

ORIGINAL ARTICLE

C-Reactive Protein Levels and Outcomes after Statin Therapy

Paul M Ridker, M.D., Christopher P. Cannon, M.D., David Morrow, M.D., Nader Rifai, Ph.D., Lynda M. Rose, M.S., Carolyn H. McCabe, B.S., Marc A. Pfeffer, M.D., Ph.D., and Eugene Braunwald, M.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) Investigators

ABSTRACT

BACKGROUND

Statins lower the levels of low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP). Whether this latter property affects clinical outcomes is unknown.

METHODS

We evaluated relationships between the LDL cholesterol and CRP levels achieved after treatment with 80 mg of atorvastatin or 40 mg of pravastatin per day and the risk of recurrent myocardial infarction or death from coronary causes among 3745 patients with acute coronary syndromes.

RESULTS

Patients in whom statin therapy resulted in LDL cholesterol levels of less than 70 mg per deciliter (1.8 mmol per liter) had lower event rates than those with higher levels (2.7 vs. 4.0 events per 100 person-years, $P=0.008$). However, a virtually identical difference was observed between those who had CRP levels of less than 2 mg per liter after statin therapy and those who had higher levels (2.8 vs. 3.9 events per 100 person-years, $P=0.006$), an effect present at all levels of LDL cholesterol achieved. For patients with post-treatment LDL cholesterol levels of more than 70 mg per deciliter, the rates of recurrent events were 4.6 per 100 person-years among those with CRP levels of more than 2 mg per liter and 3.2 events per 100 person-years among those with CRP levels of less than 2 mg per liter; the respective rates among those with LDL cholesterol levels of less than 70 mg per deciliter were 3.1 and 2.4 events per 100 person-years ($P<0.001$). Although atorvastatin was more likely than pravastatin to result in low levels of LDL cholesterol and CRP, meeting these targets was more important in determining the outcomes than was the specific choice of therapy. Patients who had LDL cholesterol levels of less than 70 mg per deciliter and CRP levels of less than 1 mg per liter after statin therapy had the lowest rate of recurrent events (1.9 per 100 person-years).

CONCLUSIONS

Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. Strategies to lower cardiovascular risk with statins should include monitoring CRP as well as cholesterol.

From the Center for Cardiovascular Disease Prevention (P.M.R., N.R., L.M.R.), the Donald W. Reynolds Center for Cardiovascular Research (P.M.R., D.M., N.R.), and the Thrombolysis in Myocardial Infarction Study Group (C.P.C., D.M., C.H.M., M.A.P., E.B.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston. Address reprint requests to Dr. Ridker at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Ave. East, Boston, MA 02215, or at pridker@partners.org.

N Engl J Med 2005;352:20-8.
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STATIN THERAPY LOWERS THE RISK OF cardiovascular events by reducing plasma cholesterol levels, and practice guidelines for patients with known cardiovascular disease emphasize the importance of reaching target goals for low-density lipoprotein (LDL) cholesterol.¹ However, we have shown that statin therapy results in a greater clinical benefit when levels of the inflammatory biomarker C-reactive protein (CRP) are elevated^{2,3} and that statins lower CRP levels in a manner largely independent of LDL cholesterol levels.³⁻⁶ These findings, along with basic laboratory evidence, have led to the hypothesis that, in addition to being potent lipid-lowering agents, statins may also have antiinflammatory properties that are important for prognosis and treatment. If so, then the level of CRP achieved as a result of statin therapy may have clinical relevance analogous to that of the LDL cholesterol levels achieved through the use of statin therapy.

We prospectively addressed this issue among 3745 patients with acute coronary syndromes who were randomly assigned to receive either intensive or moderate lipid-lowering therapy with a statin. Specifically, on an a priori basis, we hypothesized that patients with acute coronary syndromes who had lower CRP levels as a result of statin therapy would have a lower risk of recurrent myocardial infarction or death from coronary causes than those who had higher CRP levels, even after we controlled for the achieved levels of LDL cholesterol. We also evaluated whether the specific type of statin modified the effect.

