Cardiovascular Risk Reduction in Women

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Director, Women’s Cardiovascular Program
David Geffen School of Medicine at UCLA

Disclosure of Financial Relationships

- Consultant:
  - Pfizer, Genentech, Novartis

- Clinical Trials Adjudication Committee:
  - Merck
**Cardiovascular Disease: The Leading Cause of Death in US Women** *(2006 data)*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths (1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>162.2</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>42.6</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>40.0</td>
</tr>
<tr>
<td>COPD</td>
<td>35.9</td>
</tr>
<tr>
<td>Unintentional Injuries</td>
<td>25.5</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>23.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.1</td>
</tr>
<tr>
<td>Influenza/Pneumonia</td>
<td>15.5</td>
</tr>
<tr>
<td>Motor vehicle Accidents</td>
<td>8.8</td>
</tr>
</tbody>
</table>

US Trends in age-adjusted CHD mortality rates

Men and Women age 35-44 years

Percentage change in CHD incidence 1996-2005 in the (UK)

Davies A et al, Eur Heart J 2007
Mary

“Doctor…what should I be doing to prevent heart disease?”

Mary specifically asks about…

- **Risk Factors** Risk Factors related to Insulin Resistance
- **Hormone Therapy**
- **Preventive Medications**
- **Dietary Factors**
Metabolic Syndrome

Elevated Triglycerides Increase CHD Risk

For every increase in serum TG level of 89 mg/dL, risk of CHD increases 30% in men and 69% in women.


Fasting vs. Nonfasting TG Measurements

- Historically, triglycerides have been measured in the fasting state for two reasons.
  - First, because the variability in TG measurements is much smaller in the fasting state.
  - Second, calculation of LDL-C can be performed by use of the Friedewald equation, which requires fasting triglyceride concentration.

- The recommendations to measure fasting lipids did not develop from prospective clinical studies.

- Is it possible, then, that measuring fasting TG systematically underestimates the impact of hypertriglyceridemia on CHD risk?
Risk of Myocardial Infarction and Total Mortality by Nonfasting TG Level

- Prospective study of 26,509 initially healthy US women (20,118 fasting and 6,391 nonfasting) participating in the Women's Health Study. After a follow-up of a median of 11.4 years triglyceride levels were measured in blood samples obtained at time of enrollment.


<table>
<thead>
<tr>
<th>Triglyceride levels (mg/dL)</th>
<th>≤ 90</th>
<th>91 - 147</th>
<th>≥ 148</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (n = 20,118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model*, odds ratio (95% CI)</td>
<td>1 (referent)</td>
<td>1.21 (0.96 - 1.52)</td>
<td>1.09 (0.85 - 1.41)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triglyceride levels (mg/dL)</th>
<th>≤ 104</th>
<th>105 - 170</th>
<th>≥ 171</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfasting (n = 6391)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model*, odds ratio (95% CI)</td>
<td>1 (referent)</td>
<td>1.44 (0.90 - 2.29)</td>
<td>1.98 (1.21 - 3.25)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Adjusted for age, BP, smoking, use of hormone therapy, total and HDL-C, diabetes, BMI, and CRP

The EPICOR study investigated the association of Glycemic Index with coronary heart disease (CHD) in a large cohort of Italian men and women (originally recruited to the EPIC-Norfolk study).

- 47,749 participants (15,171 men and 32,578 women) completed a dietary questionnaire, and were followed for a median of 7.9 years.

- During follow-up 463 CHD major cardiovascular events were identified (158 women and 305 men).


**Carbohydrate Intake, Glycemic Index and CHD**

- The EPICOR study investigated the association of Glycemic Index with coronary heart disease (CHD) in a large cohort of Italian men and women (originally recruited to the EPIC-Norfolk study).

- 47,749 participants (15,171 men and 32,578 women) completed a dietary questionnaire, and were followed for a median of 7.9 years.

- During follow-up 463 CHD major cardiovascular events were identified (158 women and 305 men).

