Gender Differences in Cardiovascular Disease

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research support from Merck and AstraZeneca

TOPICS TO BE COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle
Mortality Rates in Women

At Every Age, More Women Die From Heart Disease Than From Cancer

- Coronary artery disease
- Stroke
- Lung cancer
- Breast cancer
- Colon cancer
- Endometrial cancer

50% of women (1 in 2) will die from CVD compared with 4% (1 in 25) who will die from breast cancer

Deaths Due to Cardiovascular Diseases

United States

Women

Men

Global Mortality from CHD (in 1000s)

<table>
<thead>
<tr>
<th>Region</th>
<th>Women</th>
<th>2020</th>
<th>% Increase</th>
<th>Men</th>
<th>2020</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>EME</td>
<td>838</td>
<td>1107</td>
<td>32</td>
<td>829</td>
<td>1209</td>
<td>46</td>
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<tr>
<td>FSE</td>
<td>559</td>
<td>702</td>
<td>26</td>
<td>488</td>
<td>612</td>
<td>52</td>
</tr>
<tr>
<td>Total developed</td>
<td>1397</td>
<td>1809</td>
<td>20</td>
<td>1297</td>
<td>1821</td>
<td>46</td>
</tr>
<tr>
<td>countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>556</td>
<td>1117</td>
<td>115</td>
<td>619</td>
<td>1405</td>
<td>127</td>
</tr>
<tr>
<td>China</td>
<td>377</td>
<td>584</td>
<td>61</td>
<td>386</td>
<td>811</td>
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<td>OAI</td>
<td>227</td>
<td>552</td>
<td>143</td>
<td>233</td>
<td>581</td>
<td>149</td>
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<tr>
<td>SSA</td>
<td>117</td>
<td>263</td>
<td>125</td>
<td>112</td>
<td>222</td>
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<td>Latin America</td>
<td>169</td>
<td>412</td>
<td>144</td>
<td>179</td>
<td>444</td>
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<tr>
<td>Middle East</td>
<td>291</td>
<td>717</td>
<td>146</td>
<td>319</td>
<td>874</td>
<td>174</td>
</tr>
<tr>
<td>Total developing</td>
<td>1737</td>
<td>3625</td>
<td>120</td>
<td>1620</td>
<td>4287</td>
<td>177</td>
</tr>
<tr>
<td>countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>World</td>
<td>3134</td>
<td>5684</td>
<td>80</td>
<td>3125</td>
<td>6258</td>
<td>100</td>
</tr>
</tbody>
</table>

Yusuf S et al, Circ 2001;104:2746

TOPICS TO BE COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle
Presentation of CHD

- Angina is most common presentation in women (myocardial infarction in men)
- Women may present with more atypical sx, such as fatigue, nausea, abdominal pain
- Most (>90%) of women will present with typical chest pain
- Chest pain is less predictive of CHD in women
- Gender differences in presentation are significant only among younger pts

Absence of Significant CHD

<table>
<thead>
<tr>
<th></th>
<th>FEMALE</th>
<th>MALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24%</td>
<td>9%</td>
</tr>
<tr>
<td>ST-segment</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>CK-MB/Troponin +</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* Restricted to patients in invasive arms, <50% stenosis

O’Donoghue et al., JAMA 2008; 300:71
Gender Differences in Acute Coronary Syndromes (ACS)

- Women are older
- More likely to have
  - Diabetes
  - Hypertension
  - Hypercholesterolemia
  - History of angina, CHF and CVD
- More women than men will have a second heart attack within 6 years after their first heart attack

ACS Outcomes: Invasive strategy benefit seen only in women with + biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB or Troponin +</td>
<td>1110</td>
<td>0.67 (0.50-0.88)</td>
</tr>
<tr>
<td>CK-MB or Troponin -</td>
<td>1486</td>
<td>0.94 (0.61-1.44)</td>
</tr>
<tr>
<td>MALE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB or Troponin +</td>
<td>2745</td>
<td>0.56 (0.46-0.67)</td>
</tr>
<tr>
<td>CK-MB or Troponin -</td>
<td>2294</td>
<td>0.72 (0.51-1.01)</td>
</tr>
</tbody>
</table>

