Statins for the Primary Prevention of Cardiovascular Events in Women With Elevated High-Sensitivity C-Reactive Protein or Dyslipidemia

Results From the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and Meta-Analysis of Women From Primary Prevention Trials

Samia Mora, MD, MHS; Robert J. Glynn, ScD; Judith Hsia, MD; Jean G. MacFadyen, BA; Jacques Genest, MD; Paul M Ridker, MD, MPH

Background—Statin therapy in women without cardiovascular disease (CVD) is controversial, given the insufficient evidence of benefit. We analyzed sex-specific outcomes in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and synthesized the results with prior trials.

Methods and Results—JUPITER participants included 6801 women ≥60 years of age and 11 001 men ≥50 years of age with high-sensitivity C-reactive protein ≥2 mg/L and low-density lipoprotein cholesterol <130 mg/dL randomized to rosuvastatin versus placebo. Meta-analysis studies were randomized placebo-controlled statin trials with predominantly or exclusively primary prevention in women and sex-specific outcomes (20 147 women; 276 CVD events; mean age, 63 to 69 years). Absolute CVD rates (per 100 person-years) in JUPITER women for rosuvastatin and placebo (0.57 and 1.04, respectively) were lower than for men (0.88 and 1.54, respectively), with similar relative risk reduction in women (hazard ratio, 0.54; 95% confidence interval, 0.37 to 0.80; \( P < 0.002 \)) and men (hazard ratio, 0.58; 95% confidence interval, 0.45 to 0.73; \( P < 0.001 \)). In women, there was significant reduction in revascularization/unstable angina and nonsignificant reductions in other components of the primary end point. Meta-analysis of 13 154 women (240 CVD events; 216 total deaths) from exclusively primary prevention trials found a significant reduction in primary CVD events with statins by a third (relative risk, 0.63; 95% confidence interval, 0.49 to 0.82; \( P < 0.001 \); \( P \) for heterogeneity = 0.56) with a smaller nonsignificant effect on total mortality (relative risk, 0.78; 95% confidence interval, 0.53 to 1.15; \( P = 0.21 \); \( P \) for heterogeneity = 0.20). Similar results were obtained for trials that were predominantly but not exclusively primary prevention.

Conclusion—JUPITER demonstrated that in primary prevention rosuvastatin reduced CVD events in women with a relative risk reduction similar to that in men, a finding supported by meta-analysis of primary prevention statin trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00239681.

(Circulation. 2010;121:1069-1077.)

Key Words: lipids ■ meta-analysis ■ prevention ■ women

The use of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins) in patients with manifest cardiovascular disease (CVD) is established, with similar benefits in women and men for relative risk (RR) reduction of \( \approx 20 \% \) to 30%, but statin use for the primary prevention of CVD is controversial, particularly for women.1–3 Specifically, for primary prevention in men, prior meta-analyses showed significant reductions in coronary events with statins versus placebo, whereas in women, the reduction was smaller and nonsignificant.4,5 Before the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), statins had not been found to reduce total or coronary mortality in women, men, or combined for primary prevention.4–6 Moreover, the recent Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study enrolled...
more women than men in large numbers, but the reduction in events was significant only in men.7

---

**Editorial see p 1063**

**Clinical Perspective on p 1077**

**JUPITER** was a multicenter randomized trial designed to assess the benefits and risks of statin therapy in apparently healthy individuals selected on the basis of elevated high-sensitivity C-reactive protein (hsCRP), a marker of higher cardiovascular risk, without a concomitant elevation in low-density lipoprotein (LDL) cholesterol.8 We conducted a prespecified sex-specific analysis in JUPITER comparing the efficacy and safety of rosuvastatin therapy in women versus men. We then performed an updated meta-analysis of statin therapy for the primary prevention of CVD events and total mortality in women, with nearly twice the number of women included in the prior meta-analysis by Walsh and Pignone4 in 2004.

