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Long-Term Effects of Pravastatin on Plasma Concentration of C-reactive Protein

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Background—Elevated plasma concentrations of C-reactive protein (CRP) are associated with increased cardiovascular risk. We evaluated whether long-term therapy with pravastatin, an agent that reduces cardiovascular risk, might alter levels of this inflammatory parameter.

Methods and Results—CRP levels were measured at baseline and at 5 years in 472 randomly selected participants in the Cholesterol and Recurrent Events (CARE) trial who remained free of recurrent coronary events during follow-up. Overall, CRP levels at baseline and at 5 years were highly correlated ($r=0.60$, $P<0.001$). However, among those allocated to placebo, median CRP levels and the mean change in CRP tended to increase over time (median change, +4.2%; $P=0.2$ and mean change, +0.07 mg/dL; $P=0.04$). By contrast, median CRP levels and the mean change in CRP decreased over time among those allocated to pravastatin (median change, −17.4%; $P=0.004$ and mean change, −0.07 mg/dL; $P=0.002$). Thus, statistically significant differences were observed at 5 years between the pravastatin and placebo groups in terms of median CRP levels (difference, −21.6%; $P=0.007$), mean CRP levels (difference, −37.8%; $P=0.002$), and absolute mean change in CRP (difference, −0.137 mg/dL; $P=0.003$). These effects persisted in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline lipid levels. Attempts to relate the magnitude of change in CRP to the magnitude of change in lipids in both the pravastatin and placebo groups did not reveal any obvious relationships.

Conclusions—Among survivors of myocardial infarction on standard therapy plus placebo, CRP levels tended to increase over 5 years of follow-up. In contrast, randomization to pravastatin resulted in significant reductions in this inflammatory marker that were not related to the magnitude of lipid alterations observed. Thus, these data further support the potential for nonlipid effects of this agent. **(*Circulation*. 1999;100:230-235.)**

Key Words: myocardial infarction ■ proteins ■ pravastatin ■ atherosclerosis

Plasma concentrations of C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, are elevated among men and women at risk for future cardiovascular events.[1] Specifically, prospective studies indicate that baseline levels of CRP are associated with increased risk of myocardial infarction and stroke among apparently healthy individuals,[2,3] those at increased risk because of older age or smoking status,[4,5] and those with symptomatic angina pectoris[6] or prior myocardial infarction.[7,8] Furthermore, the predictive value of high-sensitivity testing for CRP (hs-CRP) appears to be additive to that of total and HDL cholesterol,[9] data that suggest that screening for hs-CRP may have a role in cardiovascular risk prediction.

To date, few therapeutic modalities have been shown to influence CRP levels. However, in a nested case-control analysis of post–myocardial infarction patients randomly assigned to pravastatin or placebo in the Cholesterol and Recurrent Events (CARE) trial, those with elevated levels of CRP at baseline were found to have an increased risk of recurrent coronary events (RR=1.77, $P=0.02$).[7] Moreover, in that study, the association between CRP and subsequent risk was significant among those randomized to placebo (RR=2.1, $P=0.048$) but was attenuated and no longer significant among those assigned to pravastatin (RR=1.29, $P=0.5$). These effects were present even though those with and without elevated levels of CRP had virtually identical baseline lipid levels. This observation, as well as experimental data demonstrating that therapy with pravastatin[10,11] and cerivastatin[12] reduces the number and activity of inflammatory cells present within atherosclerotic plaques, raises the possibility that HMG-CoA reductase inhibition may have clinically important anti-inflammatory actions.

Despite these data, it is unknown whether long-term HMG-CoA reductase inhibition affects plasma concentration of CRP. The availability of baseline and 5-year follow-up blood samples in the CARE study afforded us the opportunity

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to directly address this issue for pravastatin, a potent HMG-CoA reductase inhibitor that has been shown in several large-scale trials to significantly reduce rates of myocardial infarction, stroke, and cardiovascular mortality in both high-risk and moderate-risk populations.[13–15]

