Simvastatin Lowers C-Reactive Protein Within 14 Days
An Effect Independent of Low-Density Lipoprotein Cholesterol Reduction

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Background—The early response of C-reactive protein to initiation of a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) is not known. The purpose of this study was to determine the rate at which highly sensitive C-reactive protein (hsCRP) levels change after initiation of simvastatin and whether this occurs independently of the change in LDL cholesterol.

Methods and Results—The study was a crossover, double-blind design including 40 subjects with elevated LDL cholesterol. Subjects were randomly assigned to 1 of 2 groups: simvastatin 40 mg for 14 days, then placebo for 14 days, or placebo first, then simvastatin. Simvastatin decreased LDL cholesterol by 56±4 mg/dL (P<0.0001) at day 7 and by an additional 8±3 mg/dL (P=0.02) at day 14. Baseline log(hsCRP) levels were similar in the 2 groups. By day 14, log(hsCRP) was significantly lower in patients on simvastatin when compared with placebo (P=0.011). Although there was no significant difference in fibrinogen levels, simvastatin produced a modest increase in log[lipoprotein(a)] (P=0.03) at days 7 and 14. There were no relationships between the decrease in LDL cholesterol and the decrease in hsCRP.

Conclusions—Simvastatin lowers hsCRP by 14 days, independent of its effect on LDL cholesterol. This rapid impact of a statin on hsCRP has potential implications in the management of acute coronary syndromes. (Circulation. 2002;106:1447-1452.)

Key Words: C-reactive protein ■ lipoproteins ■ fibrinogen ■ inflammation

New evidence continues to emerge supporting the role of inflammation in coronary artery disease (CAD) and emphasizing the importance of investigating interventions that target inflammatory reduction and their impact on patient outcomes. At the same time, a number of prospective studies have demonstrated that elevated C-reactive protein (CRP) is a risk factor for coronary events, independent of traditional risk factors such as hyperlipidemia and tobacco use.1-3 Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have been shown to decrease levels of CRP over time,4,5 thus emphasizing the role of statins as a potential modifier in the inflammatory process of CHD.

Statin therapy seems to be effective in the primary prevention of coronary events among patients with elevated CRP levels, even when lipid levels are relatively low.6 Ridker and colleagues7 recently reported that CRP could decrease within 8 weeks of initiation of cerivastatin. Beyond this knowledge, however, the early response of CRP to a statin and its relationship to the decrease in LDL cholesterol is unknown. This information may be clinically applicable in a variety of settings, including the management of patients with acute coronary syndromes and immediately after percutaneous intervention.

We hypothesized that simvastatin would have a relatively rapid effect on CRP levels, with a change detectable within several days of initiation. The aims of our study were (1) to determine the rate at which CRP levels change after initiation or cessation of the statin simvastatin and (2) to determine whether the alteration in CRP occurs independently of the change in LDL cholesterol.

Methods
Study Design
This study had a crossover, double-blind design and was approved by the Western Institutional Review Board. Forty subjects with elevated LDL cholesterol, as defined by the National Cholesterol Education Program: Adult Treatment Panel II (NCEP:ATP II), were included. Persons eligible for treatment according to NCEP:ATP II guidelines are (1) subjects with known CAD or a CAD equivalent, (2) subjects with ≥2 risk factors for CAD and an LDL cholesterol >130 mg/dL, and (3) subjects with no risk factors or one risk factor and an LDL cholesterol >160 mg/dL. Subjects were randomly assigned to 1 of 2 groups. One group took simvastatin for the first...
phase of the trial and placebo for the second phase, and the other group took placebo first, then simvastatin for the same intervals. Each phase lasted 14 days. Highly sensitive CRP (hsCRP) levels were measured on days 0, 1, 3, 7, and 14 of each phase. LDL cholesterol was calculated from fasting lipids measured at baseline and on days 7 and 14. To assess the specificity of the hsCRP response to simvastatin, the acute-phase reactants lipoprotein(a) \( [Lp(a)] \) and fibrinogen were also measured on the same days as hsCRP.

After a 12-hour fast, potential subjects were screened and underwent phlebotomy for liver function tests (total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphate), blood urea nitrogen (BUN), creatinine, glucose, lipid panel (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), complete blood count with differential and hsCRP level, and a urinalysis.

