Effect of Statin Therapy on C-Reactive Protein Levels: The Pravastatin Inflammation/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study

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Effect of Statin Therapy on C-Reactive Protein Levels

The Pravastatin Inflammation/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study

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Context Plasma levels of the inflammatory biomarker C-reactive protein (CRP) predict cardiovascular risk, and retrospective studies suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may lower CRP in a manner largely independent of low-density lipoprotein cholesterol (LDL-C). However, prospective trial data directly evaluating this anti-inflammatory effect of statins are not available.

Objective To test the hypothesis that pravastatin has anti-inflammatory effects as evidenced by CRP reduction.

Design, Setting, and Participants Community-based, prospective, randomized, double-blind trial including 1702 men and women with no prior history of cardiovascular disease (primary prevention cohort) and open-label study including 1182 patients with known cardiovascular disease (secondary prevention cohort) who provided at least baseline and 12-week blood samples. The study was conducted in US office-based practices from February to December 2000.

Interventions Participants in the double-blind primary prevention trial were randomly assigned to receive 40 mg/d of pravastatin (n = 865) or placebo (n = 837) for 24 weeks. Participants in the secondary prevention cohort received 40 mg/d of open-label pravastatin for 24 weeks.

Main Outcome Measure Change in CRP levels from baseline to 24 weeks.

Results In the primary prevention trial, compared with placebo, pravastatin reduced median CRP levels by 16.9% ($P<.001$) at 24 weeks, reflecting a decrease of 0.02 mg/dL in the pravastatin group while no change in CRP levels was observed in the placebo group. This effect was seen as early as 12 weeks (median reduction in CRP with pravastatin, 14.7%; $P<.001$) and was present among all prespecified subgroups according to sex, age, smoking status, body mass index, baseline lipid levels, presence of diabetes, and use of aspirin or hormone replacement therapy. No significant association was observed between baseline CRP and baseline LDL-C levels, end-of-study CRP and end-of-study LDL-C levels, or change in CRP and change in LDL-C levels over time. In linear regression analyses, the only significant predictors of change in CRP on a log scale were randomized pravastatin allocation and baseline CRP levels ($P<.001$ for both). Similar reductions in CRP levels were observed at 12 weeks (–14.3%) and 24 weeks (–13.1%) in the secondary prevention cohort treated with pravastatin ($P<.005$ for both).

Conclusions In this prospective trial, pravastatin reduced CRP levels at both 12 and 24 weeks in a largely LDL-C–independent manner. These data provide evidence that statins may have anti-inflammatory effects in addition to lipid-lowering effects.

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THE 3-HYDROXY-3-METHYLGLUTARYL coenzyme A reductase inhibitors (statins) have been hypothesized to have direct anti-inflammatory effects, an important issue since inflammation plays a major role in determining atherosclerotic plaque vulnerability.[1] Experimental data indicate that statins reduce macrophage content within atherosclerotic plaques,[2-6] suppress the expression of metalloproteinases involved in the fibrous cap dissolution,[7-9] and inhibit the expression of adhesion molecules critical for monocyte attachment and adhesion to the endothelial wall.[10] The concept that statins have anti-inflammatory as well as lipid-lowering properties also helps to explain certain paradoxes of statin therapy. In particular, statins are effective in reducing stroke risk,[11] yet epidemiologic studies have not found low-density lipoprotein cholesterol (LDL-C) to be an important risk factor for stroke. Recent data also suggest that statins may slow the development of diabetes, a disease triggered in part through inflammatory mechanisms.[12]

Measurement of low-grade systemic inflammation can be achieved in clinical settings with the use of high-sensitivity assays for C-reactive protein (CRP).[13] Prospective epidemiologic studies indicate that CRP levels

