Update on Cardiovascular Prevention in Women

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Primary Reference

• Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update

Public Health Burden

Heart Disease Statistics in the United States

• Mortality
  – Cardiovascular disease (CVD) accounts for >1/3 of deaths in the U.S.
  – Annual mortality rate: 870,000+
  – CVD is the largest cause of death among women and men.
  – More women than men die of CVD.

• Morbidity
  – 80 million* people (37.1%) are living with CVD.
    • *38.2 million U.S. women (34%).

## Public Health Burden

### Mortality Statistics, United States, 2004

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of deaths</th>
<th>% of all deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart Disease</td>
<td>652,486</td>
<td>27.2</td>
</tr>
<tr>
<td>2. Cancer</td>
<td>553,888</td>
<td>23.1</td>
</tr>
<tr>
<td>3. Cerebrovascular diseases</td>
<td>150,074</td>
<td>6.3</td>
</tr>
<tr>
<td>4. Chronic lower respiratory diseases</td>
<td>121,987</td>
<td>5.1</td>
</tr>
<tr>
<td>5. Accidents (Unintentional injuries)</td>
<td>112,012</td>
<td>4.7</td>
</tr>
<tr>
<td>6. Diabetes mellitus</td>
<td>73,138</td>
<td>3.1</td>
</tr>
<tr>
<td>7. Alzheimer disease</td>
<td>65,965</td>
<td>2.8</td>
</tr>
<tr>
<td>8. Influenza &amp; pneumonia</td>
<td>59,664</td>
<td>2.5</td>
</tr>
<tr>
<td>9. Nephritis</td>
<td>42,480</td>
<td>1.8</td>
</tr>
<tr>
<td>10. Septicemia</td>
<td>33,373</td>
<td>1.4</td>
</tr>
</tbody>
</table>


## Public Health Burden

### Heart Disease Statistics in Tennessee

- Tennessee ranks 3rd highest in heart disease annual deaths in the U.S.
- Tennessee ranks 3rd highest in stroke annual deaths in the U.S.

Public Health Burden
Trends in U.S. Adult Overweight Prevalence

Economic Burden
Heart Disease Statistics in the United States

- U.S.: $403 billion (2007) on health care or lost productivity as a result of CVD
  - $190 billion for cancer (2006)
  - $29 billion for HIV (2006)
Acute Coronary Syndrome
Markers of inflammation and plaque stability


Coronary Artery Disease
Non-invasive and Invasive Detection

Images courtesy of Philips Medical Systems, Cleveland, OH
Focused Attention on CVD Prevention in Women

**History**

- 1999: AHA Scientific Statement
- 2004: Update
  - Remaining questions:
    - Are commonly used preventive interventions (supported by observational studies) supported by clinical trial data in women?
    - Can results of studies conducted in men (e.g. PHS) be generalized to women?
- 2007: Update

**2007 AHA Update**

- Current clinical recommendations for primary and secondary prevention of chronic atherosclerotic vascular diseases in women >20 years old.
- Based on a systematic search of the highest-quality science by a multi-disciplinary working group.
Focused Attention on CVD Prevention in Women

2007 AHA Update

• Changes from the 2004 Update
  – Risk stratification
    • Greater emphasis on lifetime risk than on short-term absolute risk
  – Medication recommendation changes
    • Menopausal therapy
    • Aspirin therapy
    • Folic acid
  – New algorithm
    • Prioritization of preventive interventions
    • Evaluation of CVD risk in women*

Cardiovascular Prevention

Recommendation Differences: Women vs. Men

• ASA
• Hormone Replacement Therapy
CVD Risk Assessment in Women
The historical strategy: 10-year risk

• Framingham risk score
  – Validated and widely-accepted risk score which predicts **10-year risk** (low, intermediate, or high) of myocardial infarction and coronary heart disease death.
  – Risk factors included in this risk score: age, gender, cholesterol (total cholesterol and HDL), systolic blood pressure, whether or not the patient uses medical treatment for hypertension, and cigarette smoking.

Limitations
• Narrow focus on short-term (10-year) cardiovascular risk
• Highly weighted by age*
• Lack of inclusion of family history of coronary heart disease
• Overestimation or underestimation of risk in non-white populations
• Documentation of subclinical coronary heart disease among many adults whose Framingham score suggested low risk
CVD Risk Assessment in Women
The new paradigm: lifetime risk

- Comprehensive approach to risk stratification that classifies a patient as at high risk, at risk, or at optimal risk.
- Rationale
  - (1) The average lifetime risk for CVD in men and women is very high, approaching 1 in 2, and >1 in 3, respectively, so prevention is important in all adults;
  - (2) Clinical trial data suggesting a wide spectrum of risk in apparently healthy women; and
  - (3) Growing appreciation of the limitations of risk stratification with the Framingham risk calculation.