Restricted to TIMI IIIB, FRISC II, RITA 3, MATE, TACTICS-TIMI 18

O’Donoghue et al., JAMA 2008; 300:71
**Women and ACS**

- Women are older and have more comorbidities when diagnosed with ACS
- Women diagnosed with ACS are more likely to have normal coronaries than men
- Women with ACS have different risk/benefit than men for procedures
  - Bleeding rates are higher
  - Benefit of invasive therapy seen only in high risk women

**TOPICS TO BE COVERED**

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle
Risk Factors

- Men and women share traditional risk factors
- Diabetes has higher relative risk in women
Step 1: Age Points

Diabetes has higher risk in women

Step 2: Total Cholesterol Points

Step 3: HDL-C Points

Step 4: SBP Points

Step 5: Smoking Status Points

Step 6: Sum of Points

Step 7: 10-year CHD Risk

Diabetes has higher risk in women

Framingham Risk Score: Men

Framingham Score: Women

Useful in Determining the Need for Adjunctive Preventive Therapy


2001;285:2486-97

*Such as the Framingham Risk Score (FRS)

2003 Hu et al.

Diabetes + CHD

Diabetes alone

CHD alone

Men

Women

Natarajan et al., Arch Intern Med, 2003

Hu et al., Diabetologia, 2005
Impact of CVD in Women is underestimated by Framingham Risk Score

60% of men aged 50-59 & 92% aged 60-69 are at least intermediate risk

1% women aged 50-59 & 9% aged 60-69 are at least intermediate risk

Guidelines based on FRS may not be sufficient in women

- Women <65 y/o presenting with MI
- None had a FRS >20%.
- 82% of women not eligible for statin therapy by ATP III guidelines.

Akosah et al JACC 2003
### Framingham score estimates 10-year risk

*not lifetime risk*

<table>
<thead>
<tr>
<th></th>
<th>Age 30</th>
<th>Age 60</th>
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<tbody>
<tr>
<td>Age</td>
<td>-9</td>
<td>8</td>
</tr>
<tr>
<td>Smoker</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SBP 160 mmHg</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>LDL 190 mg/dL</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HDL 35 mg/dL</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FRS points</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>FRS 10-yr risk</td>
<td>2%</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Ridker and Cook, Circulation 2005;111:657-658*

### Lifetime Risk by Risk Factors at Age 50

#### Men

- ≥2 Major RFs
- 1 Major RF
- ≥1 Elevated RF
- ≥1 Not Optimal RF
- Optimal RFs

#### Women

- ≥2 Major RFs
- 1 Major RF
- ≥1 Elevated RF
- ≥1 Not Optimal RF
- Optimal RFs

*Lloyd-Jones, Circulation 2006*
**Lifetime risk in women**

- For women free of clinical CVD at 50 years old, ~ 40% of women will later develop CVD
- Compare with lifetime risk of breast cancer (12.5%), lung cancer (6%), and colorectal cancer (6%)
- Prevention efforts need to begin decades before age 50
- A single major RF at age 50 is associated with substantially increased lifetime risk for CVD and shorter survival


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**Clinical Case I: Short term vs lifetime risk**

- 50-year nonsmoking, nondiabetic woman with TC 250, HDL-C 60, Trig 200, LDL-C 150, SBP 160 mm Hg.
  - FRS 10-year risk of only 2%
  - Not eligible for statin Rx per ATP III or aspirin per AHA guidelines
  - But 50% lifetime risk of CVD
  - >8 years shorter median survival compared to a woman of optimal risk factors

TOPICS TO BE COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
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- Therapies
  - Aspirin
  - Statins
  - Lifestyle

Framingham Risk Scoring Assessing 10-yr CHD Risk in Women

- Gender-specific FRS based on:
  - Age
  - Smoking
  - Total cholesterol
  - HDL-C
  - SBP

- Estimates 10-year global risk of CHD

- Not included in FRS
  - Family history of premature CHD
  - Metabolic Syndrome/Insulin Resistance
  - Subclinical Atherosclerosis
  - C-reactive protein
  - Exercise capacity
  - Heart rate recovery
  - Chronic kidney disease