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are a strong independent predictor of risk for future myocardial infarction and stroke among apparently healthy men and women.[13-16] Furthermore, the addition of CRP screening to standard lipid evaluation appears to provide an improved method of determining global vascular risk.[13] This latter observation is clinically important because combined CRP and lipid screening may provide an improved method to target statin therapy, particularly in the setting of primary prevention.[17]

Despite these data, clinical evidence regarding potential anti-inflammatory effects of statin therapy have been limited. In a hypothesis generating analysis of myocardial infarction patients enrolled in the Cholesterol and Recurrent Events (CARE) trial,[18] patients with elevated CRP levels were at significantly increased risk for recurrent coronary events.[19] However, the relationship between inflammation and risk was markedly attenuated among those randomly allocated to pravastatin therapy. Moreover, in a 5-year follow-up analysis of the CARE trial, pravastatin significantly reduced plasma levels of CRP in a manner largely independent of LDL-C.[20] These data, as well as similar findings for lovastatin[17] and cerivastatin,[21] provide initial clinical evidence of nonlipid anti-inflammatory effects for these agents.

However, all of these prior studies were retrospective, relied on banked plasma samples stored for other purposes, and were performed on a post hoc basis. Thus, available data regarding the role of statins in reducing CRP can be considered only as hypothesis generating. For this reason, the Pravastatin Inflammation/CRP Evaluation (PRINCE) was designed as a prospective hypothesis-testing study with the specific aim of providing evidence to support or reject these initial observations.

METHODS

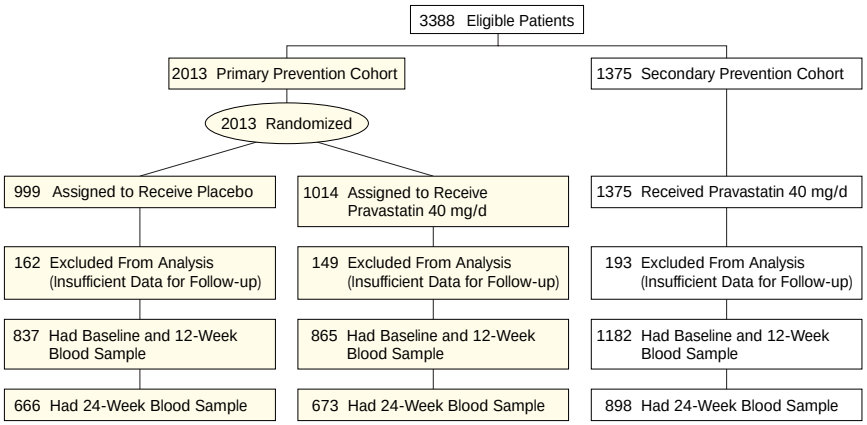
The PRINCE protocol was designed to determine whether any effect of pravastatin on CRP might be present as early as 12 to 24 weeks, whether any effects of pravastatin on CRP are dependent or independent of pravastatin-induced changes in LDL-C, and whether any anti-inflammatory effect of pravastatin in terms of reducing highly sensitive CRP (hs-CRP) is similar in magnitude among primary and secondary prevention patients.

In brief, PRINCE was a community-based study, conducted between February and December 2000, that included both a randomized double-blind trial of pravastatin 40 mg/d, vs placebo among men and women with no prior history of cardiovascular disease (primary prevention cohort), and a parallel open-label evaluation of pravastatin, 40 mg/d, among patients with a history of myocardial infarction, stroke, or arterial revascularization procedure (secondary prevention cohort; FIGURE 1). Patients in the secondary prevention cohort were not randomly allocated to receive placebo due to ethical concerns, but were included to simultaneously evaluate the magnitude of effect of pravastatin on CRP levels among individuals with known coronary disease, a group expected to have higher baseline CRP values. As described elsewhere,[22] participants eligible for PRINCE were aged 21 years or older, were free of statin use during at least the 6-month period prior to enrollment, and had no contraindications to statin therapy. Participants with a known chronic inflammatory condition or a need for anti-inflammatory therapy were not eligible. Participants in the primary prevention cohort had known baseline LDL-C levels of at least 130 mg/dL (3.5 mmol/L).