Classification of CVD Risk in Women

- High risk
- At risk
- Optimal risk

Classification of CVD Risk in Women

**High Risk**

- Established coronary heart disease
- Cerebrovascular disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- End-stage or chronic renal disease
- Diabetes mellitus
- 10-Year Framingham global risk $>20\%$


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Classification of CVD Risk in Women

**At Risk**

- 1 major risk factors for CVD, including:
  - Cigarette smoking
  - Poor diet
  - Physical inactivity
  - Obesity, especially central adiposity
  - Family history of premature CVD ($>55$ in males, $>65$ in females)
  - Hypertension
  - Dyslipidemia
- Evidence of subclinical vascular disease (eg, coronary Ca++)
- Metabolic syndrome
- Poor exercise capacity

Classification of CVD Risk in Women

**Optimal Risk**

- Framingham global risk <10% and a healthy lifestyle, with no risk factors

Guidelines for Prevention of CVD in Women

- Lifestyle Interventions
- Major Risk Factor Interventions
- Preventive Drug Interventions
- Not Useful/Potentially Harmful Interventions
Guidelines for Prevention of CVD in Women

Lifestyle Interventions

- **Cigarette smoking**
  - Women should not smoke and should avoid environmental tobacco smoke (Class I, Level B).

- **Physical activity**
  - ≥30* minutes of moderate-intensity physical activity (eg, brisk walking) on most or all, days of the week (Class I, Level B).
  - *60-90 minutes for women who need to lose weight or sustain weight loss (Class I, Level C).

- **Rehabilitation**
  - A comprehensive risk-reduction regimen is recommended to women with:
    - recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease (Class I, Level A), or
    - current/prior symptoms of heart failure and an LVEF ≤40% (Class I, Level B).

- **Depression**
  - Consider screening women with CHD for depression and refer/treat when indicated (Class IIa, Level B).

- **Weight maintenance/reduction**
  - Maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs (Class I, Level B).
  - Maintain/achieve a BMI between 18.5 and 24.9 kg/m² and a waist circumference < 35 in (Class I, Level B).

- **Dietary intake** (Class I, Level B)
  - Rich in fruits and vegetables
  - Rich in whole-grain, high-fiber foods
  - Consume fish, especially oily fish, at least twice a week
  - Limit intake of saturated fat to < 10% of energy, and if possible to < 7%
  - Limit cholesterol to < 300 mg/d
  - Limit alcohol intake to no more than 1 drink per day†
  - Limit sodium intake to < 2.3 g/d (approximately 1 tsp salt).
  - Consumption of trans-fatty acids should be as low as possible (eg, < 1% of energy).

- **Omega-3 fatty acids**
  - As an adjunct to diet, omega-3 fatty acids in capsule form (approximately 850 to 1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2 to 4 g) may be used for treatment of women with high triglyceride levels (Class IIb, Level B).


Guidelines for Prevention of CVD in Women

Lifestyle Interventions, cont’d

- **Weight maintenance/reduction**
  - Maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs (Class I, Level B).
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Guidelines for Prevention of CVD in Women

Major Risk Factor Interventions

• Blood pressure—optimal level and lifestyle
  – Encourage an optimal blood pressure of ≤120/80 mm Hg through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products (Class I, Level B).

• Blood pressure—pharmacotherapy
  – Pharmacotherapy is indicated when blood pressure is >140/90 mm Hg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes (≥130/80 mm Hg).
    • Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases.
    • Initial treatment of high-risk women‡ should be with beta-blockers and/or ACE inhibitors/ARBs, with addition of other drugs such as thiazides as needed to achieve goal blood pressure (Class I, Level A).

• Diabetes mellitus
  – Lifestyle and pharmacotherapy should be used as indicated in women with diabetes (Class I, Level B) to achieve an HbA1C <7% if this can be accomplished without significant hypoglycemia (Class I, Level C).


Guidelines for Prevention of CVD in Women

Major Risk Factor Interventions, cont’d

• Lipid and lipoprotein levels—optimal levels through lifestyle approaches
  – LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non–HDL-C <130 mg/dL (Class I, Level B).
  – If a woman is at high risk‡ or has hypercholesterolemia, intake of saturated fat should be <7% and cholesterol intake <200 mg/d (Class I, Level B).

• Lipids—pharmacotherapy (+ lifestyle therapy) for LDL-lowering, high-risk women
  – In women with CHD, treat to achieve an LDL-C <100 mg/dL (Class I, Level A).
  – In women with other atherosclerotic CVD, diabetes mellitus, or 10-year CVD absolute risk >20%, treat to achieve an LDL<100 mg/dL (Class I, Level B).
  – In very-high-risk women§ with CHD, a reduction to <70 mg/dL is reasonable and may require an LDL-lowering drug combination (Class IIa Level B).

• Lipids—pharmacotherapy for LDL-lowering, other at-risk women
  – In women with multiple (2+) risk factors and 10-year CVD absolute risk 10% to 20%, treat if LDL-C is ≥130 mg/dL with lifestyle therapy (Class I, Level B).
  – In women with multiple (2+) risk factors, even if 10-year CVD absolute risk is <10%, treat if LDL-C is ≥160 mg/dL with lifestyle therapy (Class I, Level B).
  – Regardless of the presence or absence of other risk factors or CVD, treat if LDL-C is ≥190 mg/dL (Class I, Level B).

