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C-Reactive Protein and Angiographic Coronary Artery Disease: Independent and Additive Predictors of Risk in Subjects With Angina

James S. Zebrack, MD,* Joseph B. Muhlestein, MD, FACC,*† Benjamin D. Horne, MPH,† Jeffrey L. Anderson, MD, FACC,* for the Intermountain Heart Collaboration Study Group
Salt Lake City, Utah

OBJECTIVES The objective of this study was to determine the prognostic value of C-reactive protein (CRP) independent of coronary angiographic findings.

BACKGROUND High sensitivity CRP, a marker of inflammation, predicts risk of cardiovascular events. However, it is uncertain whether it remains predictive once angiographic findings are considered.

METHODS A total of 2,554 patients with angina but without acute myocardial infarction (MI) were studied angiographically; 1,848 patients had coronary artery disease (CAD) and 706 patients did not. Coronary artery disease was quantified in five ways and combined for a CAD score. C-reactive protein was measured and patients were followed for up to five years for death or MI.

RESULTS C-reactive protein correlated with the extent of CAD, but correlation coefficients were low (0.02 to 0.08). Of angiographic measures, the CAD score best predicted future events (hazard ratio [HR] = 1.8 [1.2 to 2.6], p = 0.004, for CAD score >4). C-reactive protein ≥1.0 mg/dl was predictive in both patients without CAD (HR = 2.3 [0.9 to 5.5], p = 0.07) and with CAD (HR = 2.1 [1.5 to 3.1], p = 0.0001). Multivariate adjustment resulted in little change in HR. C-reactive protein retained predictive value within each quintile of CAD score. C-reactive protein and CAD independently and additively contributed to the risk prediction: low CRP and lowest CAD score was associated with lowest risk, and high CRP and highest CAD score was associated with the highest risk, with a 10-fold difference between extremes (2.5% vs. 24%).

CONCLUSIONS C-reactive protein correlates with extent of CAD, but the degree of correlation is low. Severity/extent of CAD and CRP are independent and additive predictors of risk. Therapy should target CRP-associated risk as well as angiographically evident stenosis. (J Am Coll Cardiol 2002;39:632–7) © 2002 by the American College of Cardiology

High sensitivity C-reactive protein (CRP), a marker of systemic inflammation, has been evaluated as a risk predictor in subjects without known coronary artery disease (CAD) (1,2), in those at risk of CAD (3,4) and in patients with stable angina (5), unstable angina (6–11) or acute myocardial infarction (MI) (12). Even small elevations of CRP, within or just beyond the "normal" range (determined by high sensitivity CRP assay) have been found to strongly predict future cardiovascular events in almost all studies. However, these studies have not adjusted for plaque burden as assessed by coronary angiography (1–11). When adjustments for CAD have been made, they generally have been limited to adjustment for one-, two- or three-vessel disease (12). In our own prior report, we limited analysis to those with angiographically severe CAD (13). In primary risk studies, angiographic information to allow for any adjustment is generally unavailable. Thus, it is possible that elevated CRP may simply be a surrogate of atherosclerosis burden. Some previous studies have shown a correlation between CRP and the presence of atherosclerosis (14), whereas others have not found a correlation (15). C-reactive protein might lose much if not all of its predictive value in both secondary and primary risk settings after adjustment for quantitative angiographic measures of CAD. On the other hand, CRP might add independently to measures of CAD extent and severity.

From the *Division of Cardiology, University of Utah School of Medicine and the †Cardiovascular Department, LDS Hospital, Salt Lake City, Utah. Supported in part by grants from the Deseret Foundation and the National Institutes of Health (NIH, 5 T32 HL-7576).

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METHODS

Study objectives. Our principal study objectives were to determine: 1) whether CRP correlates with the extent of CAD as assessed by various angiographic findings; 2) whether CRP remains an independent predictor of death or MI after adjustment for various angiographic findings; 3) whether the predictive value of CRP differs among subjects with a normal angiogram and those with mild, moderate or extensive CAD; and 4) the risk of death or MI among subgroups of CRP and CAD severity.

Patients and follow-up. The study sample included consecutive consenting patients undergoing coronary angiogra-

Abbreviations and Acronyms

ACE = angiontensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
CRP = C-reactive protein
HR = hazard ratio
MI = myocardial infarction

phy at a single hospital between 1994 and 1997 for evaluation of symptoms suggestive of stable or unstable angina. Patients with acute MI (whose CRP levels are affected by an acute-phase reaction) were excluded. Creatine kinase-MB, if drawn before angiography, was uniformly normal. This series was enrolled before widespread testing with troponin assays. Most subjects were residents of Utah, southwestern Idaho or southeastern Wyoming, a population genetically representative of U.S. Caucasians (16). The study was approved by the hospital's institutional review board.