METHODS

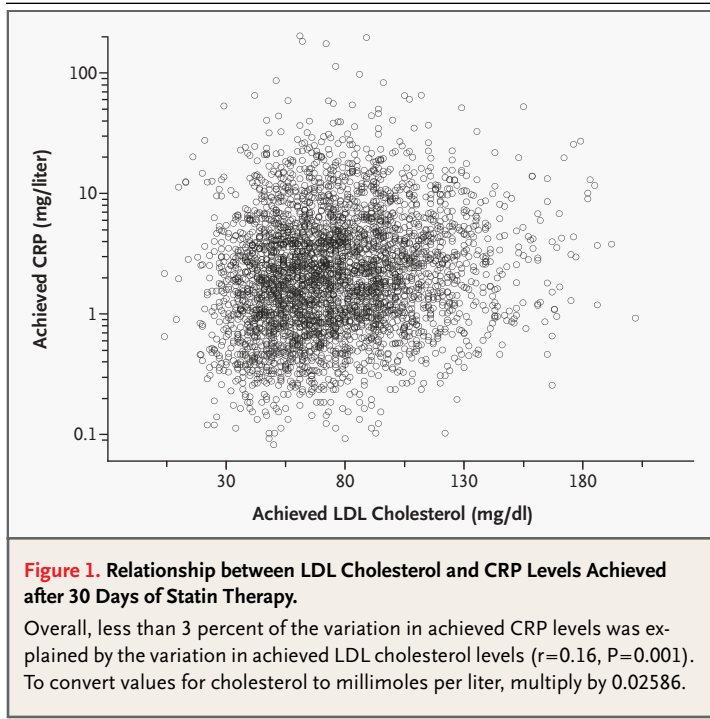
The study population was derived from the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) study, a randomized trial performed between November 2000 and February 2004 that used a two-by-two factorial design to compare the effect of intensive statin therapy (80 mg of atorvastatin orally per day) and moderate statin therapy (40 mg of pravastatin orally per day) and of gatifloxacin and placebo on the risk of recurrent coronary events after acute coronary syndromes.⁷ In total, 4162 patients who had been hospitalized within the preceding 10 days with acute coronary syndromes and who provided written informed consent were enrolled at 349 sites in eight countries. Approximately two thirds had had an acute myo-

cardial infarction, and the remainder had high-risk unstable angina. Descriptions of the study's inclusion and exclusion criteria have been presented previously.⁸

As part of the protocol, plasma samples were obtained at randomization, 30 days, 4 months, and the end of the study (mean, 24 months). For this analysis, we defined achieved LDL cholesterol levels and achieved CRP levels as the values obtained at the 30-day follow-up visit, a period adequate for the effect of statin therapy on these variables to be seen and for any residual effects of ischemia on each variable to have disappeared. Of the total cohort, 3745 participants (90.0 percent) were alive and free of a recurrent event at day 30 and had measurements of both LDL cholesterol and CRP at that time. All laboratory measurements were made in a core facility. A validated assay for high-sensitive CRP (Denka Seiken) was used.

We used Spearman correlation coefficients to evaluate the relationship between achieved LDL cholesterol levels and achieved CRP levels. We then used a multistage process to address the effect of achieved LDL cholesterol levels and achieved CRP levels on the rates of recurrent myocardial infarction or fatal coronary events that occurred after day 30 of the study. First, we divided the study population into quartiles according to the levels of achieved LDL cholesterol and achieved CRP and sought evidence that these levels were associated with the risk of recurrent myocardial infarction or death from coronary causes, both in age-adjusted analyses and after further adjustment for sex, smoking status (current smoker vs. nonsmoker), body-mass index, and the presence or absence of diabetes and a history of hypertension.

