

hsCRP and HDL Effects of Statins Trial (CHEST): Rapid Effect of Statin Therapy on C-Reactive Protein and High-Density Lipoprotein Levels

A Clinical Investigation

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Inflammation contributes to the pathogenesis of coronary heart disease and elevated serum levels of C-reactive protein (CRP) are independently associated with increased coronary risk. This study assessed whether there were differences in the effects on CRP and high-density lipoprotein (HDL) cholesterol levels among patients treated with three common statins. In a prospective, observational study, 80 dyslipidemic adults without evidence of cardiovascular disease were treated with 10 mg atorvastatin (A), 20 mg simvastatin (S), or 40 mg pravastatin (P) daily. CRP and lipid profiles were assayed before and after 12 weeks of therapy; in 21 patients, CRP levels were also measured after 1 and 4 weeks. The three treatment groups experienced comparable reductions in CRP (A: 33%, S: 42%, and P: 30%) and statistically insignificant changes in HDL cholesterol levels. CRP began to decrease after 1 week of treatment, and decreased further at 4 and 12 weeks of therapy. The change in the log-transformed CRP concentration correlated with the change in the log-transformed LDL cholesterol concentration. Subjects had similar baseline CRP levels, lipid profiles, and coronary risk factors. The authors conclude that at doses achieving similar reductions in LDL cholesterol, the three statins were associated with comparable decreases in CRP without significant changes in HDL cholesterol levels. The correlation between the reductions in CRP and LDL cholesterol differs from the findings of other published studies, and should prompt further investigation of the mechanism by which statins reduce CRP.

Inflammation has been hypothesized to play an important role in the development and progression of atherosclerosis, while increasing levels of high-density lipoprotein cholesterol (HDL-C) are associated with a decreased risk of vascular disease. A high-sensitivity assay discriminates among levels of C-reactive protein (CRP/hsCRP) within the normal range, and numerous studies have shown that higher levels predict increased risk of coronary heart disease

(CHD), peripheral vascular disease, type 2 diabetes mellitus, and stroke.¹⁻⁸ Some of these studies suggest that CRP is superior to and independent of traditional cardiovascular risk factors in predicting CHD.^{9,10} A recent analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study suggests that evaluating baseline lipid profile in the context of CRP level may be useful in targeting primary prevention candidates who are likely to benefit from statin therapy.¹¹ Furthermore, CRP levels correlated negatively with HDL-C concentrations in a population-based study.¹²

Statins are among the cardioprotective agents shown to reduce CRP levels.¹³⁻¹⁵ Jialal and colleagues¹⁶ recently published a randomized, crossover comparison of the abilities of 40 mg pravastatin, 20 mg simvastatin, and 10 mg atorvastatin to reduce CRP in a hyperlipidemic population. The trial demonstrated similar reductions in CRP among these three statins (20.3%, 22.8%, and 28.3%, respectively) after 6 weeks; all reductions were unrelated to changes in

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Author to provide.

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low-density lipoprotein-cholesterol (LDL-C) but did correlate with reductions in triglycerides. The study's results were limited by the small sample size of 22 subjects, the exclusion of patients with diabetes, and the crossover design itself, in which the CRP levels did not return to baseline in the washout phase. Intermediate time measurements of CRP between 0 and 6 weeks were not taken.¹⁶

In contrast to CRP, which has only recently emerged as a marker of risk for CHD, HDL-C has long been considered a major risk factor for CHD.¹⁷ The statins have all been reported to raise HDL-C, but these effects have in general been modest and variable. Furthermore, statins' greatest effect on raising HDL-C is evident in those subjects with low baseline levels of HDL-C. Prospective comparison between the statins has been limited to the high end of the dose range, at which at least two studies suggested an advantage to simvastatin over atorvastatin.^{18,19}

The goal of the present prospective study was to evaluate the abilities of 40 mg pravastatin, 20 mg simvastatin, and 10 mg atorvastatin to modulate levels of blood CRP and HDL-C in three groups of dyslipidemic adults in usual medical care. Secondary aims of the study were to determine the time course of the decrease in CRP and the magnitude of changes in HDL-C occurring with statin treatment.