Clinical events during follow-up were determined through telephone calls and hospital records, with supplemental information from a national death registry enabling 100% determination of vital status.

Determination of CAD severity. All angiograms were reviewed by an attending cardiologist blind to CRP level and future outcome, and each lesion was visually estimated for percent diameter stenosis rounded to the nearest 10%. The presence of a mild/moderate (10% to 60%) or a severe lesion (70% to 100%) in the left anterior descending, the circumflex or the right coronary artery defined the vessel as a mild/moderately or severely affected vessel (or both).

The extent of CAD was quantified in six ways: 1) the number of distinct lesions with 10% to 60% stenosis (range 0 to 18); 2) the number of distinct lesions with ≥70% stenosis (range 0 to 15); 3) the total number of lesions (range 0 to 22); 4) the number of vessels with 10% to 60% stenosis (range 0 to 3); 5) the number of vessels with ≥70% stenosis (range 0 to 3); and 6) a CAD score (the total number of lesions plus the number of vessels with at least one severe lesion plus the number of vessels with at least one moderate lesion [range 0 to 28]). We chose a priori to evaluate each measured angiographic finding individually and cumulatively in a CAD score and determine the strongest CAD predictor of future events.

Determination of CRP. C-reactive protein was quantified by a fluorescence polarization immunoassay (Abbott Diagnostics, Abbott Park, Illinois). All plasma was analyzed by the high sensitivity (0.05 mg/dl threshold) protocol, with a range of results of <0.05 to >6.5 mg/dl. All samples with a CRP exceeding 6.5 mg/dl were reanalyzed by a lower sensitivity (>1.5 mg/dl) protocol, with a range of results of up to 26 mg/dl. The test is standardized to the International Federation of Clinical Chemistry International Reference Preparation for Plasma Proteins. The within-run coefficient of variation for a 1.78-mg/dl standard is 3.7%. Between-run coefficients of variation are 3.9% for a 0.74-mg/dl standard and 3.0% for a 9.08-mg/dl standard.

We chose a priori to define an elevated CRP as ≥1.0 mg/dl, a commonly used cutpoint to define high risk in the literature and our previous studies in CAD populations; this level exceeds the 98th percentile for clinically normal individuals (Abbott Laboratories). We also chose to define a highly elevated CRP level as ≥2.0 mg/dl, approximately the top CRP quintile.

Statistical considerations. Baseline demographic and laboratory information is presented as mean (standard deviation) for continuous variables and frequencies for discrete variables. Comparisons among groups used analysis of variance for continuous variables and chi-square testing for discrete variables. Survival statistics were used for risk determinations. The primary outcome variable was the combination of death (all-cause) and nonfatal MI. Only the first event was counted as an end point. Secondary outcome variables were nonfatal MI alone. Cox regression analysis was used for assessment of the relative hazard of these events over time. Both univariate and multivariate analyses were performed using SPSS for Windows, version 9.0.1 (SPSS Inc., Chicago, Illinois). Cox multivariate adjustments of hazard ratios used a forced-entry approach, and multivariate modeling used a backward conditional stepwise regression approach.

Traditional risk factors used in multivariable analyses included age, gender, diabetes, smoking history (current or >10 pack years), family history of CAD, diagnosis of hypertension, diagnosis of hyperlipidemia and type of treatment after angiography (medical, angioplasty or surgery). Complete data on these risk factors were available in 2,487 of the subjects. Baseline demographic information on lipid levels, ejection fraction and blood pressure were available in 965, 2,152 and 2,472 subjects, respectively.

RESULTS

Subject population and demographics. A total of 2,554 subjects were enrolled who had angiographic and baseline demographic information and a baseline CRP level. Subjects were followed to up to five years (mean 2.1 ± 1.2 years). Patients presenting with symptoms consistent with stable angina comprised 65% of the study cohort; an unstable angina presentation made up the other 35%. Among the entire group, angioplasty was performed in 9%, bypass surgery in 19% and medical therapy only was given to 72%. Discharge rates of medications were 55% for aspirin, 35% for angiotensin-converting enzyme (ACE) inhibitors, 16% for beta-blockers and 12% for statins.