Second, we divided the study population at the approximate median value achieved for the LDL cholesterol level, 70 mg per deciliter (1.8 mmol per liter), and evaluated whether the rates of events differed between patients with values above the median and those with values below the median. In a similar manner, we divided the study population at the approximate median value achieved for the CRP level, 2 mg per liter, and determined whether the rates of recurrent events differed between patients with values above the median and those with values below the median. (None of the patients had the exact median value of either marker.) To address the relative effect of the achieved CRP level across the strata of achieved LDL cholesterol levels, we repeated this process after dividing the study cohort into



four groups on the basis of achieved LDL cholesterol levels and achieved CRP levels above or below the respective values of 70 mg per deciliter and 2 mg per liter. A test for trend across groups was performed by assigning a score of 0 to those with low levels of both variables, a score of 1 to the two intermediate groups, and a score of 2 to those with high levels of both variables. Similar analyses were performed after stratification of the study group according to their assignment to atorvastatin or pravastatin. Estimates of hazard ratios were obtained with the use of Cox proportional-hazards models. All main analyses were prespecified in the PROVE IT-TIMI 22 protocol.⁸ All P values were two-tailed, all confidence intervals computed at the 95 percent level, and all analyses adjusted for assignment to gatifloxacin or placebo.

The investigators designed the protocol; collected, held, and analyzed the data; and wrote the article.

RESULTS

The mean age of the 3745 participants at study entry was 58 years, and 22 percent were women. Forty-nine percent had a history of hypertension, 17 percent had diabetes, and 36 percent were current smokers. Although the levels of both LDL chole-

sterol and CRP were reduced by statin therapy at 30 days, the correlation between the achieved values was small ($r=0.16$, $P=0.001$), so that less than 3 percent of the variance in achieved CRP levels was explained by the variance in achieved LDL cholesterol levels (Fig. 1). This minimal level of correlation was also observed in the subgroup of patients who subsequently had recurrent coronary events ($r=0.18$, $P=0.004$).

There was a linear relationship between the levels of LDL cholesterol achieved after statin therapy and the risk of recurrent myocardial infarction or death from coronary causes. Fully adjusted relative risks for those in the second lowest, second highest, and highest quartiles of achieved LDL cholesterol level, as compared with those in the lowest quartile (the reference group) were 1.1 ($P=0.80$), 1.2 ($P=0.30$), and 1.7 ($P=0.006$), respectively (Table 1). However, despite the almost complete independence of achieved CRP and achieved LDL cholesterol levels, there was also a linear relationship between the levels of CRP achieved after statin therapy and the risk of recurrent myocardial infarction or death from coronary causes, so that fully adjusted relative risks for those in the second lowest, second highest, and highest quartiles of achieved CRP level, as compared with those in the lowest quartile of achieved CRP level (the reference group), were 1.5 ($P=0.06$), 1.3 ($P=0.15$), and 1.7 ($P=0.01$). Additional adjustment for concomitant cardiovascular medications had no effect on these estimates.

Age-adjusted rates of recurrent myocardial infarction or death from coronary causes are shown in Table 2 according to whether the level of LDL cholesterol achieved was greater than or less than 70 mg per deciliter and whether the level of CRP achieved was greater than or less than 2 mg per liter. Patients in whom statin therapy resulted in LDL cholesterol levels of less than 70 mg per deciliter had lower age-adjusted rates of recurrent myocardial infarction or death from coronary causes than did patients in whom statin therapy did not achieve this goal (2.7 vs. 4.0 events per 100 person-years, $P=0.008$) (Table 2 and Fig. 2). However, despite the minimal correlation between achieved LDL cholesterol and CRP levels, a virtually identical difference in the age-adjusted rates of events was also observed among patients in whom statin therapy resulted in CRP levels of less than 2 mg per liter as compared with those in whom statin therapy resulted in higher CRP values (2.8 vs. 3.9 events per 100 person-years, $P=0.006$) (Table 2 and Fig. 2).

Table 1. Relative Risk of Recurrent Coronary Events after Statin Therapy, According to the Quartile of LDL Cholesterol and CRP Levels Achieved.*

