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## MEASUREMENT OF C-REACTIVE PROTEIN FOR THE TARGETING OF STATIN THERAPY IN THE PRIMARY PREVENTION OF ACUTE CORONARY EVENTS

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### ABSTRACT

**Background** Elevated levels of C-reactive protein, even in the absence of hyperlipidemia, are associated with an increased risk of coronary events. Statin therapy reduces the level of C-reactive protein independently of its effect on lipid levels. We hypothesized that statins might prevent coronary events in persons with elevated C-reactive protein levels who did not have overt hyperlipidemia.

**Methods** The level of C-reactive protein was measured at base line and after one year in 5742 participants in a five-year randomized trial of lovastatin for the primary prevention of acute coronary events.

**Results** The rates of coronary events increased significantly with increases in the base-line levels of C-reactive protein. Lovastatin therapy reduced the C-reactive protein level by 14.8 percent ( $P < 0.001$ ), an effect not explained by lovastatin-induced changes in the lipid profile. As expected, lovastatin was effective in preventing coronary events in participants whose base-line ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol was higher than the median ratio, regardless of the level of C-reactive protein (number needed to treat for five years to prevent 1 event, 47;  $P = 0.005$ ). However, lovastatin was also effective among those with a ratio of total to HDL cholesterol that was lower than the median and a C-reactive protein level higher than the median (number needed to treat, 43;  $P = 0.02$ ). In contrast, lovastatin was ineffective among participants with a ratio of total to HDL cholesterol and a C-reactive protein level that were both lower than the median (number needed to treat, 983;  $P = 0.87$ ).

**Conclusions** Statin therapy may be effective in the primary prevention of coronary events among persons with relatively low lipid levels but with elevated levels of C-reactive protein. (N Engl J Med 2001;344:1959-65.)

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**B**OTH the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex-CAPS) and the West of Scotland Coronary Prevention Study demonstrated that inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (statins) reduce the risk of first coronary events.<sup>1,2</sup> However, the use of statins for primary prevention has not been widely adopted, in part because the number of persons who need to be treated to prevent one clinical event is relatively large and the cost of this approach is substantial.<sup>3</sup>

A method of distinguishing high-risk from low-risk patients might make possible better targeting of statin therapy for primary prevention.<sup>4</sup> For example, restricting statin use to those with overt hyperlipidemia improves the cost effectiveness of the therapy,<sup>5</sup> and the current guidelines of the National Cholesterol Education Program recommend that statins be prescribed for primary prevention when low-density lipoprotein (LDL) cholesterol levels exceed 160 mg per deciliter (4.14 mmol per liter).<sup>6</sup> Unfortunately, half of all coronary events occur in persons without overt hyperlipidemia.<sup>7</sup> Thus, lipid screening alone may fail to identify all high-risk subgroups that are likely to benefit from statin therapy.

Several studies suggest that measurement of the inflammatory marker C-reactive protein may provide a useful method of assessing the risk of cardiovascular disease in apparently healthy persons, particularly when lipid levels are low.<sup>8-12</sup> Furthermore, statin therapy has been shown to reduce C-reactive protein levels independently of its effect on cholesterol,<sup>13,14</sup> and

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statins may have antiinflammatory properties.<sup>15</sup> Although the addition of an evaluation of C-reactive protein levels to standard lipid screening has been shown to improve risk prediction in the primary prevention of acute coronary events,<sup>9,16</sup> there are no data demonstrating that C-reactive protein screening can identify subgroups of patients who are more or less likely to benefit from statin therapy.

To address this issue, we measured the level of C-reactive protein both at base line and after one year of follow-up among 5742 of the 6605 participants enrolled in a randomized, double-blind, placebo-controlled trial of lovastatin in the primary prevention of acute coronary events in persons with average levels of total cholesterol and below-average levels of high-density lipoprotein (HDL) cholesterol.<sup>1</sup>

## METHODS

AFCAPS/TexCAPS was a primary-prevention trial of lovastatin, conducted between 1990 and 1998, that included 6605 men and women at two sites in Texas, the Lackland Air Force Base and the University of North Texas Health Science Center.<sup>1,17</sup> Men 45 to 73 years old and postmenopausal women 55 to 73 years old who had average levels of total and LDL cholesterol and below-average levels of HDL cholesterol were eligible. Persons with uncontrolled hypertension, secondary hyperlipidemia, diabetes requiring insulin, or a body mass 50 percent greater than desirable were excluded.