**Methods**

**JUPITER Study Design and Protocol**

The JUPITER design has previously been described.8,9 A total of 17 802 asymptomatic individuals (women ≥60 years of age; men ≥50 years) without prior history of coronary disease, stroke, or diabetes mellitus who had LDL cholesterol <130 mg/dL and hsCRP ≥2.0 mg/L were randomized. Drugs that were exclusion criteria included current use of hormone therapy, previous or current use of lipid-lowering therapy, or immunosuppressant agents. Family history of premature coronary disease was defined as coronary disease in a first-degree male relative <55 years of age or female relative <65 years of age. Metabolic syndrome and Framingham Risk Score categories were defined according to Adult Treatment Panel III guidelines.10

Follow-up included laboratory evaluations and structural interviews assessing outcomes and potential adverse events. Laboratory measurements for fasting lipids, hsCRP, hepatic and renal function, fasting blood glucose levels, and hemoglobin A1c (HbA1c) were performed in a central laboratory. Estimated glomerular filtration rate was calculated from serum creatinine with the Modification of Diet in Renal Disease equation.11

**Outcomes and Adverse Events**

The trial was expected to last ~5 years, but on March 30, 2008, the Independent Data and Safety Monitoring Board terminated the trial early for benefit (after 1.9-year median follow-up; maximal follow-up, 5 years). The primary end point of the JUPITER trial was a composite end point defined as the combined end point of myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. Myocardial infarction, stroke, and cardiovascular death were confirmed according to standard criteria. Unstable angina was ischemic chest pain at rest or with minimal exertion occurring within the preceding 48 hours and requiring hospitalization with the presence of objective evidence of ischemia. Arterial revascularization was coronary artery bypass graft surgery, bypass grafting of any peripheral or carotid artery, or the performance of at least 1 percutaneous transluminal intervention.

All reported primary end points that occurred through March 30, 2008, were adjudicated by an independent end-point committee blinded to randomized treatment assignment. Adverse events were monitored and reported in a blinded manner until the date of the closeout visit and discontinuation of therapy.

**Meta-Analysis Methods**

We performed a review of peer-reviewed publications identified through searches of MEDLINE through July 2009. Bibliographies from these references were also reviewed. Criteria used for study selection included randomized placebo-controlled statin trials that included predominantly or exclusively primary prevention individuals with mean follow-up of >1 year and with sex-specific clinical outcomes on CVD or total mortality. Other criteria used were English language and validity based on the venue of publication. For this analysis, we included primary prevention trials that included women with diabetes. Three trials (Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], MEGA, and JUPITER) were considered exclusively primary prevention, whereas 2 other trials (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack [ALLHAT-LLT] and Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm [ASCOT-LLA]) were considered predominantly primary prevention because they included ~15% prior CVD. Two other trials, the Heart Protection Study (HPS) and Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER), included a substantial number of women without known CVD but did not report sex-specific outcomes for these women. We repeated the meta-analysis including these 2 trials.

**Statistical Analysis**

Statistical analyses were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC) and STATA software, version 10.1 (Stata Corp, College Station, Tex). For the JUPITER trial, all analyses were performed separately in women and men as prespecified in the trial design. Wilcoxon 2-sample tests for continuous variables and χ2 tests for categorical variables were used to compare the distribution of risk factors and levels of biomarkers across the 2 randomized treatment arms in sex-specific analyses.

Statistical tests for outcomes were performed according to intention to treat. The exposure time was calculated as the time from randomization to occurrence of the primary end point or the date of death, last study visit, withdrawal, or loss to follow-up or March 30, 2008, whichever came first. Absolute event rates were calculated per 100 person-years. Cox proportional-hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). The number needed to treat was computed on the basis of absolute 4-year values projected over an average 5-year period.12 P values for heterogeneity of treatment effect for outcomes between women and men were obtained from likelihood-ratio tests in Cox models that included treatment assignment, sex, and the interaction term. All P values were 2 tailed.

For the meta-analysis, 5 studies met the selection criteria.8,13–16 We constructed 2×2 tables for the statin and placebo arms for CVD, the primary end point of the meta-analysis. These included predominantly myocardial infarction, angina/revascularization, stroke, and CVD death, with some of the trials including peripheral vascular events8,17 and 1 trial including ischemic congestive heart failure.13 Two trials included only myocardial infarction and coronary death.14,15 Four trials reported the number of cases in the statin and placebo arms (ALL-HAT did not),14 so the total number of events could be reported only as greater than the number of events in these 5 trials (ie, >276 CVD events). Four of the 5 trials included sex-specific data on total mortality,8,14,16,17 and separate 2×2 tables were constructed for total mortality. Summary RRs were obtained from random-effects regression models. Tests for heterogeneity between studies and an estimator of between-study variance were also obtained, with plots for the individual and pooled estimates.