At study initiation, the magnitude and early time course of any hypothesized effect of pravastatin on CRP levels was unknown. However, our prior post hoc observations concerning this effect were observed among a group of 472 patients with myocardial infarction who had been followed up for 5 years.[20] Thus, the PRINCE study sample size was chosen to ensure evaluation of approximately 400 participants in each of the prespecified subgroups. Each study site obtained institutional review board approval of the PRINCE protocol prior to study initiation, and each study participant provided informed consent prior to enrollment. To achieve a broadly generalizable result, the number of patients enrolled by any one community-based physician was limited to 4, and we sought to enroll patients in all 50 states.

Study participants were asked to provide blood samples at baseline, 12 weeks, and 24 weeks. These samples were stored in liquid nitrogen until analysis. Levels of CRP were determined with a clini-

Figure 1. Participant Flow Diagram



Reasons for participant dropout after obtaining baseline and 12-week blood samples included, most commonly, failure to provide the final 24-week blood sample. Samples received but not analyzed were infrequent but included those for which the shipping tube fractured, no data form accompanied the specimen, the specimen arrived outside the protocol time table or was improperly labeled, or the specimen was hemolyzed.

Table 1. Baseline Characteristics of Pravastatin Inflammation/CRP Evaluation (PRINCE) Study Participants*

Characteristics	Primary Prevention			Secondary Prevention
	Placebo (n = 837)	Pravastatin (n = 865)	*P* Value	Pravastatin (n = 1182)
Age, mean (SD), y	57.4 (12.2)	56.8 (11.9)	.32	68.9 (10.8)
Women	45.6	42.3	.18	31.5
Smoking status				
Never	48.2	50.8	.13	30.7
Past	34.7	35.6		54.6
Current	17.1	13.6		14.6
Ethnicity				
White	86.8	84.7	.53	89.1
Black	6.5	7.9		6.7
Hispanic	4.4	4.3		2.4
Asian	1.8	2.0		1.3
Other	0.5	1.1		0.5
Body mass index, mean (SD), kg/m^2	29.4 (5.6)	29.2 (5.3)	.36	28.9 (5.5)
Diabetes mellitus	11.1	10.1	.47	28.2
Estrogen use	38.5	39.3	.53	22.1
Asprin use	26.7	29.7	.18	67.9
Cholesterol, mean (SD), mg/dL				
Total	231.0 (32.3)	230.9 (34.1)	.97	209.4 (41.5)
LDL-C	142.9 (26.3)	142.9 (26.3)	.99	125.9 (31.0)
HDL-C	40.4 (10.9)	39.9 (10.4)	.37	36.9 (11.3)
Triglycerides, median (IQR), mg/dL†	161.0 (116-231)	159.5 (114-233)	.70	168.0 (114-243)
hs-CRP, median (IQR), mg/dL†	0.21 (0.09-0.43)	0.20 (0.09-0.42)	.92	0.27 (0.12-0.53)

*Data are presented as percentages unless otherwise indicated. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and hs-CRP, highly sensitive C-reactive protein. To convert total, LDL, and HDL cholesterol from mg/dL to mmol/L, multiply by 0.0259 and to convert triglycerides, multiply by 0.0113. All *P* values are for comparisons between the randomized primary placebo and primary pravastatin cohorts.
†Interquartile range represents the 25th and 75th percentiles.

cally validated high sensitivity assay.[23] Total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured in a Centers for Disease Control and Prevention–standardized laboratory.