MATERIALS AND METHODS

Subjects

Patients were recruited from general internal medicine clinics at the UCLA Medical Center. In accordance with a protocol approved by the Institutional Review Board, all patients provided informed consent. Inclusion criteria were males and nonpregnant, non-breast-feeding females over 18 years of age, and dyslipidemia thought to warrant therapy with 40 mg pravastatin, 20 mg simvastatin, or 10 mg atorvastatin according to the patients' primary physicians. Exclusion criteria were as follows: history of coronary heart disease, use of lipid-lowering agents in the 6 months before

TABLE 1
Baseline Clinical Characteristics of the Three Treatment Groups

	Atorvastatin (n = 30)	Simvastatin (n = 21)	Pravastatin (n = 27)
Age: Mean(SD)	52 (14)	53 (8.6)	52 (13)
Days: Mean (SD)*	111 (23)	101 (17)	104. (27)
Male Sex‡	60 (18)	57 (12)	56 (15)
No. of Risk Factors††			
0	0 (0)	10 (2)	15 (4)
1	33 (10)	24 (5)	44 (12)
2	33 (10)	38 (8)	22 (6)
3	30 (9)	24 (5)	15 (4)
4	3 (1)	5 (1)	4 (1)
Diabetes Mellitus‡	23 (7)	33 (7)	22 (6)
Smoking‡	3 (1)	10 (2)	0 (0)
Family History‡	37 (11)	24 (5)	7 (2)
Hypertension‡	70 (21)	62 (13)	63 (17)

* Days from baseline measurement to follow-up.

† $P > 0.2$ for all except family history ($P = 0.032$).

‡ Values are percentages with n in parentheses.

TABLE 2

Baseline Blood Measures [Mean (SD)] of the Three Treatment Groups

	Atorvastatin (n = 30)	Simvastatin (n = 21)	Pravastatin (n = 27)	<i>P</i>
CRP	3.7 (4.3)	4.5 (4.5)	5.1 (5.1)	0.55
TC	238 (41)	239 (37)	231 (31)	0.71
HDL	47 (14)	50.3 (9.8)	51 (14)	0.48
LDL	158 (39)	159 (31)	154 (26)	0.84
TG	182 (98)	185 (115)	169 (84)	0.82

P-value is for *F*-test of H_0 : no difference in means. (TC = total cholesterol, TG = triglycerides).

Units: mg/L for CRP; mg/dL for lipid measures.

enrollment, evidence of hepatic dysfunction, history of statin intolerance, alcohol or drug abuse, major illness, surgery, and malignancy.

Study Design

The study used an observational design assessing 80 enrolled patients referred by 14 different primary physicians. Baseline fasting blood samples used to measure CRP, triglycerides, and total, HDL, and direct LDL-cholesterol levels were collected from all patients and analyzed in a common laboratory. Patients were started on therapy with 40 mg pravastatin, 20 mg simvastatin, or 10 mg atorvastatin at the discretion of their primary physicians. Patients submitted a questionnaire used to determine the number of CHD risk factors present.

A follow-up blood sample was obtained approximately 12 weeks after the initiation of statin therapy to assess these same parameters. In addition, 21 patients (8 atorvastatin, 6 simvastatin, and 7 pravastatin) provided additional specimens at 1 week and 4 weeks from which CRP was also measured. All CRP measurements were made using a highly sensitive assay with end point nephelometry (Quest Diagnostics, Van Nuys, CA).