Participants who provided written informed consent, met all the entrance criteria, and completed a 12-week run-in period during which they followed the American Heart Association Step I diet were randomly assigned to receive either lovastatin (20 mg per day) or matching placebo. The dose of lovastatin was increased in a double-blind manner to 40 mg of lovastatin per day if the LDL cholesterol level was higher than 110 mg per deciliter (2.84 mmol per liter) at the three-month visit. We conducted follow-up for an average of 5.2 years to monitor the occurrence of first acute coronary events, which were prospectively defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden death from cardiac causes. As we previously reported,<sup>1</sup> assignment to the lovastatin group was associated with a rate of reaching this primary clinical end point that was 37 percent lower than that in the placebo group (relative risk, 0.63; 95 percent confidence interval, 0.50 to 0.79;  $P < 0.001$ ).

### Laboratory Analyses

A highly sensitive latex-based immunoassay (Dade Behring, Newark, Del.) was used to determine the levels of C-reactive protein in blood obtained at the time of randomization and at one year.<sup>18</sup> Lipid levels were measured in a laboratory accredited by the Lipid Standardization Program of the Centers for Disease Control and Prevention. In total, 5742 of the 6605 participants (87 percent) had blood available for analysis and underwent successful evaluation for high-sensitivity C-reactive protein and lipid levels. The median LDL cholesterol level (149.1 mg per deciliter [3.86 mmol per liter]) and the median ratio of total to HDL cholesterol (5.96) among these 5742 participants were virtually identical to the median level and ratio (149.3 mg per deciliter [3.86 mmol per liter] and 5.98, respectively) in the study cohort as a whole.

### Statistical Analysis

After the study cohort had been divided into quartiles on the basis of C-reactive protein levels, Cox regression analysis was used to test for an association between base-line levels of C-reactive protein and the risk of acute coronary events. Adjusted risk estimates were obtained from analyses that also controlled for age, sex, smok-

ing status, hypertension, parental history with respect to coronary disease, and lipid levels.<sup>19</sup>

Spearman correlation coefficients were used to evaluate potential relations between C-reactive protein levels and lipid levels at study entry and between the change in C-reactive protein levels and the change in lipid values by the end of one year of therapy. The percentage change in C-reactive protein levels that was associated with the use of lovastatin was also computed and compared with the percentage change in C-reactive protein levels among those assigned to the placebo group.

To evaluate the efficacy of lovastatin as compared with placebo in subgroups defined according to base-line levels of lipids and C-reactive protein, we divided the study cohort into four groups of approximately equal size: those with an LDL cholesterol level lower than the median (less than 149.1 mg per deciliter) and a C-reactive protein level lower than the median (less than 0.16 mg per deciliter) (1448 participants); those with an LDL cholesterol level lower than the median and a C-reactive protein level higher than the median (1428 participants); those with an LDL cholesterol level higher than the median and a C-reactive protein level lower than the median (1420 participants); and those with an LDL cholesterol level higher than the median and a C-reactive protein level higher than the median (1446 participants). We then computed the reductions in relative risk associated with lovastatin as compared with placebo in each of these four groups, as well as the number of persons who would have to be treated for five years to prevent one acute coronary event.

To determine whether any observed effects within these groups were sensitive to the choice of lipid variable and to address the fact that the AFCAPS/TexCAPS trial enrolled participants with below-average HDL cholesterol levels, we repeated these analyses using the median base-line ratio of total to HDL cholesterol (5.96) rather than the median base-line LDL cholesterol level.

## RESULTS

The overall distribution of C-reactive protein values in this study was similar to that reported in previous studies of primary prevention.<sup>8-11</sup> The mean and median levels of C-reactive protein were 0.31 and 0.16 mg per deciliter, respectively, and the ranges of C-reactive protein levels in the four quartiles were less than 0.08 mg per deciliter, 0.08 to less than 0.16 mg per deciliter, 0.16 to 0.35 mg per deciliter, and greater than 0.35 mg per deciliter.