Drs Mora, Glynn, and Ridker had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**JUPITER Baseline Characteristics**

A total of 6801 women were randomized (3426 to rosuvastatin, 3375 to placebo) compared with 11 001 men (5475 to rosuvastatin, 5526 to placebo). Screen failure rates were 80.5% and 79.6% in women and men, respectively. Table 1 shows baseline characteristics of participants. Women were
Table 2. Baseline Characteristics of Women and Men in JUPITER

<table>
<thead>
<tr>
<th></th>
<th>Women (n=11 001)</th>
<th>Men (n=11 001)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.0 (65.0–73.0)</td>
<td>63.0 (58.0–70.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>7.6</td>
<td>21.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>62.7</td>
<td>54.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/ethnic group, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>61.7</td>
<td>77.1</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15.9</td>
<td>10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18.9</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>3.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2 (25.7–33.2)</td>
<td>27.9 (25.1–31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>46.7</td>
<td>38.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of premature CHD, %</td>
<td>12.2</td>
<td>11.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>16.4</td>
<td>16.8</td>
<td>0.51</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.6 (3.1–7.7)</td>
<td>4.1 (2.7–6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>109 (96–120)</td>
<td>108 (93–119)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54 (46–66)</td>
<td>45 (38–55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>118 (88–163)</td>
<td>118 (84–174)</td>
<td>0.64</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>192 (175–205)</td>
<td>182 (165–195)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>93 (87–101)</td>
<td>95 (88–102)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.8 (5.5–6.0)</td>
<td>5.6 (5.4–5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL·min⁻¹·1.73 m⁻² BSA</td>
<td>66.8 (58.6–77.0)</td>
<td>77.4 (66.8–88.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; BSA, body surface area. Values are median (25th to 75th percentile) when appropriate. P values were obtained from Wilcoxon 2-sample tests.

older than men (median age, 68 and 63 years, respectively), which reflected the sex-specific age entry criterion (women ≥60 years, men ≥50 years) and were less likely to be white. Women were heavier and had more prevalent hypertension and metabolic syndrome, but they smoked much less than men. Similar rates of aspirin use were noted in women and men.

Women had higher concentrations of hsCRP (4.6 versus 4.1 mg/L, respectively; P<0.001), even though they were not on hormone therapy. Women and men had similar baseline LDL cholesterol levels (109 and 108 mg/dL, respectively), although the small LDL cholesterol difference was statistically significant. High-density lipoprotein (HDL) cholesterol was higher in women by 10 mg/dL; hence, total cholesterol was also higher by 10 mg/dL. Small yet statistically significant differences were also noted for fasting glucose (lower in women) and HbA₁c (lower in men). Women had lower glomerular filtration rates (10 mL·min⁻¹·1.73 m⁻² body surface area) compared with men.

JUPITER Changes in Lipids and hsCRP

At the 12-month follow-up, the median change in hsCRP concentration in women was −1.8 mg/L (39%) with rosuvastatin and −0.6 mg/L (13%) with placebo, which were similar to the reductions in men (Table 2). In women, the median change in LDL cholesterol was −51 mg/dL (47%) on rosuvastatin and +4 mg/dL (4%) on placebo, with similar changes in men. HDL cholesterol increased by 3 and 1 mg/dL in women on rosuvastatin and placebo, respectively. Triglycerides were reduced by 17 mg/dL (14%) in women on rosuvastatin with no change in those on placebo; similar results were seen for men. Total cholesterol was higher in women at baseline and remained higher during follow-up, but the reduction was similar in women and men.

JUPITER Outcomes

As shown in Table 3, the absolute rates (per 100 person-years) of the primary end point in rosuvastatin and placebo were lower in women (0.56 and 1.04, respectively) than men (0.88 and 1.54, respectively), but the RR reduction with rosuvastatin was similar and statistically significant in both women (HR, 0.54; 95% CI, 0.37 to 0.80; P=0.002) and men (0.58; 95% CI, 0.45 to 0.73; P<0.001). The P value for a
treatment-by-sex interaction using a sex-stratified Cox proportional-hazards model was nonsignificant ($P=0.80$). The HR and 95% CI for the ratio of the relative hazards for treatment in women and men for the primary end point were 0.94 and 0.60 to 1.49, respectively.