Clinical Case II: The Reynolds Risk Score

72 year old non-diabetic women

<table>
<thead>
<tr>
<th></th>
<th>FRS</th>
<th>RRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Parental history</td>
<td>No</td>
<td></td>
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</tbody>
</table>
### Clinical Case II: The Reynolds Risk Score

72 year old non-diabetic women  

<table>
<thead>
<tr>
<th></th>
<th>FRS</th>
<th>RRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>Yes</td>
<td>4.9%</td>
</tr>
<tr>
<td>SBP</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Parental history</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**Myocardial infarction age 80**
Framingham Risk Scoring Assessing 10-yr CHD Risk in Women

- Gender-specific FRS based on:
  - Age
  - Smoking
  - Total cholesterol
  - HDL-C
  - SBP

- Estimates 10-year global risk of CHD

- Not included in FRS
  - Family history of premature CHD
  - Metabolic Syndrome/Insulin Resistance
  - Subclinical Atherosclerosis
  - C-reactive protein
  - Exercise capacity
  - Heart rate recovery
  - Chronic kidney disease

Ability of Exercise Testing to Predict Cardiovascular and All-Cause Death in Asymptomatic Women
A 20-Year Follow-up of the Lipid Research Clinics Prevalence Study

Context: The value of exercise testing in women has been questioned.
Objective: To determine the prognostic value of exercise testing in a population-based cohort of asymptomatic women followed up for 20 years.
Participants: A total of 2,994 asymptomatic North American women, aged 30 to 80 years, without known cardiovascular disease.
Main Outcome Measures: Cardiovascular and all-cause mortality.
Results: There were 427 (14%) deaths during 20 years of follow-up, of which 147 were due to cardiovascular causes. Low exercise capacity, low heart rate recovery (HRR), and sex were independent predictors of mortality.

Women who were below the median for both exercise capacity and heart rate recovery had 3.5-fold increased risk of CVD death

Mora S et al, JAMA 2003;290:1600-1607
Heart Rate Recovery

Vagal Withdrawal
Sympathetic Activation

Vagal Reactivation

Heart Rate

Exercise

Recovery

Rest  Peak  1 minute

TOPICS TO BE COVERED

– Impact of CVD in women
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– Novel risk factors
– Therapies
  • Aspirin
  • Statins
  • Lifestyle
Women’s Health Study: Major Cardiovascular Events (Nonfatal Myocardial Infarction, Nonfatal Stroke, Cardiovascular Death)

39,876 women randomized to aspirin (100 mg every other day) or placebo for an average of 10 years

RR = 0.91
95% CI 0.80 – 1.03
P = 0.13

Aspirin did not reduce risk of MI in women

39,876 women randomized to aspirin (100 mg every other day) or placebo for an average of 10 years

Cumulative incidence of MI:

Aspirin: P=0.83
Women's Health Study – Stroke and Myocardial Infarction

Total Stroke
RR = 0.83 (0.69-0.99)
P = 0.04

Ischemic Stroke
RR = 0.76 (0.63-0.93)
P = 0.009

Hemorrhagic Stroke
RR = 1.24 (0.82-1.87)
P = 0.31

Myocardial Infarction
RR = 1.02 (0.84-1.25)
P = 0.83

Aspirin in Primary Prevention

RR of MI Among Men
RR = 0.81 (0.69-0.96)
P = .01

RR of Stroke Among Men
RR = 0.99 (0.83-1.19)
P = .95

Aspirin Better Placebo Better
TOPICS TO BE COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle

Statins for Prevention of CVD: Gender Differences

Statins for patients with CVD is established
- Similar benefit in women, men
- Relative risk reduction ~20-30%

Statins for women with no CVD is controversial
- Prior meta-analyses: non-significant
- RR CHD events 0.87 (0.22-1.68), P=0.17
  N = 11,435 women

Walsh and Pignone, JAMA 2004;2243
Rosuvastatin for Primary Prevention of CVD in Women with Elevated hsCRP and Low LDL Cholesterol:

Sex-Specific Outcomes from the JUPITER Trial and Meta-Analysis of Primary Prevention Statin Trials

Samia Mora, Robert J Glynn, and Paul M Ridker

Brigham and Women’s Hospital
Harvard Medical School
Boston, MA

on behalf of the JUPITER Trial Study Group

Mora S et al Circ 2010;in press

JUPITER Trial Design

6,801 women > 60 years
11,001 men > 50 years
1,315 sites, 26 countries

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

Rosuvastatin 20 mg (N=8901)

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

Mora S et al Circ 2010;in press
### JUPITER

**Primary Trial Endpoint**: MI, Stroke, UA/Revascularization, CV Death

<table>
<thead>
<tr>
<th>Rosuva</th>
<th>Placebo</th>
<th>No. (Rate)*</th>
<th>No. (Rate)*</th>
<th>HR</th>
<th>95% CI</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>39 (0.56)</td>
<td>70 (1.04)</td>
<td>0.54</td>
<td>0.37-0.80</td>
<td>P=0.002</td>
<td>0.80</td>
</tr>
<tr>
<td>Men</td>
<td>103 (0.88)</td>
<td>181 (1.54)</td>
<td>0.58</td>
<td>0.45-0.73</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Rates are per 100 person-years

Mora S et al Circ 2010; in press

### JUPITER

**Primary Trial Endpoint**: Number Needed to Treat (5-years)

<table>
<thead>
<tr>
<th>Rosuva</th>
<th>Placebo</th>
<th>No. (Rate)</th>
<th>No. (Rate)</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>39 (0.56)</td>
<td>70 (1.04)</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>103 (0.88)</td>
<td>181 (1.54)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>142 (0.77)</td>
<td>251 (1.36)</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated based on the method of Altman and Andersen
### JUPITER

Adverse Events and Measured Safety Parameters

<table>
<thead>
<tr>
<th>Event</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuva</td>
<td>Placebo</td>
</tr>
<tr>
<td>Any SAE</td>
<td>7.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>8.9</td>
<td>8.3</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incident Cancer</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Cancer Deaths</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m² at 12 mth)</td>
<td>64.1</td>
<td>64.2</td>
</tr>
<tr>
<td>ALT &gt; 3xULN</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Fasting glucose (24 mth)</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>HbA1c (% at 24 mth)</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Incident Diabetes*</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

All values are medians or rates per 100 person-years
*Physician reported, P for heterogeneity by sex = 0.16

### Statins and the Development of Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>0.70 (0.50–0.98)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>Pravastatin</td>
<td>1.34 (1.06–1.68)</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>1.20 (0.98–1.35)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>1.20 (0.91–1.44)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Atorvastatin</td>
<td>1.11 (0.67–1.83)</td>
</tr>
<tr>
<td></td>
<td>vs Pravastatin</td>
<td></td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin</td>
<td>1.25 (1.05–1.54)</td>
</tr>
</tbody>
</table>

Rajpathak SN et al Diabetes Care 2009;32:1924
Conclusions – JUPITER sex-specific analysis

Among apparently healthy women with elevated hsCRP and non-elevated LDL cholesterol, rosuvastatin resulted in similar and significant relative risk reduction in CVD compared with men.

Women had lower absolute event rates, especially <65 years old.

Subgroup analysis suggested women with family history of premature CHD benefit more than those without family history.

Higher physician-reported diabetes in women compared with men, but test for heterogeneity by sex non-significant.

Overall safety in women similar to men.
TOPICS TO BE COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle

Are there lifestyle therapies that are anti-inflammatory interventions?

