

# Letter by Vos et al Regarding Article, “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”

To the Editor:

We read with interest the article by Mora and colleagues,<sup>1</sup> who are well supported when stating that “statins had not been found to reduce total or coronary mortality in women, men, or combined for primary prevention” but suggest that their Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study indicates differently. We respectfully disagree.

The article gives no data about cardiovascular mortality, which for men and women combined differed by only 8 (author’s response to Ridker and Glynn<sup>2</sup>; corresponding  $P=0.37$ ). In women specifically, calculating from combined data in Table 3 in the article by Mora et al,<sup>1</sup> there would have been 10 cardiovascular deaths on rosuvastatin versus 13 on placebo, which would generate a  $P$  value of 0.51. The infarct and stroke findings were also not different in women after  $\approx 6500$  on-statin years.

The only significant benefit in women in any of the 5 primary end point components was the 73% reduction in revascularizations. These are not disease end points per se but medical decisions based on hospital presentations and catheterization laboratory availability. To illustrate the softness of this end point and for perspective, we note that other research found revascularizations reduced by 90%, both for coronary artery bypass grafting and percutaneous coronary intervention, by the subject first presenting to a closer non-catheterization laboratory hospital when experiencing an acute coronary event,<sup>3</sup> and, in these circumstances, deaths in the non-catheterization laboratory cohort were significantly fewer after 6 months.

Interestingly, the reduction in revascularizations by rosuvastatin may be related to the well-known angina-reducing, nitroglycerin-mimicking (nitric oxide/endothelial nitric oxide synthase-promoting) pathway of statins,<sup>4,5</sup> an effect that could reduce the number of hospital presentations and thus interventions. It is unknown whether such beneficial nitric oxide/endothelial nitric oxide synthase effect is attenuated by tolerance over subsequent years or decades, as happens with nitroglycerin, because JUPITER was halted at a mean follow-up of 1.9 years.

In cost-benefit terms, the 21 fewer revascularizations in JUPITER after 6500 female on-statin years would represent an outlay of \$625 000 per procedure avoided at an April 2010 US pharmacy chain retail price. Put another way, 303 women would have to take rosuvastatin for 1 year at  $> \$2000$  each to avoid 1 revascularization.

With regard to total mortality in women, the authors suggest benefit and, in Figure 2A, introduce the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) using PRAVASTATIN study. However, as in JUPITER,

the mortality benefit of MEGA was not from fewer cardiovascular deaths, which were identical in the statin and nonstatin groups, but also from the anomaly of fewer deaths from cancer.

Therefore, physicians and women patients should be informed that rosuvastatin has thus far not been shown to reduce the risk of cardiovascular death, myocardial infarction, or stroke in high-risk primary prevention patients, as in the case of JUPITER, in which virtually all subjects had some form of metabolic syndrome.

The authors report risks for combined nonequipoise end points and  $P$  values for differences and heterogeneity with men that are of limited value to prescribers and patients. An alternative and more patient-centered approach would be to avoid ambiguity by reporting numbers needed to treat per year (annualized numbers needed to treat) with confidence intervals starting at year 1 for the 5 primary end point components.

We respectfully ask the authors to publish a simple table with these yearly numbers, separately for men and for women. This would be a vital clarification of JUPITER, a study likely to affect statin-prescribing decisions for years to come.

## Disclosures

None.

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# Response to Letters Regarding Article, “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”

We thank Dr Wells and colleagues and Dr Vos and colleagues for their interest in our study. Dr Wells and colleagues question combining the results of Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) with those of other statin trials for primary prevention of cardiovascular disease in women. Dr Vos and colleagues question the benefit in women, in particular regarding mortality, as well as cost-effectiveness and numbers needed to treat in JUPITER.

In JUPITER,<sup>1</sup> rosuvastatin 20 mg daily resulted in similar and significant proportional reductions in the primary end point for both women (46%;  $P=0.002$ ) and men (42%;  $P<0.001$ ). There was no significant heterogeneity of treatment effect by sex for the primary composite end point. For all individual components of the primary end point, the point estimates of effect favored active therapy over placebo for both women and men. Thus, as described in our article, JUPITER provides clear evidence of the efficacy of statin therapy in the primary prevention of cardiovascular disease, at least among women at risk as a result of elevated high-sensitivity C-reactive protein.

Our finding of benefit for women with statin treatment in the updated meta-analysis that we performed extends previous findings from meta-analyses that preceded publication of JUPITER. The summary relative risk from the present meta-analysis was 0.63 (95% confidence interval, 0.49 to 0.82;  $P<0.001$ ), a finding that is consistent with the summary relative risks from previous meta-analyses of primary prevention statin trials in women that did not include JUPITER or the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) (relative risk, 0.87; 95% confidence interval, 0.69 to 1.09)<sup>2</sup> or included MEGA but did not include JUPITER (relative risk, 0.89; 95% confidence interval, 0.79 to 1.00).<sup>3</sup> With the inclusion of the 6801 women from JUPITER in the meta-analysis, this effect is now statistically significant ( $P<0.001$ ). We observed no evidence for statistical heterogeneity between the primary prevention trials when JUPITER was included in the meta-analysis ( $P$  for heterogeneity=0.56). Only after additionally including 2 trials that were not exclusively primary prevention (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack [ALLHAT-LLT] and the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm [ASCOT-LLA]) in the meta-analysis was the  $P$  value for heterogeneity 0.053. When we repeated the analyses with and without including ALLHAT-LLT and ASCOT-LLA, we found similar overall results.

With regard to total mortality, JUPITER showed a 20% relative risk reduction in total mortality ( $P=0.02$ ) when the results for women and men were combined. There was no significant heterogeneity of treatment effect by sex for total or cardiovascular mortality. When the sex-specific total mortality results of JUPITER were combined with prior sex-specific results from statin trials for primary prevention, the summary relative risk showed a nonsignificant 22% relative risk reduction in total mortality among women allocated to statin use compared with placebo. As previously reported, the point estimate of effect associated with rosuvastatin within JUPITER for cardiovascular mortality (hazard ratio, 0.82; 95% confidence interval, 0.52 to 1.20) is almost identical to that of total mortality (hazard ratio, 0.80; 95% confidence interval, 0.67 to 0.97).

With regard to cost, independent analyses of the JUPITER trial have suggested values ranging from \$20 000 to \$40 000 dollars per quality-adjusted life year, values that are similar to or potentially more cost-effective than the treatment of hyperlipidemia or hypertension in comparable primary prevention settings.

Finally, the requested data on numbers needed to treat have previously been published<sup>4</sup> and again indicate that the strategy of using statin therapy among individuals with elevated high-sensitivity C-reactive protein is at least as effective as the strategy of using statin therapy only among those with hyperlipidemia.

## Disclosures

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. Dr Mora received research grant support from NHLBI (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 AstraZeneca, Novartis, Roche, and Sanofi-Aventis and nonfinancial research support from Amgen. Dr Ridker is coinventor on patents held by Brigham and Women's Hospital related to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Siemens and AstraZeneca; Dr Ridker has served as a research consultant to Schering-Plough, Sanofi/Aventis, AstraZeneca, Isis, Siemens, Merck, Novartis, and Vascular Biogenics. J. MacFadyen reports no conflicts.

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