Baseline demographics are presented by CAD category in Table 1. Subjects were divided into "quintiles" that included those with a normal angiogram (n = 706) and those in CAD score quartiles representing mild (n = 424, score 1 to 4), moderate (n = 537, score 5 to 8), moderately severe (n = 439, score 9 to 11) and severe CAD (n = 448, score

Table 1. Baseline Demographics

CAD score	0 (n = 706)	1 to 4 (n = 424)	5 to 8 (n = 537)	9 to 11 (n = 439)	12 to 28 (n = 448)	p Value for Trend
Age, years	59	63	65	67	67	< 0.001
Men	50%	63%	72%	79%	81%	< 0.001
Hypertension	45%	51%	56%	59%	63%	< 0.001
Hyperlipidemia	28%	43%	52%	56%	65%	< 0.001
Diabetes	10%	12%	14%	19%	23%	< 0.001
Family history of CAD	29%	30%	33%	35%	35%	0.007
Tobacco use (current or <10 pack-years)	17%	23%	24%	24%	21%	0.018
Ejection fraction	65%	66%	62%	61%	59%	< 0.001
Blood pressure, mm Hg	142/80	145/80	146/81	147/79	147/79	0.009/NS
Cholesterol/HDL, mg/dl	176/38	183/34	180/33	184/34	180/32	NS/0.004
CRP, median, mg/dl	1.15	1.18	1.21	1.23	1.28	< 0.001
Days of follow-up, mean	705	756	764	789	736	NS
Death or nonfatal MI	5.0%	7.3%	9.5%	16.2%	18.3%	< 0.001

CAD = coronary artery disease; CRP = C-reactive protein; HDL = high-density lipoprotein; MI = myocardial infarction; NS = nonsignificant, p > 0.05.

≥12). As the severity of CAD increased, each traditional risk factor increased in prevalence or severity ($p < 0.05$ for all except diastolic blood pressure and total cholesterol). Median CRP values were higher in patients with CAD than without CAD (1.15 vs. 1.23 mg/dl, $p < 0.001$), and CRP increased with increasing CAD severity ($p < 0.001$, Table 1).

Correlations of CRP with CAD severity/extent. C-reactive protein correlated with the severity/extent of CAD for the entire cohort by all measures of CAD ($p < 0.008$) except for the number of moderate lesions; however, correlation coefficients were very low (0.02 to 0.08) (Table 2). Among all measures of CAD, the strongest correlation with CRP was with the CAD score, which was used in further analyses.

Predictive value of CAD score. In the CAD group, there were 248 events of death or nonfatal MI during follow-up, with 221 of these counting as the first event. The CAD score predicted future events with a hazard ratio (HR) of 1.08 per unit increase in score (95% confidence interval [CI] 1.04 to 1.11, $p < 0.0001$) or a HR of 1.8 (CI 1.2 to 2.6, $p = 0.004$) for a CAD score >4 (vs. ≤4). After adjustment for CRP, the HR was unchanged. After adjustment for CRP and traditional risk factors, the CAD HR also was undiminished: 1.09 per unit increase in score (CI 1.05 to 1.13, $p < 0.0001$) or 1.8 (1.2 to 2.6, $p = 0.005$) for a CAD score >4.

Table 2. Correlation Coefficients for CRP and Angiographic Measures of CAD

Angiographic Marker	All Subjects (n = 2,598)		CAD Present (n = 1,904)	
	Pearson's	p Value	Pearson's	p Value
# of moderate lesions	0.02	0.25	0.02	0.46
# of severe lesions	0.05	0.007	0.06	0.12
# of total lesions	0.05	0.008	0.06	0.01
# of moderate vessels	0.07	<0.001	0.06	0.012
# of severe vessels	0.08	<0.001	0.06	0.013
CAD score	0.08	<0.001	0.06	0.006

Severe lesion is defined as ≥70% stenosis; moderate lesion is defined as 10%–60% stenosis; severe vessel is a coronary artery with at least one severe lesion (maximum 3); moderate vessel is a coronary artery with at least one moderate lesion (maximum 3). CAD score is defined as the # of total lesions plus # of severe and moderate vessels (range 0 to 28).
CAD = coronary artery disease; CRP = C-reactive protein.