Methods

The CARE study was a secondary prevention trial of cardiovascular disease conducted among 4159 patients with a prior history of MI who had total cholesterol levels <240 mg/dL and LDL cholesterol levels between 115 and 175 mg/dL. As described previously,[14] patients were eligible for inclusion if they had had an acute myocardial infarction between 3 and 20 months before randomization, were 21 to 75 years of age, had a left ventricular ejection fraction of ≥25%, and had no evidence of congestive heart failure. The primary end point of the CARE trial was death from coronary heart disease (including fatal myocardial infarction, either definite or probable; sudden death; death during a coronary intervention; and death from other coronary causes) or a symptomatic (unless during noncardiac surgery) nonfatal myocardial infarction confirmed by serum creatine kinase measurements. Overall, the randomized use of pravastatin in the CARE trial was associated with a 24% reduction in risk of this primary end point.[14]

Blood samples were collected in CARE during prerandomization clinic visits designed in part to determine baseline lipid levels for study eligibility. On average, these visits occurred 8.9 months after the qualifying acute myocardial infarction. Samples were collected in EDTA, shipped to a central collection site on cooled gel packs, and frozen at −80°C for future analyses. Follow-up blood samples were also obtained in the CARE trial at the 60-month (5-year) visit after randomization. Details of the blood collection and storage procedures used in the CARE trial are outlined elsewhere.[16]

For this analysis, we evaluated the effects of pravastatin on CRP levels among a randomly selected group of 477 participants in the CARE trial in whom both baseline and 5-year blood samples were available and who had remained free of recurrent vascular events during the trial follow-up. To avoid the potential for misclassification because of any elevation of CRP that might be due to the presence of an exogenous acute-phase stimulus, patients with either a baseline or 5-year CRP value >3 SD above the mean value were excluded from analysis on an a priori basis; in total, 5 patients (2 on placebo, 3 on pravastatin) were thus excluded. Of the remaining 472 patients, 258 had been randomly assigned in the CARE trial to receive pravastatin (40 mg PO QD), and 214 had been assigned to matching placebo. None of the study participants had previously been selected to serve as case or control subjects in an earlier analysis of inflammation within the CARE trial.[7]

Stored frozen blood samples from both baseline and 60-month visits were analyzed simultaneously by hs-CRP performed according to methods described by the manufacturer (Dade Behring).[17] Baseline and 60-month samples were assayed in pairs to minimize interassay variation and eliminate the possibility of drift over the course of the study. All assays were performed without knowledge of treatment assignment.

Means or proportions for baseline clinical characteristics were computed for those allocated to pravastatin or placebo, and the significance of any difference in means was tested with Student's *t* test; differences in proportions were tested with the χ^2 statistic. Because the distribution of CRP levels are skewed rightward, median concentrations were computed for those allocated to pravastatin and to placebo both at baseline and at 5 years, and log-normalized values of CRP were used to evaluate correlations over time. The significance of any differences in medians between drug groups was assessed by the Wilcoxon rank-sum test, and the significance of any differences in medians over time within each drug stratum was evaluated with the sign test for paired data. We also computed the absolute change in CRP level over time for each study subject, a process that resulted in a normal distribution of values. Thus, paired *t* tests were used to evaluate the significance of any differences in mean CRP changes over time within each drug stratum. Correlation coefficients were computed to assess for any evidence of association between the change in CRP observed over time with any change observed for total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides. These latter analyses were performed both on absolute change values for CRP and lipid levels and after categorization of the lipid data. Finally, linear regression models were used to compute β-coefficients associated with pravastatin use and the observed change in CRP. All probability values are 2-tailed.

TABLE 1. Baseline Clinical Characteristics of Study Participants According to Pravastatin or Placebo Assignment

	Placebo (n=214)	Pravastatin (n=258)	*P*
Age, y	59.3	58.5	0.3
Blood pressure, mm Hg			
Systolic	130.3	128.0	0.2
Diastolic	79.0	78.2	0.4
Body mass index, kg/m^2	27.0	27.2	0.6
Smoking status, %			
Never	25.2	22.1	0.7
Past	63.6	67.4	
Current	11.2	10.5	
Diabetes, %	10.3	12.0	0.6
Total cholesterol, mg/dL	208.0	208.2	0.9
LDL cholesterol, mg/dL	137.6	139.2	0.3
HDL cholesterol, mg/dL	39.0	40.7	0.1
Triglycerides, mg/dL	156.2	148.5	0.2

Results

Table 1 shows baseline clinical characteristics of the study participants according to placebo or pravastatin allocation. There were no significant differences between study groups in terms of age, blood pressure, body mass index, smoking status, prevalence of diabetes, or measured baseline levels of total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides. Overall, baseline clinical characteristics among patients in this analysis were similar to those reported in the CARE trial as a whole.[14] Aspirin use at study entry was 83%. In ongoing safety analyses, pravastatin use in the CARE trial has had no effects on hepatic function.

