Clinical Investigation and Reports

C-Reactive Protein Adds to the Predictive Value of Total and HDL Cholesterol in Determining Risk of First Myocardial Infarction

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Background—C-reactive protein (CRP) is a sensitive marker of inflammation, and elevated levels have been associated with future risk of myocardial infarction (MI). However, whether measurement of CRP adds to the predictive value of total cholesterol (TC) and HDL cholesterol (HDL-C) in determining risk is uncertain.

Methods and Results—Among 14 916 apparently healthy men participating in the Physicians' Health Study, baseline levels of CRP, TC, and HDL-C were measured among 245 study subjects who subsequently developed a first MI (cases) and among 372 subjects who remained free of cardiovascular disease during an average follow-up period of 9 years (controls). In univariate analyses, high baseline levels of CRP, TC, and TC:HDL-C ratio were each associated with significantly increased risks of future MI (all *P* values <0.001). In multivariate analyses, models incorporating CRP and lipid parameters provided a significantly better method to predict risk than did models using lipids alone (all likelihood ratio test *P* values <0.003). For example, relative risks of future MI among those with high levels of both CRP and TC (RR=5.0, *P*=0.0001) were greater than the product of the individual risks associated with isolated elevations of either CRP (RR=1.5) or TC (RR=2.3). In stratified analyses, baseline CRP level was predictive of risk for those with low as well as high levels of TC and the TC:HDL-C ratio. These findings were virtually identical in analyses limited to nonsmokers and after control for other cardiovascular risk factors.

Conclusions—In prospective data from a large cohort of apparently healthy men, baseline CRP level added to the predictive value of lipid parameters in determining risk of first MI. (***Circulation***. 1998;97:2007-2011.)

Key Words: myocardial infarction ■ epidemiology ■ C-reactive protein ■ risk factors ■ cholesterol

C-reactive protein is a sensitive marker of systemic inflammation, and prospective data from a population of apparently healthy men indicate that baseline levels predict risk of first MI.[1] Specifically, among men free of prior cardiovascular disease participating in the Physicians' Health Study, we recently reported that those with baseline levels of CRP in the highest quartile had a threefold increase in risk of developing future MI compared with those with levels in the lowest quartile (relative risk, 2.9; *P*<0.001).[1] In this population, risk estimates were stable over long periods of time, were significant among the subgroup of nonsmokers, and were independent of a number of other risk factors for cardiovascular disease. As such, these data demonstrate that CRP is a marker of cardiovascular risk not only among those with stable and unstable angina,[2–4] the elderly,[5] and selected high-risk patients[6] but also among individuals with no current evidence of cardiovascular disease.[1]

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From a clinical perspective, the question has been raised as to whether CRP adds to the ability to predict atherothrombotic risk with more confidence than currently achievable with standard lipid screening. We therefore reexamined data from the Physicians' Health Study to determine whether measuring CRP added to the predictive value of TC and HDL-C in determining subsequent risk of first MI. In addition, we sought to determine whether the risks of future MI associated with CRP were present among those with low-risk as well as high-risk profiles as assessed by baseline lipid status.

Methods

In the US Physicians' Health Study,[7] 14 916 men initially free of reported cardiovascular disease, cancer, or other chronic illness provided a baseline plasma sample before randomization and were prospectively followed up for the first occurrence of MI. Details of the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of aspirin and β-carotene in the primary prevention of cardiovascular disease and cancer, have been described elsewhere, as have the methods used to collect, store, and process baseline blood specimens.[1,7] Morbidity follow-up was >99% complete and mortality follow-up was 100% over the ≈9 years of follow-up in the present analysis. Reported MI that occurred during the study follow-up period was confirmed if medical record review demonstrated symptoms consistent with MI and the presence of either diagnostic

	Selected Abbreviations and Acronyms
	CRP = C-reactive protein
	HDL-C = HDL cholesterol
	MI = myocardial infarction
	TC = total cholesterol

ECG changes or cardiac enzymes. Silent MIs were not included because they could not be accurately dated. Deaths due to MI were confirmed when autopsy reports, symptoms, circumstances of death, and a history of coronary disease were consistent with this diagnosis.

