Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 36, No. 6, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00950-5

Statin Therapy, Lipid Levels, C-Reactive Protein and the Survival of Patients With Angiographically Severe Coronary Artery Disease

Benjamin D. Horne, MPH, Joseph B. Muhlestein, MD, FACC, John F. Carlquist, PHD, Tami L. Bair, BS, Troy E. Madsen, BA, Noal I. Hart, BS, Jeffrey L. Anderson, MD, FACC

Salt Lake City, Utah

OBJECTIVES The joint predictive value of lipid and C-reactive protein (CRP) levels, as well as a possible interaction between statin therapy and CRP, were evaluated for survival after angiographic diagnosis of coronary artery disease (CAD).

BACKGROUND Hyperlipidemia increases risk of CAD and myocardial infarction. For first myocardial infarction, the combination of lipid and CRP levels may be prognostically more powerful. Although lipid levels are often measured at angiography to guide therapy, their prognostic value is unclear.

METHODS Blood samples were collected from a prospective cohort of 985 patients diagnosed angiographically with severe CAD (stenosis $\geq$ 70%) and tested for total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and CRP levels. Key risk factors, including initiation of statin therapy, were recorded, and subjects were followed for an average of 3.0 years (range: 1.8 to 4.3 years) to assess survival.

RESULTS Mortality was confirmed for 109 subjects (11%). In multiple variable Cox regression, levels of TC, LDL, HDL and the TC:HDL ratio did not predict survival, but statin therapy was protective (adjusted hazard ratio [HR] = 0.49, p = 0.04). C-reactive protein levels, age, left ventricular ejection fraction and diabetes were also independently predictive. Statins primarily benefited subjects with elevated CRP by eliminating the increased mortality across increasing CRP tertiles (statins: HR = 0.97 per tertile, p-trend = 0.94; no statins: HR = 1.8 per tertile, p-trend $<$ 0.0001).

CONCLUSIONS Lipid levels drawn at angiography were not predictive of survival in this population, but initiation of statin therapy was associated with improved survival regardless of the lipid levels. The benefit of statin therapy occurred primarily in patients with elevated CRP. (J Am Coll Cardiol 2000;36:1774–80) © 2000 by the American College of Cardiology

Atherosclerotic cardiovascular disease accounts for nearly half of the deaths in the American population (1). Coronary artery disease (CAD) is responsible for the majority of these deaths. Major established risk factors for the development of CAD include hyperlipidemia, hypertension, smoking, diabetes and a family history of CAD (2,3). Some consider hyperlipidemia to be the most significant modifiable example of these risk factors (4).

Other factors such as inflammation have recently been linked to the risk of CAD. The inflammatory marker C-reactive protein (CRP) has been strongly associated with CAD, coronary ischemia and myocardial infarction (MI) (5–9). Recently, Ridker et al. (10) reported that, taken together, CRP and lipid levels provided a more useful prognostic marker for the assessment of primary CAD risk. This may suggest a connection between hyperlipidemia and inflammation in the pathogenesis of CAD.

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are a class of medications that primarily block mevalonate synthesis, resulting in positive effects on lipid parameters, especially low-density lipoprotein cholesterol (LDL). Clinical trials demonstrate that statins are safe and effective in treating hyperlipidemia and reducing cardiovascular events (11–15). Statins have also been reported to produce nonlipid-lowering benefits, including antithrombotic and anti-inflammatory effects (16,17). However, potential interactions between statin therapy, hyperlipidemia and inflammation in patients with preexisting CAD are unknown.

The purpose of this study was to prospectively evaluate the combined predictive value of lipid and CRP levels on survival among patients with angiographically-defined severe CAD. A second objective was to determine whether statin therapy affected survival for patients with and without elevated CRP.

METHODS

Study population. Between August 15, 1994, and February 28, 1997, 1,707 consecutive patients undergoing coronary arteriography at the LDS Hospital (Salt Lake City,

From the Cardiovascular Department, LDS Hospital and University of Utah, Salt Lake City, Utah. Supported by the LDS Hospital Deseret Foundation, Salt Lake City, Utah.

Manuscript received February 14, 2000; revised manuscript received May 8, 2000, accepted July 11, 2000.