As shown in Figure 1, log-normalized CRP levels were highly correlated over time among individuals allocated to placebo ($r=0.60$, $P<0.001$). Indeed, despite its being an acute-phase reactant, the absolute magnitude of the correlation coefficient for CRP in these data was similar to that observed for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides over the 5-year follow-up period (Table 2).

Although baseline and follow-up CRP levels were correlated, median CRP concentrations tended to increase over time among patients allocated to placebo (median change, +4.2%; $P=0.2$). By contrast, among those allocated to pravastatin, median CRP concentrations decreased significantly after 5 years of active treatment (median change, −17.4%; $P=0.004$) (Table 3). Thus, as shown in Figure 2 (bottom, solid lines), whereas no difference in medians was observed between those allocated to pravastatin or placebo at

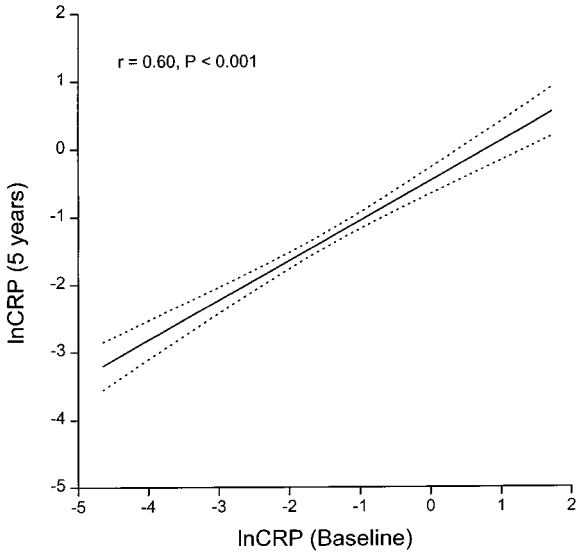

Figure 1. Relationship of log-normalized levels of CRP at baseline and at 60 months among study participants allocated to placebo. Dotted lines represent 95% CIs.

baseline ($P=0.8$), the median CRP level was 21.6% lower at 5 years for those allocated to pravastatin ($P=0.007$).

Similarly, among those allocated to placebo, mean CRP levels tended to increase over the 5-year follow-up period (mean change, +0.065 mg/dL; $P=0.04$). By contrast, among those allocated to pravastatin, mean CRP levels decreased (mean change, −0.072 mg/dL; $P=0.002$). Thus, as shown in Figure 2 (top, dotted lines), although no difference in means was observed between those allocated to pravastatin or placebo at baseline ($P=0.5$), the mean CRP level was 37.8% lower at 5 years for those allocated to pravastatin ($P=0.002$).

This difference between pravastatin and placebo groups in terms of the absolute mean change in CRP over time persisted in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (Table 4).

We performed several additional analyses designed to assess whether the change in CRP observed over time might be related to changes in lipid levels associated with each treatment group. Overall, no significant correlation was observed in these data between the magnitude of change in CRP and the magnitude of change in LDL cholesterol among those allocated to pravastatin ($r=0.10$, $P=0.1$) or to placebo

TABLE 2. Age-Adjusted Correlation Coefficients for Log-Normalized CRP Levels and for Lipid Parameters at Baseline and After 5-Year Follow-Up Among Study Participants Randomly Allocated to Placebo

Parameter	*r*	*P*
CRP	0.60	0.001
Total cholesterol	0.37	0.001
LDL cholesterol	0.32	0.001
HDL cholesterol	0.74	0.001
Triglycerides	0.49	0.001

TABLE 3. Median and Mean Concentrations of CRP at Baseline and After 5 Years of Follow-Up According to Pravastatin or Placebo Assignment