When the components of the composite primary end point were analyzed, the HR for each component favored rosuvastatin therapy for both women and men, with some sex differences noted. Women had a significant reduction in revascularization/unstable angina (HR, 0.24; 95% CI, 0.11 to 0.51), which was greater in magnitude than for men (HR, 0.63; 95% CI, 0.46 to 0.85; $P$ for heterogeneity $=0.01$). Women had nonsignificant reductions in other components of the primary end point, and a smaller reduction in nonfatal stroke compared with men ($P$ for heterogeneity $=0.04$). The HR for all-cause death was similarly reduced for women (HR, 0.77; 95% CI, 0.55 to 1.06) and men (HR, 0.82; 95% CI, 0.66 to 1.03). Although this reduction did not reach statistical significance in either sex separately, it was significant when combined ($P=0.02$). The 5-year number needed to treat to prevent 1 primary end point was calculated to be 36 in women, 22 in men, and 25 when combined.

**JUPITER Adverse Events**

The occurrence of serious adverse events was similar by sex (Table 4). Specifically, the rates of muscle disorders or myopathy were similar in women and men regardless of treatment assignment. Death resulting from cancer was examined because of prior reports of possibly increased rates of cancer-related death in women treated with statins, but we found no significant difference in cancer death in women.

Although both women and men treated with rosuvastatin had higher HbA$_{1c}$ at 12 months, a higher incidence of
physician-reported diabetes mellitus was observed in women treated with rosuvastatin versus placebo (1.53 versus 1.03 per 100 person-years, respectively; HR, 1.49; 95% CI, 1.11 to 2.01; \( P = 0.008 \)) compared with men (1.36 versus 1.20 per 100 person-years, respectively; HR, 1.14; 95% CI, 0.91 to 1.43; \( P = 0.24 \)). The test for heterogeneity of diabetes mellitus by sex was not significant (\( P \) for heterogeneity=0.16).

**JUPITER Sex-Specific Subgroups**

Subgroup analysis showed a reduction in the primary end point for both women and men (Figure 1). Two borderline-significant interactions were noted for women, whereas there was no significant interaction for any subgroup for men. First, in the 829 women who reported a family history of premature coronary disease, there was a greater proportional reduction in the primary end point compared with the women without such a history, although both were significant (HR, 0.20; 95% CI, 0.06 to 0.69; and HR, 0.63; 95% CI, 0.41 to 0.96, respectively; \( P \) for interaction=0.07). Men with and without a family history of premature coronary disease had a similar proportional reduction in the primary end point. Second, women without the metabolic syndrome appeared to have a greater reduction with rosuvastatin than those with the metabolic syndrome (HR, 0.35; 95% CI, 0.19 to 0.65; and HR, 0.77; 95% CI, 0.46 to 1.30, respectively; \( P \) for interaction=0.06).

There was no significant interaction in women stratified by Framingham Risk Scores or by HDL cholesterol. Few events occurred in women with Framingham Risk Scores \(<5%\) (\( n = 2618, 15 \) events). Women with Framingham Risk Scores of \( 5% \) to \( 10% \) (\( n = 2525 \)) and \( >10% \) (\( n = 1646 \)) had similar and significant proportional reductions in events (HR, 0.44; 95% CI, 0.22 to 0.89; and HR, 0.57; 95% CI, 0.34 to 0.97). The absolute event rates (per 100 person-years) were lower in women with scores of \( 5% \) to \( 10% \) (0.42 in rosuvastatin and 0.96 in placebo) compared with women with scores \( >10% \) (1.28 and 2.23, respectively). Similar results were found in men stratified by Framingham Risk Scores, although men had higher absolute rates. The event rates were also low for women \(<65 \) years of age, although there was no significant interaction by age. Men \(<65 \) and \( >65 \) years of age benefited from rosuvastatin therapy. Similar findings were observed when an alternative age cut point of 70 years was used.