**Definition : Glycemic Index (GI)**

A measure of the effects of 50 g of a given carbohydrate on blood glucose levels, as compared to the effects of 50 g of a standard carbohydrate (glucose or white bread).

- Carbohydrates that break down quickly and release glucose rapidly into the bloodstream have a high GI.
- Carbohydrates that break down slowly, releasing glucose gradually, have a low GI.
Risk of CHD by Carbohydrate Intake (low and high GI foods) – women and men

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO-low GI foods</td>
<td>1</td>
<td>0.96</td>
<td>0.87</td>
<td>0.99</td>
<td>0.87</td>
</tr>
<tr>
<td>CHO-high GI foods</td>
<td>1</td>
<td>1.29</td>
<td>1.44</td>
<td>1.68</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO-low GI foods</td>
<td>1</td>
<td>0.88</td>
<td>1.00</td>
<td>0.91</td>
<td>0.69</td>
</tr>
<tr>
<td>CHO-high GI foods</td>
<td>1</td>
<td>1.05</td>
<td>1.08</td>
<td>0.97</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Carbohydrate Intake, Glycemic Index and CHD

Carbohydrate Intake, Glycemic Index and CHD

- Increased intake of high GI foods increases CHD risk in women

- This may be related to increased insulin resistance

- This may be related to decreased HDL in the setting of high GI food intake

Mary specifically asks about...

- Risk Factors
- Hormone Therapy
- Preventive Medications
- Dietary Factors
WHI E+P Trial Findings, July 2002 (avg 5.2 y)

Risks
- 105% Increase Dementia
- 24% Increase CHD
- 31% Increase Stroke
- 111% Increase Pulmonary Emboli
- 24% Increase Breast Cancer

Benefits
- Fracture Reduction (Hip 23%)
- 39% Reduction Colorectal Cancer

STOPPED Early, Suggestion of Harm

Also: DVTs

Stopped 3.3 yrs early

JAMA. 2002;288:321-333

WHI E Alone Trial Findings, 2004 (avg 6.8 y)

Risks
- 49% Increase Dementia
- 39% Increase Stroke
- 34% Increase Pulmonary Emboli

Benefits
- Fracture Reduction (Hip 39%)

STOPPED Early, Suggestion of Harm

Also: DVTs

Stopped 1.7 yrs early

JAMA 2004;291:2947-58
Estrogen in the early menopausal years

- Analysis of 24,317 women 50-79 years old in WHI
  - whose age at menopause could be accurately defined
  - stratified into 3 groups: 50-59/60-69/70-79 y.o.
- CHD, stroke & mortality rates analyzed
- Stroke was increased in all women, regardless of age at menopause
- CHD was decreased in women who took E alone vs. E + P (0.95 vs. 1.23 p=0.02)
- In hormone users
  - HR for CHD if < 10 years from menopause = 0.76
  - HR for CHD if 10-20 from menopause = 1.10
  - HR for CHD if >20 years from menopause = 1.28


Hormone Therapy (CEE + MPA) by time since menopause

<table>
<thead>
<tr>
<th>Years since menopause</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.76</td>
</tr>
<tr>
<td>10–19</td>
<td>1.10</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Mary specifically asks about…

- **Risk Factors**
- **Hormone Therapy**
- **Preventive Medications**
  - Vitamins
  - Aspirin
  - Calcium
- **Dietary Factors**

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**Aspirin Evidence:**

**Primary Prevention in Women**

39,876 initially healthy† women, aged ≥45 yrs

Randomized, blinded, factorial

- **Low-Dose Aspirin**
  - 100 mg on alternate days
  - n=19,934

- **Placebo**
  - n=19,942

End points (mean, 10.1 yrs):

- Combined end point of nonfatal MI, nonfatal stroke, or total cardiovascular death
- Incidence of total malignant neoplasms of epithelial cell origin

† No history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness; no history of side effects to any of the study medications; not taking aspirin or nonsteroidal anti-inflammatory medications (NSAIDs) more than once a week (or were willing to forgo their use during the trial); not taking anticoagulants or corticosteroids; and not taking individual supplements of vitamin A, E, or beta carotene more than once a week.