Laboratory analyses were performed on those study participants who provided at least a baseline and a 12-week blood sample and who appropriately completed all procedures allowing for study follow-up. As shown in Figure 1, of the 2013 participants in the primary prevention cohort, 311 (162 placebo, 149 pravastatin) failed to provide adequate information for continued study follow-up leaving 1702 participants with at least a baseline and a 12-week blood sample for evaluation (837 placebo, 865 pravastatin). Similarly, of the 1375 participants in the secondary prevention cohort, 193 failed to provide adequate information for follow-up, leaving 1182 participants with at least a baseline and 12-week blood sample for evaluation. In all these analyses, whenever CRP levels were missing, the most recent value was carried forward, consistent with the null effect.

To address the potential impact those individuals who were randomized but who failed to provide adequate information for study follow-up might have had on the primary prevention trial outcome, we performed an additional analysis on a post hoc basis in which we assumed that all such individuals had no change in CRP levels from baseline to 24 weeks.

On an a priori basis, analyses were conducted separately in the primary and secondary prevention cohorts with the principal outcome variable being change in CRP levels at 24 weeks. Prespecified secondary study analyses included the change in CRP at 12 weeks, the relation of change in CRP to change in lipid levels, as well as subgroup analyses based on age, sex, smoking status, body mass index, lipid levels, presence of diabetes mellitus, and concurrent use of aspirin or estrogen replacement therapy.

Because the distribution of CRP levels is skewed rightward, median concentrations were computed at baseline and at study completion and the significance of any difference in distributions was assessed by the Wilcoxon rank sum test. The median change and the median percentage change in CRP levels observed over time were also computed for study patients and the significance of differences in CRP changes over time were evaluated, both between randomized treatment groups (in the primary prevention cohort) and within treatment groups (in both the primary and secondary prevention cohorts). Spearman correlation coefficients were computed to assess for any evidence of association between baseline CRP and baseline lipid levels, between end-of-study CRP and end-of-study lipid levels, and between the change in CRP observed over time and the change observed over time for each lipid parameter. Linear regression models were used to evaluate relationships between pravastatin allocation, lipid reduction, and the change in CRP levels, and to evaluate whether any observed effects were altered by baseline clinical variables. In these latter analyses, baseline levels of CRP were included because these were a major determinant of the change in CRP on a log scale. All probablility values are 2-tailed.

RESULTS

Baseline clinical characteristics of participants in the primary and secondary prevention cohorts who provided at least a baseline and a 12-week blood sample are presented in TABLE 1. No significant differences were observed in the primary prevention cohort between the 865 patients randomly allocated to receive

pravastatin and the 837 patients allocated to receive placebo in terms of baseline clinical characteristics or baseline lipid values. The 1182 patients in the open-label secondary prevention cohort were older, more likely to be men, and had a higher prevalence of diabetes mellitus and cigarette consumption.

Prior to randomization, baseline levels of CRP were virtually identical in the 2 primary prevention groups (placebo group median CRP level, 0.21; interquartile range, 0.09-0.43 mg/dL and pravastatin group median CRP level, 0.20; interquartile range, 0.09-0.42 mg/dL; $P=.92$). Baseline CRP levels were higher in the secondary prevention cohort (median, 0.27; interquartile range, 0.12-0.53 mg/dL). Lipid levels were lower in the secondary prevention cohort than in the primary prevention groups, an expected outcome since patients with myocardial infarction and known hyperlipidemia were likely to already be receiving statin therapy and, thus, were systematically excluded from enrollment.

In the study population as a whole, correlation coefficients between baseline CRP levels and baseline levels of total cholesterol, LDL-C, HDL-C, and triglycerides were all less than 0.1. Thus, virtually none of the variance in CRP levels at baseline could be attributed to the variance in any of the lipid parameters.

Allocation to pravastatin in both the primary and secondary prevention cohorts resulted in significant reductions at 24 weeks in total cholesterol (–17.2%), LDL-C (–23.0%), and triglycerides (–15.9%), as well as an increase in HDL-C (6.5%, all P values $<.001$) (TABLE 2). No change in these levels was observed at 24 weeks among participants in the primary prevention cohort randomly allocated to placebo.