**Meta-Analysis Results**

Compared with placebo, statin therapy in women significantly reduced CVD by about one-third in exclusively primary prevention trials (Figure 2A). The summary RR for the 3 trials was 0.63 (95% CI, 0.49 to 0.82; \( P < 0.001 \); \( P \) for heterogeneity=0.56). When trials that included predominantly primary prevention were analyzed together with the exclusively primary prevention trials, the summary RR was
similar but not statistically significant (0.79; 95% CI, 0.59 to 1.05; P=0.11; P for heterogeneity=0.053; Figure 2B). When we included HPS and PROSPER with the other 5 trials (data not shown), the summary RR was unchanged (0.82; 95% CI, 0.69 to 0.98; P=0.03).

The summary RR for the 3 exclusively primary prevention trials (n=13,154 women, 216 deaths) that reported sex-specific total mortality was 0.78 (95% CI, 0.53 to 1.15; P=0.21; Figure 2C). When all trials that reported sex-specific mortality outcomes in predominantly or exclusively primary prevention in women were included, the summary RR was similar (Figure 2D). HPS and PROSPER did not report sex-specific mortality data in the primary prevention arms.

### Discussion

In the JUPITER trial, statin treatment of apparently healthy individuals with elevated hsCRP and low LDL cholesterol (women ≥60 years of age, men ≥50 years of age) resulted in similar and significant proportional reductions in the primary end point for both women (46%; P=0.002) and men (42%; P<0.001).

### Figure 1. Effects of rosuvastatin on the primary composite end point according to baseline characteristics. The dashed overall line indicates the overall HR for the entire cohort (men and women combined). Hx indicates history; CHD, coronary heart disease; and BMI, body mass index.
primary CVD with allocation to statin therapy compared with placebo in women. These findings contrast with prior primary prevention trials and meta-analyses that found that among men there were significant reductions in coronary events but among women the reduction was smaller and nonsignificant.\(^4,5\) When trials that included both primary and secondary prevention populations such as PROSPER\(^19\) and HPS\(^20\) or only secondary prevention were analyzed previously, results were similar in women and men, consistent with the present meta-analysis in primary prevention in women. This argues against a sex difference in statin therapy in the primary prevention setting; rather, it suggests that the prior lack of significance may have been due to the inadequate number of events among women in these studies. Compared with prior nonsignificant sex-specific meta-analyses in primary prevention,\(^4,5\) the present meta-analysis findings of a significant reduction in CVD is likely related to the larger number of events by including the recent JUPITER and MEGA trials and using a combined CVD end point that included stroke.

Importantly, the HRs in JUPITER showed a reduction in all-cause death that, although nonsignificant in either men or women when analyzed separately, was statistically significant when they were analyzed together, as previously reported \((P=0.02).^8\) There was no evidence for an increase in cancer deaths among women or men in JUPITER. This contrasts with a significant increase in cancer deaths in the Treating to New Targets study among women with stable coronary disease.\(^18\) The JUPITER and updated meta-analysis results are, however, consistent with results from meta-analyses that showed no increase in all-cause death in either sex.\(^4,5\) In addition, the present study is the first to find a significant reduction among women for arterial revascularization or unstable angina. This may be important because women present more with angina than myocardial infarction, whereas the opposite is generally seen in men.

A finding that deserves further investigation is the somewhat higher risk of physician-reported incident diabetes in the statin arm compared with placebo that was observed in women compared with men, although the test for heterogeneity by sex was not significant. A recent study found that among women, a diagnosis of diabetes mellitus carried a 37% higher risk of subsequent CVD death than did a diagnosis of myocardial infarction, whereas the reverse was found among men, with myocardial infarction having a 43% higher risk of
CVD death compared with diabetes. Clinically, women with impaired fasting glucose or overweight/obesity were at greater risk for developing diabetes mellitus, and this subgroup had a 40% RR reduction in the primary end point in JUPITER. Interestingly, the only statin trial that showed a reduction in diabetes mellitus with statin therapy was a trial that enrolled only men, the West of Scotland Coronary Prevention Study (WOSCOPS), in which pravastatin resulted in lower incident diabetes compared with placebo. How- ever, other statin trials that included both men and women such as the HPS found a similarly small (0.6%) nonsignificant increase in incident diabetes with simvastatin that was also seen with atorvastatin (0.4%) in ASCOT-LLA. The present finding of a potential sex difference for incident diabetes underscores the importance of analyzing and reporting trial efficacy and safety data in women and men separately and combined, as has recently been recommended.

