In the recently completed Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin Multinational Trial in Heart Failure (JUPITER) trial, which was conducted with 17,802 primary-prevention patients with LDL cholesterol concentrations $<3.37$ mmol/L ($<130$ mg/dL) and high-sensitivity C-reactive protein (hsCRP) concentrations $\geq 2$ mg/L, random allocation to treatment with 20 mg rosuvastatin was associated with a 54% reduction in the incidence of myocardial infarction, a 48% reduction in stroke, a 47% reduction in the need for angioplasty or bypass surgery, a 43% reduction in venous thrombosis, and a 20% reduction in all-cause mortality (1). These effects were consistent in all of the evaluated subgroups, including among women as well as men, among minority populations, at all levels of Framingham risk, and among those with and without metabolic syndrome. Within the JUPITER trial, as had previously been shown in high-risk patients with acute coronary ischemia and among those with stable coronary disease, the clinical benefits of statin therapy compared with placebo were greatest among patients who reduced not only their LDL cholesterol concentration but also their hsCRP value (2). On the basis of these data, an advisory panel to the US Food and Drug Administration recently voted in favor of expanding the labeling for statin therapy to include those with low LDL cholesterol and increased hsCRP. Furthermore, 2009 guidelines from the Canadian Cardiovascular Society—the first national guidelines to appear since the publication of the JUPITER trial data—explicitly endorse hsCRP screening among “intermediate risk” patients, including those with low LDL cholesterol concentrations (3). The concept that low-LDL, high-hsCRP patients are at a higher than anticipated vascular risk and thus good candidates for statin therapy has also recently been confirmed in the multiethnic Atherosclerosis Risk in Communities (ARIC) study, in which patients with low LDL cholesterol values but high hsCRP concentrations had a substantially higher vascular risk than those with low values for both LDL cholesterol and hsCRP, despite both groups having identical Framingham risk scores (4). These data are almost identical to those reported in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial, in which lovastatin was highly effective at reducing cardiovascular event rates among patients with LDL cholesterol concentrations $<3.89$ mmol/L ($<150$ mg/dL) and hsCRP concentrations $>2$ mg/L, but showed no clinical benefit among those with LDL cholesterol values $<3.89$ mmol/L ($<150$ mg/dL) and lower hsCRP concentrations, despite a substantial reduction in LDL cholesterol (5).

In the December 1, 2009, issue of Circulation, McMurray and colleagues extend this paradigm to include heart failure patients who were participants in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) (6). Heart failure is an important setting in which to further test the concept of statins for patients with low LDL and high hsCRP, for multiple reasons. First, inflammation plays an important role in heart failure, and heart failure patients with increased hsCRP concentrations have consistently been found to have worse clinical outcomes. Second, in contrast to general populations, in which LDL cholesterol is a positive risk factor, low cholesterol is an independent predictor of a poor prognosis in heart failure. Thus, as McMurray and colleagues point out, heart failure is an inflammatory condition in which the usual epidemiologic relationship between cholesterol and vascular disease is reversed. Thus, a formal test of the low LDL, high hsCRP hypothesis in this setting is of both clinical and pathophysiologic interest.

Whereas JUPITER was exclusively a study of primary prevention, the CORONA trial evaluated the interaction of rosuvastatin, LDL cholesterol, and hsCRP among 4961 patients $\geq 60$ years of age and who had chronic heart failure of New York Heart Association class II to IV and a documented reduction in systolic left ventricular function. Of these patients, 1556 (31%) had entry hsCRP concentrations $<2$ mg/L, and 3405 (69%) had hsCRP values
≥2 mg/L. The baseline LDL cholesterol concentration was approximately 3.50 mmol/L (135 mg/dL) in both groups, and the left ventricular ejection fraction—a critical predictor of outcomes in heart failure—was 30% among both patients with low hsCRP concentrations and those with high hsCRP concentrations. Yet McMurray and colleagues found statistically significant interactions between rosuvastatin allocation and clinical outcomes during the CORONA trial, such that benefits were seen almost exclusively among patients with hsCRP values ≥2 mg/L at study entry. Specifically, an 11% reduction in total mortality was attributable to rosvastatin in the high-hsCRP group (hazard ratio, 0.89; 95% CI, 0.79–1.00; P = 0.05), whereas no such benefit was observed for those in the lower-hsCRP group (hazard ratio, 1.17; 95% CI, 0.95–1.43; P = 0.14, P for interaction = 0.026). Similar interactions on the basis of entry hsCRP concentrations were observed for coronary events (P for interaction = 0.023), for hospitalization for worsening heart failure (P for interaction = 0.026), for the combined end point of all-cause mortality and hospitalization (P for interaction = 0.011), and for the combined end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (P for interaction = 0.062).

Thus, taking the McMurray analysis of the CORONA trial at face value suggests that in the setting of congestive heart failure, for which the benefit of statin therapy has been equivocal to date, hsCRP evaluation may provide a mechanism to prospectively define a patient subgroup for which a clearer benefit exists.

It is unlikely that the differential effect of rosvastatin on vascular end points observed within the CORONA trial with respect to the entry hsCRP concentration relates to LDL cholesterol concentrations or to LDL reduction. Patients in the high- and low-hsCRP groups not only had virtually identical entry concentrations of LDL cholesterol but also had virtually identical 47% reductions in LDL cholesterol after the initiation of statin therapy. The 2 groups differed, however, in both baseline hsCRP concentration and hsCRP reduction. Within the CORONA trial, the median baseline hsCRP concentration was 1.1 mg/L in the low-hsCRP group and 5.6 mg/L in the high-hsCRP group, and random allocation to rosvastatin reduced the hsCRP concentration by 6% in the low-hsCRP group, compared with 33% in the high-hsCRP group.

Although it is tempting to ascribe these differential effects to the known antiinflammatory properties of rosvastatin, the CORONA data should be interpreted with appropriate caution. First, although the hsCRP stratification within the CORONA trial was done in a manner consistent with the JUPITER trial, it was nonetheless done on a post hoc basis. Second, although hsCRP is an inflammatory biomarker, it also correlates with such prothrombotic biomarkers as plasminogen activator inhibitor 1, and thus indirect selection for a prothrombotic state cannot be excluded. Furthermore, although LDL cholesterol correlates poorly with hsCRP, we do not yet know the true relationships of oxidized LDL to hsCRP, and the latter may ultimately prove important in understanding the interactions of statin therapy, LDL cholesterol, and inflammation. Finally, because both the JUPITER and CORONA trials evaluated the same agent, evidence for other statin agents is needed before these effects can be generalized. Regardless of these pathophysiologic issues, there is a remarkable consistency within multiple statin trials of primary prevention, secondary prevention, and now heart failure that tells us that individuals with increased hsCRP concentrations not only are at increased risk but also appear to preferentially benefit from aggressive statin therapy. From a research perspective, it is crucial to understand the molecular basis for these interactions. In this regard, ongoing work evaluating statin effects on the biosynthesis of isoprenoids and on the induction of nuclear factors such as Kruppel-like factor 2 has provided initial clues that need to be pursued aggressively in basic laboratory settings. From a clinical perspective, evolving guidelines must come to terms with these data, because the opportunity to maximize statin benefits through “personalized medicine,” in which the right patient receives the right drug, will become increasingly important as indications broaden. Decisions regarding a patient’s prescription need to reflect clinical trial evidence, and that evidence consistently suggests that those who obtain the greatest clinical benefit from statin therapy with the largest reductions in the rate of disease progression are those with increased inflammation, irrespective of the LDL cholesterol concentration.
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