The change in CRP at both 12 and 24 weeks for each study group is presented in TABLE 3. Among patients randomly allocated to receive placebo in the primary prevention cohort, the primary end point of median CRP change at 24 weeks was 0.00 mg/dL (interquartile range, –0.07 to 0.07; percentage change, 2.7; $P=.90$). Among patients in the primary prevention cohort randomly allocated to receive pravastatin, median CRP levels declined by 0.02 mg/dL (interquartile range, –0.10 to 0.02) corresponding to a 14.2% reduction compared with baseline levels ($P<.001$). Thus, compared with patients assigned to the placebo group, pravastatin allocation in the primary prevention cohort was associated with a 16.9% reduction in median CRP levels ($P<.001$).

The effect of pravastatin on CRP was evident as early as 12 weeks. In the primary prevention cohort, the median change in CRP among participants in the pravastatin group was –0.02 mg/dL (–14.7%) at 12 weeks with no change observed among those in the placebo group ($P<.001$). Similar reductions compared with baseline values were observed at both 12 and 24 weeks in the secondary prevention cohort treated with pravastatin ($P<.005$) (Table 3).

In an analysis in which the 311 participants in the primary prevention trial who had been randomized but who had insufficient data for follow-up were included and assigned a value of 0 for the change in CRP concentration at 24 weeks, the between-group comparison of pravastatin to placebo (reduction of CRP levels of 7.1%, $P<.001$) and the within-group comparison of baseline to 24-week CRP levels among those allocated to pravastatin (reduction of 0.012 mg/dL, $P<.001$) were statistically significant.

Compared with placebo, the effect of pravastatin on CRP levels was present and statistically significant in prespecified subgroups of patients on the basis of age, sex, smoking status, body mass

Table 2. Absolute Change and Percentage Change in Lipid Levels at 24 Weeks in Pravastatin Inflammation/CRP Evaluation (PRINCE) Participants*

Variables	Primary Prevention		Secondary Prevention	
	Placebo (n = 837)	Pravastatin (n = 865)	Pravastatin (n = 1182)	Any Pravastatin (n = 2047)
Cholesterol, mean (%)				
Total	1.1 (1.2)	−38.3 (−16.1)	−39.9 (−18.1)	−38.9 (−17.2)
Low-density lipoprotein	0.6 (1.8)	−31.8 (−21.5)	−31.8 (−24.2)	−31.8 (−23.0)
High-density lipoprotein	0.8 (1.9)	2.3 (6.6)	1.9 (6.5)	2.1 (6.5)
Triglycerides, median (%)	−3.0 (−2.2)	−18.0 (−13.0)	−27.0 (−18.1)	−24.0 (−15.9)

*Changes were measured in mg/dL. No significant differences were observed within the placebo group; all P values for changes within the pravastatin groups are less than .001.

Table 3. C-Reactive Protein (CRP) Level Changes, Pravastatin Inflammation/CRP Evaluation (PRINCE) Study Group

Variables	Primary Prevention		Secondary Prevention	
	Placebo (n = 837)	Pravastatin (n = 865)	Pravastatin (n = 1182)	Any Pravastatin (n = 2047)
CRP, median (IQR), mg/dL				
Baseline	0.21 (0.09-0.43)	0.20 (0.09-0.42)	0.27 (0.12-0.53)	0.24 (0.10-0.48)
12 Weeks	0.19 (0.09-0.42)	0.16 (0.08-0.36)	0.23 (0.10-0.48)	0.19 (0.09-0.43)
24 Weeks	0.20 (0.09-0.43)	0.16 (0.08-0.35)	0.24 (0.10-0.47)	0.20 (0.09-0.42)
CRP, median change (% change), mg/dL				
12 Weeks	0.00 (1.4)	−0.02 (−14.7)	−0.02 (−14.3)	−0.02 (−14.5)
24 Weeks	0.00 (2.7)	−0.02 (−14.2)	−0.02 (−13.1)	−0.02 (−13.8)
P value*	.90	<.001	.003	<.001

*P value designate tests of significance within groups at 24 weeks. P value for comparison between randomized placebo and pravastatin groups are less than .001.