Abbreviations and Acronyms

CAD = coronary artery disease
CI = 95% confidence interval
CRP = C-reactive protein
HDL = high-density lipoprotein
HR = hazard ratio
LDL = low-density lipoprotein
LVEF = left ventricular ejection fraction
MI = myocardial infarction
TC = total cholesterol

Utah) were enrolled in a cardiovascular registry (the Intermountain Heart Study). Patients were of unrestricted age and gender and gave written informed consent for a blood draw at angiography for use in confidential studies approved by the hospital's institutional review board. In general, patients were residents of Utah, southwestern Idaho or southeastern Wyoming, a population that is primarily of British and Northern European descent. Of these, 985 were found to have severe CAD as defined by one or more ≥70% stenosis in ≥1 coronary artery or a primary branch, and these 985 were included in this study.

Follow-up and determination of subject outcomes. Subjects were followed-up until death or until December 1998. They (or family members, in the case of subject death or disability) were interviewed by telephone survey. Deaths were verified through a national Social Security death index. Subjects unavailable by telephone but not listed in the death index were considered to be alive, thus allowing for 100% assessment of survival.

Determination of lipid levels. Lipid panels were evaluated by assay on a Vitros 950 (Johnson & Johnson Clinical Diagnostics, Rochester, New York), which measures total cholesterol (TC), triglyceride and high-density lipoprotein (HDL) levels by enzymatic methods and LDL calculated from these. The TC:HDL ratio was computed by dividing TC by the corresponding HDL level.

Determination of CRP. Testing for CRP was performed using a fluorescence polarization immunoassay (Abbott Diagnostics, Abbott Park, Illinois). Assay validation showed that 95% of healthy individuals had CRP levels <0.5 mg/dl, and 98% had levels <1.0 mg/dl (Abbott Diagnostics, List No. 9550, January 1996). The between-run coefficient of variation of this assay was 4.3% and 2.2% at mean levels of 1.10 mg/dl and 2.94 mg/dl, respectively. For analysis, CRP levels were divided into three tertiles of equal sample size.

Assessment of statin prescription. Prescription of statins at the time of hospital discharge was determined from a hospital-wide clinical database (18). The database query asked for the prescription of any of the following agents: simvastatin, pravastatin, atorvastatin, lovastatin or fluvastatin. Statin use before hospitalization was not known, and long-term compliance with therapy was not determined. Statin prescription status was available for 889 study subjects; the other 96 were excluded from the statin analysis.

Other variables examined. Subject demographics, traditional medical risk factors and clinical variables were evaluated to control for confounding factors. These included age, sex, diabetes mellitus, hypertension, smoking, family history of CAD, presenting diagnosis, clinical interventions, number of diseased coronary vessels, renal failure and left ventricular ejection fraction (LVEF). Diabetes was diagnosed by a history of fasting blood sugar greater than 126 mg/dl or a glycosylated hemoglobin >7.5%. Hypertension was defined as a history of a systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg. Family history was considered positive if a first-order relative had suffered cardiovascular death, MI or coronary revascularization before age 65. Tobacco use was considered present for active smokers or those with a history of >10 pack-years. The clinical presentation at hospitalization included stable angina (stable exertional symptoms only), unstable angina (progressive symptoms or symptoms at rest) or MI (creatine kinase-MB >6 mg/dl and creatine kinase-MB index >3%). Clinical treatment at hospitalization was categorized as medical therapy (only), percutaneous coronary interventions (including balloon angioplasty, atherectomy or stenting) and coronary artery bypass surgery (CABG). Renal failure was regarded as present if serum creatinine was ≥2.0 mg/dl.

Statistical considerations. Survival analysis evaluated the proportional hazards for mortality by Cox regression. The chi-square approximation to the likelihood ratio test was used to examine whether a univariate association with mortality existed for each known or potential risk factor. Subject age, LVEF (generally by contrast ventriculography or by echocardiogram if unavailable) and levels of TC, HDL, LDL and the TC:HDL were entered as continuous variables. C-reactive protein was evaluated as a categorical variable, comparing the third or second tertile to the first.

Multiple variable Cox regression (SPSS, v9.0) was utilized to determine hazard ratios (HR) corrected for possible confounding. The regression model was built by evaluation for significant or near-significant factors ($p < 0.10$) and for factors confounding those associations. Hazard ratios and 95% confidence intervals (CI) are presented along with two-tailed p values, designating a p value of 0.05 as nominally significant.