Predictive value of CRP for future events. In the overall study group, CRP ≥1.0 mg/dl predicted subsequent death/MI with an unadjusted HR of 2.3 (CI 1.6 to 3.2, $p < 0.0001$). In the large CAD subgroup (n = 1,848), CRP ≥1.0 mg/dl predicted events with an unadjusted HR of 2.1 (CI 1.5 to 3.1, $p = 0.0001$). Adjustment for CAD severity and traditional risk factors resulted in little change in the predictive value of CRP (Table 3), with a fully adjusted HR of 1.9 (CI 1.3 to 2.8, $p < 0.002$). In the subgroup of patients with normal angiograms (n = 706), there were 32 events of death or MI during follow-up, with 27 counting as a first event. C-reactive protein ≥1.0 mg/dl predicted an increased relative hazard for death or MI similar to that found in the CAD group (HR = 2.3 [CI 0.9 to 5.5], $p = 0.07$).

Joint predictive value of CRP and CAD score for death or MI. The entire group also was evaluated for the absolute risk of death or MI among quintiles of CAD score and low (<1.0 mg/dl; 28% of patients with CAD), moderate (1.0 to 2.0 mg/dl; 55%) or high (>2.0 mg/dl; 17%) levels of CRP. Increasing CRP and increasing CAD independently and additively contributed to the risk prediction for death or MI such that a low CRP and the lowest CAD score was associated with the lowest risk, and high CRP and the highest CAD score was associated with the highest risk (Fig. 1). A 10-fold difference was observed between these extremes (2.5% vs. 24% risk). Importantly, CRP retained its predictive value within each subgroup of CAD score, and CAD score retained its predictive value within each subgroup of CRP. Indeed, the absolute risk for death or MI among patients with lowest CAD scores and highest CRP levels was nominally greater than the risk for patients with highest CAD scores and lowest CRP levels. This occurred despite higher levels of standard risk factors in the group with more extensive CAD (Table 1).

Table 3. Hazard Ratio of Elevated CRP for Death or Nonfatal Myocardial Infarction Among Subjects With Angiographic Adjusted for Various Angiographic Markers* on Disease Severity

Adjusted for	Hazard Ratio for CRP >1.0 mg/dl	95% CI	p Value	n
Unadjusted	2.1	1.5–3.1	0.0001	1,904
# of moderate lesions	2.1	1.5–3.1	0.0001	
# of moderate vessels	2.0	1.4–3.0	0.0002	
# of severe lesions	2.0	1.4–2.9	0.0002	
# of severe vessels	2.0	1.4–2.9	0.0003	
# of total lesions	1.9	1.3–2.8	0.0007	
CAD score†	1.9	1.3–2.8	0.0009	
CAD score and traditional risk factors‡	1.9	1.3–2.8	0.0018	1,772

*Severe lesion is defined as ≥70% stenosis; moderate lesion is defined as 10%–60% stenosis; severe vessel is a coronary artery with at least one severe lesion (maximum 3); moderate vessel is a coronary artery with at least one moderate lesion (maximum 3). †Score defined as the # of total lesions plus # of severe and moderate vessels (range 0–28). ‡Traditional risk factors include age, gender, hypertension, diabetes, hyperlipidemia, family history, smoking history and treatment modality after angiography (medical, angioplasty or surgery).

CAD = coronary artery disease; CI = confidence interval; CRP = C-reactive protein.

CRP, CAD score and risk of MI. The risk of MI alone (n = 100) also increased with increasing CRP levels and with increasing CAD score. The absolute incidence of MI among patients with a normal angiogram was only 0.4% with CRP <1.0 mg/dl and 0.3% for CRP 1.0 to 2.0 mg/dl, but it was 4.0% for CRP >2 mg/dl (p = 0.0003). The incidence of MI also increased with higher CRP group (from 1.6% to 4% to 7.1%, respectively) among those with mild CAD (score 1 to 4). Among those with moderate CAD (score 5 to 8), the incidence of MI also increased with increasing CRP category (from 1.4% to 4.4% to 5.1%, respectively). Similarly among those with moderately severe CAD (score 9 to 11), the incidence of MI increased with increasing CRP category (from 5.9% to 4.7% to 9.2%, respectively). Finally, among patients with extensive CAD (score 12 to 28), rates of MI were 6.4%, 5.8% and 7.4%, respectively, by CRP category.