Our data provided minimal evidence of an association between base-line C-reactive protein levels and base-line lipid levels; the Spearman correlation coefficients for the relations between C-reactive protein levels and total, LDL, and HDL cholesterol and triglyceride levels and the ratio of total to HDL cholesterol were 0.069, 0.012,  $-0.058$ , 0.129, and 0.092, respectively. Thus, less than 2 percent of the variance in base-line C-reactive protein levels was determined by lipid factors.

Overall, the rates of coronary events increased with the base-line levels of C-reactive protein, so that the relative risks of coronary events in participants assigned to the placebo group as compared with those in the lovastatin group were 1.0, 1.2, 1.3, and 1.7 for the lowest to highest quartile of base-line levels of C-reactive protein ( $P = 0.01$ ). In unadjusted analyses, the risk of acute coronary events increased by 21 percent with each increasing quartile of base-line C-reactive protein levels (95 percent confidence in-

terval, 4 to 41 percent). In similar analyses with control for age, sex, smoking status, hypertension, parental history with respect to coronary disease, and lipid levels, the increase in risk associated with a one-quartile increase in the C-reactive protein level (17 percent; 95 percent confidence interval, 3 to 33 percent) was almost identical in magnitude to that associated with an increase of 1.0 in the ratio of total to HDL cholesterol (18 percent; 95 percent confidence interval, 5 to 33 percent).

Lovastatin therapy was associated with a statistically significant 14.8 percent reduction in the median level of C-reactive protein (95 percent confidence interval, 12.5 to 17.4 percent;  $P < 0.001$ ) at the end of the first year of treatment (Table 1). By contrast, assignment to the placebo group had no effect on the median level of C-reactive protein (median percentage change, 0.0; 95 percent confidence interval, 0.0 to 5.3 percent), although there were more participants with an increase in C-reactive protein levels than with a decrease. Thus, the difference between the lovastatin group and the placebo group in terms of the change in C-reactive protein levels over time was significant ( $P < 0.001$ ). This effect of lovastatin on the level of C-reactive protein was not related to the effect of lovastatin on lipid levels; among the participants in the lovastatin group, the Spearman correlation coefficients for the relation between the percentage change in C-reactive protein level and the percentage change in total, LDL, and HDL cholesterol and triglyceride levels and the ratio of total to HDL cholesterol were  $-0.001$ ,  $0.014$ ,  $-0.079$ ,  $-0.013$ , and  $0.061$ , respectively. Thus, virtually none of the observed variance in the effect of lovastatin on C-reactive protein levels could be explained by lovastatin-induced changes in lipid fractions.

Table 2 presents the results of efficacy analyses for lovastatin in subgroups of participants delineated ac-

ording to LDL cholesterol and C-reactive protein levels. As expected, given the overall findings of the trial, lovastatin was clinically effective among participants with LDL cholesterol levels higher than the median, regardless of their C-reactive protein levels (relative risk of acute coronary events, 0.53; 95 percent confidence interval, 0.37 to 0.77; number needed to treat, 42;  $P = 0.001$ ). However, lovastatin was also clinically effective among those with LDL cholesterol levels lower than the median and C-reactive protein levels higher than the median (relative risk, 0.58; 95 percent confidence interval, 0.34 to 0.98; number needed to treat, 48;  $P = 0.04$ ). In contrast, among the participants with LDL cholesterol and C-reactive protein levels that were both lower than the median, the point estimate did not indicate that lovastatin reduced the risk of acute coronary events (relative risk, 1.08; 95 percent confidence interval, 0.56 to 2.08;  $P = 0.74$ ). In these analyses, formal testing for a multiplicative interaction among lovastatin, lipids, and C-reactive protein indicated borderline statistical significance ( $P = 0.06$ ).

