CVD Risk Factors
Hypertension and Diabetes

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Cardiovascular Medicine
Heart and Vascular Institute

Cardiovascular Disease: US and Worldwide

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number in millions</td>
<td>Percent</td>
</tr>
<tr>
<td>CVD Prevalence</td>
<td>82.6</td>
<td>36.3</td>
</tr>
<tr>
<td>CVD Mortality</td>
<td>.814</td>
<td>33.6</td>
</tr>
<tr>
<td>CHD Mortality</td>
<td>.406</td>
<td>17</td>
</tr>
<tr>
<td>Stroke Mortality</td>
<td>.136</td>
<td>6</td>
</tr>
</tbody>
</table>

• By 2020: CVD will be the leading cause of death and disability worldwide (25 million deaths)

• By 2020: 70 to 75% of deaths from CHD and stroke will be in developing countries

WHO. 2004
American Heart Association. 2011 Heart and Stroke Statistical Update
Rationale for Primary and Secondary Prevention

- A forty year old male/female has a 49/32% chance of developing CHD during his/her lifetime
- Of 1.2 million with MI, 250,000 die within 1 hr
- 50/64% of men/women have no previous symptoms
- INTERHEART: 90% of risk: 9 modifiable RF’s: smoking, lipids, HTN, DM, lack of activity, nutrition, alcohol and psychosocial factors

Within 1st year post MI and >40 years of age:
- 18% of men and 23% of women will die
- Ischemia in 35% UA/NSTEMI; 23% of STEMI

Within 5 years post MI and 40-69 years of age:
- 33% of men and 43% of women will die
- 2nd MI in 16% of men and 22% of women
- CHF in 7% of men and 12% of women
- Stroke in 4% of men and 6% of women

Most MI’s arise from smaller stenoses

Cardiovascular Risk Factors

- Non-modifiable
  - Age: Male ≥ 45; Female ≥ 55 or premature menopause
  - Family History: <55 in male; <65 in female
- Modifiable
  - Hypertension: >140/90
  - Current Cigarette Use
  - Cholesterol: LDL > 130 (>100 known disease)
  - Low HDL: <40
  - Diabetes Mellitus
  - Sedentary Life Style
  - Obesity

High Prevalence of Risk Factors

- **98,800,000 (~45%)** over 18 with Elevated Cholesterol > 200 mg/dL
- **76,400,000 (~33%)** adults have High Blood Pressure >140/90 or on meds
  - ~60 million have prehypertension 120-139/80-89 mmHg
- **25.4 million Americans (11.4%)** have Diabetes; (projected to double by 2025)
  - 81.5 million have prediabetes
  - 75.3 million with Metabolic syndrome
- **149,300,000 (67%)** American adults (78,000,000 men and 71,300,000 women) are Overweight (BMI >25); **75,000,000 (34%)** are Obese (BMI >30)
  - 32% of children age 2 to 19 are overweight (4.6% increase over last decade)
  - Since 1991 obesity has increased 75%
- **33% of Americans 18 or older report no leisure time Physical Activity**
  - Only 30% of adults report regular physical activity lasting 30 min 5 times a week
- **25,700,000 adult men (23.1%) and 18,300,000 women (18.3%) are Smokers**
  - 20% of high school students smoke cigarettes

Impact of Risk Factors

- The WHO estimates that in North America suboptimal control of hypertension and dyslipidemia explain 58% of the total CVD burden
  - For each 20/10 increase in systolic/diastolic blood pressure above 115/75 mmHg there is a doubling of CV risk
  - Linear relationship between total and LDL-C and CVD risk
- Diabetes associated with 2 to 4 fold increase risk
- 300,000 US adults die each year of causes related to obesity
  - Associated with a loss of 3 and 7 years of life expectancy for non-smokers and smokers
- 1 in 5 deaths from cardiovascular diseases are attributable to smoking
  - 35,000 nonsmokers die/year from CVD due to environmental smoke
  - 25 to 30% increase in CHD risk
  - 2 to 3 fold risk of dying from CHD
  - Smokers die 13 to 14 years earlier than non-smokers
- 250,000 deaths/year (12%) are attributed to lack of regular exercise
  - 1.5 to 2.4 fold increased risk of CHD
**Risk Factors and Vascular Disease in the United States**

A Growing Public Health Problem

- 98.8 million adults with elevated cholesterol (44.4%)
- 41.8 million with low HDL (18.9%)
- 76.4 million with hypertension (33.5%)
- 75.0 million adults with Obesity (BMI ≥ 30: 33.7%);
- 149.3 million Overweight (BMI>25: 67.3%)
- 25.4 million adults with Diabetes (11.4%)
- 81.5 million with prediabetes (36.8%)
- 75.3 million with metabolic syndrome (34%)
- 46.6 million smokers (20.6%)
- 152 million below activity guidelines (36% no physical activity)

<table>
<thead>
<tr>
<th>CVD: One death every 39 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD: One event every 25 seconds</td>
</tr>
<tr>
<td>One death every 60 seconds</td>
</tr>
</tbody>
</table>


**Risk Factors in Tools for Risk Assessment**

- **Framingham Risk Score**
  - High risk: Clinical coronary or other CV disease, Diabetes
  - 2 or more risk factors: Age, gender, systolic BP, Total/LDL-C, HDL-
    Cigarette smoking
  - Low risk: ≤1 Risk Factor

- **Procam Score**
  - Incorporates diabetes, triglycerides and family history

- **Reynolds Score**
  - Incorporates family history and us CRP
Markers for Future CV Events*

<table>
<thead>
<tr>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein(a)</td>
</tr>
<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>IL-6</td>
</tr>
<tr>
<td>TC</td>
</tr>
<tr>
<td>LDLC</td>
</tr>
<tr>
<td>sICAM-1</td>
</tr>
<tr>
<td>SAA</td>
</tr>
<tr>
<td>Apo B</td>
</tr>
<tr>
<td>TC: HDLC</td>
</tr>
<tr>
<td>hs-CRP</td>
</tr>
<tr>
<td>hs-CRP + TC: HDLC</td>
</tr>
</tbody>
</table>

Relative Risk of Future Cardiovascular Events (95% CI)

*In healthy postmenopausal women. N=28,263.


Measures of Pre-Clinical CV Disease

- **Ankle-Brachial Index (ABI)**
  - ≤0.90 indicates peripheral artery disease and adds to predictive value for MI
  - Useful to refine the assessment of intermediate-risk patients ≥50 years

Hazard Ratios for CHD Events Associated With Coronary Calcium Scores:
US Adults Ages 45-84 Years (Reference Group CAC=0): The MESA Study


Source: Detrano et al., NEJM. 2008;358(13):1336-1345.
Defining the High Risk Patient

• Known CHD: Prior infarction, documented CAD angiographically, positive stress test, typical angina
• Other clinically significant vascular disease such as carotid artery disease, prior stroke, aortic aneurysm, PVD
• Diabetes
• > 20% ten year risk of myocardial infarction (MI) or CHD related mortality: e.g. Framingham risk score (FRS)

• Intermediate risk by clinical criteria (10 to 20% ten year risk) with other risk factors such as strong family history of premature CHD, metabolic syndrome, elevation of other markers of risk or inflammation: e.g. hs-CRP, LP(a), carotid IMT (intimal medial thickness), coronary calcification score, ABI (ankle-brachial index)

• Chronic inflammatory diseases: SLE, Rheumatoid arthritis

JNC 7 Classification of Blood Pressure

- STAGE 2: SBP ≥160 mm Hg or DBP ≥100 mg Hg
  Treatment recommended
- STAGE 1: SBP 140-159 mm Hg or DBP 90-99 mg Hg
- PRE: SBP 120-139 mm Hg or DBP 80-89 mg Hg
- NORMAL: SBP <120 mm Hg and DBP <80 mg Hg

Consider treatment in those with diabetes or renal disease who fail lifestyle modification

**CV Mortality Risk Doubles With Each 20/10 mm Hg BP**

![Diagram showing the relationship between SBP/DBP (mm Hg) and CV Mortality Risk.]

*Individuals aged 40-69 years, starting at BP 115/75 mm Hg
SBP = systolic blood pressure; DBP = diastolic blood pressure


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**Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease: Framingham Study**

![Graph showing cumulative incidence (% over time for men and women with different blood pressure categories.]

Do Patients With Prehypertension Have Additional Risk Factors?

At least 1 above optimal risk factor:
Cholesterol ≥200 mg/dl; BMI ≥25 kg/m²; Diabetes; Smoker

By Age Group
- 20-39: 83.3%
- 40-59: 92.6%
- ≥60: 93.7%

By Race
- White: 88.8%
- AA: 85.4%
- MA: 93.1%

AA indicates African American; MA, Mexican American; BMI, Body Mass Index.