DISCUSSION

Study summary and perspective. In this study, we have shown that although CRP significantly correlates with the extent of vascular disease, the degree of association is small and the independent contribution of CRP to risk assessment remains very large. Because CRP is weakly correlated with angiographic plaque burden, it appears that CRP is stimulated not only by the extent of atherosclerosis but, importantly, by other factors. We postulate that CRP is a measure of inflamed, unstable atherosclerotic plaque (both angiographically visible and occult), whereas angiography indicates the extent of visible stable and unstable occlusive

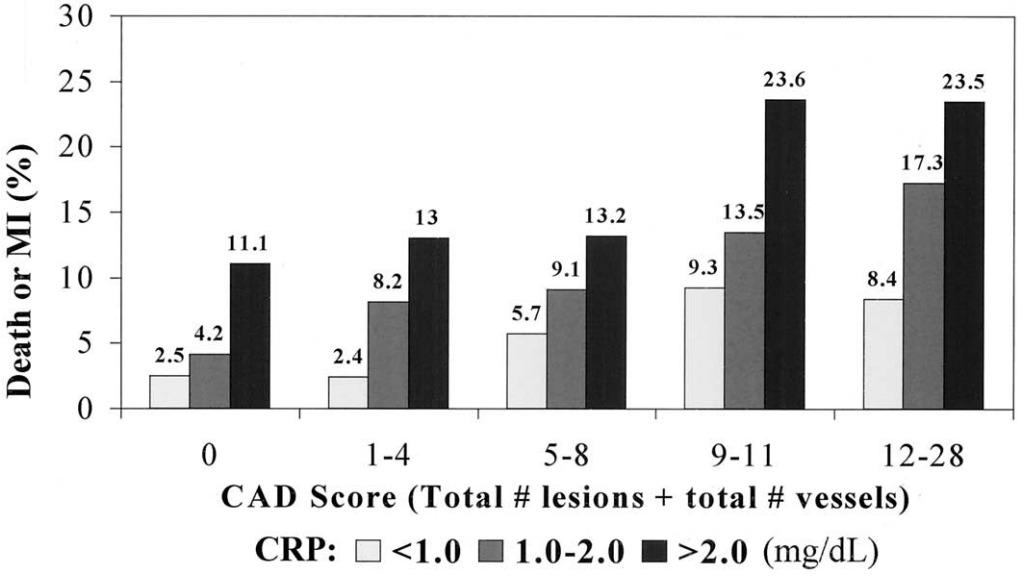

Figure 1. Cumulative incidence of all-cause mortality or myocardial infarction (MI) during follow-up by coronary artery disease (CAD) score and C-reactive protein (CRP). Among 2,554 patients presenting with stable or unstable angina, the extent of CAD was defined as a CAD score (total number of lesions + total number of moderate and severe coronary vessels). A CAD score of 0 equals a normal angiogram. Subjects with a positive score were divided into quartiles. C-reactive protein was defined as low (<1 mg/dl, 28% of patients), moderately elevated (1.0 to 2.0 mg/dl, 55% of patients) or highly elevated (>2 mg/dl, 17% of patients). The percent of each group with death or MI during follow-up is noted on each column.

plaque. C-reactive protein also may reflect systemic but nonvascular chronic inflammatory and infectious processes that impact risk of acute coronary events by influencing levels of circulating proinflammatory and prothrombotic factors.

Whatever the explanation, our study clearly shows that CRP and angiographic CAD are largely independent factors in determining risk. The value of CRP in predicting future death or MI is apparent in all ranges of CAD severity. Those with extensive CAD are at relatively high risk of death or MI regardless of CRP levels. However, in the presence of a low to moderate risk angiogram (or even a normal angiogram), CRP becomes particularly useful in distinguishing patients at substantially lower versus higher risk for death or MI. A particularly high risk is observed in subjects with lower CAD scores but highly elevated CRP despite a lower prevalence of all traditional risk factors in these patients with low/moderate CAD scores (i.e., lower cholesterol levels, absence of diabetes, hypertension, etc.). Because these patients may be considered to have "insignificant CAD" and hence to be at low risk for MI, less aggressive medical therapy may be offered to them in comparison to patients with more extensive CAD.