Statistical Analysis

We drew 1) scatterplots of the blood measurements (CRP, HDL-C, LDL-C, total cholesterol, triglycerides) at baseline, after treatment and differences (after minus baseline); 2) histograms of the lipid, demographic (age, sex), and risk factor (family history, smoking, hypertension, diabetes mellitus, and total number of risk factors) variables; and 3) boxplots of all variables broken out by treatment group. Several lipid variables and CRP measurements were

TABLE 3
Absolute [Mean (SD)] Changes in CRP, TC, HDL, LDL, and TG After 12 Weeks of Statin Treatment.

	Atorvastatin (n = 30)	Simvastatin (n = 21)	Pravastatin (n = 27)	<i>P</i>
CRP	-3.73 (19)	-2.11 (4.2)	-1.53 (3.8)	0.78
TC	-74.9 (34)	-64.1 (42)	-56.3 (48)	0.25
HDL	-2.2 (7.3)	-1.14 (5.4)	-0.74 (6.0)	0.46
LDL	-67.4 (54)	-53.9 (34)	-46.7 (29)	0.17
TG	-37.6 (104)	-47.1 (102)	-21.4 (72)	0.63

P-value is from the *F*-test of H_0 : no differences among treatment groups.

TABLE 4

Percentage [Estimate (95% Confidence Interval)] Changes in CRP, HDL, LDL, and TG After 12 Weeks of Statin Treatment.

	Atorvastatin (n = 30)	Simvastatin (n = 21)	Pravastatin (n = 27)	All (n = 78)
CRP§	-33 (-54, -2)*	-42 (-56, -23)‡	-30 (-53, 3)	-35 (-47, -20)‡
HDL	-4 (-10, 2)	-3 (-8, 2)	0 (-5, 5)	-3 (-6, 1)
LDL§	-38 (-44, -32)‡	-36 (-43, -27)‡	-31 (-37, -24)‡	-35 (-39, -31)‡
TC	-32 (-36, -27)‡	-28 (-35, -20)‡	-29 (-42, -13)‡	-30 (-35, -24)‡
TG	-24 (-36, -11)‡	-19 (-34, 0)*	-9 (-23, 9)	-18 (-26, -9)‡

* $P < 0.05$;

† $P < 0.01$;

‡ $P < 0.001$.

§ CRP and LDL were missing one observation for A10 and All.

skewed and all lipid and CRP measures were log-transformed before further analysis. The total number of risk factors other than LDL-C was defined according to National Cholesterol Education Program Adult Treatment Panel II guidelines in place at the time of study enrollment. We performed F tests for baseline continuous variables and chi-square tests of baseline categorical variables by drug group, along with F tests for differences between drug groups on changes in log transformed lipid measurements. We used paired *t* tests within each drug group to test for changes due to treatment. All results (means and confidence intervals) reported here on baseline and changes in lipid measures have been transformed back to the original scale.

We used the program SAS Proc Mixed (SAS Institute, Cary, NC, USA) for the longitudinal analysis of log CRP using a random intercept model. All cases were kept in this analysis, including those with four repeated measures and those with only baseline and final measurements. We included drug effects, risk factors, gender, and time in these models, and found no evidence of a risk-factor-by-drug or risk-factor-by-time interaction. Since there were no differences in levels or slopes due to drugs, we pooled all drug

groups before calculating decreases in CRP over time following treatment.

RESULTS

Of the 80 patients who consented for the study, 2 patients failed to return for follow-up blood testing (both patients moved out of the area). The baseline clinical characteristics, CHD risk factors, and blood measurements of the remaining 78 patients who were included in the analysis were similar between the three treatment groups (Tables 1 and 2). The only feature that significantly differed between the groups was family history of premature CHD, which was somewhat more common in the atorvastatin group (37%) compared with the simvastatin (24%) and pravastatin (7%) groups. There was no evidence of any relationship between any of the baseline characteristics and any of the changes in measured outcomes.

