Was the FDA Misled by JUPITER?

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In February 2010, the United States Food and Drug Administration (FDA) approved rosuvastatin calcium (Crestor; AstraZeneca, Wilmington, Delaware) for prevention of cardiovascular events in men older than 50 years and women older than 60 years who have high-sensitivity C-reactive protein (hs-CRP) levels greater than 2.0 mg/dL and one additional cardiovascular risk factor, representing the “missing link” between HMG-CoA reductase inhibitors (ie, statins), hs-CRP, and healthcare outcomes. The primary endpoint event was assessed with a hazard ratio that was both statistically and clinically significant (0.56; 95% confidence interval, 0.46-0.69). Although this hazard ratio is quite favorable in support of statin therapy, the outcomes benefit derived from hs-CRP lowering compared to cholesterol lowering remains unknown. This uncertainty poses a quandary, because statins have pleiotropic effects (ie, effects other than HMG-CoA reductase inhibition), and clinical trials do not typically use the statistical techniques required to separate such effects.

Fortunately, there is an indirect way to separate these pleiotropic effects—with the use of the Reynolds Risk Score (RRS) model, a cardiovascular event risk model that incorporates hs-CRP as a parameter. Except for its inclusion of this parameter to assess risk, the RRS model is similar to the Framingham Risk Score model in terms of parameters and functional form. Both are nonlinear 10-year risk models.

When the appropriate parameter values from JUPITER—representing the rosuvastatin group and placebo group at 12 months—are entered into the RRS model while controlling for gender, the 10-year risk of a cardiovascular event for the rosuvastatin group is 7.5%, and the 10-year risk of a cardiovascular event for the placebo group is 11.9%. This result yields a 10-year relative risk (RR), absolute risk reduction (ARR), and number needed to treat (NNT) of, respectively, 0.63, 4.4%, and 23. The RR and NNT values calculated from estimates made with the RRS model are similar to those values calculated in previous studies evaluating rosuvastatin for cardiovascular event risk reduction.

Calculating RR and NNT in this manner assists only in the instrumental validation of risk measurement as it applies to JUPITER results and the RRS model. It does not answer the question regarding relative impact on risk of lowering cholesterol level vs hs-CRP level. However, given the parameter values published in JUPITER, it is possible to estimate the RR as it applies to lowering either cholesterol or hs-CRP levels. This can be accomplished by holding constant all parameter values for the rosuvastatin group at their 12-month levels, while changing either the cholesterol or hs-CRP values to match those of the placebo group.

When all parameter values except for hs-CRP are the same between the rosuvastatin and placebo groups, the estimated 10-year risk of a cardiovascular event is 11.2% in the rosuvastatin group and 11.9% in the placebo group. The estimated RR, ARR, and NNT from lowering hs-CRP levels are, respectively, 0.95, 0.7%, and 143. When all parameter values except for lipid values are the same between the two groups, the estimated 10-year risk of a cardiovascular event is 7.9% in the rosuvastatin group and 11.9% in the placebo group. The estimated RR, ARR, and NNT from lowering cholesterol (primarily low-density lipoprotein cholesterol) levels are, respectively, 0.67, 4.0%, and 25.

Given this information regarding indirect estimates of RR and NNT according to statin effect, it becomes clear that the findings of JUPITER were primarily a result of cholesterol lowering as opposed to hs-CRP lowering. The fact that this conclusion has been either ignored or undetected until now is worrisome. Why did the FDA approve rosuvastatin for lowering hs-CRP levels when the benefit of this drug for that purpose is negligible and of questionable clinical significance? (The RR point estimate of 0.95, reported in the previous paragraph, could have a confidence interval with an upper bound crossing 1.00—thus suggesting clinical insignificance.)

Rosuvastatin is not a new drug and hs-CRP is not a new biomarker. Statins have most likely been lowering hs-CRP levels since their inception. Could AstraZeneca’s use of JUPITER represent an example of the pharmaceutical industry grasping at straws given their lack of success at bringing novel thera-

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pies to market? Treatment expansion of a drug is an efficient mechanism for a pharmaceutical company to squeeze revenue out of an existing product before patent expiration. AstraZeneca’s patent for rosuvastatin is scheduled to expire in 2016. Because of the established relative safety of rosuvastatin, only efficacy studies were needed to approve the drug for a new indication.

There is no doubt that results of JUPITER are significant—both statistically and clinically. However, the manner in which these results were sold to clinicians, the FDA, and the public were deceptive—damaging the credibility of the FDA and AstraZeneca.

The public health and economic ramifications of rosuvastatin’s treatment expansion are enormous. Millions of Americans will now be prescribed this statin, providing AstraZeneca and other pharmaceutical conglomerates with hundreds of millions of dollars in increased yearly revenues. Considering the misguided logic behind the FDA’s decision to expand rosuvastatin’s use, the question remains: who are the primary beneficiaries of this decision—patients or the pharmaceutical industry?

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References

Editor’s Note: Beginning on page 427, Dr MacDonald analyzes the cost-effectiveness of rosuvastatin.