RESULTS

Patient characteristics. Table 1 summarizes the overall baseline subject characteristics by statin prescription. Those given statins were younger and more frequently treated with revascularization. The distribution of statin use among the study cohort was 63% simvastatin, 15% atorvastatin, 13% pravastatin, 5% lovastatin and 4% fluvastatin.

Overall, the prevalence of standard cardiovascular risk factors was similar to other populations with known CAD. Table 2 provides the average levels of TC, LDL, HDL, the TC:HDL ratio and CRP. Despite that statins are typically

Table 1. Baseline Characteristics of the Study Population Including Percent of Subjects Receiving Prescription of Statins at Hospital Discharge

Risk Factor (n = 889)	Overall (n)	Statins	No Statin	p Value*
Statin therapy	19% (172)	19%	81%	—
Demographics				
Age (mean years ± SD)	65 ± 11	63 ± 10	66 ± 11	0.007
Gender (males)	77% (683)	71%	78%	0.06
Clinical presentation				
Stable angina	44% (393)	45%	44%	NS
Unstable angina	32% (285)	32%	32%	NS
Acute MI	24% (211)	23%	24%	NS
Coronary anatomy				
Single-vessel	35% (309)	29%	36%	0.09
Double-vessel	30% (265)	32%	29%	NS
Triple-vessel	35% (315)	39%	35%	NS
Treatment at index hospitalization				
Medical therapy only	44% (389)	29%	47%	<0.001
PCI	23% (209)	30%	22%	0.06
CABG	33% (291)	41%	30%	0.008
Cardiovascular risk factors				
Diabetes	19% (165)	20%	18%	NS
Family history	33% (291)	36%	32%	NS
Hypertension	53% (468)	53%	53%	NS
LVEF (mean ± SD)	60 ± 16%	60 ± 17%	60 ± 17%	NS
Renal failure	8% (69)	6%	8%	NS
Smoking	28% (249)	25%	29%	NS

*Statin vs. no statin.
CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

prescribed based on TC and LDL, these were similarly distributed in the statins (ranges: TC = 83 to 445 mg/dl; LDL = 26 to 322 mg/dl) and nonstatins groups (ranges: TC = 85 to 324 mg/dl; LDL= 23 to 269 mg/dl). The tertiles of CRP were: 1) <1.2 mg/dl, 2) 1.2 to 1.7 mg/dl and 3) >1.7 mg/dl. During the follow-up period (mean: 3.0 years, range: 1.8 to 4.3 years), death was confirmed for 109 subjects (11%).

Prediction of survival. Univariate Cox analyses revealed no association with survival for levels of TC ($p = 0.19$), LDL ($p = 0.30$), HDL ($p = 0.051$) or TC:HDL ratio ($p = 0.99$). Statin prescription, however, was associated with greatly improved survival (HR = 0.39; CI = [0.20, 0.78], $p = 0.002$) (Fig. 1). Survival for statin-treated subjects was 95% after an average follow-up of 1,100 days, compared with 87% for those without statins. Other univariate predictors of survival included age, LVEF, diabetes and CRP levels (Table 3).

Multiple variable Cox regression was used to adjust the univariate associations of statins and CRP for other significant or confounding factors. Patient age and index treatments were significantly different based on statin prescription status (Table 1), suggesting possible confounding. In bivariate Cox regression, however, index treatment did not confound statins; this was also found in multiple variable analysis controlling for treatment, statins and other significant factors. In contrast, analysis showed that age somewhat reduced the association of statins with survival; however, statins did retain a significant independent effect. Additionally, although interventional treatment, smoking and number of diseased vessels were each significant univariate predictors of survival, those preliminary associations were eliminated in multiple variable analysis by patient age and LVEF. Levels of TC, LDL, HDL and the TC:HDL ratio remained nonsignificant in multiple variable analysis. The final regression model included statin prescription (HR = 0.49, CI = [0.24, 0.97], $p = 0.04$) age, LVEF, CRP and diabetes (Table 4).