Benefit of Lowering BP

Summary of relative risk estimates (95% confidence intervals) for CHD events and stroke with standardized BP reduction of 10 mm Hg systolic and 5 mm Hg diastolic

Adapted from BMJ 2009:338:1665
### JNC VII Lifestyle Modifications for BP Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI=18.5-24.9)</td>
<td>5-20 mmHg/10 kg weight lost</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Diet rich in fruits, vegetables, low fat dairy and reduced in fat</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Restrict sodium intake</td>
<td>&lt;2.4 grams of sodium per day</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes on most days of the week</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>≤2 drinks/day for men and ≤1 drink/day for women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

BMI=Body mass index, SBP=Systolic blood pressure

Chobanian AV et al. JAMA. 2003;289:2560-2572

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### JNC 7 Algorithm for Treatment of Hypertension

1. **Lifestyle Modifications**
   - Not at Goal Blood Pressure (<140/90 mm Hg)
   - (<130/80 mm Hg for those with diabetes or chronic kidney disease)

2. **Initial Drug Choices**

   - **Without Compelling Indications**
     - Stage 1 Hypertension (SBP 140-159 or DBP 90-99 mm Hg)
       - Thiazide-type diuretics for most
       - May consider ACEI, ARB, BB, CCB, or combination
   - **Stage 2 Hypertension** (SBP ≥160 or DBP ≥100 mm Hg)
     - 2-drug combination for most (usually thiazide-type diuretic and ACEI, ARB, BB, or CCB)

   - **With Compelling Indications**
     - Drug(s) for the compelling indications
     - Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed

3. **Not at Goal Blood Pressure**
   - Optimize dosages or add additional drugs until goal blood pressure is achieved
   - Consider consultation with hypertension specialist

### JNC VII Compelling Indications for Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Initial Therapy Options</th>
<th>Clinical-Trial Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>Diuretic, BB, ACEI, ARB, Aldo Ant</td>
<td>MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, Val-HeFT, RALES</td>
</tr>
<tr>
<td>Post-MI</td>
<td>BB, ACEI, Aldo Ant</td>
<td>ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS</td>
</tr>
<tr>
<td>High CAD Risk</td>
<td>Diuretic, BB, ACEI, CCB</td>
<td>ALLHAT, HOPE, ANBP2, LIFE, CONVINCCE</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Diuretic, BB, ACEI, ARB, CCB</td>
<td>NKF-ADA Guideline, UKPDS, ALLHAT</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>ACEI, ARB</td>
<td>NKF Guideline, Captopril Trial, RENAAAL, IDNT, REIN, AASK</td>
</tr>
<tr>
<td>Recurrent Stroke Prevention</td>
<td>Diuretic, ACEI</td>
<td>PROGRESS</td>
</tr>
</tbody>
</table>

ACEI=Angiotensin converting enzyme inhibitor, Aldo Ant=Aldosterone antagonist, ARB=Angiotensin receptor blocker, BB=b-blocker, CAD=Coronary artery disease, CCB=Calcium channel blocker, MI=Myocardial Infarction

Chobanian AV et al. JAMA. 2003;289:2560-2572

### AHA: Treatment of Hypertension

<table>
<thead>
<tr>
<th>Area of Concern</th>
<th>BP Target Mm HG</th>
<th>Lifestyle Modification</th>
<th>Specific Drug Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>General CAD prevention</td>
<td>&lt;140/90</td>
<td>Yes</td>
<td>Any effective antihypertensive drug or combination ‡</td>
<td>If SBP ≥160 or DBP ≥100 mm Hg, start with 2 drugs</td>
</tr>
<tr>
<td>High CAD risk*</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>ACEI or ARB or CCB or thiazide diuretic or combination</td>
<td>If SBP ≥160 or DBP ≥100 mm Hg, start with 2 drugs</td>
</tr>
<tr>
<td>Stable angina</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>β -Blocker and ACEI or ARB</td>
<td>If β-blocker contraindicated: diatiazam or verapamil (if not bradycardic and no LVD) can add dihydropyridine CCB to β-blocker or thiazide for added BP control</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>β-blocker (if hemodynamically stable) and ACEI or ARB §</td>
<td>If β-blocker contraindicated: diatiazam or verapamil (if not bradycardic and no LVD) can add dihydropyridine CCB to β-blocker or thiazide for added BP control</td>
</tr>
<tr>
<td>STEMI</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>β-blocker (if hemodynamically stable) and ACEI or ARB §</td>
<td>If β-blocker contraindicated: diatiazam or verapamil (if not bradycardic and no LVD) can add dihydropyridine CCB to β-blocker or thiazide for added BP control</td>
</tr>
<tr>
<td>LVD</td>
<td>&lt;120/80</td>
<td>Yes</td>
<td>ACEI or ARB and β-blocker and aldosterone antagonist † and thiazide or loop diuretic and hydralazine/nitrates (blacks)</td>
<td>Contraindicated: verapamil, diatiazam, clonidine, moxonidine, α-blockers</td>
</tr>
</tbody>
</table>

* Diabetes mellitus, chronic kidney disease, CAD or CAD equivalent or 10-year FRS ≥10%
‡ Evidence supports ACEI (ARB), CCB, or thiazide diuretic as first-line therapy
§ If anterior MI, HTN persists, LVD or HF or diabetes
† If severe HF (NYHA III or IV, clinical HF, LVEF <40%)


19 DOS CME Course 2011

20 DOS CME Course 2011
Mortality in People with Diabetes

Causes of Death

- 65 to 75% of Mortality in diabetics is due to CVD


Type 2 Diabetes and Coronary Heart Disease

Seven-Year Incidence of Fatal/Nonfatal MI

- No diabetes: 3.5% (n=1304)
- Diabetes: 18.8% (n=69)

- No MI: 20.2% (n=890)
- MI: 45% (n=169)

DECODE: IGT Increases Mortality Risk
Collaborative Analysis of Diagnostic Criteria in Europe
N = 25,364 aged >30 years

- Diagnosed diabetes (n = 1275)
- Undiagnosed diabetes (n = 3071)
- Impaired glucose tolerance (n = 2766)*
- Normal glucose tolerance (n = 18,252)*

Follow-up (years)

Cumulative Mortality Hazard (%)

*2-hour oral glucose tolerance test (OGTT)
IGT = impaired glucose tolerance


Cardiovascular Disease in Diabetes

- Accelerated atherosclerosis is multifactorial and begins years/decades prior to diagnosis of type 2 diabetes
  - >50% of patients with newly diagnosed type 2 DM have CHD
  - Hyperglycemia, dyslipidemia, hypertension, inflammation
- Risk for CV events is 2- to 4-fold greater in DM than in non-DM
- A diabetic’s risk of CV mortality or having an MI is equivalent to a non-diabetic having had a prior MI
- Atherosclerosis accounts for ~ 65 to 75% of all diabetic mortality
  - 75% from coronary atherosclerosis
- Diabetics with MI, PCI, CABG do worse
- One of the most important risk factors for CVA in women
- Metabolic syndrome Greater than 3 fold CHD risk
  - 24 times greater risk of developing new diabetes

Goals in Management of CVD in Diabetics

• Prevent future adverse cardiovascular events
  — Correctly risk stratify patient
  — Identify and treat risk factors

• Identify extent of ischemia
  — Influence revascularization for morbidity and mortality benefits

• Improve symptomatic state
  — Enhance quality of life

• Identify subclinical disease
  — Intensify risk factor management
  — Earlier assessment for ischemia

Influence of Multiple Risk Factors on Mortality in Men With and Without Diabetes

Risk factors: cholesterol >200 mg/dL, smoking, and SBP >120 mm Hg.
SBP = systolic blood pressure.

**Abdominal obesity and increased risk of card CVD**

At presentation 90% of diabetics are overweight (30%) or obese (60%).

**The HOPE study**

<table>
<thead>
<tr>
<th>Waist circumference (cm):</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 95</td>
<td>1.29</td>
<td>1.35</td>
</tr>
<tr>
<td>95 - 103</td>
<td>1.17</td>
<td>1.16</td>
</tr>
<tr>
<td>&gt; 103</td>
<td>1.27</td>
<td>1.14</td>
</tr>
</tbody>
</table>

Adjusted for BMI, age, smoking, sex, CVD disease, DM, HDL-cholesterol, total-C; CVD: cardiovascular disease; MI: myocardial infarction; BMI: body mass index; DM: diabetes mellitus; HDL: high-density lipoprotein cholesterol


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**CVD Mortality Risk by Fitness Level in Individuals With Diabetes: ACLS**

<table>
<thead>
<tr>
<th>Maximal METs</th>
<th>Risk for CVD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7</td>
<td>Reference</td>
</tr>
<tr>
<td>7.0 - 7.9</td>
<td></td>
</tr>
<tr>
<td>8.0 - 8.9</td>
<td></td>
</tr>
<tr>
<td>9.0 - 9.9</td>
<td></td>
</tr>
<tr>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>10.0 - 10.9</td>
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<tr>
<td>10.9</td>
<td></td>
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<tr>
<td>11.0 - 11.9</td>
<td></td>
</tr>
<tr>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>12.0 - 12.9</td>
<td></td>
</tr>
<tr>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>≥ 13.0</td>
<td></td>
</tr>
</tbody>
</table>

Metabolic Response to 10-lb Weight Loss: 
Framingham Data

Small changes can add up to significant changes in long-term risk

Cholesterol Syst BP Glucose

Men Women

mg/dl mm Hg mg/dl


Diabetes Prevention Program (DPP)

• 3,234 individuals at risk for diabetes
• Randomized to placebo, metformin or lifestyle modification
• Mean follow-up 2.8 years

Benefits of Short-Term Weight Reduction on IS in Type 2 DM and in Prediabetes

**Graph:**

- **Percentage (%) Change**
  - Body Weight: -7.1 *
  - % Body Weight: -7.4 *
  - Waist / Hip: -3.3 *
  - Insulin Sensitivity: 56.8 *

- **Weight**, **BMI**, **W/H**, **Si**

*P<0.001


Fitness–Fatness and CVD Mortality in Men with Diabetes: ACLS

**BMI:**

- 18.5–24.9
- 25.0–29.9
- 30.0–34.9

**Risk for CVD Mortality**

- Low
- Moderate
- High

Does Walking Reduce Mortality in Individuals with Type 2 Diabetes?

