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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

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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.

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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

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more women than men in large numbers, but the reduction in events was significant only in men.⁷

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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 A_{1c} (HbA_{1c}) 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 $\approx 15\%$ 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 χ^2 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 events^{8,13} 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 1. Baseline Characteristics of Women and Men in JUPITER

	Women (n=6801)	Men (n=11 001)	P
Age, y	68.0 (65.0–73.0)	63.0 (58.0–70.0)	<0.001
Current smoking, %	7.6	21.0	<0.001
Hypertension, %	62.7	54.1	<0.001
Race/ethnic group, %			
White	61.7	77.1	
Black	15.9	10.4	<0.001
Hispanic	18.9	8.8	
Other or unknown	3.5	3.6	
Body mass index, kg/m ²	29.2 (25.7–33.2)	27.9 (25.1–31.2)	<0.001
Metabolic syndrome, %	46.7	38.7	<0.001
Family history of premature CHD, %	12.2	11.1	0.02
Aspirin use, %	16.4	16.8	0.51
hsCRP, mg/L	4.6 (3.1–7.7)	4.1 (2.7–6.8)	<0.001
LDL cholesterol, mg/dL	109 (96–120)	108 (93–119)	<0.001
HDL cholesterol, mg/dL	54 (46–66)	45 (38–55)	<0.001
Triglycerides, mg/dL	118 (88–163)	118 (84–174)	0.64
Total cholesterol, mg/dL	192 (175–205)	182 (165–195)	<0.001
Glucose, mg/dL	93 (87–101)	95 (88–102)	<0.001
HbA _{1c} , %	5.8 (5.5–6.0)	5.6 (5.4–5.9)	<0.001
Glomerular filtration rate, mL · min ⁻¹ · 1.73 m ⁻² BSA	66.8 (58.6–77.0)	77.4 (66.8–88.4)	<0.001

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 HbA_{1c} (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

Table 2. Lipid and Other Laboratory Measurements During Follow-Up in JUPITER

	Baseline		At 12 mo		Change From Baseline to 12 mo		<i>P</i> *
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	
Women							
hsCRP, mg/L	4.6 (3.1–7.7)	4.6 (3.1–7.6)	2.5 (1.4–4.8)	4.1 (2.4–7.0)	-1.8 (-3.6--0.6)	-0.6 (-2.2-0.8)	<0.0001
LDL cholesterol, mg/dL	109 (97–120)	109 (95–120)	55 (44–73)	112 (97–127)	-51 (-65--27)	4 (-7–17)	<0.0001
HDL cholesterol, mg/dL	54 (46–66)	54 (46–66)	58 (48–70)	55 (46–67)	3 (-2–8)	1 (-4–6)	<0.0001
Triglycerides, mg/dL	118 (88–162)	117 (88–164)	98 (76–131)	118 (89–161)	-17 (-44–3)	-1 (-23–21)	<0.0001
Total cholesterol, mg/dL	192 (175–205)	192 (175–205)	138 (121–163)	196 (177–215)	-51 (-68--27)	4 (-9–19)	<0.0001
Men							
hsCRP, mg/L	4.0 (2.7–6.6)	4.1 (2.7–6.8)	2.1 (1.2–4.1)	3.2 (1.8–5.8)	-1.7 (-3.4--0.4)	-0.8 (-2.5-0.8)	<0.0001
LDL cholesterol, mg/dL	107 (92–119)	108 (92–118)	55 (44–71)	108 (92–123)	-49 (-62--29)	3.0 (-9–15)	<0.0001
HDL cholesterol, mg/dL	46 (38–55)	45 (38–55)	49 (41–59)	47 (39–56)	3 (-2–8)	1 (-3–5)	<0.0001
Triglycerides, mg/dL	118 (83–176)	118 (84–172)	100 (73–142)	119 (86–172)	-16 (-50–7)	2 (-26–27)	<0.0001
Total cholesterol, mg/dL	182 (165–196)	182 (166–195)	129 (113–151)	185 (166–203)	-50 (-66--28)	3 (-9–17)	<0.0001

Values are median (25th to 75th percentile).