Table 2. Baseline Laboratory Values Measured at the Index Angiogram

Risk Factor (Mean ± SD)	Overall	Statin (n = 172)	No Statin (n = 717)	p Value
TC (mg/dl)	181 ± 44	182 ± 50	181 ± 42	NS
LDL (mg/dl)	120 ± 38	117 ± 43	120 ± 37	NS
HDL (mg/dl)	34 ± 14	34 ± 14	33 ± 14	NS
TC:HDL ratio (mg/dl)	6.6 ± 5.4	6.4 ± 5.4	6.6 ± 5.4	NS
CRP (mg/dl)	2.3 ± 2.5	2.2 ± 2.2	2.3 ± 2.6	NS

CRP = C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol.

Statins and CRP. The predictive value of CRP depended on the status of statin therapy (Fig. 2). For patients not prescribed statins, increasing CRP levels were associated with a graded and markedly increased risk of mortality (test of trend: HR = 1.8 per tertile, $p < 0.0001$). In contrast, among the statin group this association was eliminated such that patients had similar survival regardless of CRP level (HR = 0.98 per tertile, $p = 0.97$). These results were unchanged by multiple variable analysis (no statins: HR = 1.8 per tertile, CI = [1.3, 2.3], $p < 0.0001$; statins: HR = 0.97 per tertile, $p = 0.94$).

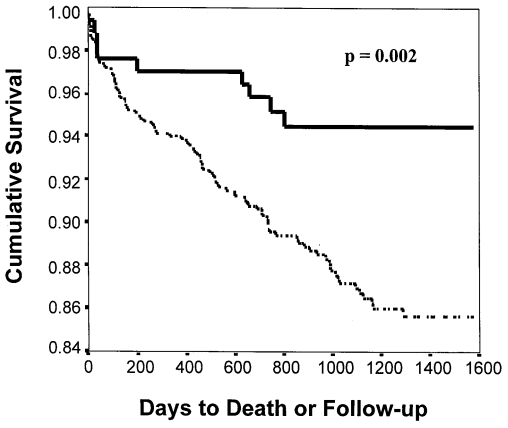

Figure 1. Kaplan-Meier survival curve showing the cumulative survival according to statin prescription. In contrast with the findings of the 4S trial, the curve separation occurred between 30 and 40 days after statin prescription. **Solid line** = statins; **dashed line** = no statins.

These differences in CRP-related survival are also illustrated by comparisons of statin status within individual CRP tertiles although the within-tertile comparisons were not statistically significant. Statins reduced death in the third tertile from 18.5% in the nonstatin group to 4.6% in the statin group (adjusted HR = 0.26, CI = [0.06,1.08], p = 0.06). Statins reduced death in the second tertile from 14.9% to 6.3% (adjusted HR = 0.65, p = 0.42) and in the first tertile from 5.8% to 4.9% (adjusted HR = 1.04, p = 0.96).

DISCUSSION

Summary of study findings. Lipid levels, including levels of TC, LDL, HDL and the TC:HDL ratio, did not predict mortality after angiographic CAD diagnosis in this population. As a result joint analysis of CRP and lipid levels was not prognostically useful for secondary risk assessment although its usefulness has been reported for prediction of first MI (10). The cholesterol-lowering statin agents, however, were found to be associated with reduced mortality. Analysis of statin prescription and levels of the inflammatory marker, CRP, showed that the clinical benefit of statin treatment was contained primarily in those patients with elevated CRP.

Cholesterol levels and cardiovascular risk. Cholesterol level is a major risk factor for the primary development of clinical CAD (2,3) and perhaps the most important among the traditional risk factors (4). Data regarding lipid levels and the prediction of cardiovascular events after the diagnosis of CAD are sparse, but, given the risk associated with lipid levels and the development of CAD, further investigation of the CAD risk after diagnosis is warranted.

Although lipid levels did not predict mortality in this or other secondary prevention studies (19,20), this does not contradict the wealth of data supporting cholesterol as a risk factor for primary development of CAD. Several possible explanations exist. First, our results may suggest that high cholesterol levels do not increase the risk of death once CAD has developed. Death after the establishment of disease may involve different (acute phase) mechanisms that do not depend heavily on processes influenced by lipid

