C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men : Results From the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992

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C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men

Results From the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992

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Background—Inflammatory reactions in coronary plaques play an important role in the pathogenesis of acute atherothrombotic events; inflammation elsewhere is also associated with both atherogenesis generally and its thrombotic complications. Recent studies indicate that systemic markers of inflammation can identify subjects at high risk of coronary events.

Methods and Results—We used a sensitive immunoradiometric assay to examine the association of serum C-reactive protein (CRP) with the incidence of first major coronary heart disease (CHD) event in 936 men 45 to 64 years of age. The subjects, who were sampled at random from the general population, participated in the first MONICA Augsburg survey (1984 to 1985) and were followed for 8 years. There was a positive and statistically significant unadjusted relationship, which was linear on the log-hazards scale, between CRP values and the incidence of CHD events (n=53). The hazard rate ratio (HRR) of CHD events associated with a 1-SD increase in log-CRP level was 1.67 (95% CI, 1.29 to 2.17). After adjustment for age, the HRR was 1.60 (95% CI, 1.23 to 2.08). Adjusting further for smoking behavior, the only variable selected from a variety of potential confounders by a forward stepping process with a 5% change in the relative risk of CRP as the selection criterion, yielded an HRR of 1.50 (95% CI, 1.14 to 1.97).

Conclusions—These results confirm the prognostic relevance of CRP, a sensitive systemic marker of inflammation, to the risk of CHD in a large, randomly selected cohort of initially healthy middle-aged men. They suggest that low-grade inflammation is involved in pathogenesis of atherosclerosis, especially its thrombo-occlusive complications. **(*Circulation*. 1999;99:237-242.)**

Key Words: proteins ■ coronary disease ■ incidence ■ epidemiology

Although atherosclerosis is clearly multifactorial, it is now universally recognized that inflammation within the lesions contributes importantly to their initiation and progression,[1] whereas histopathological and immunocytochemical observations suggest that active inflammatory processes may destabilize the fibrous cap tissue, thus triggering plaque rupture and enhancing the risk of coronary thrombosis.[2] On the other hand, prospective epidemiological studies have shown a strong and consistent association between clinical manifestations of atherothrombotic disease and systemic markers of inflammation, including white blood cell count,[3] and various hemostatic proteins that are also acute-phase reactants such as fibrinogen,[4] plasminogen-activator inhibitor type-1,[5] and von Willebrand factor.[6] A potentially important role of inflammation in the onset of acute ischemic syndromes is indicated by neutrophil activation[7] and elevated levels of various acute-phase proteins[8–10] in unstable angina and the notable temporal relationship between acute or chronic infections and coronary events.[11–13]

C-reactive protein (CRP), the classic acute-phase protein, is not directly involved in the coagulation process but is an exquisitely sensitive objective marker of inflammation, tissue damage, and infection.[14] Its plasma half-life (≈19 hours) is rapid but identical under all conditions, in contrast to the coagulation proteins and virtually all other major acute-phase reactants, so the synthesis rate of CRP is the sole determinant of its plasma concentration.[15] Excellent anti-CRP antibodies and a well-established World Health Organization (WHO)

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international reference standard for CRP[16] are available, so precise, sensitive, and robust clinical serum/plasma assays can be readily undertaken.[17,18] CRP measurement thus has many advantages in the detection and monitoring of the acute-phase response in general and the relation to atheroma and its complications in particular. Indeed, the recent use of sensitive CRP assays in a large prospective study in patients with angina pectoris[19] and in 3 nested case-control studies in initially healthy subjects[20–22] showed a consistent positive association between baseline CRP levels and cardiovascular end points. Subjects from 2 of these studies were drawn from participants in clinical trials,[20,21] raising the question of their representativeness, and 1 study[22] included only elderly subjects. Thus, to confirm the reported association between CRP levels and coronary heart disease (CHD) risk in large, unselected populations, we have measured serum CRP in 936 initially healthy men (age, 45 to 64 years) drawn from a random sample of the general population who took part in the first MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg survey in 1984 to 1985. On the basis of an 8-year follow-up, we report here the prognostic significance of CRP values for the occurrence of a first major coronary event in these men.