Historical perspective. Several trials have evaluated the predictive value of CRP for cardiovascular risk. However, much remains to be learned to explain CRP's association with risk. Levels of CRP that define increased risk vary depending on the population studied. The degree of elevation of CRP that identifies increased risk has not been clearly determined, and the clinical utility of CRP after adjustment for angiographic findings has been uncertain. C-reactive protein previously has been proposed to correlate with the extent of atherosclerosis (14). Studies have shown that lower profile plaques are more numerous than "significant stenoses" and, therefore, are statistically more likely to lead to plaque rupture than the relatively few lesions of >70% stenosis (17). Thus, it is possible that an elevated CRP simply represents a more diffuse process of coronary atherosclerosis with a higher total plaque burden. If so, the predictive value of CRP would be considerably less after adjustment for extent of disease (total number of lesions) assessed by coronary angiography. To exclude this possibility, the predictive value of CRP must be adjusted for measures of all visible atherosclerotic plaques on angiography. On the other hand, if CRP levels primarily represent plaque properties (i.e., inflammation, instability), knowledge of CRP levels would continue to be useful even in the presence of angiographic assessment of plaque burden (extent/severity). Similarly, CRP and coronary calcium score (assessed by ultrafast computed tomography) may have independent and additive prognostic value, but this has not been extensively evaluated.

Therapeutic implications. Previous studies have shown that aspirin (1) and statin therapy (18,19) are more effective in subjects with elevated CRP. Other therapies that reduce risk of MI or cardiovascular death (i.e., ACE inhibitors, beta-blockers, diet, exercise, etc.) also may be especially beneficial and cost-effective in these patients at higher than expected risk for cardiovascular events and deserve further evaluation. Thus, CRP may be useful both in determining risk category and in guiding therapy, not only in those without angiographic evaluation but even in the presence of quantitative assessments of anatomic CAD. In our patients, the rates of discharge medications in those with more severe disease were greater than in those with no or moderate disease. However, prescription rates remain suboptimal even when patients without CAD were excluded from analysis. Similarly, in recent national reports, discharge prescriptions for aspirin, statins, beta-blockers and ACE inhibitors remain suboptimal (20,21). Elevation of CRP may give physicians additional information prompting the use of optimal medical therapies. In our experience, discharge of patients undergoing angiographic assessment on a statin was associated with improved long-term compliance and reduced mortality (18,22).

Study limitations. The limitations of this study are those inherent to all prospective but nonrandomized registries. Quantification of coronary angiographic findings was limited to the visual interpretation of the attending cardiologist, which is representative of "real-world" practice. Intravascular ultrasound could be expected to give increased measures of atherosclerotic burden by identifying "intramural plaques," although this would be impractical to apply routinely. However, whether intravascular ultrasound assessments would adversely impact predictive value of CRP is unclear. The cause of death was available in fewer than half of cases, so our analyses relied on total rather than cause-specific (cardiovascular) death. However, among patients in whom cause of death could be determined, 75% were cardiovascular, and trends seen in overall event rates also were found for documented cardiovascular events alone (not shown). Use of total mortality also would tend to underestimate the predictive value of CRP for cardiovascular events. The use of medical therapy for CAD likely is more extensive in patients with more advanced angiographic CAD. If so, CRP has utility in identifying patients with less extensive CAD who are at equally high risk and who may also benefit from aggressive medical therapy. Only patients with clinical presentations suggesting stable or unstable angina who underwent angiography were included in our study. However, the vast majority of patients undergoing angiography today do so for evaluation of suspected angina. Many of these patients (about 20%) have normal angiograms. It often is difficult to determine which of these patients have true angina related to occult microvascular disease or endothelial dysfunction and which truly have noncardiac chest discomfort. C-reactive protein thus appears to be useful in evaluating risk in patients without visible CAD, although the beneficial effects of more aggressive medical therapy in these patients (18,22) should be further evaluated.

Conclusions. In a large prospectively and angiographically studied population, CRP correlated significantly with sev-

eral measures of the extent and severity of CAD, but the degree of correlation was low, suggesting that other factors are more important in determining CRP levels. When studied jointly, the extent of CAD and CRP levels retain independent predictive value for death or MI, and adjustment in multivariate analysis does not significantly alter the predictive value of either CRP or CAD score.

We postulate that CRP identifies primarily properties of plaque (i.e. inflammation, instability), whereas CAD score identifies extent of atherosclerotic plaque. Perhaps surprisingly, these two measures of atherosclerotic disease are largely independent of each other and confer additive risk. Patients presenting with chest pain who have a low or intermediate risk angiogram and high CRP levels (>1.0 to 2.0 mg/dl) are at relatively high risk and may warrant particularly aggressive risk factor reduction, medical therapy and close follow-up.

Reprint requests and correspondence: Dr. Jeffrey L. Anderson, Division of Cardiology, University of Utah School of Medicine, 50 North Medical Drive, 4A154, Salt Lake City, Utah 84132. E-mail: jeff.anderson@hsc.utah.edu.

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