In our original description of CRP in the Physicians' Health Study, we reported data from 246 initially healthy study participants who subsequently developed a first MI (cases) and from a group of 543 age- and smoking-matched study participants who remained free of cardiovascular disease during study follow-up (controls).[1] For each of these case and control subjects, blood collected at enrollment was thawed and assayed for CRP by methods described elsewhere.[1] In addition, baseline blood samples of 245 cases (99%) and 372 controls (69%) were successfully analyzed for TC and HDL-C.[8] These 617 initially healthy participants in the Physicians' Health Study form the basis for this report.

Means or proportions for baseline clinical characteristics and measured risk factors were computed for the case and control groups and compared by Student's t test or the χ^2 statistic. Univariate logistic regression analyses were used to determine whether baseline levels of CRP, TC, and the TC:HDL-C ratio were predictive of future risk of MI. In these analyses, baseline levels were divided into quartiles based on the distribution of the control values.

On an a priori basis, we evaluated the combined role of hypercholesterolemia and elevations of CRP in predicting risk of MI in three stages, which allowed us to explore from a clinical perspective the sensitivity and robustness of any findings to the choice of alternative cut points. Thus, we first used the likelihood ratio test to determine whether logistic regression models that included lipid parameters and CRP provided a significantly better fit than did logistic regression models limited to lipid parameters alone. In these analyses, lipid parameters and log-normalized CRP levels were both treated as continuous variables.

Second, logistic regression analyses were performed in which the referent group was those individuals with both TC and CRP levels below the 75th percentile cut point for each of these parameters (TC−, CRP−). In this analysis, relative risks of developing a first MI were computed for individuals with hypercholesterolemia alone (TC+, CRP−), for individuals with elevations of CRP alone (TC−, CRP+), and for individuals with both hypercholesterolemia and elevations of CRP (TC+, CRP+).

Third, we divided case and control subjects into nine groups according to tertile of TC and CRP level. In this analysis, logistic regression was used to simultaneously evaluate the risks of first MI in each of these groups, with those with the lowest tertile of both TC and CRP used as the referent group. Similar analyses were performed after case and control subjects were divided into nine groups according to tertile of the TC:HDL-C ratio.

Finally, to evaluate whether increasing levels of CRP were a predictor of risk for first MI among those with low as well as high lipid parameters, we performed stratified analyses in which tests for trends across increasing quartiles of CRP were computed separately for those with levels of TC and the TC:HDL-C ratio above or below the approximate median value for the study group.

All analyses were repeated for the subgroup of nonsmokers, and additional multivariate analyses were used to control for the presence or absence of other cardiovascular risk factors. P values are two-tailed, and 95% CIs were computed.

Results

Table 1 presents the baseline clinical characteristics of the subjects evaluated. Because study participants in our original

TABLE 1. Baseline Characteristics of Study Participants Who Subsequently Developed First MI (Cases) and Those Who Remained Free of Reported Vascular Disease During the Average 8-Year Follow-up Period (Controls)

	Cases (N=245)	Controls (N=372)	P
Age, y±SD	58.2±8.6	59.4±8.9	...
Smoking status, %			
Never	44.3	41.8	...
Past	40.6	39.9	
Current	15.2	18.3	
Diabetes, %	5.3	3.2	0.2
Body mass index, kg/m²	25.6	24.9	0.01
Systolic blood pressure, mm Hg	128.5	127.3	0.3
Diastolic blood pressure, mm Hg	80.1	79.0	0.08
TC level, mg/dL	229.4	210.9	0.001
HDL-C level, mg/dL	46.4	49.3	0.008
TC:HDL-C ratio	5.3	4.5	0.001

report were matched on smoking and age, these variables were similar among those who subsequently developed a first MI (cases) and among those who remained free of reported cardiovascular disease over the follow-up period (controls). As expected, case subjects had less favorable lipid profiles than did control subjects.

Correlations between log-normalized CRP and TC ($r=0.15$) and between log-normalized CRP and HDL-C ($r=-0.15$) were small in magnitude. Thus, <3% of the variance in CRP levels in these data was explained by the lipid parameters.

