Tough Questions About the Value of Statin Therapy for Primary Prevention: Did JUPITER Miss the Moon?

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An unusually rancorous debate that was recently described by the president of the American Heart Association as “a statistical tug-of-war” has raised more questions than answers about the risks and benefits of statins in primary prevention.^{1,2} Spending money to save money seemed like a reasonable strategy in lowering serum lipids in primary prevention of adverse cardiovascular outcomes, particularly when pravastatin and simvastatin became available by generic name in April and June 2006, respectively, soon thereafter permitting the treatment of several patients for the same drug cost as treating 1 patient with either brand pravastatin (Pravachol) or brand simvastatin (Zocor).³ Nevertheless, it has long been recognized that the small effect sizes associated with avoidance of adverse cardiovascular outcomes make the use of statins expensive even in secondary prevention, up to \$1.1 million in drug cost in 2004 dollars to prevent 1 nonfatal stroke.⁴ In an assessment of the cost-effectiveness of primary prevention, Pletcher et al. (2009) used Markov modeling to estimate the economic and clinical effects of bringing all adults in the United States into compliance with Adult Treatment Panel III (ATP III) guidelines, finding that 11.1 million adults without coronary heart disease (CHD) would undergo newly initiated (9.7 million) or intensified (1.4 million) statin treatment.⁵ The net cost, after accounting for medical cost offsets due to avoided cardiovascular events (20,000 myocardial infarctions [MIs] and 10,000 cardiovascular deaths annually), would be \$3.6 billion per year, or \$42,000 per quality-adjusted life year over a 30-year time horizon. Although the current (July 2010) market price of generic simvastatin is approximately 60% lower than the \$2.11 per tablet assumed in the model’s base-case analysis,⁶ and discounts off consumer cash price are commonly taken by health plans,⁷ Pletcher et al. note that treating all patients with low-density lipoprotein cholesterol (LDL-C) exceeding 130 milligrams per deciliter (mg per dL) would yield net cost savings only if statins cost less than \$0.10 per pill.⁵

The investment strategy for the use of statins in primary prevention dimmed further with publication of a meta-analysis by Ray et al. in June 2010.⁸ The combined results of 11 randomized controlled trials (RCTs) involving 65,229 persons with intermediate to high risk of a cardiovascular outcome but without cardiovascular disease at baseline showed that statins were not associated with reduction in the risk of all-cause

mortality over 244,000 person-years of follow-up. There were 1,447 all-cause deaths among 32,606 patients who received placebo (4.4%) versus 1,346 deaths among 32,623 patients who received statins (4.1%, risk ratio = 0.91, 95% confidence interval [CI] = 0.83-1.01). Across the 11 studies, the mortality rate for placebo ranged from 3.6 to 26.0 per 1,000 person-years versus a range from 2.4 to 27.2 per 1,000 person-years for statins, and participant age at baseline accounted for an estimated 66% of the variation in mortality rates. There was lack of significant effect on mortality despite evidence of LDL-C reduction; during a mean of 3.7 years follow-up, the mean LDL-C levels for placebo-treated and statin-treated patients were 134 mg per dL and 94 mg per dL, respectively. The results of this meta-analysis were bolstered by the absence of evidence of statistical heterogeneity among the 11 RCTs despite heterogeneity in the demographic and clinical characteristics of the study samples. The research by Ray et al. is also compelling because it is the first meta-analysis to exclude entirely the effect of statins in patients with known CHD. A previous meta-analysis of 10 RCTs in primary prevention with statins performed by Brugts et al. (2009) had found modest effects on all-cause mortality over an average 4.1 years of follow-up (rates of 5.1% and 5.7% for statin- and placebo-treated patients, respectively, odds ratio [OR] = 0.88, 95% CI = 0.81-0.96), but that meta-analysis included 4,445 participants (6.3%) with a prior history of cardiovascular disease.⁹