Variable	Quartile			
	1†	2	3	4
Achieved LDL cholesterol				
Quartile value — mg/dl	<54	54–71	72–94	>94
Relative risk adjusted for age	1.0	1.1	1.3	1.8
95% CI	—	0.8–1.6	0.9–1.9	1.2–2.5
P value	—	0.60	0.10	0.002
Relative risk adjusted for age + achieved CRP	1.0	1.1	1.3	1.7
95% CI	—	0.7–1.6	0.9–1.8	1.2–2.4
P value	—	0.70	0.20	0.006
Relative risk adjusted for age + other risk factors	1.0	1.1	1.3	1.7
95% CI	—	0.7–1.6	0.9–1.9	1.2–2.5
P value	—	0.70	0.20	0.003
Relative risk adjusted for age, achieved CRP, + other risk factors	1.0	1.1	1.2	1.7
95% CI	—	0.7–1.6	0.8–1.8	1.2–2.4
P value	—	0.80	0.30	0.006
Achieved CRP				
Quartile value — mg/liter	<0.9	0.9–1.9	2.0–4.2	>4.2
Relative risk adjusted for age	1.0	1.5	1.5	1.9
95% CI	—	1.0–2.3	1.0–2.3	1.3–2.8
P value	—	0.04	0.04	<0.001
Relative risk adjusted for age + achieved LDL cholesterol	1.0	1.5	1.4	1.8
95% CI	—	1.0–2.2	1.0–2.1	1.2–2.6
P value	—	0.06	0.07	0.004
Relative risk adjusted for age + other risk factors	1.0	1.5	1.4	1.8
95% CI	—	1.0–2.3	0.9–2.1	1.2–2.7
P value	—	0.04	0.09	0.003
Relative risk adjusted for age, achieved LDL cholesterol, + other risk factors	1.0	1.5	1.3	1.7
95% CI	—	1.0–2.2	0.9–2.0	1.1–2.5
P value	—	0.06	0.15	0.01

* All models controlled for age (in years). Models adjusted for other risk factors additionally controlled for sex, smoking status (current smoker vs. nonsmoker), diabetes (yes vs. no), history of hypertension (yes vs. no), body-mass index, and random allocation to gatifloxacin or placebo. In addition to the above covariates, the fully adjusted model for achieved LDL cholesterol also adjusted for achieved CRP, whereas the fully adjusted model for achieved CRP also adjusted for achieved LDL cholesterol. CI denotes confidence interval. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

† For each comparison, quartile 1 served as the reference group.

As also shown in Table 2, those in whom statin therapy resulted in CRP levels of less than 2 mg per liter in general had better clinical outcomes regardless of the level of LDL cholesterol achieved. For example, in the group of patients who had LDL cholesterol levels of more than 70 mg per deciliter after

statin therapy, the rates of recurrent events were 4.6 per 100 person-years among those with post-treatment CRP levels of more than 2 mg per liter and 3.2 per 100 person-years among those with CRP levels of less than 2 mg per liter. Among patients in whom statin therapy resulted in LDL cholesterol

Table 2. Age-Adjusted Rates of Recurrent Myocardial Infarction or Death from Coronary Causes, According to the LDL Cholesterol and CRP Level Achieved by Statin Therapy.

Subgroup*	No. of Patients	No. of Person-Yr	No. of Recurrent Events	Age-Adjusted Event Rate/100 Person-yr	P Value†
Prespecified analysis					
LDL cholesterol \geq 70 mg/dl	1985	3850.7	148	4.0	0.008
LDL cholesterol <70 mg/dl	1760	3511.5	95	2.7	
CRP \geq 2 mg/liter	1828	3559.3	139	3.9	0.006
CRP <2 mg/liter	1917	3802.9	104	2.8	
LDL \geq 70 mg/dl, CRP \geq 2 mg/liter	1086	2086.2	92	4.6	<0.001
LDL <70 mg/dl, CRP \geq 2 mg/liter	742	1473.0	47	3.1	
LDL \geq 70 mg/dl, CRP <2 mg/liter	899	1764.5	56	3.2	
LDL <70 mg/dl, CRP <2 mg/liter	1018	2038.4	48	2.4	
Post hoc analysis					
CRP \geq 1 mg/liter	2699	5250.7	200	3.8	<0.001
CRP <1 mg/liter	1046	2111.5	43	2.1	
LDL \geq 70 mg/dl, CRP \geq 1 mg/liter	1536	2952.3	128	4.5	<0.001
LDL <70 mg/dl, CRP \geq 1 mg/liter	1163	2298.4	72	3.1	
LDL \geq 70 mg/dl, CRP <1 mg/liter	449	898.4	20	2.3	
LDL <70 mg/dl, CRP <1 mg/liter	597	1213.0	23	1.9	

* The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

† P values are for the comparisons between two groups or among four groups.