Aspirin: Primary Prevention in Women
Womens’ Health Study (WHS)

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

Low dose aspirin did not reduce the risk of MI in low risk women

Ridker P et al. NEJM 2005;352:1293-304

Womens’ Health Study (WHS)

<table>
<thead>
<tr>
<th>Smoking status:</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (n = 5235)</td>
<td>157</td>
<td>127</td>
<td>1.30</td>
<td>1.03-1.64</td>
<td>.03</td>
</tr>
<tr>
<td>Past/never (n = 34,605)</td>
<td>319</td>
<td>392</td>
<td>0.80</td>
<td>0.69-0.93</td>
<td>.003</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary endpoints:</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>221</td>
<td>206</td>
<td>0.83</td>
<td>0.69-0.99</td>
<td>.04</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age (yrs):</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>45-54 (n = 24,025)</td>
<td>163</td>
<td>161</td>
<td>1.01</td>
<td>0.81-1.26</td>
<td>.92</td>
</tr>
<tr>
<td>55-64 (n = 11,754)</td>
<td>183</td>
<td>186</td>
<td>0.98</td>
<td>0.80-1.20</td>
<td>.84</td>
</tr>
</tbody>
</table>

Ridker P et al. NEJM 2005;352:1293-304
Aspirin Evidence: Primary Prevention in Men

Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>P</th>
<th>Aspirin Better</th>
<th>Placebo Better</th>
</tr>
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<tbody>
<tr>
<td>BDT, 1988</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PHS, 1989</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>TPT, 1998</td>
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<td></td>
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</tr>
<tr>
<td>HOT, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPP, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 0.68 (0.54-0.86)</td>
<td>P=0.001</td>
<td>Aspirin Better</td>
<td>Placebo Better</td>
</tr>
</tbody>
</table>

Stroke

<table>
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<tr>
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</tr>
<tr>
<td>PPP, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 1.13 (0.96-1.33)</td>
<td>P=0.15</td>
<td>Aspirin Better</td>
<td>Placebo Better</td>
</tr>
</tbody>
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Ridker P et al. NEJM 2005;352:1293-304

Aspirin Evidence: Primary Prevention in Women

Myocardial Infarction

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<td></td>
</tr>
<tr>
<td>WHS, 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 0.99 (0.83-1.19)</td>
<td>P=0.95</td>
<td>Aspirin Better</td>
<td>Placebo Better</td>
</tr>
</tbody>
</table>

Stroke

<table>
<thead>
<tr>
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<th>RR</th>
<th>P</th>
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<th>Placebo Better</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>WHS, 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 0.81 (0.69-0.96)</td>
<td>P=0.01</td>
<td>Aspirin Better</td>
<td>Placebo Better</td>
</tr>
</tbody>
</table>

Ridker P et al. NEJM 2005;352:1293-304
Calcium and Heart Health

- “Healthy older women randomised to calcium supplementation showed increased rates of [atherosclerosis and] myocardial infarction. This effect could outweigh any benefits on bone from calcium supplements”

Calcium and CHD

- New Zealand researchers randomized 1,471 postmenopausal women (avg age=74) to either 1 g/day calcium citrate or placebo.
- At 5 years they evaluated cardiovascular events (death, sudden death, MI, angina, other chest pain, stroke, TIA, and a composite end point of MI, stroke, or sudden death.