- N=2896 adults 18 and older with T2DM as part of the NHANES survey
- Compared individuals who walk at least 2 hrs/wk with inactive individuals
  - 39% reduction in all-cause mortality
  - 34% reduction in CVD mortality
- Mortality rates were lowest for
  - Individuals who walked 4 hours/week
    - 54% reduction in all-cause mortality
    - 43% reduction in CVD mortality
  - Individuals who reported that their walking involved moderate increases in heart rate and breathing rates
    - 43% reduction in all-cause mortality
    - 31% reduction in CVD mortality


Lifestyle Management in Diabetes

- Recommended activity
  - Perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate).
  - In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance training three times per week.
- Keep it simple and individualized
  - Increase in leisure activity is as effective as a structured exercise program
  - Home programs associated with better adherence
  - Shorter more frequent bouts of exercise
- Small amounts of weight reduction (5 to 10%) are beneficial: encourage realistic goals
- Exercise is an aid to weight loss and maintenance of weight
- Physical activity is of benefit regardless of weight and associated with CVD risk reduction regardless of BMI
  - The fitness vs. fatness debate is immaterial
    - Exercise is the treatment for both sedentary and overweight
Systolic and Diastolic Hypertension: Effect on Cardiovascular Events

Systolic Hypertension in Europe Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>CVD Events/1000 Pt-Years</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>57.6</td>
<td>62%</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=492</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>31.4</td>
<td>25%</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=4,203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>23.5</td>
<td></td>
</tr>
</tbody>
</table>

Diastolic Hypertension in HOTS

<table>
<thead>
<tr>
<th>Group</th>
<th>Events/1000 Pt-Years</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>24.4</td>
<td>48%</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=1,501</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Nondiabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=18,790</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.3</td>
<td></td>
</tr>
</tbody>
</table>


CV Risk and Albuminuria Reduction with Ramipril in Patients With Diabetes

The MICRO-HOPE Diabetic Substudy: N = 3,577 Diabetic Patients

Relative Risk Reduction (%)

- Composite End Point: 26% (p = 0.0004)
- Nonfatal MI: 22% (p = 0.01)
- Stroke: 33% (p = 0.0074)
- CV Death: 37% (p = 0.0001)
- All-Cause Mortality*: 24% (p = 0.004)

Mean Albumin/Creatinine Ratio (urine)

- Placebo
- Ramipril

*Secondary end point.

Pharmacologic Therapy: Hypertension

• Screening and diagnosis
  – Measure blood pressure at every visit. Confirm on a separate day.
  – Repeat systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg confirms a diagnosis of hypertension.

• Goals
  – Patients with diabetes should be treated to a SBP <130 DBP <80 mmHg.

• Treatment
  – Patients with a SBP 130–139 mmHg or a DBP 80–89 mmHg may be given lifestyle therapy alone for a maximum of 3 months.
  – Regimen should include either an ACE inhibitor or an angiotensin II receptor blocker (ARB).
    – If one class is not tolerated, the other should be substituted.
  – If needed to achieve targets, a thiazide diuretic should be added to those with an estimated glomerular filtration rate (GFR) ≥30 ml/min/1.73 m² and a loop diuretic for those with an estimated GFR <30 ml/min/1.73 m².
  – Two or more agents at maximal doses are generally required to achieve blood pressure targets.


Antiplatelet Agents Reduce CVD Events in Patients with Diabetes: Antiplatelet Trialists’ Collaboration

ADA Goals for Coagulopathy Associated with Diabetes

• ASA 75–162 mg/day as secondary prevention in diabetes with CVD
• Aspirin 75–162 mg/day as primary prevention in type 1 or 2 at increased CV risk (10-year risk >10%)
  – Men >50, women >60 with at least one major risk (fam hx, HBP, smoking, dyslipidemia, or albuminuria)
  – Not sufficient evidence to recommend aspirin for primary prevention in lower risk individuals
• Clopidogrel as an alternative in ASA allergy
• Smoking cessation

Glycemic Control and CVD in Diabetes

• The ACCORD trial was stopped prematurely due to an excess overall mortality among diabetic patients randomized to the intensive glycemic control (HgA1c of 6.4% vs. between 7.0% and 7.9%).
  – ADVANCE and VADT showed no benefit of tight control on CVD endpoints
  – Meta-analysis: 10 to 17% ↓CVD, no difference in mortality
• In a prespecified secondary endpoint in the PROactive trial, which examined time to fatal or nonfatal myocardial infarction (MI), patients who were treated with pioglitazone had a 28% reduction in MIs when compared to those who were treated with placebo.
• In patients with type 2 DM with excellent glycemic control (HgA1c <6.5% off glucose-lowering drugs), a study of postprandial hyperglycemia showed that nateglinide prevented progression of carotid intima-media thickness (C-IMT) when compared to a control therapy.

STENO-2: Reduction in Cardiovascular Disease Through a Multifactorial Intervention in Patients With Type 2 Diabetes

![Graph showing primary composite endpoint (%) over months of follow-up for conventional and intensive therapy.]

Intensive Treatment Goals: hemoglobin A1c, <6.5%; cholesterol, <175 mg/dL; triglycerides, <150 mg/dL; systolic blood pressure, <130 mm Hg; diastolic blood pressure, <80 mm Hg.


AHA/ACC: CHD and CHD Risk Equivalents: Lifestyle Modification/RF Goals; Class I indications

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Complete cessation</td>
</tr>
<tr>
<td>Physical activity</td>
<td>&gt;30 min activity, &gt;5-7 times weekly</td>
</tr>
<tr>
<td>Weight management</td>
<td>BMI: 18.5-24.9 kg/m²; Waist: &lt;40 in men</td>
</tr>
<tr>
<td></td>
<td>≤35 in women</td>
</tr>
<tr>
<td>Dietary</td>
<td>Moderate alcohol, sodium</td>
</tr>
<tr>
<td></td>
<td>Emphasis on fruit, vegetables, low-fat dairy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>&lt;130/80 mm Hg: Diabetes or chronic kidney disease (Consider if CHD, LVD)</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90: All others</td>
</tr>
<tr>
<td>Lipids</td>
<td>LDL-C: &lt;100/70 mg/dL Non-HDL-C &lt;130/100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>HDL-C: ≥40 mg/dL; TG: &lt;200 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>HbA1c &lt;7%</td>
</tr>
</tbody>
</table>

Smith SC. *J Am Coll Cardiol.* 2006;47:2130-9
AHA/ACC: CHD and CHD Risk Equivalents:
Drug treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Goal (Class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiplatelets agents</td>
<td>Aspirin 75 to 162 mg (I), Clopidogrel if intolerant Clopidogrel with Aspirin for up to 12 months post ACS (I)</td>
</tr>
<tr>
<td>• ACE Inhibitors</td>
<td>All post-STEMI or ACS patients with LV dysfunction (EF,40%), HBP, diabetes, chronic kidney disease (I) Consider for all other patients with coronary or peripheral vascular disease (Iia)</td>
</tr>
<tr>
<td>• Beta-blockers</td>
<td>All post-MI, ACS patients or LV dysfunction (I) Use as needed for management of BP, angina, rhythm</td>
</tr>
<tr>
<td>• Statins</td>
<td>For LDL-C &gt;100 mg/dL (I); consider for LDL-C of 70 to 100 mg/dL (Iia)</td>
</tr>
</tbody>
</table>

Gibbons RJ. J Am Coll Cardiol. 2003;41:159-168
Smith SC. J Am Coll Cardiol 2006;47:2130-9

AHA/ACC/ADA/AACE: Multiple Risk Reduction in Diabetes

<table>
<thead>
<tr>
<th>Target</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7% (&lt;6.5) Tighter control if possible without inducing hypoglycemia</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>70-130 mg/dL (&lt;110)</td>
</tr>
<tr>
<td>Postprandial</td>
<td>&lt;180 mg/dL (&lt;140)</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>&lt;130/80 ACEI or ARB in BP-lowering regimen</td>
</tr>
<tr>
<td>Lipids (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;100 (&lt;70 optional) Statin for CV history or age ≥40 yr with &gt; 1 risk factor (regardless of baseline LDL) to lower LDL 30%—40% or LDL &gt;100 with risk factors</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;40 men, &gt;50 women</td>
</tr>
<tr>
<td>TG</td>
<td>&lt;150</td>
</tr>
</tbody>
</table>

• ASA: All with CV disease history, Male ≥50, female ≥60 yr with ≥1 risk factors
• ACE inhibitor (ARB): Known CVD, age ≥40 yr with another CV risk factor

Endocr Pract. 2007;13(Suppl 1) 2007
**NHANES: Prevalence and Control**

**Hypertension**
- Prevalence: Average BP $\geq$140/90 or on medications
- Treatment: Average BP <140/90

**LDL Cholesterol**
- Prevalence: LDL-C: High $\geq$100, Intermediate $\geq$130, Low $\geq$160
- Treatment: High <100, Intermediate <130, Low <160

---

**NHANES 1999-2006**

Proportion of Diabetics Achieving RF Goals

- A1C <7%
- BP <130/80 mmHg
- LDL-C <100 mg/DL
- Non-HDL-C <130 mg/dL
- HDL-C >40/50 mg/dL

* Age adjusted

---

Low Risk Population

- Systolic BP <120 mm Hg
- Cholesterol <180 mg/dL
- BMI <25
- Non-smoker
- No history of diabetes or other cardiovascular disease

- They have a 70 to 85% reduced CVD risk
- Individuals with optimal risk factor burden have life expectancy ≥10 years more than individual with >2 RF’s
- Only 3 to 10% of adult Americans fit this definition