**P* value comparing rosuvastatin and placebo for the change from baseline to 12 months.

Table 3. Outcomes Among Women and Men in JUPITER

	Rosuvastatin (Women, n=3426; Men, n=5475)		Placebo (Women, n=3375; Men, n=5526)		HR (95% CI)	P	P for Heterogeneity
	n	Rate per 100 Person-y	n	Rate per 100 Person-y			
Women							
Primary end point	39	0.56	70	1.04	0.54 (0.37–0.80)	0.002	0.80
Nonfatal MI	8	0.12	14	0.21	0.56 (0.24–1.33)	0.18	0.24
Any MI	10	0.14	18	0.27	0.54 (0.25–1.18)	0.11	0.60
Nonfatal stroke	18	0.26	21	0.31	0.84 (0.45–1.58)	0.59	0.04
Any stroke	18	0.26	23	0.34	0.77 (0.42–1.42)	0.40	0.09
Arterial revascularization	8	0.12	29	0.43	0.27 (0.12–0.59)	0.0003	0.04
Arterial revascularization or hospitalization for unstable angina	8	0.12	33	0.49	0.24 (0.11–0.51)	<0.0001	0.01
MI, stroke, or confirmed death resulting from cardiovascular causes	36	0.52	48	0.71	0.73 (0.48–1.13)	0.16	0.06
Venous thromboembolism	12	0.17	16	0.24	0.74 (0.35–1.55)	0.42	0.43
Death resulting from any cause							
Death on known date	57	0.78	69	0.95	0.81 (0.57–1.16)	0.25	0.99
Any death	60	0.82	77	1.07	0.77 (0.55–1.06)	0.12	0.74
Men							
Primary end point	103	0.88	181	1.54	0.58 (0.45–0.73)	<0.0001	
Nonfatal MI	14	0.12	48	0.40	0.29 (0.16–0.54)	<0.0001	
Any MI	21	0.18	50	0.42	0.42 (0.26–0.71)	0.0006	
Nonfatal stroke	12	0.10	37	0.31	0.33 (0.17–0.63)	0.0003	
Any stroke	15	0.13	41	0.34	0.37 (0.21–0.67)	0.0005	
Arterial revascularization	63	0.54	102	0.86	0.63 (0.46–0.86)	0.003	
Arterial revascularization or hospitalization for unstable angina	68	0.58	110	0.93	0.63 (0.46–0.85)	0.002	
MI, stroke, or confirmed death resulting from cardiovascular causes	47	0.40	109	0.92	0.44 (0.31–0.61)	<0.0001	
Venous thromboembolism	22	0.19	44	0.37	0.51 (0.30–0.85)	0.008	
Death resulting from any cause							
Death on known date	133	1.07	166	1.32	0.81 (0.65–1.02)	0.07	
Any death	138	1.11	170	1.35	0.82 (0.66–1.03)	0.08	

MI indicates myocardial infarction. *P* values for heterogeneity of treatment effect for outcomes between women and men were obtained from likelihood-ratio tests that included treatment assignment, sex, and the interaction term.

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,¹⁸ 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

Table 4. Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events During Follow-Up in JUPITER