In univariate analyses, baseline levels of CRP, TC, and the TC:HDL-C ratio were each associated with increased risk of future MI (all P values <0.001). As shown in Table 2, the relative risk of future MI increased 38% with each increasing quartile of CRP (95% CI, 19% to 61%; $P<0.001$), 62% for each increasing quartile of TC (95% CI, 39% to 90%; $P<0.001$), and 59% for each increasing quartile of the TC:HDL-C ratio (95% CI, 37% to 86%; $P<0.001$). The 95% CIs for these risk estimates overlap and are consistent with prior reports from the entire cohort.[1,4]

To evaluate whether CRP added to the predictive value of lipids on risk of first MI, likelihood ratio tests were used to compare the fit of prediction models using CRP and lipids to the fit of models using lipids alone. In these analyses, the assessment of both parameters provided a significantly improved ability to predict risk. For example, models including both CRP and TC provided a significant improvement in prediction ($P=0.003$) compared with models including only

TABLE 2. Relative Risks of First MI Associated With Each Quartile Increase of CRP, TC, and TC:HDL-C Ratio

Parameter	RR	95% CI	P
CRP	1.38	1.19–1.61	0.0001
TC	1.62	1.39–1.90	0.0001
TC:HDL-C	1.59	1.37–1.86	0.0001

TABLE 3.   Relative Risks of First MI According to the Presence (TC+) or Absence (TC−) of TC Levels in Excess of the 75th Percentile of the Control Distribution (234 mg/dL) and/or the Presence (CRP+) or Absence (CRP−) of CRP Levels in Excess of the 75th Percentile of the Control Distribution (2.11 mg/L)

|	CRP−, TC−	CRP+, TC−	CRP−, TC+	CRP+, TC+
Crude relative risk	1.0	1.5	2.3	5.0
95% CI	...	0.9–2.4	1.5–3.7	2.5–9.8
P	...	0.1	0.0003	0.0001
Adjusted relative risk*	1.0	1.4	2.1	5.2
95% CI	...	0.8–2.3	1.3–3.4	2.5–10.5
P	...	0.02	0.002	0.0001

*Adjusted for family history of coronary artery disease, history of hypertension, body mass index, diabetes, age, and smoking status.

TC, whereas models involving CRP significantly improved prediction compared with models based solely on the TC:HDL-C ratio ($P=0.002$) or on TC and HDL-C entered as separate variables ($P=0.002$). These relationships were not significantly altered in models limited to nonsmokers or that further controlled for the effects of other cardiovascular risk factors.

Table 3 presents the relative risks of first MI in analyses in which study subjects were categorized as being above or below the 75th percentile cut point for TC and CRP. As shown, compared with those with levels of TC and CRP less than the 75th percentile cut point for each parameter (TC−, CRP−), those with elevations of TC alone (TC+, CRP−) had a 2.3-fold increase in risk, whereas those with elevations of CRP alone (TC−, CRP+) had a 1.5-fold increase in risk. In contrast, the risk of first MI associated with elevations of both TC and CRP (TC+, CRP+) was increased 5-fold (RR=5.0; 95% CI, 2.5 to 9.8; $P=0.0001$). As shown in Table 3 and in Fig 1, these effects were not significantly altered in analyses controlling for other risk factors.