With the circumspect work of Ray et al., we now have additional confidence in examining the value for money in primary prevention of cardiovascular events with statins. If the 0.3% absolute difference in the mortality rate for statin therapy (4.1%, weighted mean of 10.7 per 1,000 person-years) versus placebo (4.4%, weighted mean of 11.4 per 1,000 person-years) was statistically significant, which it was not, the effect of statin treatment was an estimated 7 fewer deaths per 10,000 person-years of treatment.⁸ At current (July 2010) real-world discounted drug prices,⁷ preventing 1 all-cause death in primary prevention would require about \$103,000 of generic simvastatin (\$72 per year times 10,000 patient-years to prevent 7 deaths), \$137,000 of generic pravastatin, or \$2 million of rosuvastatin (Crestor). Or, one can use the results from Brugts et al. to calculate the direct rosuvastatin drug cost to prevent 1 all-cause death, approximately \$975,000 (number needed to

treat [NNT] = 167 for a mean 4.1 years of treatment) at the current (mid-2010) discounted rosuvastatin drug cost of approximately \$119 per month.⁹

Risks of Statin Therapy May Outweigh the Benefits in Primary Prevention

Lack of efficacy is not the only concern with statin therapy for primary prevention of cardiovascular events. Earlier this year, Hippisley-Cox and Coupland reported that statin use was associated with increased risk of cataracts, kidney failure, muscle pain, and “moderate or serious” liver dysfunction.¹⁰ This observational study involved 2,004,692 patients in 368 general medical practices in England and Wales of whom 225,922 (10.7%) were new users of statins. Statin use was associated with decreased risk of esophageal cancer but with no apparent unintended benefit (decreased risk) for other cancers. The association of statin therapy with muscle pain was examined last year in a narrative review by Joy and Hegele (2009), who reported that the incidence of myopathy is only about 1.5%-5.0% in RCTs but occurs in up to 10% of statin users in observational analyses.¹¹ Interesting for the question of risk versus benefit in primary prevention, a June 2010 market surveillance analysis by Cham et al. found that of 354 patient reports of muscle-related adverse effects with statin therapy, 300 were determined by the study investigators to be probably or definitely drug-attributable using the Naranjo adverse drug reaction probability scale.¹² Within this group, investigators found that “most” patients “were in categories for which available [RCT] evidence shows no trend to all-cause mortality benefit with statin therapy.”

In addition to the well-recognized risk of statin-induced myopathy, Sattar et al. (2010) found that statin use was associated with a 9% increase in the risk of developing diabetes (OR=1.09, 95% CI=1.02-1.17).¹³ This study applied meta-analysis to 13 RCTs involving 91,140 patients of whom 4.7% (n=4,278, including 2,226 statin-treated and 2,052 placebo-treated patients) developed diabetes over an average of 4 years of follow-up; the number needed to harm (NNH) was 255 patients on statin therapy for 4 years to produce 1 additional case of diabetes.

JUPITER Misses the Moon?

The results of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) clinical trial were first published online on November 9, 2008, apparently opening the door to the use of statins in persons without elevated LDL-C but with elevated high-sensitivity C-reactive protein (hs-CRP) levels.¹⁴ Hypothesizing that rosuvastatin would demonstrate cardiovascular benefits in patients who “are at high vascular risk because of an enhanced inflammatory response” despite normal LDL-C levels,¹⁵ the JUPITER

investigators randomized 17,802 “apparently healthy” participants with LDL-C less than 130 mg per dL (median 108 mg per dL) and hs-CRP greater than 2.0 mg per liter (median 4.2 mg per liter) to treatment with rosuvastatin 20 mg daily or placebo. Over a median of 1.9 years of follow-up, the reported rates of the primary study endpoint (combined outcome of “[MI], stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes”) per 100 person-years of follow-up were 0.77 for patients treated with rosuvastatin versus 1.36 for the placebo group (hazard ratio [HR]=0.56, 95% CI=0.46-0.69, $P<0.001$).^{14,16} All of the cardiovascular outcomes favored rosuvastatin over placebo, but there was only a small advantage in all-cause mortality; there were 198 all-cause deaths (2.2%) in the rosuvastatin group versus 247 (2.8%) in the placebo group (HR=0.80, 95% CI=0.67-0.97, $P=0.02$).¹⁴

