Statins for Cardiovascular Disease Prevention in Women: Review of the Evidence

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Risk Factor Burden at Age 50 Predicts Lifetime Incidence of Cardiovascular Disease in Women

Framingham Study (N = 4,362 Women—30 Yr F/U)

<table>
<thead>
<tr>
<th>Attained Age, Years</th>
<th>Cumulative Incidence of a First CV Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.7</td>
</tr>
<tr>
<td>60</td>
<td>0.6</td>
</tr>
<tr>
<td>70</td>
<td>0.5</td>
</tr>
<tr>
<td>80</td>
<td>0.4</td>
</tr>
<tr>
<td>90</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CV Event = MI, USA, CHD Death, Angina Pectoris, Atherothrombotic Stroke, Claudication, or Other CV Death

Serum Total Cholesterol at Age 50 Predicts Lifetime Incidence of Cardiovascular Disease in Women


CV Event = MI, USA, CHD Death, Angina Pectoris, Atherothrombotic Stroke, Claudication, or Other CV Death
### Statin Therapy for Secondary Prevention of Cardiovascular Disease in Women & Men

**A Sex-Based Meta-Analysis -- 2012**

<table>
<thead>
<tr>
<th>Secondary Prevention Trials</th>
<th>4S SPARCL PLAC-1</th>
<th>CARE PROSPER §</th>
<th>LIPID FLORIDA REIGGER</th>
<th>MIRACL ASCOT §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>11,243 Women + 31,950 Men + CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designs</td>
<td>Statin vs. Placebo, F/U 16 wk - 6.1 Yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes on Statins</td>
<td>Any CV Event*</td>
<td>Both women and men showed significant ~20% relative risk reductions [RR’s 0.81 - 0.82  p &lt; 0.05]</td>
<td>Any Death Men showed a significant 21% relative decrease--women had a favorable risk estimate only [RR 0.92  p &gt; 0.05]</td>
<td></td>
</tr>
</tbody>
</table>

* = MI, CHD Death, CV Death, CVA, STENT, or CABG


§ Classified as a primary prevention trial in some analyses
## Primary Prevention Statin Trials Enrolling Women

<table>
<thead>
<tr>
<th>Trial</th>
<th># Women (%)</th>
<th>Mean Age, Yrs</th>
<th>% With CVD</th>
<th>% With DM</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Active Drug (mg/day)</th>
<th>% LDL Change At 1 Yr</th>
<th>F/U, Yrs</th>
<th>Sex-Specific Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/TEXCAPS</td>
<td>997/15%</td>
<td>58</td>
<td>&lt; 1%</td>
<td>&lt; 5%</td>
<td>150</td>
<td>Lova 20-40</td>
<td>- 36%</td>
<td>5.2</td>
<td>Yes</td>
</tr>
<tr>
<td>MEGA</td>
<td>5,356/68%</td>
<td>58</td>
<td>&lt; 1%</td>
<td>21%</td>
<td>155</td>
<td>Prava 10-20</td>
<td>- 25%</td>
<td>5.0</td>
<td>Yes</td>
</tr>
<tr>
<td>JUPITER</td>
<td>6,801/38%</td>
<td>66</td>
<td>0%</td>
<td>0%</td>
<td>104 + hsCRP &gt;2</td>
<td>Rosuva 20</td>
<td>- 42%</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>ASCOT</td>
<td>1,942/19%</td>
<td>63</td>
<td>14%</td>
<td>24%</td>
<td>131</td>
<td>Atorva 10</td>
<td>- 41%</td>
<td>3.3</td>
<td>Yes</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>5,051/49%</td>
<td>66</td>
<td>22%</td>
<td>34%</td>
<td>145</td>
<td>Prava 40</td>
<td>~ 10%</td>
<td>4.9</td>
<td>Yes</td>
</tr>
<tr>
<td>PROSPER</td>
<td>3,000/52%</td>
<td>75</td>
<td>44%</td>
<td>12%</td>
<td>147</td>
<td>Prava 40</td>
<td>- 40%</td>
<td>3.3</td>
<td>No</td>
</tr>
<tr>
<td>HPS</td>
<td>5,082/25%</td>
<td>NR</td>
<td>85%</td>
<td>29%</td>
<td>131</td>
<td>Simva 40</td>
<td>- 49%</td>
<td>5.4</td>
<td>No</td>
</tr>
<tr>
<td>CARDS</td>
<td>909/32%</td>
<td>62</td>
<td>31%</td>
<td>100%</td>
<td>117</td>
<td>Atorva 10</td>
<td>- 44%</td>
<td>4.1</td>
<td>No</td>
</tr>
<tr>
<td>ASPEN</td>
<td>811/34%</td>
<td>61</td>
<td>31%</td>
<td>100%</td>
<td>113</td>
<td>Atorva 10</td>
<td>-38%</td>
<td>4.0</td>
<td>No</td>
</tr>
</tbody>
</table>
Limitations of Primary Prevention
Statin Trials Enrolling Women