	Women			Men		
	Rosuvastatin (n=3426)	Placebo (n=3375)	<i>P</i>	Rosuvastatin (n=5475)	Placebo (n=5526)	<i>P</i>
Monitored adverse events, n						
Any serious adverse event	503 (7.7)	481 (7.4)	0.61	849 (7.6)	896 (7.9)	0.31
Muscular weakness, stiffness, or pain	552 (8.9)	509 (8.3)	0.24	869 (8.1)	866 (7.9)	0.77
Myopathy	5 (0.07)	4 (0.06)	0.76	5 (0.04)	5 (0.04)	0.99
Rhabdomyolysis	0	0	...	1 (0.01)	0	0.32
Newly diagnosed cancer	100 (1.4)	94 (1.4)	0.74	198 (1.7)	220 (1.8)	0.32
Death resulting from cancer	12 (0.2)	17 (0.2)	0.33	23 (0.2)	41 (0.3)	0.03
Gastrointestinal disorder	724 (12.0)	734 (12.5)	0.54	1,029 (9.8)	977 (9.0)	0.13
Renal disorder	166 (2.4)	135 (2.0)	0.09	369 (3.2)	345 (2.9)	0.29
Bleeding	99 (1.4)	106 (1.5)	0.54	159 (1.3)	169 (1.4)	0.63
Hepatic disorder	57 (0.8)	63 (0.9)	0.53	159 (1.3)	123 (1.0)	0.02
Laboratory values						
Creatinine, >100% increase from baseline, n	6 (0.09)	6 (0.09)	0.98	10 (0.08)	4 (0.03)	0.10
Glomerular filtration rate at 12 mo, mL · min ⁻¹ · 1.73 m ⁻²	64.1 (56.1–71.6)	64.2 (56.6–70.9)	0.66	71.0 (63.6–79.7)	70.5 (62.7–79.4)	0.006
Alanine aminotransferase >3× ULN on consecutive visits, n	3 (0.04)	5 (0.07)	0.47	20 (0.16)	12 (0.10)	0.15
HbA _{1c} at 24 mo, %	5.9 (5.7–6.2)	5.9 (5.6–6.1)	<0.0001	5.9 (5.6–6.1)	5.8 (5.6–6.0)	<0.0001
Glucose at 24 mo, mg/dL	96 (89–104)	95 (88–104)	0.37	99 (92–107)	99 (91–108)	0.18
Other events						
Newly diagnosed diabetes (physician reported), n	108 (1.5)	71 (1.0)	0.008	162 (1.4)	145 (1.2)	0.29
Hemorrhagic stroke, n	3 (0.04)	3 (0.04)	0.99	3 (0.02)	6 (0.05)	0.32

ULN indicates upper limit of normal. Values are number of events (rates per 100 person-years) or median (25th to 75th percentile) as appropriate.