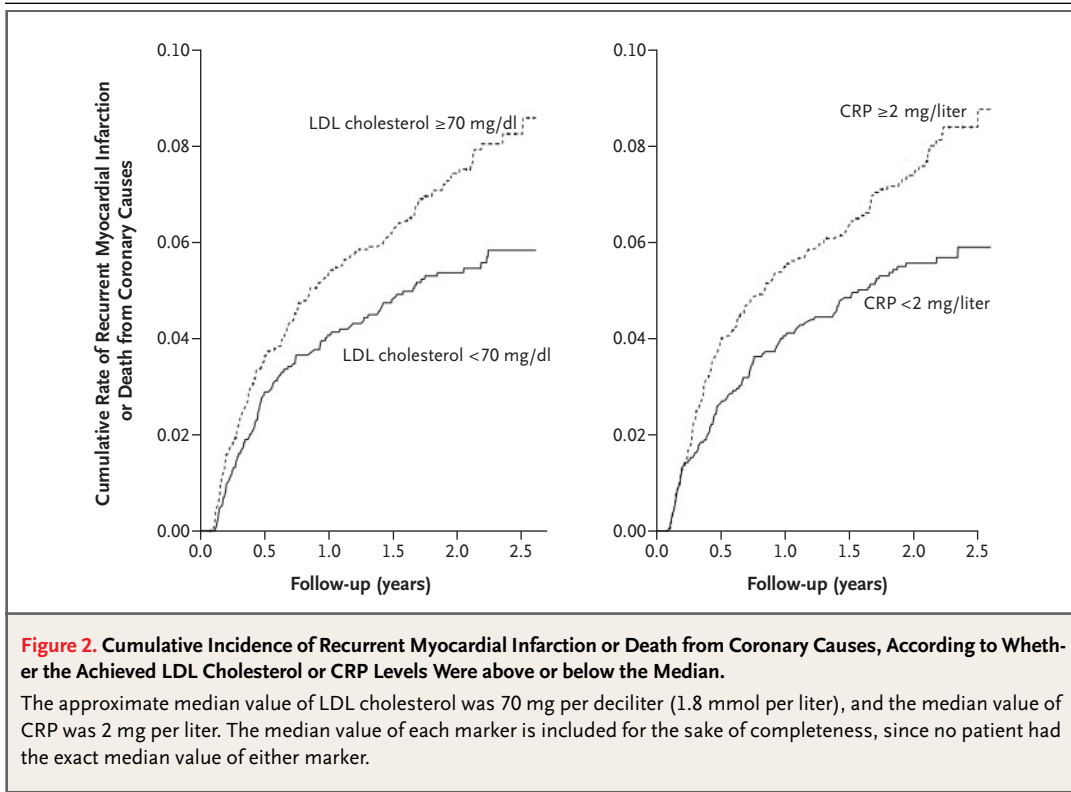
ol levels of less than 70 mg per deciliter, the respective rates of events were 3.1 and 2.4 per 100 person-years. These differences are presented graphically in Figure 3 in terms of the cumulative incidence of recurrent myocardial infarction or death from coronary causes.

Hazard ratios for recurrent coronary events among patients whose values were above the median for LDL cholesterol and below the median for CRP, those whose values were below the median for LDL cholesterol and above the median for CRP, and those whose values were above the median for both LDL cholesterol and CRP, as compared with those whose values of achieved LDL cholesterol and CRP levels were below the median (the reference group), were 1.3, 1.4, and 1.9, respectively (P for trend across groups <0.001). Almost identical results were observed in analyses that eliminated patients with prior statin use.