There was also a blemish on rosuvastatin in the JUPITER trial in the finding of a higher incidence of physician-reported diabetes (270 [3.0%] in the rosuvastatin group compared with 216 [2.4%] in the placebo group, $P=0.01$)¹⁴ despite an a priori hypothesis by study investigators that rosuvastatin might *reduce* the incidence of diabetes because hs-CRP levels “predict the onset of diabetes.”¹⁵ Still, the results of JUPITER suggested an apparent hit-the-moon achievement in improving the targeting of primary prevention efforts, with an author-estimated NNT of just 25 patients to prevent 1 primary endpoint outcome event over a 5-year period based on the available median 1.9 months of follow-up.¹⁴ The results also represented a huge market opportunity for rosuvastatin, despite a practical cost analysis that puts the price tag at approximately \$178,000 in rosuvastatin drug cost to prevent 1 major event (i.e., 25 patients treated for 5 years at current real-world rosuvastatin drug cost in mid-2010).⁷

Criticism of the JUPITER trial results began immediately. Within days of online publication of the JUPITER trial results, 2 *BMJ* editorialists pointed to weaknesses related particularly to generalizability and clinical relevance.¹⁷ The clinical relevance was described by Donner-Banzhoff and Sönnichsen as doubtful because, despite the large relative risk reduction, the absolute reduction in risk of the primary endpoint was only 0.59 events per 100 person-years. They also argued that participants were not truly at low risk of cardiovascular disease by traditional standards because, despite normal LDL-C levels and absence of cardiovascular disease, more than one-half had a Framingham risk score exceeding 10%, and 41.4% had metabolic syndrome. The inclusion of patients with metabolic syndrome and high Framingham risk scores in the JUPITER sample was likely intentional because of previous research showing that, as the JUPITER trial authors observed in their study protocol description, hs-CRP “adds prognostic information on risk at all levels of LDL-C, at all levels of the Framingham Risk Score, and at all

levels of the metabolic syndrome.”¹⁵ Still, Donner-Banzhoff and Sönnichsen raised the important point that to obtain a true test of the effect of hs-CRP screening *in routine care* would require comparing hs-CRP plus conventional risk factors versus conventional risk factors alone as predictors of treatment benefit, something that JUPITER did not do.¹⁷

Criticisms of the trial’s external validity are particularly important because a key ostensible purpose of JUPITER was to bolster the appropriate use of statins for primary prevention in routine care. Observing in 2003 that “almost half of all cardiovascular events occur among apparently healthy men and women who have normal or even low levels of [LDL-C],” the JUPITER study chairman advocated for “better screening methods ... to detect high-risk individuals for whom the [NNT] is small enough to make prophylactic statin therapy cost-effective.”¹⁵ Yet, consistent with the criticisms of the *BMJ* editorialists, the external validity of JUPITER’s findings was undermined by 2 factors. First, a 4-week placebo run-in period, during which patients had to take more than 80% of all study tablets to continue with the protocol,¹⁴ meant that the JUPITER trial participants were probably more compliant than most patients in routine clinical practice. Second, the list of JUPITER trial exclusion criteria was lengthy and contained many common conditions and treatments including current use of post-menopausal hormone-replacement therapy; past or current use of lipid-lowering therapy; diabetes; liver disease; uncontrolled hypertension (defined as systolic blood pressure exceeding 190 millimeters mercury [mm Hg] or diastolic blood pressure exceeding 100 mm Hg); cancer (except for basal-cell or squamous-cell skin carcinoma) within 5 years before enrollment; uncontrolled hypothyroidism; “recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study;” and inflammatory conditions including severe arthritis, lupus, or inflammatory bowel disease.¹⁴ Of 26,286 potential study participants who met the primary entry criteria of LDL-C less than 130 mg per dL and hs-CRP of at least 2.0 mg per liter, 3,948 (15.0%) withdrew consent; 957 (3.6%) were excluded for diabetes; 1,202 (4.6%) were excluded for other conditions, predominantly hypothyroidism and liver disease; and 856 (3.3%) were excluded for “other” conditions that were not detailed.¹⁸ Of the 19,323 potential participants remaining, 1,521 (7.9%) were excluded for “poor compliance,” leaving 17,802 participants, 67.7% of the initial clinically eligible pool, available for randomization.¹⁸

More Criticism Heaped on JUPITER

Among the criticisms raised by Donner-Banzhoff and Sönnichsen in 2008 was lack of plausibility of the JUPITER study findings in light of previous work. The evidence that was already known at the time included the results from the

CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial in patients with mild to severe systolic heart failure. Over a median follow-up period of 32.8 months, 10 months longer than JUPITER, rosuvastatin in the CORONA trial significantly lowered both LDL-C and hs-CRP by relative amounts similar to those observed in the JUPITER trial.^{19,20} However, rosuvastatin in the CORONA trial performed no better than placebo on the primary composite outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke).¹⁹ There was also no difference between rosuvastatin and placebo on 3 of 4 pre-specified secondary endpoint outcomes, including death from any cardiovascular cause, all-cause death, or any coronary event; however, there were fewer cardiovascular hospitalizations in the rosuvastatin-treated group.¹⁹ Later, Kaul et al. applied a Bayesian analysis of CORONA and JUPITER trial results to find small rosuvastatin treatment effects including an absolute difference of only 0.23% for the combined endpoint of cardiovascular death, MI or stroke (i.e., the CORONA primary endpoint outcome, a subset of the JUPITER primary endpoint outcome), thereby increasing the NNT for the CORONA endpoint outcome from 119 to 434.²⁰

By June 2010, criticism of JUPITER grew into what one press account described as “an avalanche”² with the publication of 4 articles on the topic of primary prevention with statins in the June 28, 2010, issue of the *Archives of Internal Medicine*. These articles included the meta-analysis by Ray et al., 2 technical critiques of JUPITER’s methods and findings, and an accompanying editorial.^{2,8,20,21} Much of the criticism focused on the decision of the JUPITER Independent Data and Safety Monitoring Board (IDSMB) to terminate the trial after a median follow-up of 1.9 years, raising the possibility that the benefits observed for rosuvastatin treatment represented early effects that would have diminished over time because of regression to the mean, had the entire planned (3- to 4-year) follow-up been completed.

The critique by de Lorgeril et al., including a reanalysis of the JUPITER data, is notable both because it has been the subject of intense media attention^{1,2} and because a key component of the reanalysis appears to have been based on an erroneous premise. Specifically, de Lorgeril et al. argued that because “an ‘unequivocal reduction in cardiovascular mortality’ was announced in March 2008 as the main justification for the premature trial termination, the absence of cardiovascular mortality data in the published article is striking.”²¹ On that basis, de Lorgeril et al. reanalyzed the JUPITER data to calculate a cardiovascular mortality rate (fatal stroke plus fatal MI), producing an estimate of 12 cardiovascular deaths in each study group, concluding that “such a lack of effect on cardiovascular mortality associated with a strong effect on nonfatal complications strongly suggests a bias in the data set and should have led to the continuation of the trial rather than to its premature

ending.”²¹ Putting aside the ongoing debate over whether the analysis by de Lorgeril et al. was accurate,² a question that cannot be resolved here, there appears to be no evidence that anyone connected with the JUPITER trial justified termination of the trial based mainly (or at all) on a specific finding of reduction in cardiovascular mortality. Instead, as indicated on JUPITER’s clinicaltrials.gov web page, the trial was stopped because of “unequivocal evidence of a reduction in cardiovascular morbidity and mortality,” (emphasis added).²² Although not sufficiently specific for a clinical trial web page, this language was consistent with the trial’s primary endpoint outcome, which encompassed both fatal and nonfatal cardiovascular events. The same language was used in press reports in March 2008 when the decision to terminate the trial was announced.²³ The study report indicated further that in making its decision, the IDSMB took into account “the size and precision of the observed treatment benefit, as well as effects on the rates of death and other secondary end points being monitored and on major subgroups.”¹⁴ Additional clarification was added by the JUPITER study chairman in 2009, when he reported that the trial was halted early because of “a 44% reduction in the trial primary end point of all vascular events ($P < 0.00001$), a 54% reduction in myocardial infarction ($P = 0.0002$), a 48% reduction in stroke ($P = 0.002$), a 46% reduction in need for arterial revascularization ($P < 0.001$), and a 20% reduction in all cause mortality ($P = 0.02$).”¹⁶

A more on-point critique was made by Kaul et al. (2010), who observed that important questions about the value of hs-CRP as a potential causal factor for cardiovascular events remain unresolved. Noting that a 2009 report from the U.S. Preventive Services Task Force did not endorse hs-CRP as a cardiovascular risk factor because “evidence that changes in CRP level lead to primary prevention of CHD events is inconclusive,”²⁴ Kaul et al. made 2 main criticisms of the JUPITER trial analysis.