Guidelines for Prevention of CVD in Women

Major Risk Factor Interventions, cont’d

• Lipids—pharmacotherapy for low HDL or elevated non–HDL, high-risk women
  – Utilize niacin or fibrate therapy when HDL-C is low or non–HDL-C is elevated in high-risk women after LDL-C goal is reached (Class IIa, Level B).

• Lipids—pharmacotherapy for low HDL or elevated non–HDL, other at-risk women
  – Consider niacin or fibrate therapy when HDL-C is low or non–HDL-C is elevated after LDL-C goal is reached in women with multiple (2+) risk factors and a 10-year CVD absolute risk 10% to 20% (Class IIb, Level B).

Preventive Drug Interventions

• Aspirin, high risk
  – Aspirin therapy (75 to 325 mg/d)¶ should be used in high-risk‡ women unless contraindicated (Class I, Level A).

• Aspirin—other at-risk or healthy women
  – In women >65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa, Level B).
  – In women <65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy (Class IIb, Level B).

• Beta Blockers
  – Beta blockers should be used indefinitely in all women after MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated (Class I, Level A).

• ACE inhibitors/ARBs
  – ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure or an LVEF ≤40% or with diabetes mellitus (Class I, Level A).
  – In candidate women who are intolerant of ACE inhibitors, ARBs should be used instead (Class I, Level B).

• Aldosterone blockade
  – Use aldosterone blockade after MI in women who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker, have an LVEF ≤40% with symptomatic heart failure, and do not have significant renal dysfunction or hyperkalemia (Class I, Level B).

Guidelines for Prevention of CVD in Women

*Not Useful/Potentially Harmful Interventions*

- **Menopausal therapy**
  - Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD (Class III, Level A).

- **Aspirin for MI in women <65 years of age†**

- **Antioxidant supplements**

- **Folic acid**

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**Hormone Replacement Therapy**

*Unanticipated Results from Randomized Clinical Trials*

**Women’s Health Initiative: Results**

- **CEE/MPA arm**
  - Major clinical outcomes
    - CHD
    - Breast CA
    - Stroke
    - PE
    - Colorectal CA
    - Endometrial CA
    - Hip fracture
    - Death due to other causes
  - Composite outcomes
    - Total cardiovascular disease
    - Total cancer
    - Combined fractures
    - Total mortality
    - Global index

- **CEE only arm**
  - Major clinical outcomes
    - CHD
    - Breast cancer
    - Stroke
    - PE
    - Colorectal cancer
    - Endometrial Cancer
    - Hip fracture
    - Death due to other causes
  - Composite outcomes
    - Total cardiovascular disease
    - Total cancer
    - Combined fractures
    - Total mortality
    - Global index

**WHI Conclusion:** Given that no overall benefit was demonstrated in the CEE-only arm and that increased overall risk was demonstrated in the CEE/MPA arm, CEE is no longer recommended for chronic disease prevention in postmenopausal women.

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Guidelines for Prevention of CVD in Women

*Not Useful/Potentially Harmful Interventions*

- **Menopausal therapy**
  - Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD (*Class III, Level A*).

- **Aspirin for MI in women <65 years of age**
  - Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI (*Class III, Level B*).

- **Antioxidant supplements**
  - Antioxidant vitamin supplements (e.g., vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD (*Class III, Level A*).

- **Folic acid**
  - Folic acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD (*Class III, Level A*).


**Guideline Implementation**

- Widespread documentation of lack of adherence to CVD prevention guidelines, even among women at high risk of CVD in managed-care settings in the U.S.

- Suggested algorithm
Evaluation of cardiovascular disease risk

Implement Class I Lifestyle Recommendations in women at ALL risk levels

Is she at high risk of CVD?

Yes

Recent CVD event, procedure, or CHF symptoms?

Implement Class I recommendations

Consider Class II recommendations

No

10-Year Framingham global risk >20%

Implement Class I recommendations

Consider Class II recommendations

Research Needs and Future Directions

- Testing of the impact of the guidelines
- Development of effective methods to implement guidelines in healthcare settings
- Evaluation of the roles of each of the following in risk stratification and responsiveness to preventive interventions
  - Genetics
  - Gender and sex hormones
  - Responses to unique phases in a woman’s lifespan (adolescence, pregnancy, menopause)
  - Novel risk factors and screening technologies

CVD Risk Assessment and Preventive Care in Women

2007 AHA Guidelines

- Endorse an approach to risk stratification that places greater emphasis on lifetime risk than on short-term absolute risk (as defined by the Framingham 10-year risk score);
- Acknowledge that nearly all men/women are at risk for CVD, and thereby underscore the importance of a heart-healthy lifestyle; and
- Emphasize the evaluation and appropriate assignment of CVD risk in men/women and prioritization of preventive interventions accordingly.