Fig 2 illustrates the relative risks of first MI in analyses in which study participants were stratified into nine groups according to tertile of TC as well as tertile of CRP. As shown, risks of future MI increased with each of these parameters such that those in the highest tertile of both TC and CRP had a relative risk of first MI 5.3 times that of individuals in the lowest tertile of both parameters (95% CI, 2.4 to 11.7; $P=0.0001$). Similarly, Fig 3 illustrates the relative risks of first MI in analyses in which study participants were stratified into nine groups according to tertile of the TC:HDL-C ratio as well as tertile of CRP.
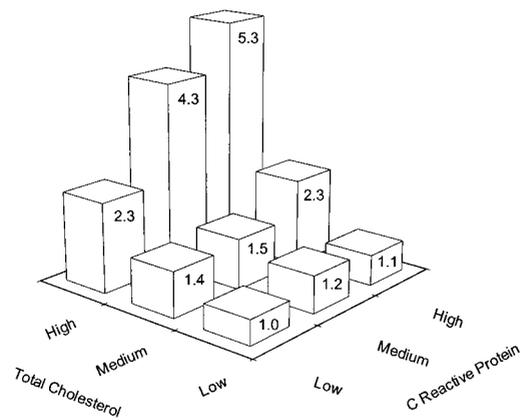
Figure 2. Relative risks of first MI among apparently healthy men associated with high (>223 mg/dL), middle (191 to 223 mg/dL), and low (<191 mg/dL) tertiles of TC and high (>1.69 mg/L), middle (0.72 to 1.69 mg/L), and low (<0.72 mg/L) tertiles of CRP.
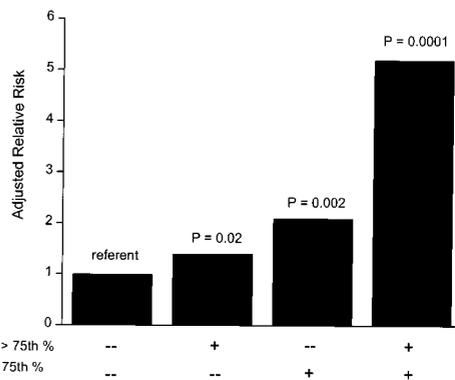
Figure 1. Adjusted relative risks of first MI according to baseline levels of TC above (TC+) or below (TC−) 75th percentile of control group (234 mg/dL) and baseline CRP levels above (CRP+) or below (CRP−) 75th percentile of control group (2.11 mg/L).
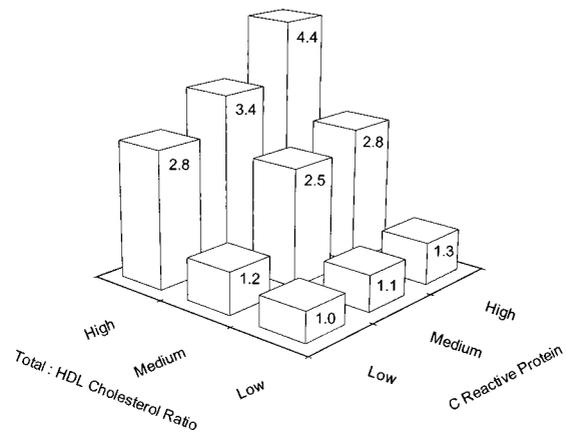
Figure 3. Relative risks of first MI among apparently healthy men associated with high (>5.01), middle (3.78 to 5.01), and low (<3.78) tertiles of the TC:HDL-C ratio and high (>1.69 mg/L), middle (0.72 to 1.69 mg/L), and low (<0.72 mg/L) tertiles of CRP.

TABLE 4.   Relative Risks of First MI According to Baseline Levels of CRP, Stratified by Baseline Lipid and Lipoprotein Levels

| | Quartile of CRP (range, mg/L) | | | | |
	1 (≤0.55)	2 (0.56–1.14)	3 (1.15–2.10)	4 (≥2.11)	*P* for Trend
TC ≤210					
All subjects					
RR	1.0	1.5	1.6	2.5	.03
95% CI	...	0.6–3.5	0.7–3.6	1.1–5.6	
P	...	0.4	0.3	0.03	
Nonsmokers					
RR	1.0	1.4	1.2	2.1	.1
95% CI	...	0.6–3.3	0.5–3.0	0.9–5.0	
P	...	0.5	0.6	0.09	
TC >210					
All subjects					
RR	1.0	2.4	3.1	3.1	.001
95% CI	...	1.2–4.9	1.6–5.9	1.6–6.0	
P	...	0.01	0.001	0.001	
Nonsmokers					
RR	1.0	2.2	3.1	3.6	.001
95% CI	...	1.1–4.7	1.5–6.2	1.7–7.6	
P	...	0.03	0.002	0.001	
TC:HDL-C ≤4.0					
All subjects					
RR	1.0	2.0	2.2	3.0	.03
95% CI	...	0.7–5.4	0.8–5.7	1.1–7.9	
P	...	0.2	0.1	0.03	
Nonsmokers					
RR	1.0	2.0	1.7	2.7	.08
95% CI	...	0.7–5.6	0.6–4.5	1.0–7.5	
P	...	0.2	0.4	0.05	
TC:HDL-C >4.0					
All subjects					
RR	1.0	1.6	2.2	2.3	.008
95% CI	...	0.8–3.1	1.2–4.2	1.2–4.2	
P	...	0.2	0.01	0.01	
Nonsmokers					
RR	1.0	1.5	2.2	2.6	.004
95% CI	...	0.8–3.0	1.1–4.2	1.3–5.1	
P	...	0.2	0.02	0.007	