First, Kaul et al. presented results from an analysis of data provided to the U.S. Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee in December 2009.²⁵ These data, Kaul et al. argued, suggest that “[hs-CRP] appears to be an insufficient predictor of risk and treatment response in JUPITER.”²⁰ These data included findings that (a) the cardiovascular event rates in the placebo group were approximately equal for subgroups of different hs-CRP levels, suggesting “flat” dose-response for hs-CRP; (b) treatment group patients with lower hs-CRP levels experienced greater treatment benefits; and (c) significant treatment benefit was observed for patients who “met the age and elevated [hs-CRP] level criteria plus at least 1 additional risk factor” but not for patients who met the “age and elevated [hs-CRP] level criteria alone.”²⁰ However, as Kaul et al. pointed out, some of these analyses were post hoc, and analyses of treatment response by

baseline LDL-C level and hs-CRP level were underpowered.

Second, Kaul et al. argued that the decision to put an early halt to any trial, including the JUPITER trial, creates important “perils” including “a false-positive result, an overoptimistic result, a less-convincing result, or a missed opportunity to gather essential data on adverse effects.”²⁰ In supporting this point, Kaul et al. referred to a systematic review and meta-regression analysis by Bassler et al. (2010), which compared 91 truncated RCTs with 424 matching nontruncated RCTs.²⁶ For truncated RCTs compared with nontruncated RCTs, the pooled ratio of relative risks was 0.71 (95% CI=0.65-0.77). For example, applying this ratio to a nontruncated trial showing a relative risk of 0.80 or a 20% risk reduction, a truncated trial would show a relative risk of 0.57 (0.80×0.71) or a 43% risk reduction.^{20,26} Kaul et al. also pointed to the results of the Optimized Phase 3 Tifacogin in Multicenter International Sepsis Trial (OPTIMIST) and the Candesartan in Heart failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trial, both of which showed significant benefits for study drugs compared with placebo at early assessments ($P = 0.006$ and 0.0006 , respectively). Both trials continued “and the apparent early benefit of the intervention disappeared on final evaluation.”²⁰

For clinicians, Kaul et al. concluded that JUPITER’s results do not warrant stratifying treatment decisions by hs-CRP level; that the risk reductions estimated in JUPITER are likely “overexuberant” and should not be expected in clinical practice; and that statins should be used only “judiciously” for primary prevention when patients do not modify lifestyle risk factors including diet, exercise and weight loss.²⁰ Still, despite the controversy about how JUPITER’s findings *should* be applied in routine practice, rosuvastatin was the only branded statin to increase its U.S. market share despite generic competition for the 2 sequential years ending in 2009; sales of rosuvastatin grew by 29% in 2009 to \$4.5 billion.²⁷

Fibrates Take Their Lumps with the Statins

A meta-analysis of 10 RCTs performed by Saha et al. (2007) found that fibrates join statins in the low return on investment in prevention of adverse cardiovascular outcomes and all-cause mortality.²⁸ Although fibrates were effective at lowering triglycerides and total cholesterol and increasing high-density lipoprotein cholesterol (HDL-C), nonfatal MI was the only endpoint outcome that was reduced by fibrates. Fibrates did not reduce fatal MI, stroke, or cardiovascular mortality. Noncardiovascular mortality was higher with fibrates, and all-cause mortality appeared to be higher with fibrates versus placebo (but the all-cause comparison was not statistically significant, $P = 0.08$), but the exclusion of clofibrate studies resulted in no significant difference in all-cause mortality and noncardiovascular mortality for fibrates compared with placebo.

Primary Prevention with Statins: Cost and Implications for Routine Clinical Practice

Based on the JUPITER trial results, on December 15, 2009, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of rosuvastatin for primary prevention in persons with elevated CRP without reference to LDL-C level, the first statin with this indication. Steven Nissen, MD, chair of cardiovascular medicine at the Cleveland Clinic, was quoted as saying at the time that if the FDA accepts the advisory committee's recommendation, "the number of Americans eligible for statin therapy [would expand] by millions."²⁹ Other experts noted that FDA approval for this indication would have the unintended consequence of increasing demand for hs-CRP laboratory tests.²⁹ The FDA approved the supplemental indication for rosuvastatin on February 8, 2010.³⁰ The revised label for rosuvastatin includes the indication for "primary prevention of cardiovascular disease in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women" who have CRP of 2 mg per liter or greater and the presence of at least 1 additional cardiovascular disease risk factor (e.g., hypertension, low HDL-C, smoking, or a family history of premature CHD).³¹