Methods

MONICA Project, Augsburg Center

The objectives and design of the MONICA project have been described elsewhere.[23,24] The first cross-sectional study of the MONICA Augsburg (Germany) center was carried out in 1984 to 1985. The study population and data collection procedures have also been reported previously.[25,26] Briefly, 4022 of the 5069 eligible individuals 25 to 64 years of age initially sampled at random from a study population of 282 279 inhabitants of a mixed urban/rural area participated in the study (response rate, 79.3%). The present report is based on all men (age, 45 to 64 years) who participated in the first survey (n=1074). Of these subjects, 43 were not included in the analyses because of previous myocardial infarction. Eight were excluded because their medical histories suggested disease other than CHD, possibly associated with an acute-phase reaction. In the remaining 1023 men, measurements of CRP were missing from 74 (7.2%); in 13 other men, at least 1 control variable could not be obtained. Thus, a total of 936 men 45 to 64 years of age had data on all variables studied.

Survey Methods

Participants completed a standardized questionnaire, including medical history, lifestyle, and drug history.[26] Blood pressure, body height (m), body weight (kg), body mass index (BMI, m/kg^2), smoking behavior, and alcohol consumption (g/d) were determined as described elsewhere.[26–28] Leisure-time physical activity (LTPA) was assessed on a 4-level graded scale for winter and summer time (0, <1, 1 to 2, and >2 h/wk).[29] The number of education years was calculated on the basis of the highest level of formal education completed.

Laboratory Procedures

Nonfasting blood samples were taken from all subjects at baseline in 1984 to 1985 and stored at −70°C. Serum concentrations of CRP were measured in a sensitive immunoradiometric assay with monospecific polyclonal and monoclonal antibodies produced by immunization with highly purified CRP.[15] Briefly, 96-well microtiter plates (Costar Co) activated with *N*-oxysuccinimide were coated with the IgG fraction of polyclonal goat anti-human CRP antiserum offered at 100 μg/mL. Serum samples, 100 μL at 1:100 dilution, were added to each well and incubated at 37°C for 4 hours and at 4°C overnight. The plates were then washed, and bound CRP was detected by incubation with ^{125}I-radiolabeled monoclonal anti-human CRP antibody, followed by rinsing and counting of retained radioactivity in each well. CRP concentrations were determined by use of a 5-point standard curve calibrated with the WHO international reference standard for CRP immunoassay, standard 85/506, produced at the Immunological Medicine Unit, Royal Postgraduate Medical School (London, UK). Recovery of pure CRP[15] spiked into serum was 100%, and the assay range was 0.05 to 10 mg/L, with coefficients of variation within assays of 4% and between-assay coefficients of ≈12% across the whole range. Samples with values >10 mg/L were remeasured at appropriately higher dilutions. All samples were measured in triplicate, and values were averaged for analysis. Total and HDL cholesterol levels were measured by enzymatic methods.

Follow-Up Procedure

Within the population-based Augsburg Coronary Event Register, all death certificates of residents of the study area who were 25 to 74 years of age were screened in the 3 health departments for suspected cases of acute myocardial infarction (AMI) occurring since October 1, 1984. Additional information was gained from standardized questionnaires sent from the health departments to the last attending physician and/or coroner. On the basis of both the information from the death certificate and the questionnaire, the register team decided whether a case fulfilled the MONICA algorithm for fatal CHD. Data on cases of fatal and nonfatal AMI occurring in hospital were actively collected by register nurses. No information could be obtained on nonfatal events in patients outside hospital (<1% of AMI patients) or on patients with silent AMI. Detailed information on the case-finding procedure and on data-quality aspects has been published elsewhere.[30]

An incident was defined as a first fatal or nonfatal AMI, including sudden cardiac death. According to the MONICA manual,[27,31] diagnosis of a major CHD event was based on symptoms, cardiac enzymes (creatine kinase, aspartate aminotransferase, and lactate dehydrogenase), and serial changes from 12-lead ECGs evaluated by Minnesota coding,[32] necropsy results, and history of CHD in fatal cases.