**Subjects**

Men and women aged 25 to 75 years who were candidates for treatment with a statin on the basis of the NCEP:ATP II guidelines were included. Patients currently being treated for hyperlipidemia with a statin were also eligible, but they stopped their medication for a minimum of 7 days before day 0.

Exclusion criteria included active hepatic or renal dysfunction, any type of connective tissue disease, chronic inflammatory disease, malignancy or history of malignancy, any acute illness, leukocytosis \((>10,000\) white blood cells\) or thrombocytosis \((>450,000\) platelets\), anemia \((\text{hematocrit} <40\%)\), diabetes mellitus, or subjects taking corticosteroids. Patients admitted to the hospital for an acute coronary syndrome within 6 months of the start of the study were also excluded. Tobacco use, which has been shown to increase CRP, and aspirin use, which has been shown to decrease CRP, were not exclusion criteria because patients served as their own controls. All patients previously on aspirin were continued on a standardized dose of 81 mg daily. Patients were instructed to avoid using nonsteroidal anti-inflammatory agents while participating in the study.

**Measurements**

HsCRP and fibrinogen were measured by the Laboratory Corporation of America in Denver, Colorado. HsCRP samples were frozen at \(-20^\circ\text{C}\) and measured at 522 nm using the Integra-Immunoturbimetric method (Roche Cobas Integra 700). The method is sensitive to 0.3 mg/L. A 6-point calibration methodology was performed with each new reagent lot. For precision, the coefficient of variance for the low range was 1.8% at a mean of 6.2 mg/L (total coefficient of variance was 2.9%). The normal range of hsCRP was 0.0 to 4.9 mg/L. Fibrinogen was measured by a mechanical clot detection assay (STA analyzer, Stago Diagnostica). Lp(a) samples were frozen at \(-70^\circ\text{C}\) and sent to the University of Washington in Seattle, Washington. The plasma apolipoprotein A (apoA) concentration was determined by a direct-binding, double monoclonal antibody–based enzyme-linked immunoassay (ELISA) performed as previously reported. The capture monoclonal antibody \((a-6)\) in the assay is directed to an epitope present in apoA kringle 4 type 2 and the detection antibody \((a-40)\) is directed to a unique epitope located in apoA kringle 4 type 9. This assay has been extensively evaluated, was demonstrated to measure Lp(a) accurately, independently of apoA size polymorphism, and is considered the reference method in the standardization of Lp(a) assays. Lp(a) concentrations are expressed in mmol/L. Lp(a) concentrations have been described previously as reported, 75 mmol/L is the cutoff for whites and approximately corresponds to the 80th percentile.

Lipids were measured in serum after a 12-hour fast on days 7 and 14 of both the first and second phases of the study. LDL cholesterol was calculated from measured fasting lipids. In cases where triglyceride levels were \(\geq 500\) mg/dL, LDL cholesterol was not calculated. (baseline, \(n=3\); day 7 of simvastatin, \(n=2\); day 14 of simvastatin, \(n=1\)). Additionally, the incidence of subjects with a serum triglyceride level \(\leq 400\) and \(<500\) mg/dL were as follows: baseline, \(n=2\); day 7 placebo, \(n=2\); day 7 simvastatin, \(n=1\); day 14 placebo, \(n=4\); day 14 simvastatin, \(n=1\).

**Statistical Analyses**

Statistical analyses were performed using SAS software version 8 (SAS Institute Inc). Significance tests were 2-sided, with significance level at 0.05. Outcomes for hsCRP and Lp(a) were natural-log–transformed to satisfy assumptions of normality and equal variance. All statistical models and significance tests were performed on these logged variables, and in some cases we give median values on the original scale to facilitate clinical interpretation. All data are presented as the mean ± SEM.