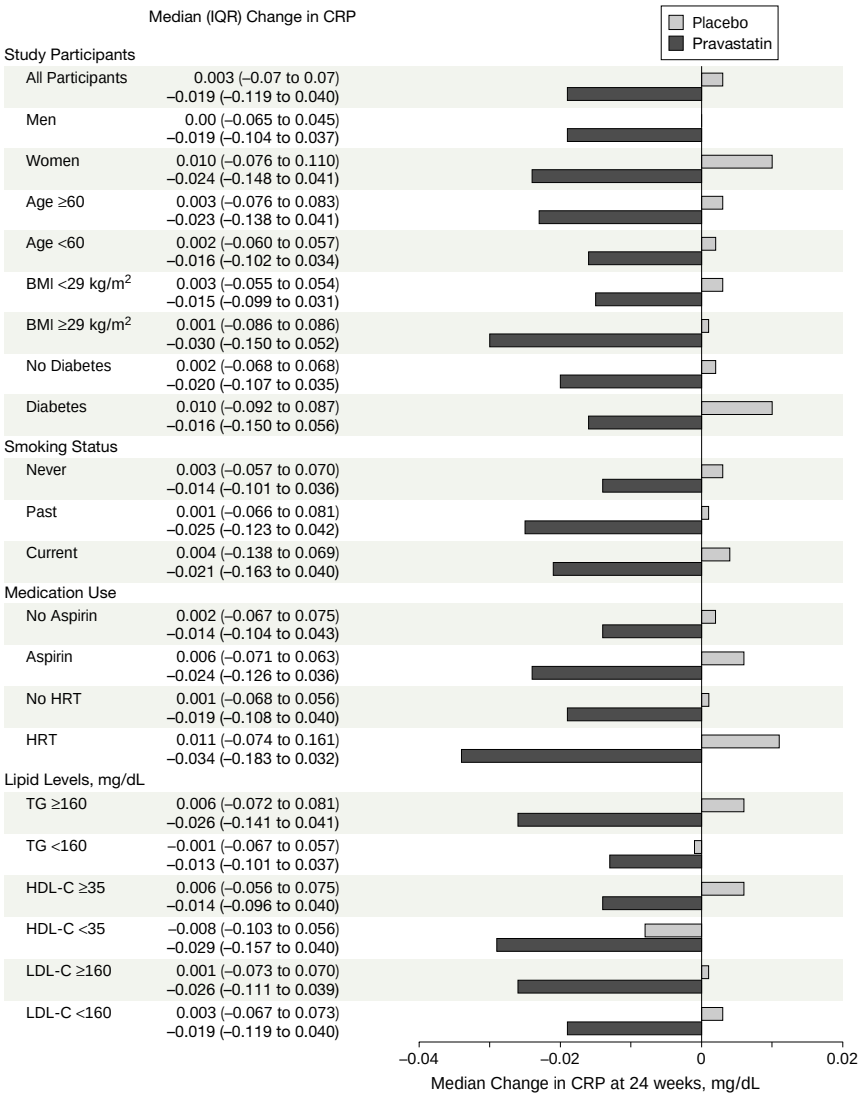
index, and median baseline levels of LDL-C, HDL-C, and triglycerides (all *P* values <.02; FIGURE 2). Similar effects were observed among persons who had never smoked (*P*<.001) and past smokers (*P*<.001) although the reduction in CRP with pravastatin use was not statistically significant among the subgroup of current smokers. With regard to prior drug use, the magnitude of CRP reduction associated with pravastatin use among those taking aspirin was similar to that observed among those not taking aspirin while the magnitude of CRP reduction among women taking estrogen was similar to that observed among women not taking estrogen. With the exception of body mass index, for which higher levels were associated with greater CRP reduction, there was little evidence that any of these baseline risk factors significantly modified the effect of pravastatin on CRP.