We evaluated the robustness of these analyses by stratifying the study cohort on the basis of the median base-line ratio of total to HDL cholesterol, rather than on the basis of the base-line LDL cholesterol level, and the results were nearly identical (Table 3). Specifically, lovastatin was highly effective among participants with a base-line ratio of total to HDL cholesterol that was higher than the median (number needed to treat, 47;  $P = 0.005$ ). However, lovastatin was also highly effective among those with a ratio of total to HDL cholesterol lower than the median and a C-reactive protein level higher than the median (number needed to treat, 43;  $P = 0.02$ ). In contrast, lovastatin was far less effective among those with a ratio of total to HDL cholesterol lower than the median who also had a C-reactive protein level lower

**TABLE 1. MEDIAN C-REACTIVE PROTEIN LEVELS AT BASE LINE AND AFTER ONE YEAR OF THERAPY IN THE LOVASTATIN AND PLACEBO GROUPS.\***

TREATMENT	MEDIAN C-REACTIVE PROTEIN LEVEL		MEDIAN CHANGE	MEDIAN PERCENT CHANGE
	BASE LINE	ONE YEAR		
	mg/dl (95% CI)			% (95% CI)
Lovastatin (n=2885)	0.16 (0.15 to 0.17)	0.13 (0.12 to 0.14)	-0.02 (-0.02 to -0.01)	-14.8 (-17.4 to -12.5)
Placebo (n=2834)	0.15 (0.15 to 0.16)	0.16 (0.16 to 0.17)	0.0 (0.00 to 0.01)	0.0 (0.0 to 5.3)†

\*Data are shown for the 5719 study participants who provided both base-line and one-year blood samples and who were free of any acute coronary event during the first year of follow-up. Confidence intervals (CIs) of the medians are nonparametric.

† $P < 0.001$  for the comparison with the lovastatin group.

**TABLE 2.** NUMBERS OF ACUTE CORONARY EVENTS, RATES OF EVENTS, RELATIVE RISKS, AND NUMBERS NEEDED TO TREAT WITH LOVASTATIN TO PREVENT ONE EVENT, ACCORDING TO BASE-LINE LEVELS OF LDL CHOLESTEROL AND C-REACTIVE PROTEIN.\*

SUBGROUP	LOVASTATIN GROUP		PLACEBO GROUP		RELATIVE RISK OF ACUTE CORONARY EVENTS (95% CI)	NO. NEEDED TO TREAT
	NO. OF EVENTS/ NO. OF PARTICIPANTS	RATE OF EVENTS	NO. OF EVENTS/ NO. OF PARTICIPANTS	RATE OF EVENTS		
LDL <median	41/1444	0.027	54/1432	0.036	0.74 (0.49–1.11)	113
LDL >median	44/1450	0.029	77/1416	0.053	0.53 (0.37–0.77)	42
LDL <median, C-reactive protein <median	19/726	0.025	17/722	0.022	1.08 (0.56–2.08)	—
LDL <median, C-reactive protein >median	22/718	0.029	37/710	0.051	0.58 (0.34–0.98)	48
LDL >median, C-reactive protein <median	15/709	0.020	37/711	0.050	0.38 (0.21–0.70)	33
LDL >median, C-reactive protein >median	29/741	0.038	40/705	0.055	0.68 (0.42–1.10)	58

\*The rates of events and the numbers needed to treat to prevent one event were calculated on the basis of five patient-years at risk. CI denotes confidence interval.

**TABLE 3.** NUMBERS OF ACUTE CORONARY EVENTS, RATES OF EVENTS, RELATIVE RISKS, AND NUMBERS NEEDED TO TREAT WITH LOVASTATIN TO PREVENT ONE EVENT, ACCORDING TO BASE-LINE RATIO OF TOTAL TO HDL CHOLESTEROL AND C-REACTIVE PROTEIN LEVEL.\*

SUBGROUP	LOVASTATIN GROUP		PLACEBO GROUP		RELATIVE RISK OF ACUTE CORONARY EVENTS (95% CI)	NO. NEEDED TO TREAT
	NO. OF EVENTS/ NO. OF PARTICIPANTS	RATE OF EVENTS	NO. OF EVENTS/ NO. OF PARTICIPANTS	RATE OF EVENTS		
Cholesterol ratio <median	36/1412	0.024	55/1459	0.036	0.63 (0.41–0.95)	86
Cholesterol ratio >median	49/1482	0.032	76/1389	0.053	0.59 (0.41–0.85)	47
Cholesterol ratio <median, C-reactive protein <median	19/762	0.024	20/763	0.025	0.88 (0.47–1.67)	983
Cholesterol ratio <median, C-reactive protein >median	17/650	0.025	35/696	0.050	0.47 (0.27–0.85)	43
Cholesterol ratio >median, C-reactive protein <median	15/673	0.021	34/670	0.050	0.42 (0.23–0.77)	35
Cholesterol ratio >median, C-reactive protein >median	34/809	0.041	42/719	0.057	0.72 (0.46–1.13)	62