- Inability to classify many trials
- Low numbers of women in early trials
- Low numbers of older women
- Methodologic problems in large early trial
- Lack of sex-specific analyses
- Lack of reporting of individual events
- Short durations of follow up
Lipid Drug Therapy for Primary Prevention of Coronary Disease in Women
A Systematic Review – 2004

<table>
<thead>
<tr>
<th>Primary Prevention Trials to 2004</th>
<th>AF/TEXCAPS COLESTIPOL</th>
<th>ALLHAT ACAPS</th>
<th>ASCOT HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>11,435 Women “No” CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designs</td>
<td>Lipid Drug vs. Placebo, F/U 2.8 – 5.2 Yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Outcomes on Drug (Statins in all except 1 Trial) | Any CHD Event*
Non-significant but favorable risk estimate [RR 0.87 p > .05]
Excluding ALLHAT yielded significant 23% risk reduction [RR 0.77 p < .05] |              |          |
|                                  | Any Death
Non-significant but favorable estimate [RR 0.95 p=NS] |              |          |

* = MI, USA, CHD Death, PCI or CABG

## Statin Therapy for Primary Prevention of Coronary Disease in Women vs. Men

### A Sex-Based Meta-Analysis – 2010


<table>
<thead>
<tr>
<th>Primary Prevention Trials to 2008</th>
<th>AF/TEXCAPS WOSCACS</th>
<th>ALLHAT PROSPER</th>
<th>ASCOT MEGA</th>
<th>HPS ACAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>19,052 Women + 30,194 Men “No” CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Designs</strong></td>
<td>Statin vs. Placebo, Mean F/U 3.9 Yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes on Statins</strong></td>
<td>Any CHD Event*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women had borderline 11% risk reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[RR 0.89  p = 0.05]</td>
<td></td>
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<tr>
<td></td>
<td>Men had a significant 41% risk reduction</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>[RR 0.59  p &lt; 0.05]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Death  Both women and men had non-significant favorable risk estimates</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>[RR 0.96 - 0.93  p &gt; 0.05 for both]</td>
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</tbody>
</table>

= MI, USA, CHD Death, PCI or CABG.

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Does The Argument To Withhold Statins in Women At Risk “Stretch the Limits” of Evidence Based Medicine?

**No**

- *P* values >0.05 indicate insufficient evidence to support treatment

**Ye**

- ‘*P* < 0.05’ is an arbitrary cutoff
- *P* values reflect only the strength of evidence against the ‘null’ hypothesis
- *P*-values must be interpreted within the context of other trial data and human physiology

Baum, S. Evidence Based Medicine. What’s the Evidence? Clinical Cardiology 2012;35:259
Evidence Suggests
 Few Sex-Based Differences in
 Atherosclerotic Plaque Histology or Biology

Raised plaques exist in a large proportion of women and men by middle age

Plaques in women are histologically identical to those in men

There is no evidence that plaques in women are less vulnerable to rupture

There is no evidence that statins stabilize vulnerable plaques after rupture, but not before

# Statin Therapy for Primary Prevention of Cardiovascular Disease in Women with Elevated hsCRP

**JUPITER Trial -- 2010**

<table>
<thead>
<tr>
<th>Females</th>
<th>N=6,801  &gt; 60 Yr  0 CVD  LDL-C &lt;130  hsCRP &gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Rosuvastatin 20 mg  vs.  Placebo  F/U 2 Yr</td>
</tr>
<tr>
<td>Endpoint</td>
<td>MI  CVA  USA  STENTS  CABG or CV Death</td>
</tr>
</tbody>
</table>

**Outcomes in Women on Statins**

- **Primary Endpoint - Any CV Event**
  - Women had a significant 46% decrease in relative risk [HR 0.54  p = 0.002].
  - Those with FHx CAD had an 80% decrease [HR 0.20, p <.05]

- **Unstable Angina or Revascularization**
  - Women had a significant 76% decrease in relative risk [HR 0.24  p=.0001]

- **Any MI, CVA or CV Death** [HR 0.73  p=0.16]
- **Any Death**  [HR 0.77  p = 0.12]