Definitions for AHA 2020 Goals

<table>
<thead>
<tr>
<th>Metric</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Never or quit &gt;12 months</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;25 kg/m² or &lt;85th percentile in children</td>
</tr>
<tr>
<td>Activity</td>
<td>150+ min/wk moderate; 75+ vigorous 60+ min daily in children</td>
</tr>
<tr>
<td>Diet</td>
<td>4-5 components</td>
</tr>
<tr>
<td>TC</td>
<td>&lt;200 mg/dl in adults &lt;170 in children</td>
</tr>
<tr>
<td>BP</td>
<td>&lt;120/&lt;80 mm Hg in adults; &lt;90th percentile in children</td>
</tr>
<tr>
<td>FPG</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

Prevalence of poor, intermediate and ideal CV Health for 7 metrics: NHANES 2005-6

Only 17% of US adults have 5 or more metrics with ideal levels (11% men, 24% women)
Women and Cardiovascular Disease

Michael B. Rocco, M.D.
Medical Director, Stress Testing and Cardiac Rehab
Sections of Preventive Cardiology and Clinical Cardiology
Cardiovascular Medicine
Heart and Vascular Medicine
Clinical Manifestation

Similarities
Differences


A Total CVD                      D Chronic Lower Respiratory Diseases
B Cancer                         E Diabetes Mellitus
C Accidents                      F Alzheimer’s Disease

Source: CDC/NCHS
Prevalence of CVD in adults age 20 and older by age and sex (NHANES: 2005-2006). Source: NCHS and NHLBI. These data include coronary heart disease, heart failure, stroke and hypertension.

Women vs Men After MI

- Within the 1st year post MI:
  - 25% men and 38% women die
- Within 6 years post MI:
  - 2nd MI in 18% males; 35% females
  - CHF in 22% males; 46% females
  - Stroke in 9% males; 18% females
- Women <65 have twice the mortality as men
- CABG doubles the risk compared with men
  - <50: triple the risk
- Increased bleeding complications with interventions (PCI, LYSIS, CABG)
Cardiovascular Disease Mortality Trends for Males and Females
United States: 1979-2002

Source: NCHS and NHLBI.

Awareness of CVD Among Women
Telephone survey of 1024 women over 25 years old in 7-03

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>2000</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness of CHD as leading killer</td>
<td>30%</td>
<td>34%</td>
<td>46%</td>
</tr>
<tr>
<td>CHD perceived as their major threat</td>
<td>7%</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>Breast cancer perceived as their major threat</td>
<td>34%</td>
<td>36%</td>
<td>35%</td>
</tr>
</tbody>
</table>

- Disconnect between awareness of risk and perceived threat to them as individuals
- Only a third identified standard risk factors as causes of heart disease; 19% identified hypertension, 7% diabetes, 1% high triglycerides
- Increase perception that antioxidant, vitamins and aromatherapy could reduce risk of heart disease
- Women obtain most of their knowledge about heart disease form the mass media
Myocardial Infarction (MI) Without Chest Pain or Discomfort and Unrecognized MI by Age and Sex

### Gender Differences in Atherosclerosis

- Plaque erosion as the etiology of coronary thrombosis and AMI occurs at a higher frequency in women than in men.

- In an autopsy study of 291 patients who died of AMI and had coronary thrombosis, the prevalence of plaque erosions was 37% in women and 18% in men.

---


Gender Differences in Atherosclerosis

### Myocardial Infarction (MI) Without Chest Pain or Discomfort and Unrecognized MI by Age and Sex*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women, %</th>
<th>Men, %</th>
<th>Age Group, Odds Ratio (Women vs Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI without chest pain or discomfort</td>
<td>(n=155,515)</td>
<td>(n=229,313)</td>
<td>30-39 y</td>
</tr>
<tr>
<td>All Patients</td>
<td>37</td>
<td>28</td>
<td>1.52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unrecognized MI</th>
<th>(n=2013)</th>
<th>(n=2252)</th>
<th>45-54 y</th>
<th>55-64 y</th>
<th>65-74 y</th>
<th>75-84 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Heart Study</td>
<td></td>
<td></td>
<td>(M, 18% W, 46%)</td>
<td>(M, 26% W, 45%)</td>
<td>(M, 36% W, 29%)</td>
<td>(M, 36% W, 40%)</td>
</tr>
<tr>
<td>All Patients</td>
<td>34</td>
<td>67</td>
<td>0.56</td>
<td>1.75</td>
<td>0.01</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Abbreviations: M, men; W, women.

*An odds ratio greater than 1.0 means that women have greater odds to present with MI without chest pain or discomfort or unrecognized MI compared with men. Men = reference group.

Gender Differences with MI

- Older
- Higher risk baseline characteristics and comorbidities
- Diagnostic uncertainties/delays in symptom recognition and treatment
  - Women less likely to receive intensive Rx or catheterization
  - Concern with increased bleeding with thrombolytics, PCI or CABG
  - Lack of clinical trials
    - “do-no-harm” adage
- Less likely to be treated with guideline prescribed therapies
- Lack of awareness and delayed presentation
  - 29% of women vs. 37% of men presented <2 hours from symptom onset- NRMI database
  - 31% of women vs. 27% of men presented to ER > 6 hours after onset of symptom – Medicare database

Vaccarino V et al., NEJM 1999;341:217-25
Gan SC et al., NEJM 2000;343:8-15

Gender Differences in ACS Outcome and Rx

- **Crusade:** Women (41% of 35,875 patients)
  - Older (73 vs 65)
  - More likely to have diabetes and hypertension
  - Less likely to receive acute heparin, ACEI, GpIIb/IIa
  - Less utilization of cath and revascularization
  - Higher unadjusted in-hospital event rate
    - Death: 5.6% vs 4.3%; Reinfarction: 4.0% vs 3.5%
    - CHF: 12.1% vs 8.8%; Stroke: 1.1% vs 0.8%
    - Transfusion: 17.2% vs 13.2%
  - After adjustment for risk factors only transfusion remained higher
  - Less likely to receive discharge ASA, ACEI and statins

- **Guidelines Applied in Practice (GAP)**
  - 2857 MI survivors (1373 women) in 33 hospitals in Michigan
  - Standard orders and a discharge tool to increase use of guidelines
  - Men more likely to receive pre-discharge prescriptions of recommended drugs. Men had increased utilization of ASA, beta-blockers, ACEI and statins while women had improvement only of ASA and beta-blocker use

Blankens et al. JACC 2005:45;1832
Abstract at ACC: Jami SM et al. JACC 2005:45
Treatment: Acute Coronary Syndrome

- **ACS:** Meta analysis of 8 trials (3075 women / 7075 men; 12 mo. f/u)
  - Death/Mi/re-ACS Invasive vs. Conservative
    - Women 0.81 (95% CI 0.65-1.01) 21% vs. 25%
    - Men 0.73 (95% CI 0.55-0.98) 21.2% vs. 26.2%

- **CABG:**
  - Similar procedural mortality and MI rate between men and women
  - Less IMA use, more likely to have angina after CABG
  - Longer ICU and hospital stay, increased bleeding

- **Thrombolytics:**
  - Equivalent benefit as men (12-14% ↓ death)
  - Risk of hemorrhagic stroke is equivalent after adjusting for age and BMI (GUSTO I, ISIS III)
  - Less likely to undergo cath and revasc

---

Complications

- **Women more likely to have bleeding complications with fibrinolytic therapy** Hochman et al., NEJM 1999;341:226-32
- **Women have more bleeding complications after PCI** Chiu et al., Am Heart J 2004;148:998-1002
- **Women have more bleeding complications with GP IIb/IIIa inhibitors** Cho et al., JACC 2000;36:81-6
- **Higher complications rates with CABG due to bleeding**
  - Average PRBC transfusion 2.2u in Men vs. 3.6 in women Scott et al., Anesthesia & Analgesia 2003;97:958-63
  - 52.6% of men need transfusion vs. 79.6% women Scott et al., Anesthesia & Analgesia 2003;97:958-63
  - Women have longer length of stay, intubation time, ICU stay then men Butterworth et al., Anesthesiology 2000;92:414-24
Gender Differences in CVD

• Similar mortality but delayed
• Reasons for differences in outcomes multifactorial
  – Biological factors
  – Education and awareness gap
  – Lack of women in clinical trials
  – Lack of utilization of proven treatments
  – Older and increased comorbidities
• Controlling for differences in comorbidities, women can see the same advantages of interventions as men
  – Except for bleeding/vascular complications

• Prevalence and strength of risk factors
  – Increased prevalence of HTN, DM, depression, decreased tobacco use
  – Increased relative risk from HTN, DM, tobacco, TG

Risk Factors
Prevalence of CV Risk Factors in Adult Men and Women

Importance of Risk Factors in Women

• Smoking
  – More potent risk factor in women than in men
  – Women who smoke DOUBLE their risk of developing CAD
  – The Nurse’s Health Study cohort showed a strong causal relation between smoking and stroke in women

• Hypertension
  – Greater in women with aging
  – Causes stroke in women more frequently than in men
  – Stronger risk factor for the development of heart failure

• High Cholesterol
  – LDL as predictive in women as in men
  – Added impact of low HDL and elevated TG’s
  – Effect of loss of estrogen with menopause:
    – ↑ Total Cholesterol, LDL-C Triglycerides, ↓ HDL
Most Risk Factors for Nonfatal MI are the Same in Men and Women - NOT DIABETES

Risk Factor

Diabetes
High TC (≥6.5 mmol/L)
High TC (≥6.3 mmol/L)
HTN (≥170/95 mmHg)
Overweight (BMI ≥30 kg/m²)
WHR (≥0.85)
Physical inactivity
Smoking
Job strain