<table>
<thead>
<tr>
<th>Vascular event</th>
<th>Calcium group (n = 732)</th>
<th>Placebo group (n = 739)</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>24</td>
<td>10</td>
<td>2.12 (1.01 - 4.47)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke</td>
<td>34</td>
<td>23</td>
<td>1.42 (0.83 - 2.43)</td>
<td>0.21</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3</td>
<td>3</td>
<td>1.01 (0.20 - 4.99)</td>
<td>1.0</td>
</tr>
<tr>
<td>Composite end point</td>
<td>61</td>
<td>38</td>
<td>1.47 (0.97 - 2.23)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

- When unreported events were added RR of MI fell to 1.49 (p=0.16) RR of composite end point fell to 1.21 (p=0.32).

Bolland MJ et al. BMJ. 2008;336:262-266
Calcium and CHD Meta-analysis

- 15 studies included (longer than 1y, n > 100)
  - Elemental calcium ≥ 500 mg/day
  - Trials including vitamin D EXCLUDED
- Events
  - Myocardial infarction, heart attack
  - Stroke, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular accident,
  - Sudden death
- Identifying Events
  - Self reports, hospital admissions/discharges
  - Blinded review by physicians

Bolland et. al. BMJ 2010; 341:c3691

RESULTS  Median follow up: 3.6 y

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>Placebo</th>
<th>HR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>143</td>
<td>111</td>
<td>1.31</td>
<td>1.02-1.67</td>
<td>0.035</td>
</tr>
<tr>
<td>Stroke</td>
<td>167</td>
<td>143</td>
<td>1.2</td>
<td>0.96-1.50</td>
<td>0.011</td>
</tr>
<tr>
<td>Any event</td>
<td>293</td>
<td>254</td>
<td>1.18</td>
<td>1.00-1.39</td>
<td>0.057</td>
</tr>
<tr>
<td>Death</td>
<td>519</td>
<td>487</td>
<td>1.09</td>
<td>0.96-1.23</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Bolland et. al. BMJ 2010; 341:c3691

>805 mg calcium/day associated with even greater risk of MI (HR 1.85, CI 1.28-2.67)
Authors’ Conclusions

- Calcium supplements without co-administered vitamin D are associated with an increased incidence of MI
- Treatment of 1000 people with calcium for five years would cause 14 MI, 10 strokes, 13 deaths and prevent 26 fractures
- Further study of effects of calcium on vascular system needed
- Reassessment of calcium supplements in prevention and treatment of osteoporosis is warranted

Bolland et. al. BMJ 2010; 341:c3691

Limitations / Contradictory Evidence

- Limitations of the Meta-analysis
  - Excluded trials that included calcium plus vitamin D
  - CVD events were not the primary outcome in any of the studies
  - Data was not gathered in a uniform manner
  - There was incomplete data for 15% of participants
- Contradictory Evidence: Women’s Health Initiative investigators published a secondary analysis of cardiovascular event risk with calcium plus vitamin D supplementation. Overall, these investigation found no significant increase or decrease in cardiovascular events among 36,000 postmenopausal women aged 50-79 years of age (mean age 62 years) over a 7 year study period.*

Mary specifically asks about…

- Risk Factors
- Hormone Therapy
- Preventive Medications
- Dietary Factors Which diet?

Americans Are Turning To Fad Diets

Which diet?
Popular Diets- 12 months
160 participants- 40 per group- Average 220 pounds

<table>
<thead>
<tr>
<th>Diet</th>
<th>Drop outs</th>
<th>Weight Loss</th>
<th>HDL</th>
<th>LDL</th>
<th>Insulin levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>48%</td>
<td>-3.9%</td>
<td>+15.4%</td>
<td>-8.6%</td>
<td>-7.7%</td>
</tr>
<tr>
<td>Zone</td>
<td>30%</td>
<td>-4.6%</td>
<td>+14.6%</td>
<td>-6.7%</td>
<td>-16.8%</td>
</tr>
<tr>
<td>Ornish</td>
<td>50%</td>
<td>-6.2%</td>
<td>+2.2%</td>
<td>-16.7%</td>
<td>-19.9%</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>35%</td>
<td>-4.5%</td>
<td>+18.5%</td>
<td>-7.7%</td>
<td>-8.8%</td>
</tr>
</tbody>
</table>