\*The rates of events and the numbers needed to treat to prevent one event were calculated on the basis of five patient-years at risk. CI denotes confidence interval.

than the median (number needed to treat, 983;  $P=0.87$ ) (Table 3).

The rates of events among the participants in the placebo group who had lipid levels lower than the median and C-reactive protein levels higher than the median were just as high as the rates of events among those with overt hyperlipidemia (Tables 2 and 3). Moreover, lovastatin was clinically effective in reducing the risk of acute coronary events among participants with lipid levels lower than the median and C-reactive protein levels higher than the median, but not among those with lipid levels and C-reactive protein levels that were both lower than the median (Fig. 1).

In these data, the observed efficacy of lovastatin in preventing acute coronary events was not statistically significant among the participants with lipid levels and C-reactive protein levels that were both higher than the median (Fig. 1). However, in each of the two subgroups defined according to these criteria, the point estimates of effect indicate an overall net benefit with lovastatin. Furthermore, there was no evidence of any statistically significant difference between the efficacy of lovastatin among the participants with lipid levels and C-reactive protein levels that were both higher than the median and its efficacy among those with lipid levels higher than the median but C-reactive protein levels lower than the median; these data suggest that any small differences between the results in these subgroups probably represent the effects of chance. Finally, because the rates of events were high among participants with lipid levels and C-reactive protein levels that were both higher than the median, the number needed to treat in these subgroups was well below the number considered the threshold for justifying treatment for primary prevention. Indeed, the number needed to treat among participants with lipid levels and C-reactive protein levels that were both higher than the median was of similar magnitude to that found in subgroups in which the efficacy of lovastatin was clearly statistically significant (Tables 2 and 3).

### DISCUSSION

Among the participants in AFCAPS/TexCAPS, base-line C-reactive protein levels were an independent predictor of first acute coronary events. Furthermore, lovastatin appeared to be highly effective in reducing the risk of acute coronary events in participants with elevated C-reactive protein levels but no hyperlipidemia. Indeed, among participants with either an LDL cholesterol level or a ratio of total to HDL cholesterol that was lower than the median but a C-reactive protein level higher than the median, the number needed to treat with lovastatin to prevent one clinical event was virtually identical to that among participants with lipid levels higher than the median. These analyses thus raise the possibility that statin therapy may be clinically effective in persons with-