The SHEEP Study

Odds Ratio

SHEEP = Stockholm Heart Epidemiology Program

Men Women


Diabetes as a CVD Risk Factor in Women

Annual CHD Deaths/1000

18 16 14 12 10 8 6 4 2 0

Men Women

17 17

8 4

Diabetes No diabetes

• >9 million women with diabetes
• Stronger risk factor in women vs men
• Women with diabetes have more adverse CV risk profiles
• Risk of MI in diabetic women is 3 to 4 times that of nondiabetic
  • Doubles the risk of recurrent MI
• Eliminates the 10 year gender gap and relative premenopausal cardioprotective effect

Kannel WB, McGee DL. JAMA 1979;241:2035-2038
Unique Risk Factors

- Gestational Diabetes (Diab Res Clin Pract 2007)
- Early Menopause (Basic Res Cardiol 2000; 95:177-83)
  - Natural
  - Surgically induced
  - Chemically induced (Breast cancer)

- Autoimmune disease
  - 80% autoimmune patients are women
  - RA (Circ 2003;107:1303-7)
  - Psoriasis (JAMA 2006:296:1735-41)

Women with Diabetes are Under Treated

3849 patients; more than half women
5 academic centers 2000 to 2003

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No CHD N=2699</th>
<th>P value</th>
<th>CHD N=1150</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL drugs</td>
<td>0.82</td>
<td>.01</td>
<td>0.77</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.63</td>
<td>.0001</td>
<td>0.70</td>
<td>.0001</td>
</tr>
<tr>
<td>BP &lt;140/90</td>
<td>1.0</td>
<td>NS</td>
<td>0.88</td>
<td>.0001</td>
</tr>
<tr>
<td>HbA1c &lt;7.0</td>
<td>0.84</td>
<td>.005</td>
<td>0.63</td>
<td>.0001</td>
</tr>
<tr>
<td>LDL &lt; 100 mg/dL</td>
<td>0.75</td>
<td>.007</td>
<td>0.80</td>
<td>.006</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>.92</td>
<td>NS</td>
<td>1.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Wexler et al Diabetes Care 2005;28:514
Trends in the prevalence of total serum cholesterol (200+) in adults age 20 and older, by sex, race/ethnicity

Statin Trials: Therapy Reduces Major Coronary Events in Women

*M4S = primarily CHD death and nonfatal MI;
CARE = coronary death, nonfatal MI, angioplasty, or bypass surgery;
AFCAPS/TexCAPS = fatal/nonfatal MI, unstable angina, or sudden cardiac death.

Hypertension Treatment Effect by Gender

<table>
<thead>
<tr>
<th></th>
<th>Total Mortality</th>
<th>CV Death</th>
<th>Fatal CVA</th>
<th>All CVA</th>
<th>Fatal CV Event</th>
<th>Major CV Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>0.91 (0.81-1.01)</td>
<td>0.86 (0.74-1.01)</td>
<td>0.71 (0.53-0.96)</td>
<td>0.62 (0.52-0.73)</td>
<td>0.92 (0.74-1.16)</td>
<td>0.74 (0.66-0.83)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>0.88 (0.80-0.97)</td>
<td>0.80 (0.70-0.91)</td>
<td>0.57 (0.41-0.78)</td>
<td>0.66 (0.56-0.78)</td>
<td>0.83 (0.71-0.97)</td>
<td>0.78 (0.71-0.86)</td>
</tr>
</tbody>
</table>

Aspirin and Primary Prevention of CVD in WHS According to Age Group

**Estrogen: Benefit**

- Beneficial alteration of lipid profile
- Antioxidant effect
- Reduction of serum fibrinogen
- Inhibition of neointimal hyperplasia, smooth muscle cell collagen biosynthesis
- Potentiation of endothelium derived relaxing factor
- Increased prostacyclin biosynthesis
- Decrease insulin resistance
- May cause favorable distribution of body fat

---

**Meta-analysis of HRT trials**

Peto odds ratio plot [fixed effects]

- WHI: 1.09 (0.69, 1.72)
- PHASE: 3.90 (0.87, 17.52)
- MERS: 7.09 (0.84, 1.42)
- ESPRIT: 0.68 (0.33, 1.73)
- IRWPE: 7.16 (0.47, 3.95)
- combined [fixed]: 7.08 (0.86, 1.30)

Cho et al., Cardiology 2005
**Meta-Analysis of Randomized Clinical Trials of Hormone Therapy**

<table>
<thead>
<tr>
<th>Younger women (mean age &lt; 60 or &lt; 10 yrs since menopause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD: OR = 0.68 (95% CI, 0.48-0.96)</td>
</tr>
<tr>
<td>Total Mortality: OR = 0.61 (95% CI, 0.39-0.95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Older women (mean age &gt; 60 or ≥ 10 yrs since menopause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD: OR = 1.03 (95% CI, 0.91-1.16)</td>
</tr>
<tr>
<td>Total Mortality: OR = 1.03 (95% CI, 0.90-1.18)</td>
</tr>
</tbody>
</table>

CHD = nonfatal MI or cardiac death

---

**Hormone Therapy: Decision Making Flowchart**

- **Significant symptoms of menopause (moderate-to-severe hot flashes, night sweats)?**
  - No: **No HT**
  - Yes: **Free of contraindications to HT and no h/o CHD, stroke, or TIA?**
    - No Increased risk for stroke (< 10% by Framingham stroke score)?
      - Yes: Assess CHD risk and years since last menstrual period
      - No: **No HT**

**Assess CHD risk and years since last menstrual period**

<table>
<thead>
<tr>
<th>CHD Risk Over 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Very low (&lt; 5%)</td>
</tr>
<tr>
<td>Low (5% to &lt; 10%)</td>
</tr>
<tr>
<td>Moderate (10% to 20%)</td>
</tr>
<tr>
<td>High (more than 20%)</td>
</tr>
</tbody>
</table>

- 5-10: HT OK (Choose transdermal)
- > 10: No HT

**Decision about duration of use:** continued moderate-to-severe symptoms; patient preference; weigh baseline risks for breast cancer vs osteoporosis

---


From Manson J and Bassuk S Harrison’s Principles of Internal Medicine 2008
Then and Now

4-03: Cover in TIME: Women and Heart Disease

- HERS/WHI underscore the need to critically review guidelines specific to women
  - Only recently has there been an increase in proportion of women in clinical trials.
  - Care making inferences from men to women
  - Need to assess level of risk and have risk based treatment strategies

- New emphasis on educating women and health care providers
  - AHA's "Go Red for Women" campaign
  - NHLBI's "The Heart Truth" campaign
  - W.A.T.C.H: Women's Agenda Targeting Cholesterol in Heart Disease

- First female specific CVD prevention guidelines published in 1999
  - First evidence based guidelines in 2004
  - Updated evidence based guidelines in 2007 and 2011


Source: NCHS and NHLBI.
AHA Evidence-Based Guidelines for CVD Prevention in Women

• Assess stratify based on risk, treat according to risk category

• Urge lifestyle changes
  – ≥30 minutes moderate-intensity physical activity daily
  – Smoking cessation/environmental smoke avoidance
  – Weight maintenance/reduction; BMI 18.5 to 24.9, waist circ <35 in
  – Heart-healthy diet
  – Consider omega 3 fatty acids and folic acid supplementation

• Encourage optimal BP <120/80 mm Hg with lifestyle approaches
  – Prescribe Rx for BP ≥140/90 (lower with diabetes or target organ damage)
  – ACEI contraindicated in pregnancy

• Encourage optimal lipid levels with lifestyle approaches and Rx
  – LDL-C <100 mg/dL HDL-C >50 mg/dL
  – TG <150 mg/dL Non–HDL-C <130 mg/dL

• Use lifestyle/Rx in patients with diabetes to achieve HbA1c (<7%)

• Evaluate for depression in women with CVD

---

Descriptions of Risk Groups

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| High risk   | •Established CHD, CVD, PAD, AAA  
  •End-stage or chronic renal disease  
  •Diabetes mellitus  
  •10-yr Framingham risk >20%  
  •10-yr predicted CVD risk ≥10% |
| At risk     | •≥1 major risk factor for CVD including poor diet, physical inactivity, obesity, family Hx of premature CVD  
  •Evidence of subclinical vascular disease  
  •Metabolic syndrome  
  •Poor exercise capacity or abnormal HR recovery on stress  
  •Systemic autoimmune collagen vascular disease (SLE, RA)  
  •Hx of preeclampsia, gestational diabetes, pregnancy induced HTN |
| Optimal risk| •Framingham risk <10% and healthy lifestyle with no risk factors |
AHA Evidence-Based Guidelines for CVD Prevention in Women

Women at High Risk

• Class I Recommendations
  – Smoking cessation/environmental smoke avoidance
  – Physical activity/cardiac rehabilitation
  – Diet therapy
  – Weight maintenance/reduction
  – Blood pressure control
  – Lipid control with LDL-C-lowering agents
  – Statin therapy in women for LDL-C <100 mg/dL (<70mg/dL in very high risk)
  – Aspirin therapy (75-162 mg)
  – Beta-blocker therapy unless contraindicated after ACS, LV dysfunction
  – ACE inhibitor therapy (ARBs if contraindicated) after MI, LV dysfunction, CHF, DM
  – Glycemic control in diabetics

• Class IIa Recommendation:
  – Evaluation/referral for depression

• Class IIb Recommendations:
  – Omega 3 fatty-acid supplementation
  – Consider statin in women > 60 with usCRP >2
  – Niacin or fibrates when HDL <50, non-HDL >130