	Baseline, mg/dL	5 Years, mg/dL	Difference, %	*P*
Median levels				
Placebo	0.24	0.25	+4.2	0.2
Pravastatin	0.23	0.19	−17.4	0.004
Mean levels				
Placebo	0.36	0.43	+19.4	0.04
Pravastatin	0.38	0.31	−18.4	0.002

($r=0.02$, $P=0.8$). A similar lack of correlation between the change in CRP and changes in total cholesterol ($r=0.10$, $P=0.1$ for pravastatin and $r=0.02$, $P=0.8$ for placebo) and triglycerides ($r=0.06$, $P=0.3$ for pravastatin and $r=0.05$, $P=0.4$ for placebo) was observed. Finally, no correlation was observed between the change in CRP and the change in HDL cholesterol among those on pravastatin ($r=-0.09$, $P=0.2$), whereas a modest correlation was observed among those on placebo ($r=-0.15$, $P=0.03$).

We explored this issue further in analyses that categorized absolute LDL changes observed at the end of the treatment period into increments of 25 mg/dL. As shown in Figure 3, allocation to pravastatin tended to reduce CRP levels at all LDL change increments, whereas placebo allocation tended to be associated with elevations of CRP. This appeared to be the case even among those individuals who, despite placebo allocation, experienced a reduction in LDL levels over the 5-year follow-up period. For example, in a subgroup analysis limited to study participants with a 0- to 50-mg/dL decrease in LDL cholesterol during trial follow-up, a 0.05-mg/dL decrease in CRP was observed among those assigned to pravastatin (n=144) compared

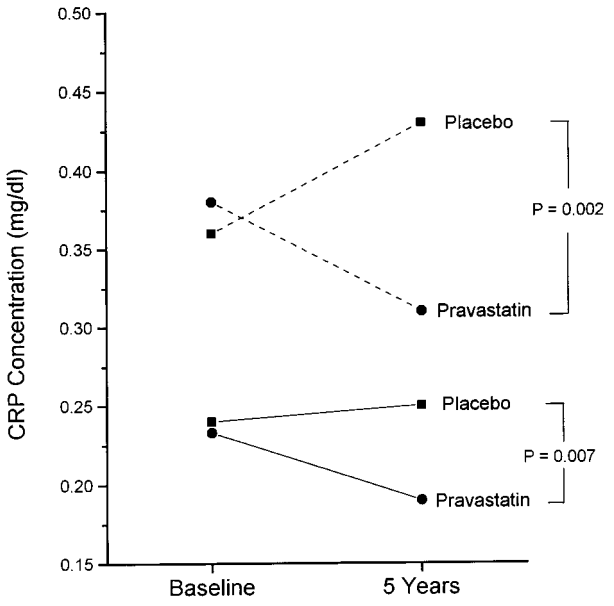

Figure 2. Median (solid lines) and mean (dotted lines) levels of CRP at baseline and at 60 months, according to placebo or pravastatin assignment.

TABLE 4. Change in Mean CRP Concentration Over 5 Years of Follow-Up According to Pravastatin or Placebo Assignment

		Change in CRP Concentration Over Time, mg/dL			
	n	Placebo	Pravastatin	Net Difference	*P*
All subjects	472	+0.065	−0.072	−0.137	0.003
Age >60 y	221	+0.051	−0.083	−0.134	0.03
Age ≤60 y	251	+0.079	−0.063	−0.142	0.004
Body mass index >27 kg/m^2	217	+0.091	−0.035	−0.126	0.04
Body mass index ≤27 kg/m^2	255	+0.045	−0.106	−0.151	0.001
Smokers	51	+0.355	−0.217	−0.573	0.002
Nonsmokers	421	+0.029	−0.055	−0.084	0.02
Blood pressure, mm Hg					
Systolic >128	234	+0.039	−0.082	−0.121	0.04
Systolic ≤128	238	+0.089	−0.063	−0.152	0.003
Diastolic >78	266	+0.032	−0.061	−0.093	0.05
Diastolic ≤78	206	+0.108	−0.087	−0.195	0.002
LDL cholesterol >138 mg/dL	233	+0.029	−0.064	−0.093	0.05
LDL cholesterol ≤138 mg/dL	239	+0.099	−0.081	−0.180	0.003
HDL cholesterol >35 mg/dL	289	+0.082	−0.055	−0.137	0.007
HDL cholesterol ≤35 mg/dL	183	+0.041	−0.101	−0.142	0.02
Triglycerides >160 mg/dL	191	+0.097	−0.099	−0.196	0.002
Triglycerides ≤160 mg/dL	281	+0.042	−0.056	−0.098	0.04

with a 0.10-mg/dL increase among those assigned to placebo (n=102) (P=0.01) (Figure 3).