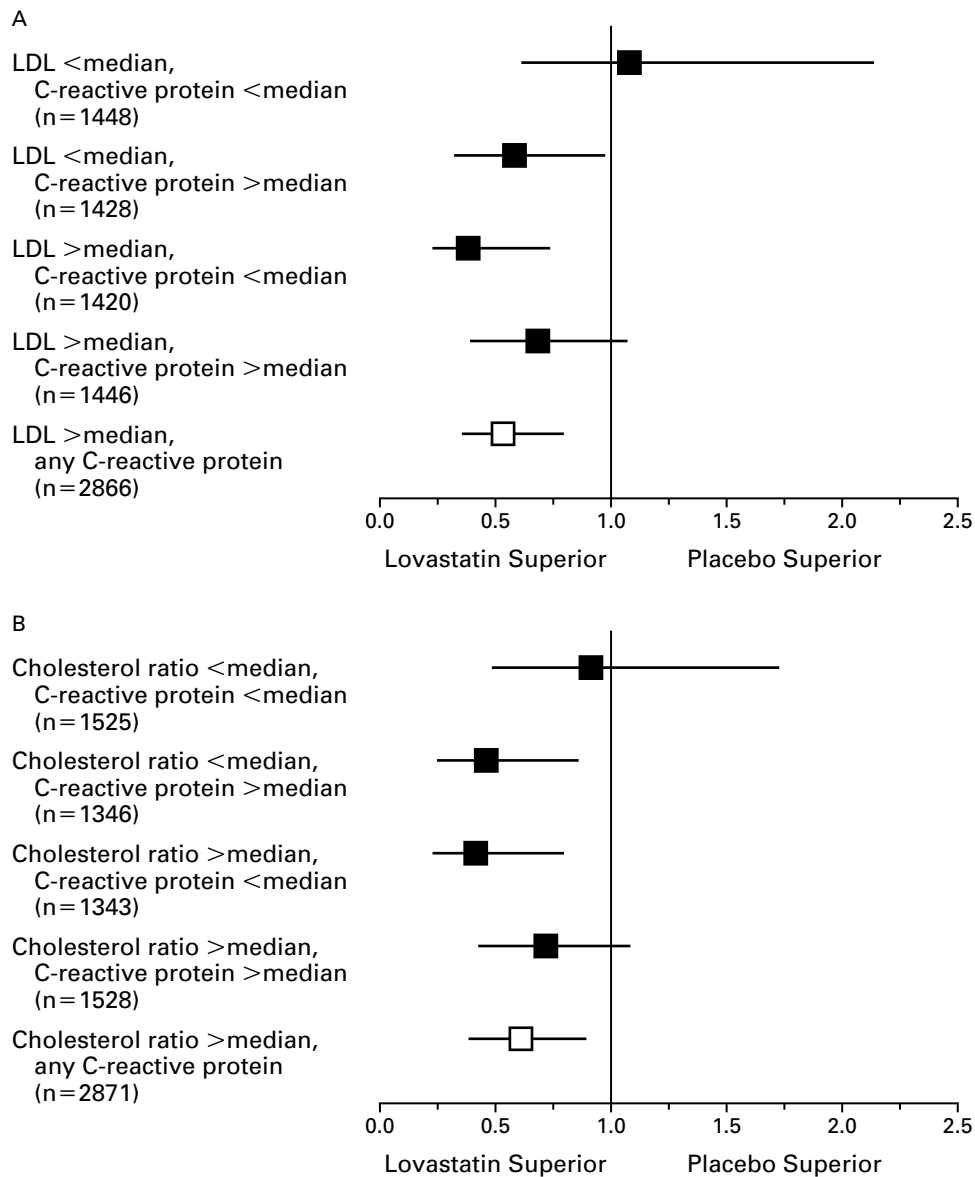
out hyperlipidemia and suggest that evaluation of the C-reactive protein level may provide a method for the appropriate targeting of statin therapy for primary prevention.<sup>20</sup> Finally, lovastatin significantly reduced C-reactive protein levels independently of its effect on lipids.

The results of this study have several implications. First, the current data confirm in a large population of apparently healthy men and women that C-reactive protein can be used to determine the risk of acute coronary events. The effect of the C-reactive protein level on risk was independent of all other factors, including lipid levels, known to predict clinical coronary outcomes. Thus, as in our earlier studies,<sup>8,9,16</sup> the current data are consistent with the hypothesis that the addition of an evaluation of the C-reactive protein level to the standard lipid evaluation may provide an improved method of identifying persons at high risk.

Second, in this double-blind trial, the use of lovastatin resulted in a 14.8 percent reduction in median C-reactive protein levels after one year ( $P<0.001$ ), whereas no change in C-reactive protein levels occurred in participants in the placebo group. Thus, the current data also confirm the findings of the Cholesterol and Recurrent Events (CARE) trial, in which assignment to pravastatin therapy led to a 17.4 percent reduction in median C-reactive protein levels over a five-year period.<sup>13</sup> As in the CARE trial, the effect of lovastatin on C-reactive protein levels in our study appeared to be unrelated to any effect of HMG-CoA reductase inhibition on plasma lipid levels. Together, these clinical data provide evidence of nonlipid effects of this class of agents<sup>13-15</sup> and suggest that statins may lead to the stabilization of plaque in part through antiinflammatory mechanisms.<sup>21-23</sup>