As expected from the trial design, lipid changes from the comparably dosed statins were similar (Tables 3 and 4). Specifically the differences between LDL-C reductions with 10 mg atorvastatin (43%), 20 mg simvastatin (34%), and 40 mg pravastatin (30%) daily were not statistically significant. The modest reductions in triglyceride levels (24%, 19%, and 9%, respectively) were statistically equivalent. In addition, all three statins failed to significantly change HDL-C levels.

Plasma CRP levels were similar among the groups at baseline and at the 12-week follow-up evaluation, with a 42% reduction in mean CRP from baseline with simvastatin, 33% with atorvastatin, and 30% with pravastatin. The mean reduction in CRP with pravastatin did not reach significance when analyzed alone. The differences in log-transformed CRP levels during the study were similar between the three groups, but the response was wide-ranging (Fig. 1). The considerable variation in CRP response to statin treatment permitted this study to have power to detect a true 67% difference between the effects of any two drugs.

The subset of 21 patients who underwent additional measurements of CRP at intermediate time points showed wide variation in their responses to each of the statins. Longitudinal analysis provided evidence for a linear decrease in log CRP over time ($P < 0.0001$), with no evidence of nonlinearity over time. The estimated decrease

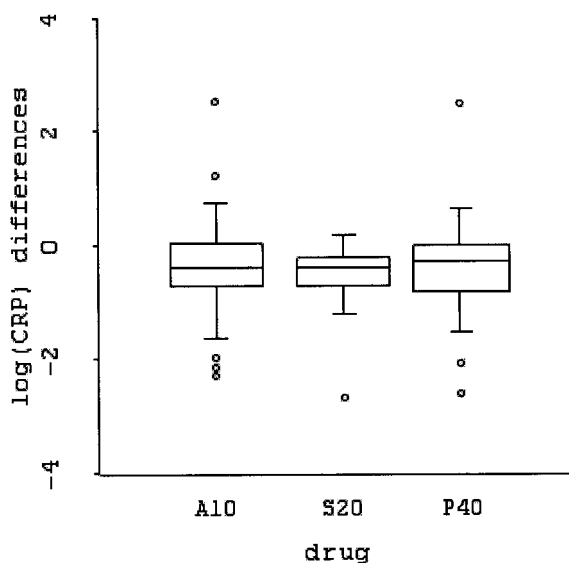


Figure 1. Boxplots of differences in log-transformed CRP concentrations following 12 weeks of statin treatment. A10 = atorvastatin, S20 = simvastatin, P40 = pravastatin.

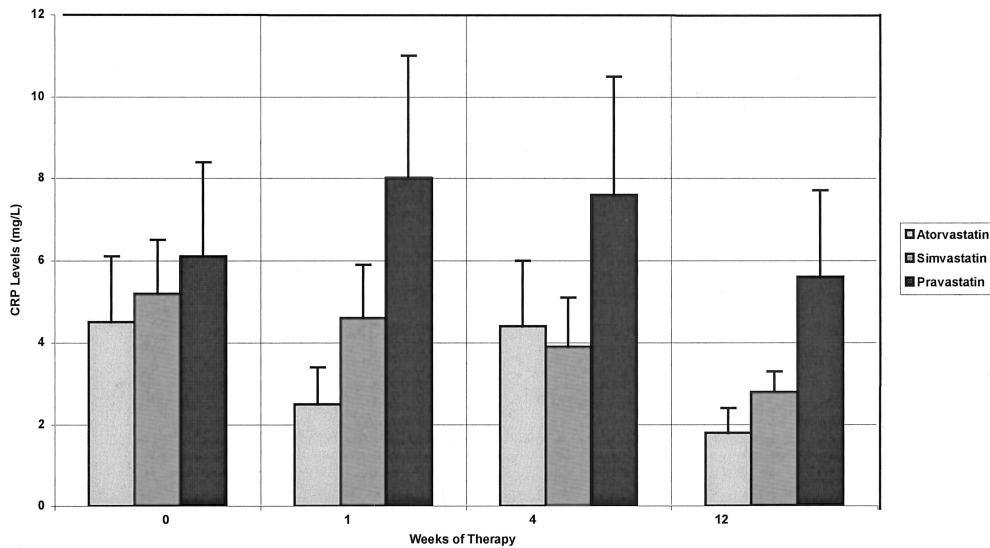


Figure 2. Sample mean (bar height) and SD (error bar) CRP levels over time in substudy of 21 individuals receiving statin treatment.