The study was designed as a 2-treatment, 2-period crossover design. Patterns in outcomes across time were analyzed using a 3-factor ANOVA with factors of treatment (placebo or simvastatin), time (0, 1, 3, 7, and 14 days), and period (1, 2). Linear mixed statistical models, as implemented in SAS PROC MIXED, with a random subject effect were used to account for repeated measurements on subjects. All 2-way and 3-way interactions were initially included, and nonsignificant interactions were subsequently removed to yield simpler models. To examine differences in time patterns between treatments (simvastatin and placebo), the time by treatment interaction was tested, and if it was significant, the difference between the 2 treatments was estimated and tested at each time. If it was not significant, no such tests were made. To allow for possible effects of crossover between treatments, models that allowed different effects of simvastatin and placebo during each period, and also depending on whether they were administered during the first or second period of treatment, were considered. In no cases were interactions involving period significant. There was a significant difference between periods for log\([Lp(a)]\), so a period effect was included in that model to adjust for the difference. Graphic examination of model residuals and random effect estimates indicated the assumption of normality was satisfied after log-transformation of hsCRP and Lp(a).

Correlations between changes in LDL cholesterol from 0 to 7, 0 to 14, and 7 to 14 days and changes in outcomes in log(hsCRP), fibrinogen, and log\([Lp(a)]\) during the same or a later period were examined using Pearson correlations and significance tests; correlations were evaluated separately for the simvastatin and placebo treatments. Subjects who had one or more missing LDL cholesterol values were omitted from correlation analyses (\(n=5\)). All subjects had a level of hsCRP \(\geq 0.3\) mg/L on day 0 of each phase. The sample size of 40 subjects was required to detect a difference in means of 25%, assuming that the common SD of the differences was 1.90 ± 2.21.

**Results**

Characteristics of the 40 subjects are represented in Table 1. Men \((n=19)\) and women \((n=21)\) were significantly different in several areas, including weight \((P=0.004)\), baseline systolic blood pressure \((P=0.03)\), diastolic blood pressure \((P=0.009)\), and baseline HDL cholesterol \((P=0.009)\). Importantly, log(hsCRP) was significantly higher for women compared with men at baseline \((P=0.01)\); median hsCRP was 2.8 mg/L for women and 1.1 mg/L for men.

There was a decrease in log(hsCRP) from day 1 to 14 for patients on simvastatin compared with placebo (Figure 1). On the original scale, median hsCRP decreased from 2.55 mg/L at day 0 to 1.60 mg/L at day 14 for patients on simvastatin, compared with 2.00 mg/L and 2.20 mg/L at days 0 and 14 for patients on placebo. There was a significant time by treatment interaction \((P=0.043)\), indicating different patterns across time for placebo and simvastatin. Tests comparing simvastatin and placebo at each time show that at day 14, log(hsCRP) was significantly lower for patients on simvastatin than on placebo \((P=0.011)\). Median hsCRP at day 14 was 1.60 mg/L for patients on simvastatin and 2.20 mg/L for patients on placebo. The
significant difference between observations during periods 1 and 2 \((P=0.043)\) was adjusted for in the analysis.

When comparing placebo versus simvastatin groups, there was no significant difference in fibrinogen levels \((P=0.33; \text{Table 2})\). Table 2 also shows mean±SEM of log[Lp(a)] and fibrinogen levels at days 0, 1, 3, 7, and 14 for placebo and simvastatin. For log[Lp(a)] there was a significant time by treatment interaction \((P=0.012)\), indicating different patterns across time for placebo and simvastatin. At days 7 and 14, log[Lp(a)] was significantly higher in patients on simvastatin compared with placebo \((P=0.03\) and \(P=0.03\) respectively). The observed difference in log[Lp(a)] of 0.07 between simvastatin and placebo at days 7 and 14 represents 7.3% higher values for simvastatin compared with placebo on the original Lp(a) scale.

On the original scale, median Lp(a) was 23.65 nmol/L at 7 days and 23.60 nmol/L at 14 days for patients on simvastatin, compared with 22.45 nmol/L and 22.75 nmol/L for patients on placebo.

For fibrinogen, there was no significant time by treatment interaction \((P=0.33)\), indicating no difference in the patterns across time for placebo and simvastatin.

Figure 2 shows mean LDL cholesterol levels at days 0, 7, and 14 for placebo and simvastatin. There was a very significant time by treatment interaction \((P=0.0001)\), indicating different patterns across time for placebo and simvastatin. Tests comparing simvastatin and placebo at each time show that at days 7 and 14, LDL cholesterol was significantly lower for patients on simvastatin \((P=0.0001\) at both times). There was a significant difference between observations during periods 1 and 2 \((P=0.020)\), which was adjusted for in the analysis.

