Rosuvastatin in Patients with Elevated C-Reactive Protein

**TO THE EDITOR:**  Ridker et al. (Nov. 20 issue) report the results of Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),\(^1\) which showed that rosuvastatin significantly reduced cardiovascular events in patients with elevated levels of C-reactive protein. However, broad application of their results in primary prevention is premature, since the baseline therapy that many patients in the study were receiving did not meet existing standards. Although about 50% of the patients had intermediate Framingham risk scores, which would have qualified such men (and possibly women) for aspirin therapy,\(^2,3\) only 16.6% of the patients were receiving aspirin. One quarter of the patients had a systolic blood pressure of at least 145 mm Hg, indicating that their hypertension was not being treated according to existing national goals.\(^4\) Almost 16% of the patients were current smokers.

It is impossible to tell how many of the patients were receiving “optimal therapy” at baseline, defined as meeting current targets in all three of the following areas: the use of aspirin when indicated, hypertension treated to national goals, and no tobacco use. Future substudies should examine the number of patients who would need to be treated to prevent one cardiovascular event in the subgroup of patients who were already receiving optimal therapy at baseline. Public health might be better served by improving compliance with existing standards.

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**TO THE EDITOR:** JUPITER is notable for the unacknowledged exclusion of a population that may be at increased risk for dose-related adverse effects of rosuvastatin. In 2005, the label for Crestor was amended to read, “The result of a large pharmacokinetic study conducted in the U.S. demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients.”\(^1\) Decreased activity of an organic anion-transporting polypeptide, OATP1B1, may account for differences in the pharmacokinetics of rosuvastatin.\(^2,3\)
Although Ridker et al. state that “by design, the study population was diverse,” no Asian countries are included among the study sites, and the demographic breakdown of the 17,802 patients according to race or ethnic group includes only white, black, Hispanic, and “other or unknown.” It would appear that there may have been a conscious choice to exclude people of Asian descent from JUPITER.

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TO THE EDITOR: Although the JUPITER study investigators report event rates for most individual components of the primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and revascularization), they do not report event rates for death from cardiovascular causes, even though the trial was terminated early in part because of apparent mortality benefits. We therefore attempted to calculate the rates of death from both cardiovascular and noncardiovascular causes from the numbers provided in the article.

On the basis of our calculations, in the rosuvastatin group, as compared with the placebo group, the number of deaths from cardiovascular causes was not significantly reduced (31 vs. 37 deaths), although the number of deaths from any cause was significantly reduced (167 vs. 210 deaths). This finding is at odds with extensive data from previous statin trials. In addition, the authors suggest that their results support treating patients on the basis of elevations in C-reactive protein. However, they provide no results showing that C-reactive protein is an independent predictor of the relative or absolute benefit of therapy, since the treatment effects seen with rosuvastatin could have been mediated by reductions in low-density lipoprotein (LDL) cholesterol. Multivariable models that adjust for baseline levels of LDL cholesterol and changes in LDL cholesterol over time would further clarify the role of C-reactive protein.

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TO THE EDITOR: Ridker et al. describe a modest but significant benefit from rosuvastatin, as compared with placebo, in a large group of patients with LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2 mg per liter or more. Although they state that there was no heterogeneity of results for subgroups of patients according to sex, race or ethnic group, or known coronary risk factors, they did not make a similar statement regarding subgroups stratified according to the baseline level of high-sensitivity C-reactive protein or cholesterol, the very measures that are affected by the study intervention.

Could the authors provide data showing whether there was a gradient of risk for cardiovascular events and death according to baseline levels of C-reactive protein or a gradient of benefit from rosuvastatin according to the extent of the baseline elevation? Furthermore, could they reassure clinicians that there was no incremental risk among patients with the lowest baseline cholesterol levels who were treated with a lipid-lowering statin? Was the clinical benefit explained by changes in levels of C-reactive protein, and how could clinicians monitor the intervention in practice in order to achieve a clinical benefit?