was 2.7% (95% CI: 1.5%, 3.8%) after 1 week of statin therapy and 27% (95% CI: 16%, 37%) after 12 weeks. Mean and median CRP decreased steadily in the simvastatin group, while median (but not mean) CRP decreased steadily in the atorvastatin group. Curiously, the subjects receiving pravastatin experienced an intermediate trend toward increased levels of CRP, but this increase was no longer evident by week 12 (Fig. 2).

We found a modest correlation (coefficient = 0.33, $P = 0.004$) between changes in log-transformed CRP and LDL-cholesterol levels (Fig. 3). Other relationships that were evident in our longitudinal analyses included a higher mean CRP concentration among women versus men ($P < 0.01$). There was also a linear relationship between log-transformed CRP and increasing numbers of risk factors ($P = 0.01$). Each individual risk factor was associated with a 35% increase (95% CI, 8.2–68%) in log CRP. Hypertension and diabetes mellitus appeared to be associated with the greatest increases in CRP, in that CRP levels in patients without diabetes were 48% (95% CI: 29–62%) of those found in the diabetes patients, and levels in normotensive subjects were 37% (95% CI: 22–59%) of those found in subjects with hypertension. CRP levels did not differ between subjects with a family history of premature CHD and those without such a background.

DISCUSSION

Our sample population is representative of patients managed in clinical practice, and included a large fraction of diabetic patients. The results of this statin trial are consistent with prior studies of CRP reduction with statins. The broader makeup and size of our sample and the parallel study group design allow for additional confidence in concluding similarity among the CRP effects of the three statins. Our time-course substudy indicated that CRP levels had not leveled off by 12 weeks, suggesting that studies of longer duration are needed to characterize more fully anti-inflammatory effects seen during the long-term phase of

statin therapy. The nonrandomized design did not result in differences in baseline characteristics between the groups in the current study. Like previous studies, this study lacked power to adequately exclude differences between the treatment groups.

Our study showed a mild correlation between CRP and LDL-C reduction transformed to a log scale, which differs from other studies suggesting no relationship between change in LDL and change in CRP. Some of these studies did not use log-transformed levels of either measurement. However, the Pravastatin Inflammation/CRP Evaluation (PRINCE) trial reported no correlation between the change in log-transformed CRP and LDL levels. The median changes in CRP with 40 mg pravastatin in the PRINCE trial were considerably smaller (–16.9%) compared with placebo than the mean CRP reductions from baseline in CHEST, perhaps reflecting concomitant dietary or risk factor modification in the latter study.⁶ In the comparative trial by Jialal et al, the failure of physiologic measures to return to baseline at the end of the washout period likely led to underestimation of the true magnitude of CRP reduction in that study as well.¹⁶ The lesser degrees of CRP

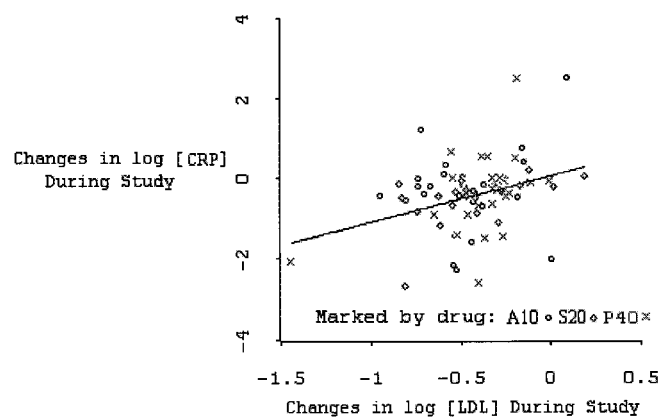


Figure 3. Relationship between log-transformed changes in CRP and LDL-cholesterol with statin treatment (correlation coefficient = 0.33, $P = 0.004$).

reduction in these two studies compared with those seen in CHEST may have limited the ability to detect a true relationship between CRP and LDL.