There was no significant association between the changes in LDL cholesterol from day 0 to 7, day 0 to 14, or day 7 to 14 and the change in outcome log(hsCRP) during the same periods. Figure 3 shows the lack of association between log(hsCRP) compared with the changes in LDL cholesterol for subjects on simvastatin \((r=0.00, P=0.98)\); the corresponding Spearman nonparametric correlation using untransformed hsCRP is \(r=-0.12, P=0.50\). Moreover, there were no significant correlations between the change in LDL from day 0 to 7, day 0 to 14, or day 7 to 14 and the corresponding change in outcome in log(hsCRP), fibrinogen, or log[Lp(a)] for either placebo or simvastatin. The changes in outcomes from day 7 to 14 were

### Table 1. Baseline Demographic Data for 40 Subjects

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.8 (3)</td>
<td>48.2 (3)</td>
</tr>
<tr>
<td>Ethnicity (white/black/Hispanic/other)</td>
<td>17/2/0/2</td>
<td>17/0/1/1</td>
</tr>
<tr>
<td>History of CVD event, stroke, or peripheral vascular disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Current smokers</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.5 (3.2)</td>
<td>89.3 (3.0)*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 (3)</td>
<td>133 (3)†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 (1)</td>
<td>79 (2)*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>261 (11)</td>
<td>252 (10)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>176 (47)</td>
<td>269 (47)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>60 (4)</td>
<td>46 (2)*</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>170 (10)</td>
<td>152 (8)</td>
</tr>
<tr>
<td>HsCRP, mg/L</td>
<td>2.8 (1, 3, 4.8)</td>
<td>1.1 (0.8, 2.5)†</td>
</tr>
<tr>
<td>Log(hsCRP)</td>
<td>0.86 (0.21)</td>
<td>0.14 (0.18)†</td>
</tr>
<tr>
<td>Lp(a), nmol/L</td>
<td>36.8 (12.5, 88.5)</td>
<td>13.7 (2.5, 66.2)</td>
</tr>
<tr>
<td>Log[Lp(a)]</td>
<td>3.49 (0.34)</td>
<td>2.63 (0.39)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>392 (18)</td>
<td>330 (13)</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SEM).

HsCRP and Lp(a) were not normally distributed and were therefore log transformed. Both are shown below on the original scale (median [lower, upper quartile]) and on the logged scale (mean [SEM]).

*\(P<0.01\), †\(P<0.05\), for comparing females and males.
also not correlated with the change in LDL cholesterol during the preceding period (day 0 to 7; data not shown).

**Discussion**

Emerging data continue to substantiate CRP as an independent predictor of cardiovascular disease (CVD) events.\(^1\)\(^,\)\(^1\)\(^5\)\(^–\)\(^1\)\(^7\)

Although many acute-phase reactants have been studied, CRP has most consistently been found to be useful in predicting subjects who are at greatest risk of both first and recurrent CVD events. For example, a baseline elevation in CRP confers up to a 3-fold risk of myocardial infarction in subjects who are at greatest risk of both first and recurrent CVD events. For example, a baseline elevation in CRP confers an almost 4-fold risk of 30-day death or myocardial infarction.\(^1\)\(^8\)

After a myocardial infarction, higher CRP levels correlate with lower event-free survival rates and higher cardiac event rates.\(^4\) In patients undergoing percutaneous transluminal angioplasty, a baseline elevation in hsCRP confers an almost 4-fold risk of 30-day death or myocardial infarction.\(^1\)\(^8\)

Although it has been shown that statins lower hsCRP over time\(^5\)\(^–\)\(^5\)\(^5\), this is the first study to show that treatment with simvastatin lowers hsCRP levels within 14 days, independently of the effect on LDL cholesterol and the acute-phase reactants Lp(a) and fibrinogen. This suggests that statins may inhibit inflammatory or noninflammatory processes that lead to the development of CAD by another mechanism.

