
- Malaysia: 6.8%
- Africa: 1.9%

For ACE-1/ARB:
- North America/Europe: 46.8%
- South America: 40.2%
- Middle East: 26.2%
- South Asia: 12.8%
- China: 7.8%
- Malaysia: 6.4%
- Africa: 6.8%

For Statins:
- North America/Europe: 56.7%
- South America: 37.3%
- Middle East: 4.8%
- South Asia: 2.0%
- China: 15.9%
- Malaysia: 2.0%
- Africa: 1.4%

Future Needs for CVD Epidemiologic Studies

• Role in personalized medicine such as identifying characteristics of patients most likely to respond to different therapies (lipid-lowering, diabetes, antihypertensive)

• Identify novel biomarker strategies that can improve risk prediction beyond traditional risk factor assessment

• Better identification of lifestyle characteristics that predict low risk status / those unlikely to suffer CVD events
Do we need yet another risk factor? No doubt there is room for skepticism but:

“Whenever a new discovery is reported to the scientific world they first say ‘it is probably not true’. When the truth of the new proposition has been demonstrated beyond question they say ‘yes it may be true but it is not important.’ Finally when sufficient time has elapsed to fully evidence its importance they say ‘yes, surely it is important, but it is no longer new.”

Michell DeMontagne
I have some bad news for you. While your cholesterol has remained the same, the research findings have changed.