C-reactive protein (CRP) levels are an independent predictor of future myocardial infarction and stroke among apparently healthy men and women,1-5 and the addition of CRP testing to standard lipid screening seems to provide an improved method to determine vascular risk.2,6 These data, as well as accumulating evidence that CRP may have direct inflammatory effects at the endothelial level,7 have implications for the use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). For example, in the Cholesterol and Recurrent Events (CARE) trial, random allocation to pravastatin both attenuated the excess vascular risk associated with low-grade, systemic inflammation8 and significantly reduced CRP levels over a 5-year follow-up period.9 Moreover, in that study, the change in CRP attributable to pravastatin was unrelated to changes in LDL cholesterol (LDL-C), an observation supporting the hypothesis that statin therapy may have important nonlipid anti-inflammatory effects.

Despite these observations, whether the effect of pravastatin on CRP is generalizable to other statin agents is uncertain,10 the time course of the CRP effect attributable to statins is largely unknown, and no dose-response data are available. We evaluated these issues in an 8-week randomized trial of cerivastatin given at either 0.4 or 0.8 mg daily in a cohort of 785 patients with primary hypercholesterolemia.
TABLE 1. Plasma Levels of LDL-C, HDL-C, and CRP at Baseline and After 8 Weeks of Treatment With Cerivastatin Among 785 Patients With Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Baseline, mg/dL</th>
<th>8 Weeks, mg/dL</th>
<th>Change, mg/dL</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>192.7</td>
<td>112.8</td>
<td>-79.1</td>
<td>-41.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>49.0</td>
<td>52.7</td>
<td>3.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mean)</td>
<td>0.33</td>
<td>0.25</td>
<td>-0.08</td>
<td>-24.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (median)</td>
<td>0.15</td>
<td>0.13</td>
<td>-0.02</td>
<td>-13.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

evidence of association between the change in CRP observed over time and the change observed for LDL-C or HDL-C. Log-normalized values were used to assess any correlation between baseline CRP levels and baseline levels of either LDL-C or HDL-C. All analyses were repeated according to randomized dose assignment, and all probability values are 2-tailed.

Results

The mean age of study participants was 56.9 years (range, 24 to 76 years), 62% were male, and 92% were white. Fourteen percent were current smokers, and 36% had a past smoking history.

Table 1 displays baseline and 8-week plasma levels of LDL-C and HDL-C for all 785 subjects evaluated. As expected, LDL-C levels significantly decreased from a mean of 192.7 mg/dL at baseline to 112.8 mg/dL after 8 weeks (41.0% reduction, P<0.001). Similarly, HDL-C levels increased from a mean of 49.0 mg/dL at baseline to 52.7 mg/dL at 8 weeks (7.8% increase, P<0.001).

As also shown, median CRP levels decreased from 0.15 mg/dL at baseline to 0.13 mg/dL at 8 weeks; this 13.3% reduction in median levels was attributable to cerivastatin (P<0.001). Accordingly, mean levels of CRP decreased from 0.33 mg/dL to 0.25 mg/dL, an average reduction of 24.5% (P<0.001). Although 61% of participants had a net reduction in CRP, 39% had no change or an increase in CRP, and 18 participants (2%) had a net increase in excess of 1 mg/dL, suggesting possible intercurrent infection.

The effects of both low-dose (0.4 mg) and high-dose (0.8 mg) cerivastatin on LDL-C, HDL-C, and CRP are displayed in Table 2 and in the Figure. Both doses of cerivastatin led to significant reductions in LDL-C and elevations of HDL-C and, as expected, a dose-response effect was observed for LDL-C (mean LDL reduction, 37.3% for 0.4 mg of cerivastatin and 42.2% for 0.8 mg of cerivastatin; P<0.001). In contrast, there was no clear dose-response effect of cerivastatin on CRP levels (median CRP reduction, 11.1% for 0.4 mg of cerivastatin and 13.3% for 0.8 mg of cerivastatin; P=NS).

We performed several additional analyses designed to address whether the change in CRP observed over time might be related to changes in lipid levels associated with cerivastatin use. In the total cohort, no substantive correlation was observed between the magnitude of change in CRP and the magnitude of change in LDL-C (r=-0.08), or between the magnitude of change in CRP and the magnitude of change in HDL-C (r=-0.04). Indeed, <2% of the variance in the percent change in CRP over time could be attributed to the percent change in either lipid parameter. This lack of correlation was observed both at low and high doses of cerivastatin. Similarly, we observed minimal evidence of correlation between baseline CRP levels and baseline lipid levels and between end-of-study CRP levels and end-of-study lipid levels (all r values <0.1).

Discussion

In this randomized intervention study performed among 785 patients with primary hypercholesterolemia, we observed highly significant reductions in plasma concentrations of CRP associated with both low-dose (0.4 mg) and high-dose (0.8 mg) cerivastatin given over an 8-week period. In contrast to LDL-C, we did not observe a significant dose-response effect for cerivastatin on CRP. Finally, there was no evidence that the change in LDL-C (or HDL-C) attributable to cerivastatin was related to the change in CRP that was also observed with the use of this agent.

We think these data have clinical relevance and importantly extend prior observations. First, the magnitude of reduction in median CRP levels observed in this study of cerivastatin (13.3%) is very similar to the magnitude of reduction in median CRP levels previously observed in the CARE trial of pravastatin (17.4%)9 and in data from our group in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of lovastatin (median reduction, 14.8%). Thus, on the basis of the consistency of these 3 studies, which together include serial CRP evaluation...
in >7000 patients, it seems that the effects of statins on CRP may represent a class effect.

Second, as also observed in the CARE trial of pravastatin and in the AFCAPS/TexCAPS trial of lovastatin, the change in CRP observed in the current study of cerivastatin was not related to the change in LDL-C achieved by this agent. Thus, <2% of the variance in the percent change in CRP could be accounted for by the percent change in LDL-C. This latter observation is important because it supports the hypothesis that mechanisms in addition to LDL reduction may be important for statin therapy. Because primary prevention studies have consistently found that individuals with low LDL-C but high CRP levels are at high vascular risk, these data also support the hypothesis that statin therapy might be effective even in the absence of overt hyperlipidemia, an issue in need of direct testing in future clinical trials.

Finally, the current data demonstrate that the effect of statins on CRP is present after as early as 8 weeks; these data expand on prior work that showed effects either at 1 year or at 5 years.9 In addition to the mechanistic implications of these data, the fact that CRP levels decline as early as 8 weeks also has implications for the timing of the initiation of statin therapy in several clinical settings, and again supports the hypothesis that plaque stabilization may be a critical mechanism of effect for these agents.

To date, the specific pathways by which statins reduce CRP and exert anti-inflammatory effects remain uncertain. However, intensive research efforts have demonstrated that statins impact several different components of the inflammatory cascade.13 With specific regard to cerivastatin, reduced macrophage content within atherosclerotic plaque has been demonstrated with this agent,14 as has direct suppression of the growth of macrophages and their subsequent expression of matrix metalloproteinases and tissue factor.15 Other studies suggest that statins may have important anti-inflammatory effects at the level of the vessel wall, data which are particularly intriguing given the recent demonstration that CRP can directly induce the expression of several cellular adhesion molecules critical to early atherogenesis.7

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