*No significant difference between diets at any time point.*

Low Fat vs. Low Carb vs. Mediterranean Diets

- 2-year trial
- took place in an isolated workplace that facilitated retention in the study,
- randomly assigned 322 moderately obese subjects to one of three diets:
  - a low-fat, restricted-calorie diet
  - a Mediterranean, restricted-calorie diet
  - or a low-carbohydrate, non-restricted-calorie diet

Weight Changes during 2 Years According to Diet Group

Changes in Lipids According to Diet Group

Conclusion

- Mediterranean and low-carbohydrate diets may be effective alternatives to low-fat diets
- More favorable effects on lipids were seen with the low-carbohydrate diet and more favorable effects on glycemic control were seen with the Mediterranean diet

Mary

“Doctor…what do the national guidelines say?”
Lifestyle Interventions

- Cigarette smoking
  - DON'T! (Class I; LOE B)

- Physical activity
  - 150 min/wk of moderate exercise or 75 min/wk of vigorous exercise, performed in episodes of at least 10 min, (Class I; LOE B)
  - Muscle strengthening activities on ≥2 d per week (Class I; LOE B)

- Cardiac rehabilitation
  - RECOMMENDED (Class I; LOE B).

- Dietary intake
  - Diet rich in fruits, vegetables, and whole grains. Limit saturated fat, cholesterol, alcohol, salt, and sugar. Avoid trans-fatty acids (Class I LOE B)
Lifestyle Interventions (cont.)

- **Weight maintenance/reduction**
  - Maintain or lose weight through physical activity and appropriate caloric intake to achieve appropriate body weight (BMI <25 kg/m², waist size <35 inches) (*Class I; LOE B*).

- **Omega-3 fatty acids**
  - Consumption of omega-3 fatty acids in the form of fish or in capsule form for women with hypertriglyceridemia or for primary or secondary prevention of CHD (*Class IIb; LOE B*).

Major Risk Factor Interventions

- **Blood pressure management**
  - Pharmacotherapy when blood pressure is ≥140/90 mm Hg (≥130/80 mm Hg in the setting of chronic kidney disease and diabetes. (*Class I; LOE B*).

- **Lipid Management**
  - LDL-C–lowering drug therapy is recommended (along with lifestyle) in women with CHD, other atherosclerotic CVD, diabetes mellitus or 10-year absolute risk >20% to achieve an LDL-C <100 mg/dL (*Class I; LOE A*).
  - LDL-C–lowering with lifestyle therapy in all others, even if LDL > 190 mg/dL. (*Class I LOE B*).
Major Risk Factor Interventions (cont.)

- **Lipid Management (cont.)**
  - *In women >60 years of age and with an estimated CHD risk >10%, statins could be considered if hsCRP >2 mg/dL after lifestyle modification and no acute inflammatory process is present (Class IIb; LOE B)*
  - Niacin or *fibrate therapy* can be useful when HDL-C is low (<50 mg/dL) or non–HDL-C is elevated (>130 mg/dL) in high-risk women after LDL-C goal is reached (*Class IIb; LOE B*).

- **Diabetes Management**
  - Lifestyle and/or pharmacotherapy to achieve HbA1C <7. (*Class Ila LOE B*).

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**ACCORD Lipid Protocol**

- Lipid Trial question: will combination therapy with a statin plus a fibrate would reduce cardiovascular events compared to statin therapy alone in people with T2DM
- All participants on open-labeled simvastatin, 20 to 40 mg/day
- randomized to placebo or fenofibrate, 54 to 160mg/day (based on GFR)