Are exercise, weight loss, and diet effective because they are anti-inflammatory?
Increased body weight and physical inactivity both raise CRP

C-Reactive Protein > 3 mg/L  \( P = 0.01 \)

Adjusted Odds Ratio

\( P < 0.001 \)

Normal Weight  Overweight  Obese

active  inactive

Mora S et al, JAMA 2006; 295:1412

Risk reduction in CVD by activity level
Women’s Health Study

Age and treatment adjusted relative risk,
11 year follow-up

Mora S et al, Circulation 2007;116:2110

Reference <200 kcal/wk N=6,789
200-599 kcal/wk N=6,732  - 27%
600-1499 kcal/wk N=7,681  - 32%
\geq 1500 kcal/wk N=5,853  - 41%
Exercise Evidence: Role of Physical Inactivity

Physical Inactivity

- Inflammation
- Dyslipidemia
- Age
- Diabetes Mellitus
- Obesity
- Genetics
- Hypertension
- Smoking
- Hypercoagulability

Atherosclerosis

Physical Activity and CVD Risk in Women

% of Risk Reduction Explained by Various Risk Factors

- All Risk Factors 59%
- Inflammatory Markers 32.6%
- Blood Pressure/ Hypertension 27.1%
- Traditional Lipids 19.1%
- Novel Lipids 15.5%
- Body Mass Index 10.1%
- Hemoglobin A1c/ Diabetes 8.9%
- Homocysteine 0.7%

Mora S et al, Circ 2007;116: 2110
**Effect on Obesity and Diabetes**

*Nurse’s Health Study*

<table>
<thead>
<tr>
<th>Reduction: Each hour a day spent walking briskly</th>
<th>Increase: Each two hours a day spent watching TV</th>
<th>Increase: Each two hours a day spent sitting or driving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of obesity</td>
<td>Risk of DM</td>
<td></td>
</tr>
</tbody>
</table>

Exercise reduces the incidence of obesity and DM

DM=Diabetes mellitus

Hu FB et al. JAMA 2003;289:1785-91

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**Simplified Approach to Prevention**

An ABC approach to prevention organizes important lifestyle changes and pharmacologic treatment

<table>
<thead>
<tr>
<th>A</th>
<th>Antiplatelet therapy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ACE inhibitor/Angiotensin receptor blocker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Blood pressure control</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Cholesterol management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cigarette smoking/tobacco cessation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>Diet and weight management</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>E</th>
<th>Diabetes mellitus prevention and management</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>F</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise, cardiac rehabilitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G</th>
<th>Follow-up</th>
</tr>
</thead>
</table>

---
Clinical Case III
Primary Prevention

S.M. is a 66-year-old woman
She seeks evaluation because she is “concerned about her overall health”
She denies symptoms of myocardial ischemia
She continues to smoke “from time to time” and has been told that her blood pressure has “run high in the past”
She denies a history of vascular disease or diabetes mellitus
Pertinent physical exam findings includes a BP of 145/92 mm Hg and a body mass index of 29.6 kg/m²
A fasting lipid profile demonstrates a total cholesterol level of 222 mg/dL, a HDL-cholesterol level of 42 mg/dL, a triglyceride level of 155 mg/dL and a LDL-cholesterol level of 149 mg/dL

Case III
Framingham Risk Score

Step 1: Age Points

<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>
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<td>65-69</td>
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<tr>
<td>70-74</td>
<td>14</td>
</tr>
<tr>
<td>75-79</td>
<td>16</td>
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</table>

Step 2: Total Cholesterol Points

<table>
<thead>
<tr>
<th>TC (mg/dL)</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;150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>150-199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>200-239</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>240-279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>2</td>
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</table>

Step 3: HDL-C Points

<table>
<thead>
<tr>
<th>HDL-C (mg/dL)</th>
<th>Points</th>
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<tbody>
<tr>
<td>&lt;40</td>
<td>-40</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
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<tr>
<td>&gt;49</td>
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</table>

Step 4: SBP Points

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>1</td>
</tr>
<tr>
<td>130-139</td>
<td>2</td>
</tr>
<tr>
<td>140-159</td>
<td>3</td>
</tr>
<tr>
<td>&gt;160</td>
<td>4</td>
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</table>

Step 5: Smoking Status Points

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Points</th>
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<tbody>
<tr>
<td>Nonsmoker</td>
<td>0</td>
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<tr>
<td>Smoker</td>
<td>9</td>
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</table>

Step 6: Sum of Points

<table>
<thead>
<tr>
<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>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
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<tr>
<td>10</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>9</td>
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<tr>
<td>12</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
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<td>13</td>
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<td>7</td>
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<td>11</td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
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</table>