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

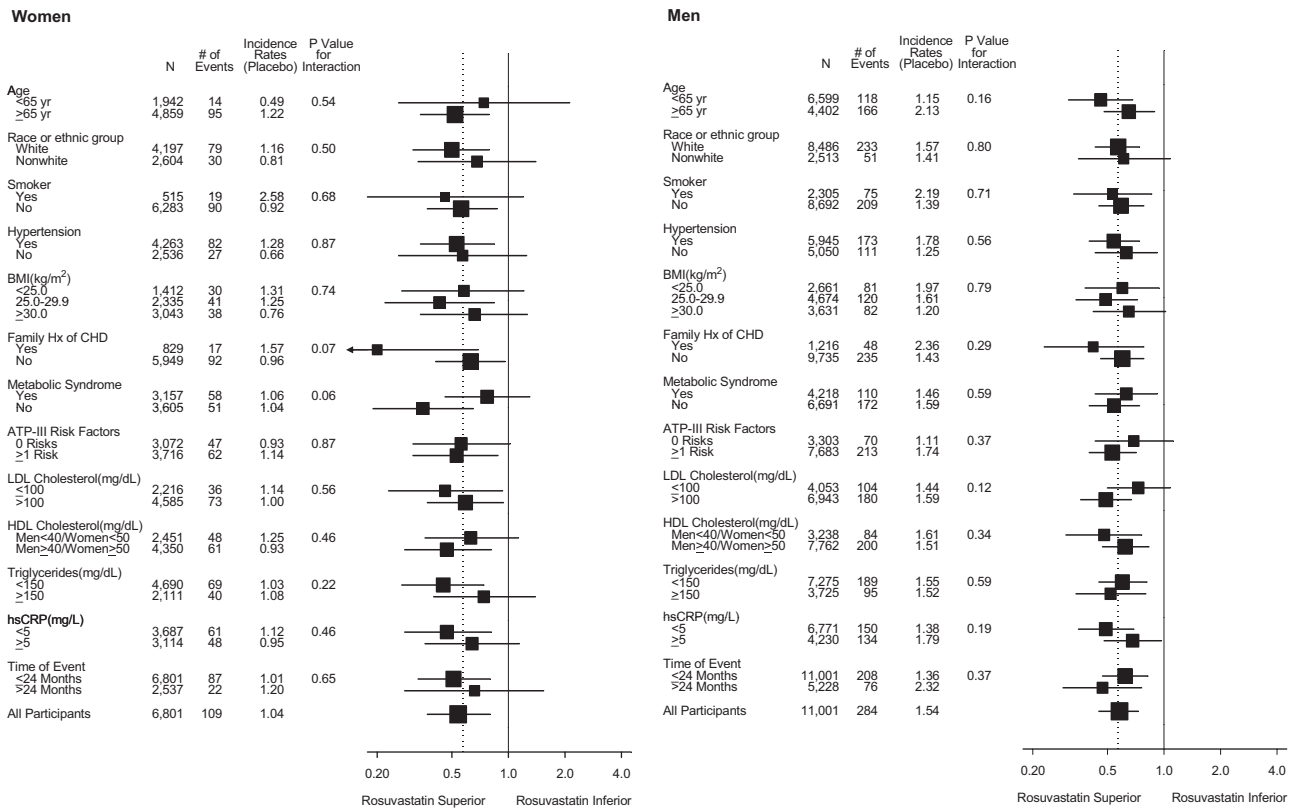


Figure 1. Effects of rosuvastatin on the primary composite end point according to baseline characteristics. The dashed overall line indicates the overall HR for the entire cohort (men and women combined). Hx indicates history; CHD, coronary heart disease; and BMI, body mass index.

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%; $P<0.001$). Absolute event rates were lower in women, even though women were older and generally had more cardiovascular risk factors than men. There was no significant heterogeneity of treatment effect by sex for the primary composite end point or all-cause mortality. In this updated meta-analysis of statin therapy for primary prevention in women, statin allocation yielded a significant RR reduction in CVD by one-third, similar to prior results seen in men and in second-

ary prevention in women. Statin allocation had a smaller, nonsignificant reduction in total mortality for primary prevention in women.

In JUPITER, sex differences were noted in 2 components of the primary end point, with women having a significantly greater reduction compared with men in revascularization/unstable angina and men having a greater reduction in stroke. Subgroup analysis suggested that women with a family history of premature coronary disease may benefit more from rosuvastatin therapy than those without, whereas in men, the benefit was similar for those with and without a family history. Women and men with Framingham Risk Scores $<5\%$ and women <65 years of age had low event rates, although there was no suggestion of heterogeneity by categories of Framingham risk in either women or men.

The JUPITER findings demonstrate for the first time that the proportional cardiovascular benefit from rosuvastatin therapy for primary prevention was similar and significant in women and men who were selected for therapy on the basis of an elevated hsCRP level. JUPITER differs from prior statin trials in using elevated levels of hsCRP as an entry criterion; previous statin trials selected participants mostly on the basis of dyslipidemia. hsCRP has been shown to identify asymptomatic women and men who are at increased risk of CVD events independently of their LDL cholesterol.⁹ This finding underscores the importance of selecting individuals with adequate baseline risk to ensure a significant benefit of therapy.

When put in context with the updated meta-analysis in women, there was overall about a one-third reduction in