The mechanism by which elevated CRP levels might increase the risk for CVD events has been debated. Several theories have been proposed.\(^1\)\(^,\)\(^1\)\(^9\)\(^–\)\(^2\)\(^1\) One holds that the acute-phase response is activated by ongoing arterial inflammation. That is, the uptake of oxidized LDL cholesterol and LDL phospholipids within an arterial atheromatous plaque causes the release of interleukin-6 (IL-6) and other inflammatory mediators from the plaque itself. This, in turn, stimulates the hepatic production of CRP and other acute-phase reactants\(^2\)\(^2\) that may contribute to atherothrombosis. A second theory holds that the secretion of IL-6 may come from sources such as adipose tissue\(^2\)\(^3\)\(^,\)\(^2\)\(^4\) or a site of chronic infection. IL-6 and other mediators would induce hepatic production of CRP,\(^2\)\(^5\) which enters the systemic circulation and thereby contributes to atherothrombosis.\(^2\)\(^3\)\(^,\)\(^2\)\(^4\) These 2 proposed mechanisms are not mutually exclusive; resultant atherothrombosis may be a consequence of both. At this point, the degree to which hsCRP or other inflammatory mediators actually contribute to the formation of atheromas or coronary thrombosis in humans is unknown.

Statins could reduce hsCRP by a number of mechanisms. One possibility is by a reduction of inflammation within the artery, presumably by reducing the amount of LDL available for oxidative metabolism. This would likely be a time-dependent process unlikely to occur by 14 days. However, although the simvastatin-mediated decrease in LDL cholesterol occurred by 7 days, there was no relationship between this decrease and the subsequent change in hsCRP. An effect of simvastatin to reduce hsCRP production by the liver is possible, but without precedent at present. Finally, the effect of statins could be to decrease the production and/or circulation of mediators of hsCRP production.
eg, tumor necrosis factor-α or IL-6. Decreases in leucocyte function antigen-1 may also relate.26

An intriguing finding in this study was that treatment with simvastatin increased Lp(a). This finding has questionable clinical implications, although the role of Lp(a) as an independent risk factor for premature atherosclerotic vascular disease has been documented in several large studies.27–29 Lp(a) has been considered a lipoprotein particle with both atherogenic and thrombogenic potential because of its structural similarities to both LDL and plasminogen. The impact of statins on Lp(a) concentrations is controversial, with some studies showing an increase30 and others showing no effect.31–32 Further investigation into the effect of statins on Lp(a) concentrations may be warranted.

The results of the present study may have important long-term clinical implications. The effect of simvastatin on hsCRP was independent of its effect on LDL cholesterol, supporting data from other studies which have shown that treatment with statins decrease the risk of both first and recurrent coronary events in patients with elevated hsCRP, irrespective of LDL cholesterol levels.4,6,14,33 The protective effect of statin therapy was recently emphasized when Heeschen and colleagues34 reported that cessation of statin therapy at the time of presentation with an acute coronary syndrome was associated with a 3-fold increase in cardiac risk compared with patients who continued to take their statin. At the same time, cardiac risk was higher in patients who had never taken a statin when compared with those who had.

The data also show that simvastatin lowers hsCRP rapidly, potentially decreasing the risk for CVD events in the short term. Because hsCRP can be lowered in as little as 2 weeks, the administration of a statin in the setting of an acute coronary syndrome may have a role as powerful as that of early treatment with aspirin, a β-blocker, or an ACE inhibitor. This rapid effect may also be important after percutaneous intervention, where an elevated baseline CRP predicts a heightened risk of death or myocardial infarction.18 If treatment with a statin was initiated immediately after percutaneous intervention with a statin therapy was recently emphasized when Heeschen and colleagues34 reported that cessation of statin therapy at the time of presentation with an acute coronary syndrome was associated with a 3-fold increase in cardiac risk compared with patients who continued to take their statin. At the same time, cardiac risk was higher in patients who had never taken a statin when compared with those who had.

The authors recognize that the present study may differ from ones in which patients present with an acute inflammatory process, because basal CRP levels can increase several hundred-fold in inflammatory states.15 This points to a need for further study in this population. In addition, the short study duration raises questions regarding whether the maximal reduction in CRP was reached, highlighting the need for further investigation of longer-term statin therapy and its effect in multiple populations prone to CVD (eg, diabetes mellitus).

Overall, the 14-day hsCRP-lowering effect of simvastatin, independent of its effect on other acute-phase reactants and lipids, could change the way physicians manage all patients at risk for CAD, both in the early setting and in the prevention of long-term events.

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References


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