Case-control analysis of prerandomization blood samples from the participants in the Cholesterol and Recurrent Events (CARE) trial revealed that subjects in whom recurrent coronary events developed within the 5-year follow-up period exhibited higher baseline levels of CRP than control subjects.²⁰ This association was not apparent in the patients who received pravastatin, suggesting that an antiinflammatory role of this agent may have contributed to its success in reducing cardiovascular morbidity. The reduction in CRP did not correlate with the reduction in lipid levels seen in subjects receiving pravastatin.²¹ Further research will be necessary to determine the relationship between statins' antiinflammatory and LDL-lowering effects.

This study also found a progressive decrease in median CRP levels beginning after 1 week of statin therapy, and continuing at each successive time point with simvastatin and atorvastatin. This rapid effect may help explain recent evidence supporting statin usage in acute coronary syndromes.²² Furthermore, the reduction in CRP occurred without any increase in HDL cholesterol concentration from baseline to 12 weeks. Previously, the PRINCE trial showed comparable reductions in CRP after 12 and 24 weeks of pravastatin therapy compared with placebo. These observations suggest a mechanism by which statins reduce CRP. As the half-life of CRP is relatively short, it seems possible that a major mechanism for statin-induced reduction may be indirect. Future study will be necessary to determine the mechanism(s) by which statins reduce CRP, the relationship between CRP and LDL, and how CRP itself might factor into clinical decision-making. Based on these results, differences in CRP effects should not play a role in statin selection.

The use of CRP in clinical settings is limited by the nonspecific nature of this inflammatory marker. While CRP has been correlated with the progression of atherosclerosis in patients with cardiovascular risk factors,²³ it is also correlated with the activity of many inflammatory conditions common to an internal medicine setting such as upper respiratory infections,²⁴ influenza,²⁵ autoimmune diseases,²⁶ inflammatory bowel diseases,²⁷ and trauma.²⁸ While the presence of a known inflammatory condition was an exclusion criterion for this study, it is likely that the patients whose CRP levels rose in excess of 100% over the course of the study had an interval development of a nonatherosclerotic inflammatory condition. The majority of the subjects were enrolled in the winter months, when respiratory illnesses or other winter-related conditions may have contributed to variance in CRP levels.

In contrast to the CRP results and to results of other large-scale statin trials, HDL-C did not increase with statin treatment in the present study, suggesting that, in a population not selected for low levels of HDL-C, none

of these agents is likely to significantly raise HDL-C. This finding does not imply that statins should not be used in patients with low levels of HDL-C; on the contrary, this patient population is particularly likely to benefit from statins.²⁹ However, a marked improvement in HDL-C will likely have to be achieved using other means. The subjects in this study were selected from a broad-based internal medicine clinic and did not exhibit low mean HDL-C levels at baseline. Since statins raise HDL-C most significantly when baseline levels are low, this study feature may account for the lack of significant HDL-C increases observed.³⁰ Furthermore, many of the subjects were newly diagnosed with dyslipidemia and/or diabetes, and may have initiated dietary and/or lifestyle changes that might have moderated the effects of HDL-C.³¹

In conclusion, these results suggest that atorvastatin, simvastatin, and pravastatin have similar antiinflammatory properties and effects on HDL cholesterol levels when dosed to achieve comparable reductions in LDL cholesterol levels in an outpatient practice setting. Although there may be a role for using C-reactive protein levels to determine primary CHD prevention patients who are likely to benefit from statin treatment,³² the reduction of CRP itself appears to be a class effect.

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