This study has potential limitations. The median duration of follow-up in JUPITER was 1.9 years (maximum, 5 years) because of early termination of the trial for benefit, and long-term safety data for rosuvastatin in a primary prevention setting are limited. Although there was a substantial proportion of women <65 years or with low Framingham Risk Scores, the event rates were low in these subgroups, and the question of whether they would significantly benefit from statin therapy remains. Limitations of the meta-analysis included the fact that the number of both CVD and total deaths could not be determined exactly because 1 trial did not report sex-specific event rates, and the degree of LDL cholesterol lowering differed among the trials.

Conclusions
Statin treatment of apparently healthy women with elevated hsCRP and nonelevated LDL cholesterol resulted in similar and significant proportional reductions in CVD compared with men. Absolute event rates were lower in women, with a greater benefit for revascularization/unstable angina in women and a greater benefit for stroke in men. Subgroup analysis suggested that women with a family history of premature coronary disease may benefit more from rosuvastatin therapy that those without. Women and men with Framingham Risk Scores <5% had low event rates, although there was no suggestion of heterogeneity by categories of Framingham risk in either women or men. When these results are taken together with the results of the updated meta-analysis in women, statin therapy resulted in about a one-third relative reduction in primary CVD in women, a benefit similar to that seen in previous meta-analyses of men.

Source of Funding
JUPITER was funded by AstraZeneca. The sponsor collected data and monitored study sites but played no role in the conduct of the analyses or drafting of the manuscript.

Disclosures
Dr Mora received research grant support from the National Heart, Lung, and Blood Institute (K08 HL094375), AstraZeneca, and Merck. Dr Glynn received grant support from AstraZeneca and Bristol-Myers Squibb. Dr Hsia is employed by AstraZeneca. Dr Genest received research grants from Merck, AstraZeneca, and Resverlogix and speaker’s fees from Merck, AstraZeneca, and GlaxoSmithKline. Dr Ridker received research support from Astra- Zeneca, Novartis, Roche, and Sanofi-Aventis and nonfinancial re- search support from Amgen. Dr Ridker is coinventor on patents held by Brigham and Women’s Hospital related to the use of inflamma- tory biomarkers in CVD that have been licensed to Siemens and AstraZeneca and has served as a research consultant to Schering- Plough, Sanofi-Aventis, AstraZeneca, Isis, Siemens, Merck, Novar- tis, and Vascular Biogenics. J.G. MacFadyen reports no conflicts.

References
12. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319:1492–1495.


**CLINICAL PERSPECTIVE**

The use of statins in patients with manifest cardiovascular disease is established, with similar benefits seen in women and men, but statin use for the primary prevention of cardiovascular disease is controversial, particularly for women. We analyzed sex-specific outcomes in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and conducted an updated meta-analysis of statin use for women in primary prevention (20 147 women; >276 cardiovascular disease events; mean age, 63 to 69 years). JUPITER was a multicenter randomized trial designed to assess the benefits and risks of statin therapy in apparently healthy individuals selected on the basis of elevated high-sensitivity C-reactive protein, a marker of higher cardiovascular risk, without a concomitant elevation in low-density lipoprotein cholesterol. JUPITER participants included 6801 women ≥60 years of age and 11 001 men ≥50 years of age with high-sensitivity C-reactive protein ≥2 mg/L and low-density lipoprotein cholesterol <130 mg/dL who were randomized to rosuvastatin 20 mg/d versus placebo. Absolute cardiovascular disease rates for rosuvastatin and placebo in JUPITER were lower for women than for men, but there were similar and significant relative risk reductions in both women (by 46%) and men (by 42%). In women, there was significant reduction in revascularization/unstable angina and nonsignificant reductions in other components of the primary end point. Furthermore, in this updated meta-analysis of statin therapy for primary prevention in women, statin allocation yielded a significant relative risk reduction in cardiovascular disease by one-third, similar to prior results in men and in secondary prevention in women.
Statins for the Primary Prevention of Cardiovascular Events in Women With Elevated High-Sensitivity C-Reactive Protein or Dyslipidemia: Results From the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and Meta-Analysis of Women From Primary Prevention Trials
Samia Mora, Robert J. Glyn, Judith Hsia, Jean G. MacFadyen, Jacques Genest and Paul M Ridker

Circulation. 2010;121:1069-1077; originally published online February 22, 2010; doi: 10.1161/CIRCULATIONAHA.109.906479

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/9/1069

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/