Because study participants were randomly assigned to receive either 80 mg of atorvastatin or 40 mg of pravastatin daily, we had the additional op-

portunity to assess the relative effect of these two agents on the reduction in CRP levels and to assess whether the main effects observed in the total cohort according to the LDL cholesterol and CRP levels achieved were modified by the choice of statin therapy. With regard to CRP, the median levels were similar in the atorvastatin and pravastatin groups at randomization (12.2 and 11.9 mg per liter, respectively; P=0.60), but they were significantly lower in the atorvastatin group than in the pravastatin group at 30 days (1.6 vs. 2.3 mg per liter, P<0.001), 4 months (1.3 vs. 2.1 mg per liter, P<0.001), and the end of the study (1.3 vs. 2.1 mg per liter, P<0.001) (Fig. 4).

Despite these differences, there was substantial overlap between the two groups in terms of achieved CRP levels; 57.5 percent of those treated with atorvastatin had CRP levels below 2 mg per liter after 30 days, whereas 44.9 percent of patients in the pravastatin group had such levels (P<0.001). The levels of LDL cholesterol were identical in the two groups at randomization and, as expected, were significantly

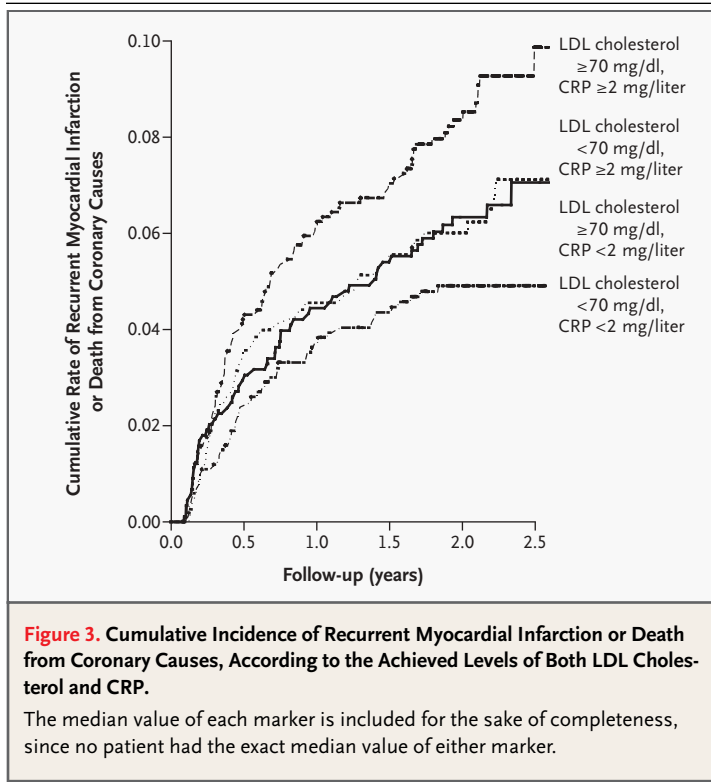


lower in the atorvastatin group than in the pravastatin group at day 30, four months, and the end of the study. At 30 days, 72.3 percent of those assigned to receive atorvastatin had met the LDL cholesterol goal of a level of less than 70 mg per deciliter, as compared with 21.7 percent of those assigned to pravastatin ($P < 0.001$). The magnitude of the correlation between achieved LDL cholesterol and achieved CRP levels was small for both agents ($r = 0.04$, $P = 0.07$ for pravastatin, and $r = 0.15$, $P = 0.001$ for atorvastatin).

Despite the greater ability of atorvastatin than of pravastatin to reduce LDL cholesterol levels to below 70 mg per deciliter and CRP levels to below 2 mg per liter, there was little evidence that either agent led to better clinical outcomes once the target levels of both LDL cholesterol and CRP were achieved. Specifically, although atorvastatin was superior to pravastatin overall in the PROVE IT-TIMI 22 trial,⁷ there was no observed residual effect of randomization on clinical outcomes once the achieved levels of LDL cholesterol and CRP were accounted for (fully adjusted hazard ratio for atorvastatin as compared with pravastatin = 1.00; 95 percent confidence interval, 0.75 to 1.34; $P = 0.90$).