Lipid Trial Primary Outcome: Nonfatal MI, Nonfatal Stroke or CVD Death


### Primary Outcome By Treatment Group and Baseline Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate % Events (# in grp)</th>
<th>Placebo % Events (# in grp)</th>
<th>Feno to Placebo Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.9% (2765)</td>
<td>11.3% (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>9.1% (851)</td>
<td>6.6% (845)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>11.2% (1914)</td>
<td>13.3% (1910)</td>
<td></td>
<td>0.0106</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>8.1% (1930)</td>
<td>9.5% (1922)</td>
<td></td>
<td>0.2520</td>
</tr>
<tr>
<td>Age 65+</td>
<td>15.2% (927)</td>
<td>14.7% (931)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td>9.7% (855)</td>
<td>8.2% (888)</td>
<td></td>
<td>0.0877</td>
</tr>
<tr>
<td>White</td>
<td>10.9% (1909)</td>
<td>12.7% (1885)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Prev</td>
<td>7.3% (1757)</td>
<td>7.3% (1745)</td>
<td></td>
<td>0.4525</td>
</tr>
<tr>
<td>Secondary Prev</td>
<td>16.2% (1008)</td>
<td>18.1% (1008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycemia Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Std Glycemia</td>
<td>10.1% (1381)</td>
<td>11.6% (1370)</td>
<td></td>
<td>0.3579</td>
</tr>
<tr>
<td>Int Glycemia</td>
<td>10.9% (1374)</td>
<td>10.9% (1383)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Preventive Drug Interventions

- **Aspirin**
  Aspirin (75–325 mg/d) in women with CHD unless contraindicated (*Class I; LOE A*).
  - **Aspirin** (75–325 mg/d) is reasonable in **women with diabetes** (*Class IIa; LOE B*).
  - **Aspirin** (81 mg daily or 100 mg every other day) can be useful in women ≥65 years of age, if ... benefit for ischemic stroke and MI prevention is likely to outweigh risk of GI bleeding and hemorrhagic stroke (*Class IIa; LOE B*).
  - **Aspirin** (81 mg daily or 100 mg every other day) may be reasonable for women <65 years of age for ischemic stroke prevention (*Class IIb; LOE B*).

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**Diabetes aspirin use questioned**

**The POPADAD**

- 1200 patients (56% women) > 40 yo with diabetes, asymptomatic peripheral artery disease (ABI ≤ 0.99), no symptomatic CVD
- Randomized to receive aspirin 100 mg qd or placebo for 8 y
- Relative risk with 100 mg aspirin vs. placebo
  - CV mortality 1.23 (CI=[0.79, 1.93])
  - total CV events 0.98 (CI=[0.76, 1.26])
- “The trial does not provide evidence to support the use of aspirin… in primary prevention of CV events and mortality in the population with diabetes studied”

**JPAD: Total Atherosclerotic Events According to the Treatment Groups**

- Prospective, randomized, open-label, controlled trial
- 2567 Patients (45% women) randomized to low-dose aspirin group (81 or 100 mg/day) or no aspirin
- Inclusion Criteria: Type 2 diabetes 30 - 85 years old
- Exclusion Criteria: arteriosclerotic disease, atrial fibrillation, history of ulcer, and use of antithrombotic medication

![Log-Rank Test, \( P = 0.16 \)
HR (95% CI): 0.80 (0.58–1.10)](image)

**ADA Recommendations: Antiplatelet Agents**

- Consider aspirin therapy (75–162 mg/day) (C)
  - As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)
  - Includes most men >50 years of age or women >60 years of age who have at least one additional major risk factor
    - Family history of CVD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

Class III Interventions (Not Useful/Effective and May Be Harmful)

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

- **Antioxidant Supplements**
  - *Antioxidant vitamin supplements* (eg, vitamins A, C, E) **should not be used for the primary or secondary prevention of CVD** (Class III, LOA A).

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

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

**CONCLUSIONS**

- CHD is the leading cause of death in women and incidence appears to be increasing

- Risk Factor Modification remains the cornerstone of CV risk reduction

- Preventive Strategies may differ by sex

- Evidence-based therapies should be utilized

- Therapies of no proven benefit (or of potential harm) should be avoided

- As always…evidence continues to evolve