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TO THE EDITOR: Ridker et al. do not adequately address the issue of the development of new-onset diabetes in patients receiving rosuvastatin. Although this issue has not been systematically investigated, the risk of diabetes was increased by a factor of 1.25 (95% confidence interval [CI], 1.05 to 1.51) among patients receiving rosuvastatin. The discordance of the effects of rosuvastatin on vascular outcomes and the risk of diabetes is per-
plexing, particularly since the two conditions are believed to share a common inflammatory basis.\(^1\) We therefore used the available published data from large-scale, placebo-controlled trials of statins to evaluate the relationship between statin therapy and incident diabetes.

Among 59,006 patients, the risk of diabetes for patients receiving a statin was similar to that for patients receiving placebo (relative risk, 1.06; 95% CI, 0.91 to 1.23). The risk of diabetes appears to increase with increased potency of the lipid-lowering agent. For the two large, placebo-controlled trials of pravastatin, the West of Scotland Coronary Prevention Study (WOSCOPS) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, the relative risk of diabetes in the pravastatin group was 0.81 (95% CI, 0.64 to 1.02). For the two large, placebo-controlled trials of rosuvastatin, JUPITER and the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), the relative risk of diabetes in the rosuvastatin group was 1.22 (95% CI, 1.05 to 1.42). For drugs with intermediate potency, simvastatin and atorvastatin, the values fell in between these extremes.

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**TO THE EDITOR:** JUPITER was stopped early, after a median follow-up of 1.9 years. The number of patients who would need to be treated for 2 years to prevent the occurrence of one primary end point was 95. Ridker et al. extrapolate these results by a projection over a 5-year treatment period. This estimation should be viewed critically, since the study has most of the characteristics of a truncated trial.

The majority of randomized clinical trials that are stopped early because of an observed benefit of the treatment under investigation are industry-funded drug trials that are stopped at the first interim analysis, with the results published in a high-impact medical journal. The hazard ratio of 0.56 for the primary end point in JUPITER is close to the median risk ratio of 0.53 among 143 truncated randomized trials.\(^3\) Truncated trials overestimate the treatment effect.\(^2\) This factor was important in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, in which early stopping was resisted.\(^3\) Because rosuvastatin would be given long-term for primary prevention, the JUPITER study investigators should have continued follow-up to determine whether the positive results would have continued or would have declined to a more modest effect.

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**TO THE EDITOR:** JUPITER was designed to continue until 520 confirmed primary end points had been documented. The study was terminated early because of the efficacy of rosuvastatin. However, the statistical results are reported as if the trial had been designed as a fixed-length trial with 393 primary end points, even though the analysis was sequential. This leads to bias in the reporting.

The correct P value for the sequential analysis, as conducted, is P<0.05, not P<0.00001, as reported. In addition, the point estimate of the treatment effect from a trial that was terminated early for efficacy is biased in favor of the treatment.\(^4\) Thus, although it can be agreed that rosuvastatin lowered the risk of cardiovascular disease in this study, the methods used to report the results overestimate the strength of the association.

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TO THE EDITOR: Ridker et al. used conventional Kaplan–Meier analyses to describe the probability of the occurrence of major cardiovascular events over time. Such analyses assume that the event of interest is as likely to occur in the future in patients for whom data have been censored as in those remaining in the trial. This assumption is obviously not the case for patients who died from noncardiovascular causes. The censoring of “competing deaths” estimates the actuarial rather than the actual cumulative incidence.\(^1\)–\(^3\) Hence, the absolute difference in risk is inflated, and the respective number of patients who would need to be treated to prevent one occurrence of the end point becomes too low. If we assume that there was a 30% relative overestimation\(^3\) of the actual cumulative incidence, the number needed to treat increases by the same magnitude, from 95 to 124. Since the number of competing deaths from noncardiovascular causes might increase with time, the difference may particularly affect the projected numbers needed to treat at 4 and 5 years. A competing-risk method would have been preferable to determine the actual cumulative incidence and estimates of the number who would need to be treated.

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THE AUTHORS REPLY: We agree with Gibbons that improved compliance with current guidelines remains important for primary prevention of cardiovascular disease. However, in our trial, the 5-year number needed to treat for nonsmokers, patients without hypertension or the metabolic syndrome, and those with low Framingham scores are all similar to or smaller than the 5-year values of 50 to 60 previously reported for statins among white men with hyperlipidemia.