Similarly, for those in whom atorvastatin therapy resulted in LDL cholesterol levels of less than 70 mg per deciliter, the rates of recurrent events were 3.1 per 100 person-years for those with post-treatment CRP levels of more than 2 mg per liter and 2.3 per 100 person-years for those with CRP levels of less than 2 mg per liter, whereas the corresponding event rates for patients in whom pravastatin resulted in LDL cholesterol levels of less than 70 mg per deciliter were 3.4 and 2.5 per 100 person-years ($P = 0.70$ for the difference between agents). Thus, achieving target levels of both LDL cholesterol and CRP was of substantially greater importance for subsequent event-free survival than was the specific type of statin therapy received.

We performed additional post hoc analyses to evaluate those in whom statin therapy resulted not only in a target LDL cholesterol level below 70 mg per deciliter but also in a CRP level below 1 mg per liter. Although only 15.9 percent of the study population reached these very aggressive target goals, this subgroup had the lowest age-adjusted rate of recurrent events (1.9 per 100 person-years) (Table 2); 81.8 percent of patients in this subgroup had been assigned to receive atorvastatin.



As indicated above, all analyses were adjusted for random assignment to gatifloxacin or placebo. This agent had no significant effect on CRP levels in this population.

DISCUSSION

Our data indicate that among patients with acute coronary syndromes who are treated with a statin, achieving a target level of CRP of less than 2 mg per liter is associated with a significant improvement in event-free survival, an effect present at all levels of LDL cholesterol achieved. Our data also demonstrate that the relationship between the reduction in LDL cholesterol and that in CRP varies greatly from patient to patient, regardless of the intensity of lipid-lowering regimen used; this finding is consistent with those of previous studies of subjects without acute ischemia.³⁻⁶ In our study, less than 3 percent of the variation in achieved CRP levels was explained by the variation in achieved LDL cholesterol levels. Thus, these data suggest that strategies that aggressively lower cardiovascular risk by means of statin therapy may need to include monitoring of the levels of inflammation as well as cholesterol.

We believe our data have clinical relevance for

several reasons. First, although the PROVE IT-TIMI 22 study demonstrated the importance of achieving LDL cholesterol levels of less than 70 mg per deciliter after acute coronary syndromes, the current analyses indicate that subsequent event-free survival is also linked to the achievement of CRP levels of less than 2 mg per liter. This concept is supported by observations made by Nissen et al.,⁹ which appear elsewhere in this issue. Nissen et al. used intravascular ultrasonography to show that the magnitude of change in CRP levels and the magnitude of change in LDL cholesterol levels were both independent predictors of plaque regression after statin therapy.⁹ Thus, while confirming the importance of achieving LDL cholesterol levels of less than 70 mg per deciliter in very-high-risk patients, as was recently advocated,¹⁰ our observations regarding the clinical relevance of the CRP levels achieved as a result of statin therapy may also be important for future guidelines designed to address the appropriate use of statin therapy.

Second, we believe our data are of pathophysiological importance, since they provide evidence that reducing inflammation in general and perhaps the levels of CRP in particular may well have a role in altering the atherothrombotic process. To date, a consistent series of prospective epidemiologic studies has demonstrated that CRP levels independently predict the risk of first coronary events at all levels of LDL cholesterol and across a full spectrum of Framingham risk categories¹¹⁻¹⁶ and that CRP levels have prognostic value in patients with acute coronary syndromes.¹⁷⁻²⁰ However, although statin therapy has been shown to lower CRP levels in a manner that is largely independent of LDL cholesterol levels,^{2-6,21,22} evidence linking a greater reduction in CRP levels to reduced rates of vascular events has been lacking. In the current analysis, we found evidence of incremental benefit for those in whom statin therapy resulted in CRP levels of less than 2 mg per liter, whether or not LDL cholesterol levels were also reduced to the target value of less than 70 mg per liter. In this regard, our data are consistent with laboratory work indicating the importance of inflammation as a determinant of plaque instability,²³ as well as experimental data indicating that statins have lipid-lowering and antiinflammatory effects.²⁴ Our data also provide support for ongoing efforts to find agents capable of lowering CRP as a potential method of reducing vascular risk.