Third, although our study is hypothesis-generating, the fact that lovastatin was highly effective among participants without marked hyperlipidemia but with elevated levels of C-reactive protein may have implications for the use of HMG-CoA reductase inhibitors in primary prevention. As outlined in the current guidelines of the National Cholesterol Education Program, strategies to target statin therapy in primary prevention rely largely on LDL cholesterol screening, an approach that results in a reduction in the number needed to treat to prevent one event and improves the cost effectiveness of these agents.<sup>5,6</sup> However, as the current data suggest, lovastatin may be highly effective among persons with average and below-average LDL cholesterol levels who have C-reactive protein levels higher than the median. Thus, if the number needed to treat is used to estimate the effect of therapy in primary prevention, then C-reactive protein screening might provide an additional method for targeting the use of statins, particularly when lipid levels are normal or low.

In the current study, the magnitude of the increase



**Figure 1.** Relative Risks (and 95 Percent Confidence Intervals) Associated with Lovastatin Therapy, According to Base-Line Lipid and C-Reactive Protein Levels.

Data are shown for LDL cholesterol levels (Panel A) and the ratio of total to HDL cholesterol (Panel B). Open boxes reflect analyses for all participants with LDL cholesterol levels higher than the median (in Panel A) and ratios of total to HDL cholesterol higher than the median (in Panel B).

in risk associated with higher levels of C-reactive protein is somewhat smaller than that observed in previous studies.<sup>8-11</sup> Several aspects of the design of our study probably account for this difference. For example, obese persons and diabetic patients requiring insulin were excluded from the study. Since these groups have elevated C-reactive protein levels and are at increased risk for cardiovascular disease,<sup>24</sup> their exclu-

sion would tend to lead to underestimation of the predictive value of the C-reactive protein level. Similarly, because C-reactive protein and lipid levels appear additive in their ability to predict the risk of cardiovascular disease,<sup>9,16</sup> the further exclusion from the study of persons with severe hyperlipidemia would also tend to reduce the predictive value of the C-reactive protein level. Finally, nearly 20 percent of the par-

ticipants in AFCAPS/TexCAPS were taking aspirin, a drug that has also been shown to reduce the effect of C-reactive protein on vascular risk.<sup>8</sup> For all of these reasons, estimates of the risk associated with C-reactive protein derived from data from our study cohort would be expected to be lower than those found in unselected populations.<sup>20</sup> These issues would not, however, affect the validity of observations made in the context of this study with regard to statin therapy and C-reactive protein, since the participants were assigned to treatment groups in a double-blind manner, without knowledge of C-reactive protein values.

From a clinical perspective, it is important to recognize that half of all heart attacks occur among persons without overt hyperlipidemia<sup>7</sup> and thus that novel approaches to the determination of the risk of cardiovascular disease as well as to intervention are needed to improve resource allocation in the primary prevention of myocardial infarction.<sup>25</sup> In a recent study of patients with a history of myocardial infarction, randomized use of statin therapy reduced the risk of recurrent coronary events associated with elevated levels of C-reactive protein.<sup>26</sup> In the current study of primary prevention, statin therapy was found to reduce the risk of acute coronary events associated with C-reactive protein, even in the absence of hyperlipidemia. Thus, these hypothesis-generating clinical studies, together with the recognition that, biologically, atherosclerosis is in part an inflammatory disease<sup>21</sup> and that the lowering of lipid levels may represent an antiinflammatory process,<sup>22</sup> appear to provide a rationale for considering wider use of statins than is typically achieved in current practice. Nonetheless, despite large differences in the number needed to treat in this study, the absolute number of events that occurred in each of the four subgroups of participants was small, and formal testing for a multiplicative interaction among lovastatin, lipids, and C-reactive protein indicated borderline statistical significance ( $P=0.06$ ). Thus, randomized trials of statin therapy among persons without overt hyperlipidemia but with evidence of systemic inflammation are needed in order to test these hypotheses directly.

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Dr. Ridker is named as a coinventor on patent applications filed for the use of inflammatory markers in coronary artery disease. Drs. Gotto, Clearfield, Downs, and Weis have either served as consultants to Merck (the manufacturer of lovastatin) or received honorariums from Merck.

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