AHA Evidence-Based Guidelines for CVD Prevention in Women

Women at Risk (10%-20% Risk)

• Class I Recommendations:
  – Smoking cessation/environmental smoke avoidance
  – Physical activity
  – Heart-healthy diet or lipid-lowering diet
  – Weight maintenance/reduction
  – Treat individual CVD risk factors as indicated
  – Blood pressure control
  – Lipid control

• Class IIa Recommendation:
  – Aspirin therapy (75-162 mg) if BP controlled

Circulation. 2011;123
AHA Evidence-Based Guidelines for CVD Prevention in Women

Women at Optimal Risk

- Class I Recommendations
  - Avoid environmental smoke avoidance
  - Physical activity
  - Heart-healthy diet or lipid-lowering diet
  - Weight maintenance/reduction

Class III (Not Recommended for CVD Prevention):
- Hormone therapy in postmenopausal women
- Antioxidant supplements
- Folic acid supplementation
- Aspirin therapy in low risk women

Class I: Atrial Fibrillation and Stroke Risk
- Aspirin 75 to 325 mg contraindication to warfarin or CHADS2 <2
- Coumadin for INR 2 to 3
- Dibagatran as alternative: without CRF, liver disease, valvular disease

Summary

- Cardiovascular Disease is the leading cause of death in women
  - Increased awareness, change in misconceptions
- Cardiovascular risk factors are prevalent in women and associated with poorer outcomes
  - Screen and treat early
  - Screen for diabetes
  - Lipid management with statin, target HDL > 50 and TG’s <150 mg/dL
- Differences exit between men and women in terms of disease presentation and response to therapies particularly bleeding/vascular complications
  - Radial approach, smaller catheters, weight and renal adjusted med dosing
- Although data is improving, awareness and utilization remains low
  - Risk assessment at entry into the health system
  - Education
- New guidelines for prevention can assist physicians and empower women to take control of their healthcare and reduce their risk
- Future research on risks and treatments of heart disease must focus on women as well as men
Rationale for Primary and Secondary Prevention

Most MIs arise from smaller stenoses

Multiple plaque rupture in ACS

90% of Patients with Newly Diagnosed Diabetes Are Overweight or Obese

National Health Interview Survey, 2003; N = 31,000 aged 18 to 79 years


Steno-2: Death from Any Cause, and from CVD and Cardiovascular Events

HR=0.54; P=0.02
Absolute RR= 20%

HR=0.41; P<0.001
Absolute RR=29%

Diabetes Mellitus and Metabolic Syndrome

- An estimated 25.4 million Americans have diabetes; (projected to double by 2025)
  - 81.5 million have prediabetes
- 800,000 to 1.2 million new cases of type II diabetes a year in US
- WHO predicts number of adults with diabetes in the world will rise from 171 million in 2000 to 366 million in 2030

75.3 million with Metabolic syndrome
- Abdominal obesity
- Atherogenic dyslipidemia
- Elevated triglycerides
- Small LDL particles
- Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Prothrombotic state
- Proinflammatory state

NCEP-ATP III: Risk Assessment—CHD Risk Categories

10-year CHD risk (%)

0 Low
10 Intermediate
20 High

0-1 RF
≥2 RFs (calculate Framingham risk)

CHD, Diabetes, Atherosclerotic disease

For persons without known CHD, other forms of atherosclerotic disease, or diabetes:
- Count the number of risk factors.
- Use Framingham scoring for persons with ≥2 risk factors* to determine the absolute 10-year CHD risk.

---


**PROCAM Score**

**Prospective Cardiovascular Münster Study**

Score of ≥53 associated with a 10-year risk of acute coronary event of ≥20%

- **Age, y**
  - 35–39 0
  - 40–44 6
  - 45–49 11
  - 50–54 16
  - 55–59 21
  - 60–65 26
- **Triglycerides, mg/dL**
  - <100 0
  - 100–149 2
  - 150–199 3
  - ≥200 4
- **Smoker**
  - No 0
  - Yes 8
- **Diabetes mellitus**
  - No 0
  - Yes 6
- **MI in family history**
  - No 0
  - Yes 4
- **HDL-C mg/dL**
  - <35 11
  - 35–44 8
  - 45–54 5
  - ≥55 0
- **Systolic BP, mm Hg**
  - <120 0
  - 120–129 2
  - 130–139 3
  - 140–159 5
  - ≥160 8

**SCORE RISK**

- <20–45 = <10%
- 45–53 = 10–19%
- >53 = >20%

---

**Prognostic Value of CRP Is Additive to the Framingham Risk Score and LDL-C**

Women's Health Study (N=27,939)

- **CRP (mg/L)**
  - <1.0
  - 1.0-3.0
  - >3.0

- **LDL-C (mg/dL)**
  - <130
  - 130-160
  - >160

---


Blood Pressure: Lower is Better

Ischemic Heart Disease Mortality

Age at Risk (Y)

Age at Risk (Y)

Prospective Studies Collaboration. Lancet. 2002;360:1903-1913

Resistant HTN

• Identifiable causes
  – Renal parenchymal disease
  – Renovascular disease
  – Primary aldosteronism
  – Obstructive sleep apnea
  – Pheochromocytoma
  – Cushing’s syndrome
  – Thyroid disease
  – Aortic coarctation
  – Intracranial tumour
## Antihypertensives for Comorbidities: Consensus Statements and Guidelines for Use

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>ACEI</th>
<th>ARB</th>
<th>Aldosterone antagonist</th>
<th>β-Blocker</th>
<th>CCB</th>
<th>Diuretic</th>
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<tbody>
<tr>
<td>Heart failure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Post-MI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High CHD risk</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Blood Pressure Control Recommendations

**Goal: <140/90 mm Hg or <130/80 if diabetes or chronic kidney disease**

- **Blood pressure 120/80 mm Hg or greater:**
  - Initiate or maintain lifestyle modification: weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits vegetables and low fat dairy products

- **Blood pressure 140/90 mm Hg or greater (or 130/80 or greater for chronic kidney disease or diabetes):**
  - As tolerated, add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors with addition of other drugs such as thiazides as needed to achieve goal blood pressure

Circulation 2006;113:2363-2372 and J Am Coll Cardiol 2006;47:2130-2139
Impact of Risk Factors

- Diabetes
  - ~65 to 75% of all diabetic mortality is due to CVD
  - 75% from coronary atherosclerosis
  - 25% from cerebral or peripheral vascular disease
  - 71,382 deaths from diabetes in 2007
  - A diabetic's risk of CV mortality or having an MI is equivalent to a non-diabetic having had a prior MI
  - Up to 4 fold increase CHD in women, 2 fold increase in men
  - One of most important risk factors for stroke in women

- Metabolic syndrome
  - Greater than 3 fold CHD risk
  - 24 times greater risk of developing new diabetes

Atherosclerosis in Diabetes

- Accelerated atherosclerosis is multifactorial and begins years/decades prior to diagnosis of type 2 diabetes
  - Hyperglycemia, dyslipidemia, hypertension, inflammation
  - >50% of patients with newly diagnosed type 2 DM have CHD
- Risk for CV events is 2- to 4-fold greater in DM than in non-DM
- A diabetic's risk of CV mortality or having an MI is equivalent to a non-diabetic having had a prior MI
- Diabetics with MI, CABG do worse
- Atherosclerosis accounts for ~ 65 to 75% of all diabetic mortality
  - 75% from coronary atherosclerosis
  - One of most important risk factors for stroke in women
- IVUS: halting of progression of atherosclerosis highest in individuals on therapy with LDL <70 mg/dL and SBP <120 mmHg
- Metabolic syndrome Greater than 3 fold CHD risk
  - 24 times greater risk of developing new diabetes

References:

DOS CME Course 2011
Diabetes and Metabolic Syndrome increases risk for CHD

Diabetes
- n=2432
- 7 year fu
- CV Mortality %
  - No prior MI: 2.1
  - Prior MI: 15.9

Metabolic Syndrome
- n=3606
- 7 year fu
- CV Mortality %
  - No MS: 2.2
  - MS: 12

---

Isomaa B et al. *Diabetes Care.* 2001;24:683

Diabetes and Long-Term Survival Following Acute MI: Comparability of Risk with Prior MI

**NIH-ONSET STUDY**

Proportion Alive following Acute MI

- No diabetes
- No diabetes with prior MI
- Diabetes
- Diabetes with prior MI

With diabetes=1536
Without Diabetes=399

---

### CVD Endpoint Trials with Type II DM Trials

<table>
<thead>
<tr>
<th></th>
<th>UKPDS</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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</thead>
<tbody>
<tr>
<td>Pt</td>
<td>3867</td>
<td>10251</td>
<td>11140</td>
<td>1791</td>
</tr>
<tr>
<td>Age</td>
<td>53</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>F/U yrs</td>
<td>5.0</td>
<td>3.4</td>
<td>4.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Target</td>
<td>FPG&lt;6</td>
<td>HgA1c&lt;6%</td>
<td>HgA1c&lt;6.5</td>
<td>HgA1c&lt;6.0</td>
</tr>
<tr>
<td>DM (yrs)</td>
<td>0</td>
<td>10</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CVD %</td>
<td>2</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>HgA1c (base)</td>
<td>7.1</td>
<td>8.3</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Result</td>
<td>No diff</td>
<td>Increase death</td>
<td>No diff</td>
<td>No diff</td>
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</table>