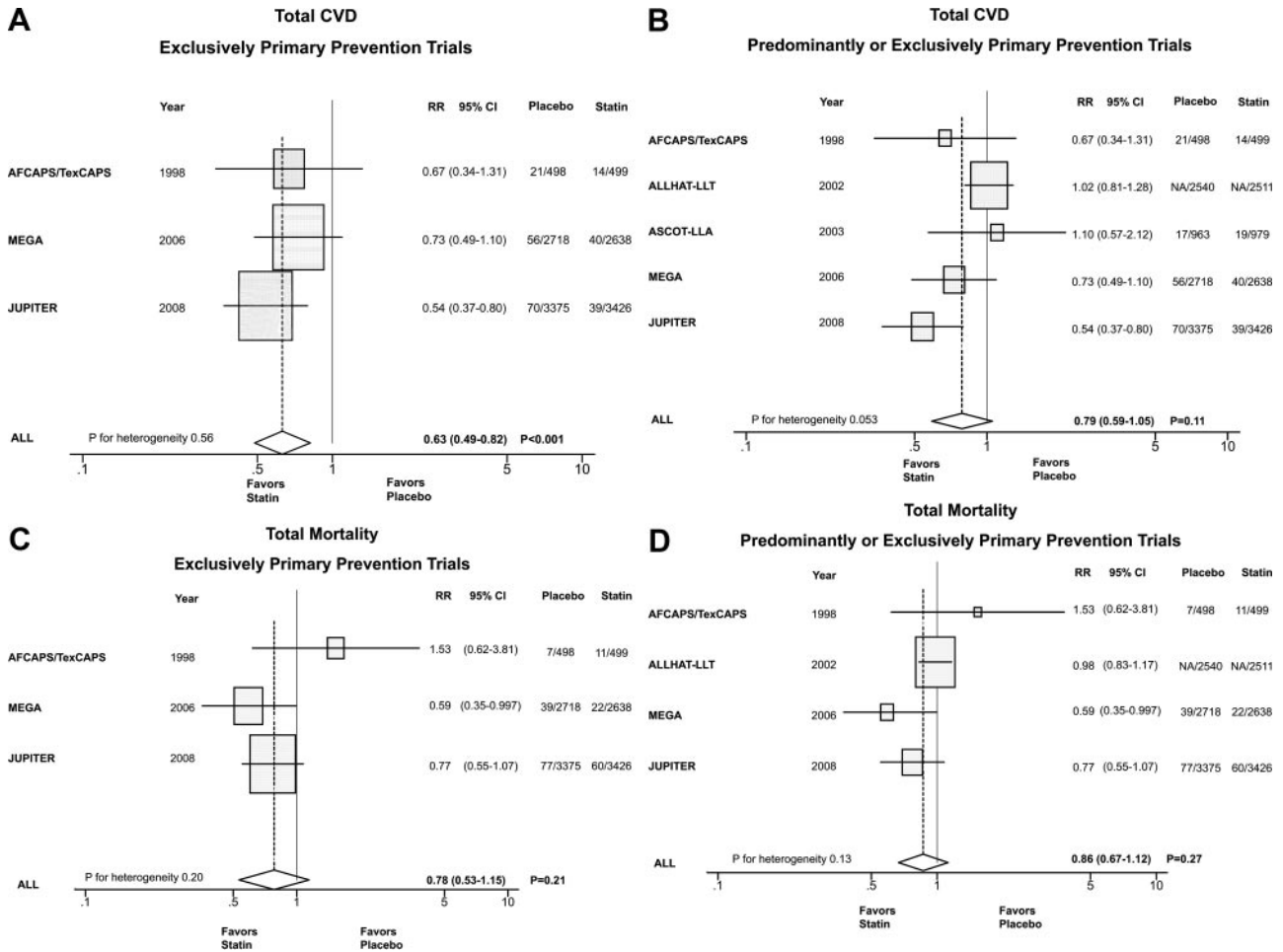


Figure 2. RR of allocation to statin vs placebo in women in relation to CVD in exclusively primary prevention trials (A) and predominantly or exclusively primary prevention trials (B) and of total mortality (C and D). The size of the squares is proportional to the number of events. Mean age, percent diabetic, and statin dose were as follows: AFCAPS/TexCAPS: 63 years, 3%, and lovastatin 20 to 40 mg/d, respectively; ALLHAT-LLA: 66 years, 35%, and pravastatin 20 to 40 mg/d; ASCOT-LLA: 63 years, 24%, and atorvastatin 10 mg/d; MEGA: 60 years, 18%, and pravastatin 10 to 20 mg/d; and JUPITER: 69 years, 0%, and rosuvastatin 20 mg/d.

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 PROSPER¹⁹ and HPS²⁰ 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.²¹ 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.²² However, 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 simvastatin²⁰ that was also seen with atorvastatin (0.4%) in ASCOT-LLA.¹⁵ 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.²³

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 than 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.

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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.

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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.