A population-level strategy to treat persons with elevated CRP with primary prevention for cardiovascular disease would be expensive. Relying in part on an analysis by Woloshin et al (2007),³² Shah et al. (2009) assumed a rosuvastatin drug cost of \$115 per month and "a conservative strategy" in which patients would be eligible for treatment only if they had 2 or more risk factors, an estimated 10%-20% risk of coronary artery disease over the next 10 years (using Framingham risk scores), and a CRP of more than 3 mg per liter (i.e., a threshold higher than the current FDA-approved indication).³³ Under this assumed conservative strategy, Shah et al. estimated that \$345,238 in rosuvastatin drug cost would be required to prevent 1 MI, stroke, or death from cardiovascular disease. The population-level rosuvastatin cost in the U.S. would be \$2.9 billion per year to treat an additional 2.1 million Americans for 1.9 years.^{32,33} Under a "broad" strategy of treating all individuals with CRP exceeding 3 mg per liter, the additional treated population would number 25.3 million.³²

The cost of hs-CRP testing would also be expensive. The cost of the hs-CRP laboratory test (Current Procedural Terminology [CPT] code 86141)³⁴ is highly variable, typically in the range of \$45-\$85 but as much as \$120, and multiple hs-CRP tests are necessary to determine an average value.²⁴ Assuming testing of *only* those who meet the other high-risk ("conservative strategy") criteria specified by Shah et al. and applying a conservative estimate of 2 hs-CRP tests per person tested, \$50 per hs-CRP test,³⁵ and 3 persons tested for every person prescribed rosuvastatin for elevated hs-CRP (greater

than 3 mg per liter), 6.3 million persons would be tested twice for a total cost of about \$630 million.

There are also many unanswered questions about how a test-and-treat strategy would work in routine clinical practice. For example, Woloshin et al. warned about overdiagnosis and estimated that widespread CRP testing would not address the problem of undertreatment of persons at high risk of CHD because most patients who would become eligible for treatment based only on CRP would have the lowest CHD risk.³² And, as Shah et al. pointed out, it is not clear whether practitioners would choose to test patients who have inflammatory disorders, such as severe arthritis, lupus, and inflammatory bowel disease.³³ These patients were excluded from the JUPITER trial, and the value of hs-CRP as a predictor of their cardiac risk is questionable, adding uncertainty about the potential value of treatment if providers choose to test and treat them.

Can the Return-on-Investment of Primary Prevention with Statins Be Improved?

The limited evidence currently available suggests that the direct drug cost of rosuvastatin to prevent 1 all-cause death in persons without evident CHD ranges somewhere between approximately \$1 million (Brugts et al., NNT=167, 4 years of treatment) and \$2 million (Ray et al., 1 death in 1,429 person-years of treatment), at current (mid-2010) discounted drug cost.⁷ Since there are no head-to-head trials that would suggest that rosuvastatin is any better than other statins in primary prevention, the statin drug cost to prevent 1 all-cause death can be reduced by about 95% with generic simvastatin or by about 93% with generic pravastatin, to a range of approximately \$100,000 to \$137,000 per death avoided. This is still a high price to pay, before consideration of the potential clinical and economic impact of adverse effects, which are currently unknown for long-term therapy with statins in primary prevention.³⁶

Despite the potential importance of the notion that we should more accurately target primary prevention to those most likely to benefit from it, there seems to be insufficient evidence to focus on hs-CRP at the present time, let alone "[commit] low-risk subjects without clinical disease to 20 years or more of drug treatment," as one editorialist observed at the time of JUPITER's publication.³⁶ In particular, we currently lack experimental comparisons of hs-CRP with traditional risk factors as predictors of benefit from statin treatment. There are also numerous questions about how to apply clinical trial evidence from JUPITER's highly select sample to routine clinical practice, even putting aside the controversy over JUPITER's methods and findings. Whether better evidence will "tip the scale" toward a role for hs-CRP in primary prevention remains to be seen. In an era of evidence-based practice, clinicians and patients should await the answer.

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DISCLOSURES

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