Finally, in linear regression models, pravastatin use was a significant predictor of change in CRP over time (P=0.001). However, in linear regression models that included change in LDL as well as pravastatin use, change in LDL was not a predictor of change in CRP (P=0.2), whereas the effect of pravastatin remained statistically significant (P=0.02). Moreover, the β-coefficient for pravastatin use in models including change in LDL was similar to that in models excluding change in LDL (β-coefficients, −0.11 and −0.14, respectively). Thus, these latter findings indicate that the effect of pravastatin on change in CRP over time is only slightly attenuated in analyses controlled for change in LDL.

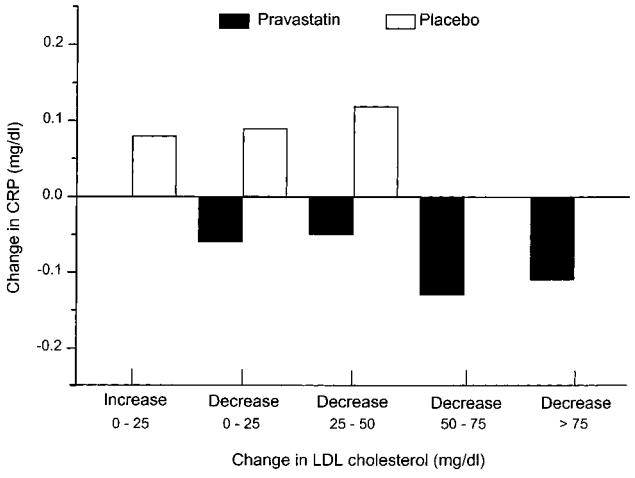

Figure 3. Mean change in CRP levels over time according to observed changes in LDL cholesterol. Data are shown for those allocated to pravastatin (solid bars) or to placebo (open bars).

Discussion

In this study of post–myocardial infarction patients enrolled in the CARE trial and followed up for 5 years, we found that CRP levels tended to increase among those treated with standard therapy plus placebo. In contrast, randomization to pravastatin resulted in significant reductions in this inflammatory marker, such that those allocated to active therapy had median CRP levels 21.6% lower than those on placebo at the end of the treatment period (P=0.007). This effect was present in the total study cohort as well as in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline lipid levels. Moreover, the magnitude of change in CRP associated with randomized treatment assignment did not correlate with the magnitude of change in lipid levels observed during follow-up. For example, allocation to placebo was associated with increased CRP levels (and allocation to pravastatin was associated with decreased CRP levels) regardless of the magnitude of LDL reduction achieved. This appeared to be the case even among those individuals who, despite placebo allocation, experienced a reduction in LDL levels over the 5-year follow-up period. Finally, in linear regression analyses that controlled for change in LDL, pravastatin use remained a statistically significant predictor of change in CRP over time (P=0.02), and the β-coefficient associated with pravastatin use was minimally altered.

Previous data evaluating the effects of HMG-CoA reductase inhibition on plasma concentrations of CRP are scant.[18] However, the possibility that statin therapy might have clinically relevant anti-inflammatory effects has been suggested previously in both experimental and clinical settings. For example, HMG-CoA reductase inhibitors, such as prava-

statin, have been shown to inhibit endogenous cholesterol synthesis in macrophages, a process that may reduce macrophage activation.[19] Similarly, treatment with pravastatin as well as cerivastatin has been shown to reduce the number of inflammatory cells present within atherosclerotic plaques, possibly in a cholesterol-independent manner.[10–12] Recent experimental data also indicate that lipid-lowering reduces matrix metalloproteinase activity, an effect mediated in part by inhibition of macrophage function.[20,21] These latter data thus suggest that part of the plaque-stabilizing effects of statin therapy may relate to reduced inflammatory-cell function.