Full prescribing data for rosuvastatin among Asians were not available in 2002. Thus, Fugh-Berman is correct that Asian participation was marginal. The safety of rosuvastatin has subsequently been established and the 20-mg dose approved for patients of Asian descent.

The calculations by Chan et al. are incorrect partly because they do not account for deaths from vascular causes, such as aneurysm rupture. Furthermore, because we prespecified very strict confirmation criteria, many out-of-hospital deaths from cardiovascular causes were classified as being from noncardiovascular causes for trial purposes. On the basis of these strict criteria, the numbers of confirmed deaths from cardiovascular causes were 35 in the rosuvastatin group and 43 in the placebo group, with a hazard ratio in the rosuvastatin group of 0.82 (95% CI, 0.52 to 1.27), which was similar to the reported hazard ratio for death from any cause of 0.80 (95% CI, 0.67 to 0.97). Our trial is consistent with the notion that achieving very low levels of high-sensitivity C-reactive protein and LDL cholesterol can enhance statin benefits\(^1\)–\(^2\) — analyses that will interest Chan et al., along with Jenny-Avital. As anticipated, the absolute risk of a cardiovascular event increased with increased levels of highsensitivity C-reactive protein and decreased with decreased levels.

We partially disagree with Mak and Chan. If the “protective” effect on diabetes incidence reported in WOSCOPS is treated as hypothesis-generating, then a summary of published hypothesis-testing trials demonstrates that all statins modestly increase the risk of diabetes, with no heterogeneity according to potency. In our study, many of the patients in whom diabetes developed were obese or had an impaired fasting glucose level, groups in which large reductions in vascular events were associated with rosuvastatin.

The independent data and safety monitoring board for our trial followed rigorous principles in its prespecification that early termination of the study because of an observed benefit would require proof beyond a reasonable doubt. Members of the board were experienced in monitoring publicly and privately funded trials and viewed the trial’s prespecified statistical boundary as only one
component required for proof. Although the formal statistical boundary was conservative and evaluated only after accrual of ample data, the board elected to continue the trial for an additional 6 months after the boundary was crossed. Data that were accrued thereafter independently confirmed both the magnitude and statistical significance of the apparent benefit. We thus respectfully disagree with Pierard and Davis. The board appropriately protected the interests of society and the trial participants and provided a valid estimate of the treatment effect.4

The evaluation by Koller et al. ignores the significant reduction in death from any cause that we observed. If death from any cause is added to our primary composite outcome (a standard approach to account for competing risks), then the absolute risk difference increases and the number needed to treat declines.

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Obesity and Risk of Death

TO THE EDITOR: A challenging issue with the study reported on by Pischon et al. (Nov. 13 issue)1 is where to measure the waist. The accepted standard for measuring the waist circumference put forth by the third National Health and Nutrition Examination Surveys (NHANES III) protocol,2 as noted by Mahley in the Williams Textbook of Endocrinology,3 is: “to measure waist circumference, locate the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration.” However, Pischon et al. report that in their study, “waist circumference was measured either at the narrowest circumference of the torso or at the midpoint between the lower ribs and the iliac crest.” International acceptance of measurement tools is paramount.

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TO THE EDITOR: Pischon et al. support the use of waist circumference or waist-to-hip ratio in addition to body-mass index (BMI) in assessing the risk of death. Engeland et al. found that height is inversely associated with mortality among men and to some degree among women.4 My recent study2 and a meta-analysis,3 both of which used cross-sectional data, provide support for the superiority of measures of central obesity — especially waist-to-height ratio — over BMI for discriminating the presence or absence of cardiologic and metabolic risk factors. Pischon et al. appropriately adjusted for height when calculating the mortality risk associated with anthropometric indexes. It would be helpful if the authors would determine the relative risk of death according to waist-to-height ratio and its comparison with other anthropometric data. For a fair comparison, height should not be adjusted for other studied anthropometric indexes.

Pischon et al. indicated that they observed no significant association between hip circumference and mortality risk. Larger hip circumference was shown to be an independent predictor of a lower mortality rate in a Swedish female cohort.4 Did Pischon et al. confirm that?

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1. Engeland A, Bjorge T, Selmer RM, Tverdal A. Height and