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Statin Therapy for Primary Prevention of Cardiovascular Disease In Women With Elevated hsCRP or Dyslipidemia

An Updated Sex-Based Meta-Analysis—Post JUPITER – 2010

RR for Total CVD* in Statin vs. Placebo Treated Women In the 3 Exclusively Primary Prevention Trials (N=13,154)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>RR</th>
<th>95% CI</th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>1998</td>
<td>0.67</td>
<td>(0.34-1.31)</td>
<td>21/498</td>
<td>14/499</td>
</tr>
<tr>
<td>MEGA</td>
<td>2006</td>
<td>0.73</td>
<td>(0.49-1.10)</td>
<td>56/2,718</td>
<td>40/2,638</td>
</tr>
<tr>
<td>JUPITER</td>
<td>2008</td>
<td>0.54</td>
<td>(0.37-0.80)</td>
<td>70/3,375</td>
<td>39/3,426</td>
</tr>
</tbody>
</table>

* Favors Statin
Favors Placebo

P for heterogeneity 0.56

0.63 [0.49-0.82 p < 0.001]

Mora, S et al.
Circulation
2010;121:1069-77

*= MI, CHD, Death, CV Death, CVA, STENT, or CABG
# Statin Effects in Women vs. Men

## Most Recent Sex-Based Meta-Analysis -- 2012

<table>
<thead>
<tr>
<th>18 Trials</th>
<th>A to Z CORONA SEARCH</th>
<th>AFTEXCAPS GREASE JUPITER</th>
<th>ALLHAT GISSI-P HPS</th>
<th>ASCOT LIPID PROSPER</th>
<th>AURORA MEGA PROVEIT</th>
<th>CARE 4S TNT</th>
</tr>
</thead>
</table>

### Subjects
40,275 Women + 100,960 Men ± CVD

### Designs
Statin vs. Placebo or More vs. Less Statin

### Outcomes on Statins
CV Events were significantly reduced 17% in women and 23% in men in primary and secondary prevention trials, regardless of baseline risk

- [OR-Women 0.83, OR-Men 0.77 \( p < .001 \)]

Total Deaths were reduced significantly by 13% in women in primary prevention trials

- [OR 0.87 \( p \sim 0.01 \)]

Kostis, WJ et al. JACC 2012;59:572-82.
Remaining Questions About Statins for Primary Prevention in Women

How Do We Assess Global Risk, and At What Level of Risk Do We Treat?

- Which Risk Score is Best For Women?
  - ATP III Score predicts MI or CHD death only
  - Updated Framingham Score includes all CVD
  - Reynolds Score adds hsCRP, family history

- Do We Treat at >5%, >10% or >20% Risk?
  - Cost efficacy is greater in high risk women, but majority of events will occur in women with low and intermediate 10-year risk
Remaining Questions About Statins for Primary Prevention in Women

What Costs Are We Willing to Pay?

• Drug Costs Are Low and Gender Neutral
  – A generic statin = $ 0.06 tab/day x 1 yr = $ 22

• Cost Efficacy is Lower in Women
  – Absolute risk reduction (ARR) is low in primary prevention [~0.5 % / year in women in JUPITER]
  – Since the NNT to prevent 1 event = 1 / ARR, an ARR of ~ 0.5% / year (or 2.5% in 5 years) translates to needing to treat ~40 women for 5 years to prevent 1 event [at a cost of $4,500 to $255,000]

*NNT = Number Needed To Treat
Remaining Questions About Statins for Primary Prevention in Women

What Side Effect Risks Are Acceptable?

- Diabetes Mellitus
  - Risk: ~9% - 13% from meta-analyses
  - Risk Factor: Pre-Diabetes

- Neuro-Cognitive Dysfunction
  - Risk: Unknown—reports based only on FDA AERS

- Liver Injury
  - Risk: “Transaminitis” 1/100; Liver Failure 1/1,000,000

- Myopathy
  - Risks: Myositis 5/100,000; Rhabdomyolysis 1.5/100,000
  - Risk Factors: Age, Small BMI, CKD, Drug interactions

Summary: What To Tell Patients

- The lifetime risk of CV disease in women is closely tied to the risk factor burden at age 50.
- In women *with* CV disease, statins significantly reduce the risk of CV events.
- In those *at risk of* CV disease, early statin trials showed benefits for men, but non-significant results in women were due to trial limitations.
- Recent meta-analyses show statins reduce CV events in at-risk women with elevated lipids or hsCRP, especially those with a family history of early CHD—and may reduce the risk of death.
- Specific clinical benefits, cost efficacy, and the risk-to-benefit ratio may be different in women and must be considered when treating.