With regard to previous clinical evidence, a previous report from the CARE trial has shown that elevated levels of CRP after myocardial infarction were associated with increased risk of recurrent coronary events,[7] data that extend evidence indicating that this inflammatory marker is a potent cardiovascular risk factor among low-risk individuals[2,3] as well as those with significant preclinical atherosclerosis[4,5] or angina pectoris.[6,8] However, in the CARE trial, the association between elevated levels of CRP and risk was significant only among those randomized to placebo (RR=2.11, P=0.048) but was attenuated and nonsignificant among those randomized to pravastatin (RR=1.29, P=0.5). Furthermore, the risk reduction attributable to pravastatin in the CARE trial was substantially greater among those with evidence of inflammation (54%) than among those without evidence of inflammation (25%); this effect was present even though baseline lipid levels were similar in these 2 groups.[7] Thus, the current finding that pravastatin reduces CRP levels supports previous observations regarding interrelations between inflammation, pravastatin, and the risk of recurrent coronary events.

The observation in these data that the magnitude of CRP reduction associated with pravastatin use did not correlate with the magnitude of LDL reduction achieved is intriguing and merits further investigation. Several large-scale randomized trials demonstrate that therapy with HMG-CoA reductase inhibitors significantly reduces the risk of subsequent myocardial infarction, stroke, and cardiovascular mortality.[13–15,22,23] However, it has also been suggested that these risk reductions are greater than that expected on the basis of LDL reduction alone.[24] Furthermore, in the West of Scotland Coronary Prevention Study trial, those on pravastatin fared better than those on placebo even when matched for LDL levels achieved.[25] Thus, in this context, the present data also provide mechanistic support for the possibility that therapy with pravastatin may have important nonlipid effects.

Potential limitations of these data require consideration. For example, the magnitude of change in median CRP levels observed over time in our study were modest (+4.2% for placebo, −17.4% for pravastatin), and there was variation in both the degree and direction of change observed for individuals within each treatment stratum. However, the mean changes observed in these data were stable in analyses stratified by all available baseline variables as well as in analyses stratified by LDL change over time, an observation that suggests that our sample size was more than adequate to discern important small to moderate effects. In addition, because CRP is an acute-phase reactant, it is at least theoretically possible that the differences observed over time might have been the result of an unanticipated exogenous anti-inflammatory stimulus rather than an effect of pravastatin. We believe, however, that the randomization of our study subjects between pravastatin and placebo and the consistency of effects across subgroups makes such a possibility highly unlikely. Finally, to limit any potentially misleading effects due to outlying values, we chose prospectively to exclude from our analysis individuals with CRP levels >3 SD above the mean at either baseline or 60 months. This decision proved to have minimal impact on our analysis, because only 5 individuals were excluded on this basis (2 on placebo, 3 on pravastatin). Furthermore, post hoc inclusion of these individuals did not result in any change in median CRP levels, the analyses we believe to be most informative given the skewed nature of this inflammatory parameter.

In sum, the present data support several conclusions. First, among patients on standard therapy plus placebo followed up over a 5-year period, CRP levels were correlated, median CRP levels were stable, and the mean change in CRP over time tended to increase. The general stability of CRP over long follow-up periods thus supports the use of this inflammatory marker as a novel means for cardiovascular risk detection.

Second, long-term HMG-CoA reductase therapy with pravastatin appears to result in significantly reduced levels of CRP. These data suggest that CRP may be a modifiable marker of risk, an important observation in that previous studies indicate that individuals with elevations of CRP but normal lipid levels are at significantly increased risks of developing cardiovascular disease.[9]

Finally, previous studies of inflammation in the CARE trial indicate that the efficacy of pravastatin is greater among those with elevated levels of CRP, an effect that is independent of baseline lipid levels.[7] In the present analysis, we found that pravastatin resulted in changes in CRP that also did not correlate with changes in LDL cholesterol. Thus, taken together, these data provide additional insights into the role of inflammation in atherogenesis and the mechanisms by which HMG-CoA reductase therapy reduces the risk of recurrent coronary events.

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