Table 3. Death Rate and Univariate Significance for the Various Risk Factors

Risk Factor	Death Rate	p Value
C-reactive protein		
1st tertile	5%	(reference)
2nd tertile	13%	0.0009
3rd tertile	15%	0.0001
Age		
<75 yrs	7%	<0.0001
≥75 yrs	24%	
Gender		
Female	14%	0.10
Male	10%	
Clinical presentation		
Stable angina	12%	(reference)
Unstable angina	9%	NS
Acute MI	12%	NS
Coronary anatomy		
Single-vessel	7%	(reference)
Double-vessel	11%	0.09
Triple-vessel	16%	0.0004
Treatment at index hospitalization		
Medical therapy only	15%	(reference)
PCI	6%	0.009
CABG	9%	0.002
Diabetes		
No	10%	0.04
Yes	15%	
Family history		
No	12%	NS
Yes	10%	
Hypertension		
No	11%	NS
Yes	11%	
LVEF		
<40%	28%	<0.0001
≥40%	8%	
Renal failure		
No	11%	NS
Yes	15%	
Smoking		
No	12%	0.03
Yes	8%	

CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 4. Final Multiple Variable Cox Regression Model Showing the Independent Protective Effect of Statins

Risk Factor (n = 889)	Hazard Ratio	CI	p Value
Age	1.08 per year	1.05, 1.10	<0.0001
LVEF	0.97 per % increase	0.96, 0.99	<0.0001
CRP	1.6 per tertile	1.3, 2.1	0.0002
Diabetes	1.7	1.1, 2.6	0.02
Statins	0.49	0.24, 0.97	0.04

CI = 95% confidence interval; CRP = C-reactive protein; LVEF = left ventricular ejection fraction.

Lipid levels, including total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, were not predictive of long-term death in this model.

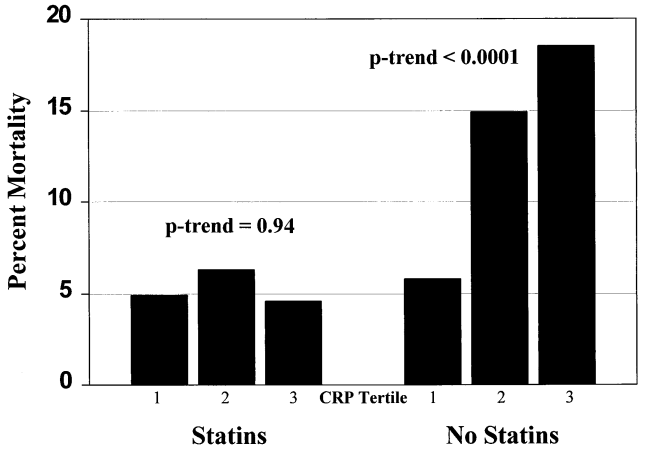

Figure 2. Percent mortality for statin prescription stratified by CRP levels. For patients receiving statins the risk due to increasing CRP was eliminated. In contrast, among those not prescribed statins, a significant trend toward higher mortality existed across increasing CRP tertiles. CRP = C-reactive protein.

levels. Second, once a patient has developed CAD, the lack of association for lipids may indicate that the lipid levels are too high for that particular patient, regardless of whether the absolute lipid levels are above what might be considered a typical at-risk level. If so, lipid-lowering treatment may be warranted. Finally, statins may work through mechanisms unrelated or only indirectly dependent on lowering of plasma lipid levels (i.e., anti-inflammatory effects, lowering of plaque oxidized-LDL, etc.).

Statins and risk. In multiple clinical trials of cholesterol reduction and event prevention using statin agents, lowering of LDL levels has been shown to protect against first MI, subsequent MI and cardiovascular-related mortality. Several studies found that, in patients with known CAD, statin use decreased the risk of subsequent mortality and coronary events (11,12). Other randomized studies of statins found that patients with average or "normal" lipid levels also benefit from statin use (13–15). Additional evidence indicates that statins slow the progression of CAD in addition to reducing coronary events (21,22).

In this study, among patients with a wide range of lipid levels and with angiographic evidence for CAD, statin prescription was protective against future mortality. This finding is consistent with the randomized clinical trials. Such a benefit, even among patients with "normal" lipid levels, may indicate that a percentage reduction in lipid levels should be the goal for patients after diagnosis, not an absolute reduction from "abnormal" to "normal" levels (23,24).