Step 7: 10-year CHD Risk

<table>
<thead>
<tr>
<th>TC (mg/dL)</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;150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>150-199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>200-239</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<tr>
<td>240-279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
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<td>&gt;280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

10-year Risk

<table>
<thead>
<tr>
<th>9</th>
<th>10-year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>15%</td>
</tr>
<tr>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>3%</td>
<td>22%</td>
</tr>
<tr>
<td>4%</td>
<td>27%</td>
</tr>
<tr>
<td>5%</td>
<td>24%</td>
</tr>
<tr>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>7%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Case III
Primary Prevention

A  Antiplatelet therapy
    Anticoagulant therapy
    Angiotensin converting enzyme inhibitor
    Angiotensin receptor blocker

B  Blood pressure control
    β-blocker

C  Cholesterol management
    Cigarette smoking/tobacco cessation
    Cardiac rehabilitation

D  Diet and weight management
    Diabetes mellitus prevention and management

E  Education
    Exercise, physical activity and fitness
    Ejection fraction assessment

F  Follow-up

Aspirin
Primary Prevention

RR of MI in Men

RR = 0.68 (0.54-0.86)
P = 0.001

RR of CVA in Men

RR = 1.13 (0.96-1.33)
P = 0.15

RR of MI in Women

RR = 0.99 (0.83-1.19)
P = 0.95

RR of CVA in Women

RR = 0.81 (0.69-0.96)
P = 0.01

CVA = Cerebrovascular accident, MI = Myocardial infarction, RR = Relative risk
Ridker P et al. NEJM 2005;352:1293-304
Aspirin Recommendations
Primary Prevention

Aspirin (81 mg daily or 100 mg every other day) in at risk women ≥65 years of age

Aspirin in at risk women <65 years of age for ischemic stroke prevention

Aspirin in optimal risk women <65 years of age

CHD = Coronary heart disease

JNC 7 Blood Pressure Treatment Algorithm

Lifestyle modifications

Not at goal BP (SBP >140/90 mm Hg) (SBP >130/80 mm Hg for those with diabetes mellitus or chronic kidney disease)

Initial drug choices

Stage 1 hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg): Thiazide-type diuretic for most. May consider ACEI, ARB, BB, CCB or combo.

Stage 2 hypertension (SBP ≥160 or DBP ≥100 mm Hg): Two-drug combination for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).

Drugs for compelling indications: Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed.

Optimize dosages or add additional drugs until goal BP is achieved. Consider consultation with hypertension specialist.

BP = Blood pressure, DBP = Diastolic blood pressure, JNC = Joint National Committee, SBP = Systolic blood pressure
Chobanian AV et al. JAMA 2003;289:2560-2572
HMG-CoA Reductase Inhibitor: Primary Prevention
Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA)

10,305 patients with HTN randomized to atorvastatin (10 mg) or placebo for a median of 3.3 years*

Cumulative incidence of MI and fatal CHD (%) vs follow-up (yr)

Statins provide significant benefit in moderate- to high-risk individuals by lowering LDL-C levels below current goals

CHD = Coronary heart disease, RR = Relative risk
* Study was stopped prematurely
** Post-treatment LDL-C level

ATP III LDL-C Goals and Cut-points for Drug Therapy

<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>High/Very High</td>
<td>High and very high risk: CHD or CHD risk equivalents (10-year risk &gt;20%) &lt;100 mg/dL (optional goal: &lt;70) &gt;100 mg/dL</td>
<td>&gt;100 mg/dL (&lt;100 mg/dL: consider drug options)</td>
<td></td>
</tr>
<tr>
<td>Moderately High</td>
<td>Moderately high risk: 2+ risk factors* (10-year risk 10% to 20%) &lt;130 mg/dL (optional goal: &lt;100) &gt;130 mg/dL</td>
<td>&gt;130 mg/dL (100-129 mg/dL: consider drug options)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate risk: 2+ risk factors* (10 year risk &lt;10%) &lt;130 mg/dL &gt;130 mg/dL</td>
<td>&gt;160 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>Lower risk: 0-1 risk factor* &lt;160 mg/dL &gt;160 mg/dL</td>
<td>&gt;190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
<td></td>
</tr>
</tbody>
</table>