### NHANES 1999-2006

National Health and Nutrition Examination Surveys

<table>
<thead>
<tr>
<th></th>
<th>1999-2002</th>
<th>2003-2006</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Diabetes</td>
<td>6.5</td>
<td>7.8</td>
<td>.03</td>
</tr>
<tr>
<td>BMI</td>
<td>31.77</td>
<td>32.27</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>116</td>
<td>108.2</td>
<td>.009</td>
</tr>
<tr>
<td>A1C</td>
<td>7.62</td>
<td>7.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>132.9</td>
<td>130.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>BP Med Use</td>
<td>62.8%</td>
<td>76.2%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lipid Med Use</td>
<td>42.8%</td>
<td>54.9%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Glucose Control: Meta-Analysis

<table>
<thead>
<tr>
<th>Trials</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ray et al (Lancet 2009;373:1765-72)</td>
<td>Nonfatal MI ↓ 17% Reduce CHD ↓ 15% No change in death</td>
</tr>
<tr>
<td>Turnbull et al (Diabetologia 2009;52:2288-98)</td>
<td>Reduce MI 15% No change in death</td>
</tr>
</tbody>
</table>

### Definitions for AHA 2020 Goals

<table>
<thead>
<tr>
<th>Poor</th>
<th>Intermediate</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>No</td>
<td>Never quit &amp; &lt;10 mo</td>
</tr>
<tr>
<td>Alcohol aged ≥12 y</td>
<td>Yes</td>
<td>≤10 drinks per mo</td>
</tr>
<tr>
<td>Trained at ≥2 y</td>
<td>≥2 drinks per day</td>
<td>&lt;2 drinks per day</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Active</td>
<td>Slightly sedentary</td>
</tr>
<tr>
<td>Healthy diet score</td>
<td>≥6 components</td>
<td>3–5 components</td>
</tr>
<tr>
<td>Added sugar</td>
<td>0–3</td>
<td>≤3</td>
</tr>
<tr>
<td>Added fat</td>
<td>0–3</td>
<td>≤3</td>
</tr>
<tr>
<td>Added salt</td>
<td>0–3</td>
<td>≤3</td>
</tr>
</tbody>
</table>

---

*American Heart Association. 2011 Heart and Stroke Statistical Update.*
Definitions for AHA 2020 Goals

Only 17% of US adults have 5 or more metrics with ideal levels (11% men, 24% women)

Ankle-Brachial Index

- Ratio of ankle to arm systolic blood pressure (SBP)
  - ABI ≤0.90 indicates peripheral artery disease\(^1\)\(^-\)\(^3\)
  - ABI ≤0.90 at baseline added predictive value for fatal MI\(^3\)
- ABI is useful to refine the assessment of intermediate-risk patients ≥50 years\(^1\)\(^,\)\(^2\)

---

Hazard Ratios for CHD Events Associated With Coronary Calcium Scores: US Adults Ages 45-84 Years (Reference Group CAC=0) (The MESA Study).

Source: Detrano et al., NEJM. 2008;358(13):1336-1345.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>E</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>34.4</td>
<td>27.2</td>
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<tr>
<td></td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>3.8</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>2.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Source: CDC/NCHS

A Total CVD  D Chronic Lower Respiratory Diseases
B Cancer     E Diabetes Mellitus
C Accidents  F Alzheimer’s Disease

Treatment of Risk Factors
Gender and Biological Differences in CVD

- Onset of CVD lags men by ~10 years
- Prevalence and strength of risk factors
  - Increased prevalence of THN, DM, depression, decreased tobacco
  - Increased relative risk from HTN, DM, tobacco, TG’s
  - Low LDL-C
  - Increased comorbidities
- Increased diffuse atherosclerosis/nonobstructive CHD
- Increased microvascular and endothelial dysfunction
- Increased stroke and complications in AF
Gender and Biological Differences in CVD

- Atherosclerosis
  - Stiffer arteries
  - Plaque erosion > rupture
  - Increased smooth muscle dysfunction
  - Genetics
  - Increased thrombotic isk
  - Increased inflammation levels (autoimmune disease)
- Increased CHF with normal systolic function
- Smaller body size
- Differences in pain perception
- Influence of hormones on physiology

Acute Coronary Syndrome

- Meta analysis of 8 ACS trials
  - 3075 women / 7075 men
  - Invasive vs. Conservative therapy
  - 12 month follow up
- Death/MI/re-ACS Invasive vs. Conservative
  - Women 0.81 (95% CI 0.65-1.01) 21% vs. 25%
  - Men 0.73 (95% CI 0.55-0.98) 21.2% vs. 26.2%
- Positive Biomarkers (+ troponin or + CKMB)
  - Women 0.67 (95% CI 0.50 -0.88) 33% reduction in death/MI/ACS and 23% reduction in death or MI
  - Men 0.56 (95% CI 0.46 -0.67)
- Negative Biomarkers (-Troponin or – CKMB)
  - Women 0.94 (95% CI 0.61-1.44) with NS 35% INCREASE in death /MI
  - Men 0.72 (95% CI 0.51-1.01)

JAMA 2008;300:71-80
CABG & Women

- Outcomes between men and women similar
- Similar procedural mortality and MI rate between men and women
- No lesion difference between men and women
- Less IMA use, more likely to have angina after CABG
- Longer ICU and hospital stay
- Increase bleeding

Women and Thrombolytics

- Equivalent benefit as men (12-14% ↓ death)
- Risk of hemorrhagic stroke is equivalent after adjusting for age and BMI (GUSTO I, ISIS III)
- Higher bleeding complications
- Higher rates of shock, CHF, rupture, VF, AF, and reinfarction
- Less likely to undergo cath and revasc
PCI Bleeding Risk

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>Blood transfusion</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>0.3%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

CABG Bleeding Rates

Average PRBC transfusion 2.2u in Men vs. 3.6 in Women
Scott et al., Anesthesia & Analgesia 2003;97:958-63

52.6% of men need transfusion vs. 79.6% women
Scott et al., Anesthesia & Analgesia 2003;97:958-63

Women have longer length of stay, intubation time, ICU stay then men
Butterworth et al., Anesthesiology 2000;92:414-24

Cleveland Clinic

Vascular Complications

<table>
<thead>
<tr>
<th></th>
<th># Women/Men</th>
<th>Female</th>
<th>Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chacko 2006</td>
<td>1537/4465</td>
<td>4.8%</td>
<td>2.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major Bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Bleed</td>
<td></td>
<td>22.2%</td>
<td>18.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>Cho 2002</td>
<td>1771/4824</td>
<td>3.0%</td>
<td>1.4%</td>
<td>0.004</td>
</tr>
<tr>
<td>Major Bleed*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Bleed*</td>
<td></td>
<td>6.7%</td>
<td>2.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Patient treated with abciximab. Major and minor bleed as defined by TIMI bleeding criteria.
† Major bleeding was defined as a hemoglobin drop >4 g/dL, overt bleeding with hemoglobin drop >3 g/dL; > 2 U blood transfusion or retroperitoneal, intraocular, or intracranial hemorrhage. Minor bleeding was defined as over bleeding that did not meet major bleeding criteria.
‡ Clarify definitions
Age-adjusted prevalence of obesity in Adults ages 20-74 by sex and survey.

High blood pressure in Adults by age and sex
**CVD Mortality in Women:**

HDL Levels Lipid Research Clinic Follow-Up  
Impact of TG Levels on Relative Risk of CHD: Framingham Heart Study

---

**Nurses Health Study: Waist Circumference and CHD Risk**

<table>
<thead>
<tr>
<th>Waist Circumference (in)</th>
<th>Relative Risk for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28</td>
<td>1.0</td>
</tr>
<tr>
<td>28 to &lt; 30</td>
<td>1.25</td>
</tr>
<tr>
<td>30 to &lt; 32</td>
<td>1.29</td>
</tr>
<tr>
<td>32 to &lt; 34</td>
<td>2.42</td>
</tr>
<tr>
<td>34 to &lt; 36</td>
<td>2.13</td>
</tr>
<tr>
<td>36 to &lt; 38</td>
<td>2.25</td>
</tr>
<tr>
<td>≥ 38</td>
<td>3.06</td>
</tr>
</tbody>
</table>

*Age-adjusted and multivariate relative risks; P = .002 for trend*
Prognostic Value of Functional Capacity in Asymptomatic and Symptomatic Women

Why Focus on Lipid Management?

- LDL predicts CVD in women similar to men
- HDL and triglycerides are stronger predictors in women
- Women are less likely than men to receive optimal lipid management
  - Minority women are less likely to receive optimal preventive care compared to white women
  - Evidence supports that women receive equal benefit from lipid management although less likely to receive than men
- Effect of loss of estrogen with menopause:
  - ↑ Total Cholesterol, LDL-C Triglycerides
  - ↓ HDL
Aspirin and Primary Prevention in Women

39,876 women over 45 years old followed 10 years
Randomized to aspirin 100 mg qod vs placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin, N=19,934</th>
<th>Placebo, N=19,942</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CV Event</td>
<td>477</td>
<td>522</td>
<td>0.91</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>221</td>
<td>266</td>
<td>0.83</td>
<td>0.04</td>
</tr>
<tr>
<td>Fatal and Nonfatal MI</td>
<td>198</td>
<td>193</td>
<td>1.02</td>
<td>0.83</td>
</tr>
<tr>
<td>Mortality</td>
<td>609</td>
<td>642</td>
<td>0.95</td>
<td>0.32</td>
</tr>
<tr>
<td>CVD Death</td>
<td>120</td>
<td>126</td>
<td>0.95</td>
<td>0.68</td>
</tr>
<tr>
<td>Transfusion for GI bleed</td>
<td>127</td>
<td>91</td>
<td>1.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Subanalysis in women over 65 demonstrated significant 26% reduction in major CV events, 34% reduction in MI and 30% reduction in stroke


HERS: Combined HRT:

All-Cause Mortality

CHD Events

Log rank \( P=0.56 \)

*0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate.