We performed several additional analyses designed to assess whether the observed pravastatin-induced changes in CRP were related to pravastatin-induced changes in lipid parameters. First, in correlational analyses limited to patients in the pravastatin group, we found minimal evidence of association between the change in CRP concentration at 24 weeks and the change in total cholesterol (r=0.02), LDL-C (r=0.04), HDL-C (r=−0.09), or triglyceride (r=−0.01) levels.

Second, in linear regression models, pravastatin allocation and baseline CRP levels were the major determinants of the change in CRP over time on a log scale (both *P*<.001). However, in linear regression models that included change in LDL-C levels and pravastatin use, change in LDL-C levels was not a predictor of change in CRP levels (*P* = .44), whereas the effect of pravastatin remained statistically significant (*P*<.001). In addition, the β coefficient for pravastatin use in models including change in LDL-C levels was similar to that in models that excluded change in LDL-C levels. As such, the effect of pravastatin on change in CRP levels over time was not attenuated in analyses controlling for the change in LDL-C levels, at least for the levels of LDL-C reduction achieved.

Also, because of the skewed nature of CRP levels, we evaluated for evidence of association between change in CRP and change in LDL-C levels according to baseline CRP levels. In this post hoc subgroup analysis, a statistically significant association was observed among those with baseline CRP levels in the highest quartile only (*P*=.03). However, even in this subgroup, the magnitude of association between change in CRP and change in LDL-C levels was small in absolute magnitude (Spearman r = 0.10).

Figure 2. Change in Median C-Reactive Protein (CRP) Levels Among All Participants According to Baseline Clinical Characteristics



Lightface print indicates placebo values; boldface print, pravastatin values; HRT, hormone replacement therapy; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. To convert HDL-C and LDL-C from mg/dL to mmol/L, multiply by 0.0259, and to convert tryglycertides, multiply by 0.0113.

COMMENT

In this prospective, randomized, double-blind evaluation of primary prevention patients, we found significant

reductions in CRP associated with pravastatin use at the end of 24 weeks of therapy. This effect was present among all subgroups evaluated, was seen as early as 12 weeks, and was not significantly related to pravastatin-induced changes in lipid parameters. In a parallel cohort study of patients with a prior history of known cardiovascular disease, open-label pravastatin use was also associated with almost identical reductions of CRP levels of 14.3% and 13.1% at 12 and 24 weeks, respectively.

The current data are derived from a prospective hypothesis-testing study and thus provide confirmation of prior work based on retrospective analyses for pravastatin, lovastatin, and cerivastatin.[17,19-21] In these studies, the median reductions in CRP levels were similar in magnitude and only minimally related to changes in LDL-C. Thus, it appears likely that reduction in CRP levels is a class effect of statin therapy. Also consistent with prior work, the absolute change in CRP levels associated with pravastatin use in PRINCE was modest (–0.02 mg/dL). However, on a percentage basis, the magnitude of this effect in the randomized primary prevention cohort (–14.7%) was similar to the effect of pravastatin on total cholesterol levels (–16.1%) and larger than the effect on HDL-C levels (6.6%).

Several a priori subgroups evaluated in PRINCE provide additional clinical information regarding inflammation, statins, and atherosclerotic heart disease. First, prior work has shown that aspirin use modifies the risk associated with elevated CRP levels, both in primary prevention[14] and in the setting of unstable angina.[24] However, in retrospective data from the CARE trial, which evaluated patients with a history of myocardial infarction, the effect of pravastatin on CRP levels was at least additive to any effects of aspirin on CRP since almost all participants in the CARE study were taking aspirin daily.[20] Our data thus extend this observation since the magnitude of CRP reduction was virtually identical among PRINCE participants who were taking prophylactic aspirin compared with those who were not.