Third, our data demonstrating the concomitant importance of both lipid reduction and CRP reduc-

tion provide insight into mechanisms by which more aggressive statin regimens augment the reduction in vascular risk. In our study, patients assigned to receive 80 mg of atorvastatin daily were significantly more likely than those assigned to receive 40 mg of pravastatin daily to have a decrease in the levels of both LDL cholesterol and CRP to the target values, data that are consistent with those in other studies.²⁵ Nonetheless, once target levels were met, we found little evidence of a differential outcome according to the specific statin given, suggesting that achieving the target levels of LDL cholesterol and CRP was more important in determining the outcomes than was the specific choice of agent. The observation that the treatment group was not associated with the outcome after adjustment for the LDL cholesterol and CRP levels achieved provides strong support for the hypothesis that the appropriate use of more aggressive therapy to achieve these targets will reduce risk. Clinical trials testing two doses of the same statin will be needed to evaluate this issue fully.

Given that the participants had recently had a myocardial infarction or had high-risk unstable angina and thus had a clear indication for long-term statin therapy, we believe our findings should not be generalized beyond situations involving secondary prevention. Post hoc analysis of a recent primary-prevention trial suggests that apparently healthy persons who have elevated CRP levels but low lipid levels can benefit from statin therapy.³ However, whether statin therapy should be used for primary prevention among persons with elevated levels of CRP who do not have hyperlipidemia remains highly controversial and is the subject of an ongoing multinational trial.^{26,27}

In summary, these secondary-prevention data demonstrate that the aggressive use of statin therapy to achieve target levels of both LDL cholesterol

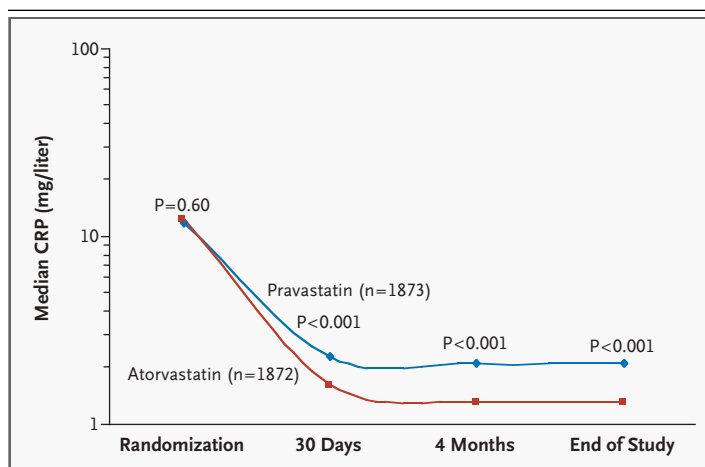


Figure 4. Median Levels of CRP at Randomization, 30 Days, 4 Months, and the End of the Study, According to Whether Patients Received 80 mg of Atorvastatin or 40 mg of Pravastatin Daily.

and CRP decreases the risk of recurrent myocardial infarction or death from coronary causes among patients with acute coronary syndromes. These data also provide strong evidence to support the hypothesis that therapies designed to reduce inflammation after acute coronary ischemia may improve cardiovascular outcomes.

Supported by grants from the Donald W. Reynolds Foundation, the Doris Duke Charitable Foundation, Bristol-Myers Squibb, and Sankyo.

Dr. Ridker reports being a coinventor of approaches related to the use of inflammatory biomarkers in cardiovascular disease for which patents are held by the Brigham and Women's Hospital and having received research support or lecture honoraria from Bristol-Myers Squibb, AstraZeneca, Merck, Pfizer, and Dade Behring. Dr. Pfeffer reports having received research support or lecture honoraria from Bristol-Myers Squibb, Merck, and Pfizer; Dr. Cannon, research support from Bristol-Myers Squibb, Sanofi, and Merck and consulting fees from AstraZeneca and GlaxoSmithKline; Dr. Morrow, research support or lecture honoraria from Dade Behring, Beckman Coulter, Bayer Diagnostics, and Biosite; Dr. Rifai, honoraria from Dade-Behring, Denka Seiken, and Bayer; and Dr. Braunwald, research support from Bristol-Myers Squibb, Merck, and AstraZeneca.

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