Hulley S et al. JAMA. 1998;280:605-613

Outcomes in WHI Trial of Estrogen, Progestin

- Estimated hazard ratios (nominal 95% CI):
  - CHD (primary outcome): 1.29 (1.02-1.63) 286 cases
  - Stroke: 1.41 (1.07-1.85) 212 cases
  - Invasive breast cancer (primary adverse outcome): 1.26 (1.00-1.59) 290 cases
  - Hip fracture: 0.66 (0.45-0.98) 106 cases

- Overall health risks exceed benefits: 41% increase in stroke, 29% increase in CHD events

- Adverse outcomes: Absolute incidence is low, but will increase over longer time needed to prevent chronic disease
  - Increase 7 CHD, 8 CVA, 8 PE, 8 Breast Ca per 10,000/yr
  - Decrease 8 Colorectal Ca, 5 Hip fractures per 10,000/yr

- Researchers’ conclusions on estrogen/progestin:
  - Not recommended for primary prevention of CHD
  - Consider other treatments to prevent osteoporosis


WHI: CHD, Stroke Outcomes in Estrogen-Alone Arm

<table>
<thead>
<tr>
<th>Events</th>
<th>Year</th>
<th>CHD*</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>26</td>
<td>0.91 (95% CI, 0.75-1.12)</td>
<td>1.39 (95% CI, 1.10-1.77)</td>
</tr>
<tr>
<td>Placebo</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Primary outcome.

Absolute Excess Risks (Cases per 10,000 Pts) by Age in Combined Trials of WHI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>-2</td>
<td>-1</td>
<td>+19*</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-10</td>
<td>-4</td>
<td>+16*</td>
</tr>
<tr>
<td>Global index†</td>
<td>-4</td>
<td>+15</td>
<td>+43*</td>
</tr>
</tbody>
</table>

* P = .03 compared with age 50-59 years or < 10 years since menopause
† Global index = composite outcome of CHD, stroke, pulmonary embolism, breast, colorectal, and endometrial cancers, hip fracture, and mortality


WHI: Adjusted Risk for CHD According to Baseline Use of HRT and CRP and IL-6

<table>
<thead>
<tr>
<th>HRT increases inflammatory markers; elevated markers increase risk for CHD</th>
<th>OR (95% CI) by Biomarker Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>C-reactive protein†</td>
<td>2.6 (1.0-6.7)</td>
</tr>
<tr>
<td>Current users</td>
<td>2.3 (1.0-5.0)</td>
</tr>
<tr>
<td>Nonusers</td>
<td>2.4 (0.9-6.5)</td>
</tr>
<tr>
<td>Interleukin 6‡</td>
<td>1.0 (0.7-3.2)</td>
</tr>
<tr>
<td>Current users</td>
<td>2.2 (1.1-4.6)</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1.4 (0.6-0.3)</td>
</tr>
<tr>
<td></td>
<td>2.4 (1.1-5.0)</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio
† Tertile defined as low (< 0.14 mg/dL); intermediate (0.14-0.38 mg/dL); and high (≥ 0.38 mg/dL)
‡ Tertile defined as low (< 1.20 pg/mL); intermediate (1.20-1.86 pg/mL); and high (≥ 1.86 pg/mL)

AHA Evidence-Based Guidelines for CVD Prevention in Women

Lifestyle Interventions

Cigarette smoking
Women should not smoke and should avoid environmental tobacco smoke. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program (Class I, Level B).

Physical activity
Women should accumulate a minimum of 30 minutes of moderate-intensity physical activity per day, brisk walking on most, and preferably all, days of the week (Class I, Level C).

Rehabilitation
A comprehensive risk-reduction regimen, such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program, should be 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 on LVD (<49%) (Class I, Level B).

Dietary intake
Women should consume a diet rich in fruits and vegetables; choose whole-grain, high-fiber foods; consume fish, especially oily fish, at least twice a week; limit intake of saturated fat <10% of energy, and if possible to <7%; cholesterol to <200 mg; sodium intake to no more than 1,500 mg per day; and sodium intake to <2.3 g per day (approximately 1 tsp salt). Consumption of trans-fatty acids should be as low as possible (<1% of energy) (Class I, Level B).

Weight maintenance/reduction
Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and normal behavioral programs when indicated to maintain a body mass index (BMI) between 18.5 and 24.9 kg/m² and a waist circumference <35 in (Class I, Level B).

Group 2 fatty acids
As an adjunct to diet: omega-3 fatty acids in capsule form (approximately 800 to 1000 mg of EPA and DHA) may be considered in women with CVD, and higher doses 2 to 4 g may be used for treatment of women with high triglyceride levels (Class IIa, Level B).

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


AHA Evidence-Based Guidelines for CVD Prevention in Women

Major Risk Factor Interventions

Blood pressure—optimal level and therapy
Exchange 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 or near target 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 clinical disease. For treatment of high-risk women should be on blockers and/or ACE inhibitors/RAS.

Lipids and lipoproteins levels—optimal levels and lifestyle
The following levels of lipids and lipoproteins are considered through lifestyle approaches: LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non-HDL-C (total cholesterol minus HDL cholesterol) <150 mg/dL. If a woman is at high risk, or has a history of/or diabetes, HDL-C below 50 mg/dL should be considered (Class I, Level E).

Lipids—pharmacotherapy for LDL, lowering risk, high-risk women
Uttile LDL-C-lowering drug therapy with or without lifestyle therapy in women with CVD to achieve an LDL-C <100 mg/dL, (Class I, Level B) and non-HDL-C <150 mg/dL in women with other conditions (10% or more risk in 10 years, risk factors, or diabetes mellitus) (Class IIa, Level B).

Lipids—pharmacotherapy for LDL, lowering risk, high-risk women
Use LDL-lowering therapy if LDL-C level is >150 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk >10% (Class I, Level B).

Lipids—pharmacotherapy for HDL, elevated HDL, risk women
Use HDL-lowering therapy if HDL-C level is >60 mg/dL with lifestyle therapy and multiple risk factors over 10 year absolute risk <10% (Class Level B).

Lipids—pharmacotherapy for HDL, elevated HDL, low-risk women
Use HDL-lowering therapy if HDL-C level >60 mg/dL, without lifestyle therapy and multiple risk factors over 10 year absolute risk <10% (Class Level B).

Diabetes mellitus
Lifestyle and pharmacotherapy should be used in women with diabetes (Class I, Level C) to achieve an HDL-C >40 mg/dL if can be accomplished without significant hypoglycemia (Class I, Level C).

AHA Evidence-Based Guidelines for CVD Prevention in Women

Preventive drug interventions

Aspirin, high risk
Aspirin therapy (75 to 325 mg/day) 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) and in women <65 years of age when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy (Class IIb, Level B).

β-Blockers
β-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 (please contraindicated) in women after MI and in those with clinical evidence of heart failure or an EF <40% or with diabetes mellitus (Class I, Level A). In women after MI and in those with clinical evidence of heart failure or an EF <40% or with diabetes mellitus who are resistant to β-blockers, ARBs should be used instead (Class I, Level A).

Aldosterone blockade
Use aldosterone blockade after MI in women who do not have significant renal dysfunction or hypertension who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, and have LVEF <40% with symptomatic heart failure (Class IIa, Level A).

<table>
<thead>
<tr>
<th>TABLE 6. Class III Interventions (Not Useful/Effective and May Be Harmful) for CVD or MI Prevention in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasal therapy</td>
</tr>
<tr>
<td>Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD (Class III, Level A).</td>
</tr>
<tr>
<td>Antioxidant supplements</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>Folic acid</td>
</tr>
<tr>
<td>Folic acid, with or without H4 and B12 supplementation, should not be used for the primary or secondary prevention of CVD (Class III, Level A).</td>
</tr>
<tr>
<td>Aspirin for MI in women ≥65 years of age</td>
</tr>
<tr>
<td>Routine use of aspirin in healthy women &lt;65 years of age is not recommended to prevent MI (Class III, Level A).</td>
</tr>
</tbody>
</table>
AHA Evidence-Based Guidelines for CVD Prevention in Women

Evaluation of Cardiovascular Disease Risk:
- Medical history
- Symptoms of cardiovascular disease
- Physical examination including BMI, body mass index, waist size
- Labs including fasting lipoprotein and glucose
- Framingham risk assessment for cardiovascular disease or diabetes
- Depression screening in women with cardiovascular disease

Implement Class I Lifestyle Recommendations (Implement in Women at All Risk Levels):
- Smoking cessation
- Heart-healthy eating pattern
- Regular physical activity
- Weight management

Is Woman at High Risk of Cardiovascular Disease?
- Total blood cholesterol level
- Cardiovascular disease
- Peripheral arterial disease
- Abnormal blood pressure
- Diabetes mellitus
- Chronic renal disease
- Global 10-year risk >20%

Yes

AHA Evidence-Based Guidelines for CVD Prevention in Women

Recent cardiovascular event, procedure, or side effect from a failure?—Yes

Refer to rehabilitation

Impotent Class I Recommendations:
- BP control
- LDL lowering (goal <100 mg/dL)
- Aspirin/antithrombotic agents
- Statins
- Angiotensin-converting enzyme/angiotensin receptor blocker
- Glycemic control in diabetic women
- Adenosine blocker in heart women

Consider Class II Recommendations:
- HDL (<40 mg/dL in women)
- Omega-3 fatty acids
- Depression referral/training

Impotent Class I Recommendations:
- TG lowering
- LDL lowering in selected women
- ACP lipids

No