Second, recent data indicate that postmenopausal hormone replacement therapy (HRT) is associated with elevated levels of CRP,[25,26] an issue of clinical concern as randomized trials suggest a small early hazard of thrombosis when HRT is initiated.[27] Thus, the observation in these data that pravastatin reduces CRP among women taking and not taking HRT should also provide reassurance regarding the role of statins among postmenopausal women.

Third, our data demonstrate that the effects of pravastatin on CRP initially observed in the CARE trial of secondary prevention are also present among individuals with no prior history of cardiovascular disease. This observation is important because a major role of CRP evaluation is likely to be in the primary prevention setting, where combined inflammatory and lipid screening appears to provide an improved method of determining global vascular risk.[13,28] Moreover, recent evidence from the Air Force/Texas Coronary Atherosclerosis Prevention Study[17] suggests that the use of statins may be effective in the primary prevention of acute coronary events among those with elevated levels of CRP, even in the absence of overt hyperlipidemia. Taken together, these 2 studies suggest that the effect of statins on CRP levels may have clinical importance, even if the absolute effect size is small for most participants.

Our observation that the change in CRP concentration is largely unrelated to the change in LDL-C concentration is of pathophysiologic interest and supports the concept that pravastatin has clinically relevant anti-inflammatory effects. However, limitations of our study should be addressed, particularly in regard to this observation. Because PRINCE was designed as a community-based randomized trial, we elected to use a single fixed dosage of pravastatin (40 mg/d), which has been shown in several large-scale trials to substantially reduce cardiovascular event rates.[18,29,30] Potential reductions in CRP concentration at lower dosages of pravastatin were, thus, not evaluated.

In addition, because the PRINCE trial was not designed as an end point trial, these data do not demonstrate that CRP reduction per se necessarily leads to cardiovascular event reduction; to date, no clinical trial has evaluated a targeted anti-inflammatory therapy that did not also have important antiplatelet or lipid-lowering effects. A further potential limitation of our study is that not all participants fully completed the protocol, a common problem with community-based evaluations. Of the 8652 blood samples to be collected in this study, 597 (6.9%) were either missing or insufficient in quantity. To address this issue, all analyses were performed so that the most recent CRP value was carried forward in those instances for which data were missing. In addition, to account for patients who were randomized but had insufficient data for follow-up, we conducted an additional analysis in which we assumed that those with missing values had no change in CRP levels from baseline. We believe these conservative approaches were appropriate because they would tend, if anything, to bias our data toward the null. However, our use of a community-based protocol increases the generalizability of these data and suggests that our results are likely to have application for usual outpatients in unselected settings.

In summary, this large-scale hypothesis-testing trial provides direct confirmation that pravastatin therapy reduces CRP levels and that these effects are largely independent of changes in LDL-C levels. Thus, the PRINCE data provide evidence supporting anti-inflammatory effects of statins and suggest that further laboratory investigations regarding the effects of these agents on adhesion molecules, cytokine function, metalloproteinases, and tissue factor may be fruitful. Furthermore, since elevated CRP levels appear to provide a simple clinical surrogate for plaque vulnerability and a method to improve global risk prediction,[13,28] data from the PRINCE study showing that pravastatin reduces inflammation should help

improve use of lipid-lowering therapy in categories of patients for whom completed randomized trials have shown clear efficacy. Future trials are needed to directly test whether patients with low LDL-C levels but high CRP levels also achieve a substantial benefit from statin therapy.[17]

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Author Contributions: Dr Ridker, as principal investigator of the PRINCE study, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Albert, Ridker.
Analysis and interpretation of data: Albert, Rifai, Ridker.
Drafting of the manuscript: Albert, Ridker.
Critical revision of the manuscript for important intellectual content: Albert, Danielson, Rifai, Ridker.
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