Table 4 presents the relative risks of first MI according to baseline levels of CRP in analyses in which the study population was stratified according to baseline lipid profile. As shown, statistically significant associations were found between baseline level of CRP and risk of first MI for study participants with low as well as high levels of TC and the TC:HDL-C ratio. Similar relationships were found in analyses limited to nonsmokers.

Discussion

In these prospective data deriving from a large cohort of apparently healthy men, baseline CRP level added to the predictive value of TC and HDL-C in determining risk of first MI. Indeed, interactive models evaluating elevations of CRP and lipids raise the possibility that the joint effects of both risk factors may be slightly greater than the product of the individual effects of each risk factor considered separately. Moreover, baseline level of CRP is a predictor of risk of first MI for men at low as well as high risk as determined by their lipid profiles. These relationships were minimally altered in analyses either limited to nonsmokers or adjusted for other risk factors, including hypertension, body mass, diabetes, and family history of coronary disease. Finally, these results were

robust to the choice of several cut points for both CRP and lipid parameters.

The present data describing at least additive relationships between CRP and lipids in terms of risk prediction extend prior findings relating CRP to cardiovascular disease.[1–6] Specifically, elevated levels of CRP are associated with increased risks of MI or sudden death among those with stable and unstable angina pectoris,[2–4] as well as coronary heart disease in the elderly[5] and coronary mortality among high-risk patients.[6] However, because CRP levels increase in response to acute ischemia and are chronically elevated among smokers,[9] it had been uncertain whether the inflammation detected by CRP in these studies is causal or due to the effects of other factors, such as ischemia or cigarette consumption. Moreover, these prior studies did not evaluate whether the effects of CRP were present among those with high- as well as low-risk lipid profiles or whether the risks associated with CRP were additive to those determined by standard lipid analysis.

All the apparently healthy men in the Physicians' Health Study were free of any history of cardiovascular disease when blood samples were obtained. Thus, the potential for confounding by the presence of symptomatic ischemia in these data is unlikely. Moreover, the risks of future MI associated with CRP in the Physicians' Health Study were present for nonsmokers, providing evidence against the possibility that observed effects are simply the result of cigarette consumption.[9]

The fact that lipid parameters and CRP levels were measured only once at baseline in our study is a potential limitation, because random fluctuation in these parameters over time would tend to increase the variance in our data. However, if random, such variation would most likely bias our findings toward a null result and lead to an underestimation of true predictive values. Conversely, because assays for CRP as well as all lipid parameters were performed on the same baseline plasma sample, these data are compatible with the potential utility of simultaneous assessment of inflammatory markers and lipid parameters as a method of risk detection.

It is currently estimated that up to half of all MIs in the United States occur among individuals with moderate to low risk as determined by assessment of TC and HDL-C levels.[10] The present data raise the possibility that assessment of CRP may provide a method of determining risk of future MI among apparently low-risk individuals, including nonsmok-

ers. Because relatively simple interventions such as exercise, weight loss, and diet restriction can lead to substantial reductions in risk of first MI,[10] assessment of CRP might have clinical utility if improved risk stratification leads to improved compliance with lifestyle modification. Confirmation of these data in other prospective cohorts is thus of critical importance, as are studies in women, for whom data are lacking on the predictive value of inflammatory markers.

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