* Risk factors for CHD include: cigarette smoking, hypertension (blood pressure ≥140/90 mmHg or on antihypertensive medication), HDL-C <40 mg/dl (≥60 mg/dl is a negative risk factor), family history of premature CHD, age ≥45 years in men or ≥55 years in women
ATP = Adult Treatment Panel, CHD = Coronary heart disease, LDL-C = Low-density lipoprotein cholesterol, TLC = Therapeutic lifestyle changes
Cigarette Smoking and Mortality
Most preventable causes of death in U.S. in 1990 & 2000

<table>
<thead>
<tr>
<th>Causes</th>
<th># (% in 1990)</th>
<th># (% in 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>400,000 (19)</td>
<td>435,000 (18)</td>
</tr>
<tr>
<td>Poor diet and physical activity (obesity)</td>
<td>300,000 (14)</td>
<td>400,000 (17)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>100,000 (5)</td>
<td>85,000 (4)</td>
</tr>
<tr>
<td>Microbial agents</td>
<td>90,000 (4)</td>
<td>75,000 (3)</td>
</tr>
<tr>
<td>Toxic agents</td>
<td>60,000 (3)</td>
<td>55,000 (2)</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>25,000 (1)</td>
<td>43,000 (2)</td>
</tr>
<tr>
<td>Firearms</td>
<td>35,000 (2)</td>
<td>29,000 (1)</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td>30,000 (1)</td>
<td>20,000 (&lt;1)</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>20,000 (&lt;1)</td>
<td>17,000 (&lt;1)</td>
</tr>
<tr>
<td>Total</td>
<td>1,060,000 (50)</td>
<td>1,159,000 (48)</td>
</tr>
</tbody>
</table>

Mokdad AH et al. JAMA 2004;291:1238-1245

Cigarette Smoking Cessation Guidelines

**Goals**
- Complete cessation
- No environmental tobacco smoke exposure

**Recommendations**
- Ask about tobacco use at every visit
- In a clear, strong and personalized manner, advise the patient to stop smoking
- Urge avoidance of exposure to second-hand smoke at work and home
- Assess patient’s willingness to quit smoking
- Develop a plan for smoking cessation and arrange follow-up
- Provide counseling, pharmacologic therapy and referral to a formal cessation program
Simplified Approach to Prevention

An ABC approach to prevention organizes important lifestyle changes and pharmacologic treatment

| A | Antiplatelet therapy  
ACE inhibitor/Angiotensin receptor blocker |
<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td>B</td>
<td>Blood pressure control</td>
</tr>
</tbody>
</table>
| C | Cholesterol management  
Cigarette smoking/tobacco cessation |
| D | Diet and weight management  
Diabetes mellitus prevention and management |
| E | Education  
Exercise, cardiac rehabilitation |
| F | Follow-up |

ALOHA

Say Farewell to Heart Disease

A Assess CVD risk and stratify
L Lifestyle changes
O Other interventions (eg, drug therapies)  
based on strength of recommendation
H Highest priority = highest-risk women
A Avoid Class III interventions (hormone therapy, antioxidants, etc) not effective, may be harmful

TOPICS COVERED

- Impact of CVD in women
- Gender differences in presentation
- Traditional risk factors
- Novel risk factors
- Therapies
  - Aspirin
  - Statins
  - Lifestyle

References for Preventive Guidelines and Therapies

2002-2007 ACC/AHA guidelines

- Evidence-Based Guidelines for CV Disease Prevention in Women
- Prevention of Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease
- Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease
- Management of Patients with Chronic Stable Angina
- Management of Patients With ST-Elevation Myocardial Infarction
- Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction
- Update for Coronary Artery Bypass Graft Surgery
- Evaluation and Management of Chronic Heart Failure in the Adult

The full-text guidelines and executive summaries are also available on the ACC and AHA websites at www.americanheart.org

ACC = American College of Cardiology, AHA = American Heart Association, CV = Cardiovascular