In addition, it has been proposed that statins may produce beneficial effects other than through their direct plasma lipid-lowering capability (16,17). These benefits may include inhibition of vascular smooth muscle cell proliferation (25–27), prevention of thromboembolism (28–30), improvement of endothelial function (27,31–33) and alteration of the immune (inflammatory) response (16,34). Reduction in plaque oxidized LDL may also be a mechanism of benefit and may be poorly reflected by circulating lipid levels. These proposals are supported by the positive benefit of statins that was found in our study, and this benefit appears regardless of baseline lipid levels.

Interestingly, and in contrast with the findings of the 4S trial (11), the separation in the survival curve began quickly —between 30 and 40 days after initiation of statin therapy. This finding requires further evaluation.

Statins and CRP. Plasma CRP, a nonspecific marker of inflammation, has received much attention as a predictor of risk. Ridker et al. (5) showed it to predict cardiovascular events in a prospective study of presumably healthy physicians. We have found CRP to be associated with CAD and a history of MI and also with mortality after CAD diagnosis in large, angiographically-defined populations (9,35). Ridker et al. (19) have reported results from a retrospective substudy of the CARE trial that are consistent with the findings of our present study. In the CARE trial, patients with elevated CRP at baseline who were randomized to pravastatin experienced a greater reduction in MI or mortality compared with placebo than did those with nonelevated baseline CRP levels.

Our larger, prospective observational study of patients who were angiographically diagnosed with severe CAD confirms the results of the CARE study. Together, they indicate that statins are more beneficial for patients with elevated CRP than in those whose CRP is normal at baseline. Moreover, the reduction in cardiovascular risk due to statins for patients with high CRP may be the result of an actual lowering of CRP levels (30,36,37).

Study strengths and limitations. This study was a prospective, but observational, evaluation of mortality. The failure to randomize to statins or to use a single statin agent limited the ability of the study to discern between possible differences in the effects of the various statin agents. In addition, the actual statin doses and the patient compliance with therapy were not known. However, inadequate dosing and noncompliance would bias the outcome in favor of the null hypothesis. The benefits found in this study, which are attributed to statins, could be confounded by, or due in part to, selection biases associated with statin use. However, potential confounders were adjusted for by multiple variable Cox regression, including baseline lipid levels and clinical treatment, and the effect of statins remained independently significant.

The use of statins before hospitalization was also not known. This may have produced a bias toward greater significance for statin therapy by predisposing the statin group to a relatively lesser severity of disease. Because statin prescription has not been based on CRP levels in the past, however, the association of CRP and statins to mortality may not be affected.

Baseline CRP levels might have been influenced by myocardial injury (due to MI). However, the presenting clinical status was controlled in the multiple variable analysis

and did not alter the overall association of CRP to mortality. Additionally, CRP has been measured by various methods in the literature. We analyzed CRP by tertiles instead of an actual concentration, and, thus, the results are unlikely to relate to the specific CRP measurement method.

The unrandomized, observational nature of this study may be considered to be a strength. This study utilized a design that better approximates real-world actual use in which drug assignment is not randomized, compliance with therapy is not tracked, and patients are not excluded from therapy due to solely study-based criteria. Each of these points increases the generalizability of this study's results to the overall CAD patient population. At the same time, though, the results also confirm a similar study completed among a randomized study population.

Conclusions. This study suggests four possible conclusions: 1) although lipid levels are useful in primary prevention, they are not predictive of death when drawn at the time of angiographic CAD diagnosis; 2) prescription of statins for patients who have a broad range of lipid levels and are newly diagnosed with CAD is associated with a reduction in mortality; 3) CRP is a strong predictor of mortality in patients with CAD, as previously described; and 4) statin therapy is particularly beneficial in patients with angiographically-severe CAD whose CRP level is relatively elevated and, thus, statins may exert an anti-inflammatory effect on atherosclerosis.

Reprint requests and correspondence: Dr. J. Brent Muhlestein, Department of Cardiology Research, LDS Hospital, 8th Avenue & C Street, Salt Lake City, Utah 84143. E-mail: ldbmuhle@ihc.com.

