Statin Therapy for Elevated hsCRP: More Evidence Is Needed

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Recently, the US Food and Drug Administration (FDA) approved rosuvastatin for the primary prevention of cardiovascular (CV) events in older adults with no clinical evidence of cardiovascular disease. The FDA noted that individuals to be considered for this new indication must meet the following criteria: age ≥50 years (men) or ≥60 years (women), high-sensitivity C-reactive protein (hsCRP) level of ≥2 mg/L, and the presence of at least 1 additional risk factor (hypertension, low high-density lipoprotein cholesterol [HDL-C], smoking, or family history of premature coronary heart disease). The FDA based its approval solely on results from the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a prospective, randomized, double-blind, placebo-controlled multicenter trial funded by the maker of rosuvastatin, AstraZeneca.[1]

The JUPITER trial assessed the effects of rosuvastatin versus placebo on the occurrence of major CV events in 17,802 subjects who met the inclusion criteria (age ≥50 years for men and ≥60 years for women, low-density lipoprotein cholesterol [LDL-C] <130 mg/dL, and hsCRP ≥2 mg/L); these patients were followed over approximately 2 years. Enrolled subjects were assigned to receive either rosuvastatin 20 mg daily or placebo. The study results showed about 44% relative risk reduction and 1.2% absolute risk reduction in the primary end point of combined myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes. The study also showed a 47% relative risk reduction in the secondary end point of combined myocardial infarction, stroke, or death from CV causes. There was no significant difference in the overall occurrence of adverse events, although there was a higher incidence of new onset of diabetes in the rosuvastatin group.

Although rosuvastatin lowered hsCRP to a statistically significant degree in this study, one has to be careful not to prematurely tag hsCRP the new culprit for CV events. The most current evidence on the predictive utility of hsCRP for CV events continues to be equivocal.[2,3] It is unclear to what degree the hsCRP reduction contributed to the results from the JUPITER trial. However, even if this reduction was deemed to be a significant contributor, then the question becomes whether a similar reduction in hsCRP could be achieved by other, more cost-effective means. For example, could the results from the JUPITER trial have been achieved by aggressive lifestyle modification such as exercise, smoking cessation, and diet?

It is unknown whether results similar to those from the JUPITER trial could be realized with a lower dose of rosuvastatin or other statins. Approval of rosuvastatin for this indication could open the door for other statins to be approved for the same indication without investigating the effectiveness of lower doses and non-statin therapies.

Concerns about the long-term adverse effects from statins are relevant because most patients who meet the criteria for this new indication would likely take rosuvastatin for about 20 to 30 years. The long-term cost of this therapy, including the cost of screening for high hsCRP, is an issue as well.

In addition, there is the issue of clinical utility. About 80% of the subjects screened for this study were excluded. Given that fact, how well will the results of the JUPITER trial translate into actual clinical practices?

Clearly, rosuvastatin is known to be effective for lowering LDL-C. As shown in the JUPITER trial, it significantly lowered both LDL-C and hsCRP. However, it is unlikely that rosuvastatin would have any significant direct effect on risk factors such as hypertension, low HDL-C, smoking, and family history of premature death. Traditionally, primary prevention of CV events has focused mainly on nonpharmacologic means such as lifestyle modifications and aggressive management of those conditions known to increase the risk of developing CV events (eg, hypertension).

It is unclear at this point what the medical community thinks about approval of rosuvastatin for this new indication. Clinicians might regard the news with skepticism. Many might wonder how to use this information in real-world settings. Others might face the often-subtle challenge of explaining the new use for rosuvastatin to some of their patients who are yearning for more information.

The often-cozy relationship between the FDA and drug companies has in the past drawn

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heavy criticism and remains a hot topic of debate.[4] The FDA has done important work throughout its existence. However, many wonder whether this recent approval is just another successful campaign by a drug company to expand the boundaries of an illness or condition to increase their market share[5] and whether the FDA succumbed to pressure to expand indications for this drug.

I think this new indication for rosuvastatin is unlikely to have any significant impact on clinical practices. As clinicians, it is our responsibility to ensure that we are up to date on the most current evidence-based, cost-effective medicine. However, we also must learn to differentiate between clinically relevant drug approvals and the relentless attempts by drug companies to expand boundaries of illnesses for profit. With such education, we will be better equipped to reject the growing trend of "more drugs, for more patients, for more profits."

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