REFERENCES

1. National Heart, Lung and Blood Institute Fact Book: fiscal Year 1995. Bethesda, Maryland: US Department of Health and Human Services Monograph. March, 1996:30–52.
2. Farmer JA, Gotto AM, Jr. Dyslipidemia and other risk factors for coronary artery disease. In: Braunwald E, editor. Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia: WB Saunders, 1997:1126–60.
3. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992;152:56–64.
4. LaRosa JC, Hunninghake D, Bush D, et al. The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung and Blood Institute. Commissioned by the Task Force on Cholesterol Issues, American Heart Association. Circulation 1990;81:1721–33.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1996;336:973–9.
6. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C-reactive protein and its relation to cardiovascular risk factors: a population-based cross-sectional study. Br Med J 1996;312:1061–5.
7. Maseri A. Inflammation, atherosclerosis and ischemic events—exploring the hidden side of the moon. N Engl J Med 1997;336:1014–6.
8. Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB, for the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 1997;349:462–6.
9. Anderson JL, Carlquist JF, Muhlestein JB, Horne BD, Elmer SP. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. J Am Coll Cardiol 1998;32:35–41.
10. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining the risk of first myocardial infarction. Circulation 1998;97:2007–11.
11. The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
12. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
13. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
14. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
15. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS—Air Force/Texas Coronary Atherosclerosis Prevention Study. J Am Med Assoc 1998;279:1615–22.
16. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. Lancet 1996;348:1079–82.
17. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins. Implications for cardiovascular event reduction. J Am Med Assoc 1998;279:1643–50.
18. Evans RS. The HELP system: a review of clinical applications in infectious diseases and antibiotic use. MD Comput 1991;8:282–8.
19. Ridker PM, Rifai N, Pfeffer MA, et al. for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998;98:839–44.
20. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 1997;337:230–6.
21. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Interventional trial. Circulation 1994;89:959–68.
22. Jukema JW, Bruschke AVG, van Boven JA, et al. Coronary artery disease/myocardial infarction: effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). Circulation 1995;91:2528–40.
23. Pedersen TR, Olsson AG, Faergeman O, et al. for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453–60.
24. Thompson GR, Hollyer J, Waters DD. Percentage change rather than plasma level of LDL-cholesterol determines therapeutic response in coronary heart disease. Curr Opin Lipidol 1995;6:386–8.
25. Corsini A, Pazzucconi F, Pfister P, Paoletti R, Sirtori CR. Inhibitor of proliferation of arterial smooth muscle cells by fluvastatin. Lancet 1996;348:1584.
26. Bellosta S, Bernini F, Ferri N, et al. Direct vascular effects of HMG-CoA reductase inhibitors. Atherosclerosis 1998;137 Suppl: S101–9.
27. Sato I, Ma L, Ikeda M, Morita I, Murota S. Simvastatin, a potent HMG-CoA reductase inhibitor, inhibits the proliferation of human

and bovine endothelial cells in vitro. J Atheroscler Thromb 1998;4: 102–6.
28. Lacoste L, Lam JYT, Hung J, Letchacovski G, Solymoss CB, Waters D. Hyperlipidemia and coronary disease: correction of the increased thrombogenic potential with cholesterol reduction. Circulation 1995; 92:3172–7.
29. Tsuda Y, Satoh K, Kitadai M, Takahashi T, Izumi Y, Hosomi N. Effects of pravastatin sodium and simvastatin on plasma fibrinogen level and blood rheology in type II hyperlipoproteinemia. Atherosclerosis 1996;112:225–33.
30. Dangas G, Badimon JJ, Smith DA, et al. Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. J Am Coll Cardiol 1999;33:1294–304.
31. Egashira K, Hirooka Y, Kai H, et al. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with coronary artery disease. Circulation 1994;89: 2519–24.
32. Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995;332:481–7.
33. Anderson TJ, Meridith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995; 332:488–93.
34. Kurakata S, Kada M, Shimada Y, Komai T, Komoto K. Effects of different inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, pravastatin sodium and simvastatin on sterol synthesis and immunological functions in human lymphocytes in vitro. Immunopharmacology 1996;34:51–61.
35. Muhlestein JB, Horne BD, Carlquist JF, et al. C-reactive protein and cytomegalovirus antibody levels predict mortality in patients with angiographically defined coronary artery disease (abstr). J Am Coll Cardiol 1999;33 Suppl A:317A.
36. Strandberg TE, Vanhanen H, Tikkanen MJ. Effect of statins on C-reactive protein in patients with coronary artery disease. Lancet 1999;353:118–9.
37. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999;100:230–5.