Addresses of all participants in the first survey (1984 to 1985) were checked at 2-year intervals, and information on survival was collected. If a subject had died, information on the cause of death was obtained. The results reported here comprise the 8-year follow-up of participants in the first survey (as of December 31, 1992).

Statistical Analysis

The number of events was rather small relative to the number of variables considered (10 to 20 events per regression term should be available for a reliable analysis). We therefore used variables in their simplest form if warranted, used a forward stepping procedure to discard unneeded variables, and did not investigate interactions.

CRP was used as a continuous variable, transformed to natural logarithms for greater symmetry of the distribution (ln mg/L). Covariables controlled for possible confounding effects were age (years), BMI (ln kg/m^2), total cholesterol (ln mg/dL), HDL cholesterol (square root mg/dL), smoking status (never smoked, ex-smoker, current smoker), alcohol consumption (square root g/d), systolic and diastolic blood pressures (ln mm Hg), education (ln years), winter and summer LTPA (0, <1, 1 to 2, and >2 h/wk), and diabetes by history (no, yes). The categorical variables, recognizing their ordinal character, were used as continuous variables, transformed to orthogonal polynomial coefficients if necessary.

Cox proportional hazards regression[33] was used to model time to event in the presence of censoring. An individual was considered censored when he died from another cause or left the study area or when the observation period ended. The crude relation of CHD and CRP was checked for departures from linearity, poorly fitted observations, overly influential observations, and validity of the proportional hazards assumption by use of residual plots and nonparametric smoothing functions.

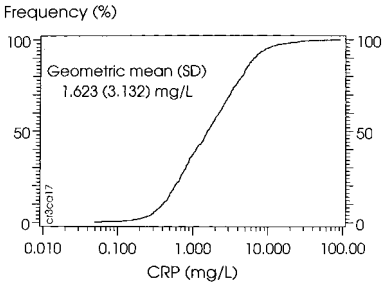

Figure 1. Empirical distribution of CRP on logarithmic scale. Geometric mean (SD) is shown.

To investigate possible nonlinear transformations of the covariables for adjusting the crude relation, we compared the hazard rate ratio (HRR) for CRP from the model including the covariable in its simplest form with HRR from models including more complex forms (polynomials, splines). Model validity was assessed in a fashion analogous to the crude analysis. The resulting variables were then added to the crude model in a forward stepping manner, at each step adding the variable that changed the absolute value of HRR the most when added to the variable terms already in the model. Age was forced into the model from the beginning. As a stepping criterion, we used 5% change, although some authors recommend 10%.[34]

All computations and graphics were performed on a personal computer under Windows NT 4 with SAS software, version 6.12,[35] and S-PLUS, version 4.0.[36]

Results

The empirical cumulative distribution of log-CRP values in our study sample of 936 men 45 to 64 years of age was remarkably smooth and symmetrical (coefficient of skewness, 0.13; SE=0.08) (Figure 1), and the coefficient of kurtosis was also close to zero (0.09; SE=0.16), indicating that CRP levels in this population approximated a log-normal distribution. The minimal CRP value was 0.05 mg/L, the maximal value was 90.8 mg/L, and the antilogs of the mean (geometric mean) and SD were 1.623 and 3.132 mg/L, respectively.

The cohort was followed up for a maximum of 8.2 years. During this time, 53 first major CHD events (5.7%) occurred, of which 26 were fatal and 27 were nonfatal. Of the 53 events, 48 occurred after 7.5 years, together with 72 censored observations that were fairly evenly distributed over the time period. The last event occurred after 7.9 years, at which point there was a total of 433 censored observations, and the estimated survival probability was 0.94. The average annual incidence rate was 7.64 per 1000 person-years (95% CI, 5.72 to 9.99).

Table 1 reports unadjusted associations of CRP levels with the covariables, computed as group means of categorized variables. The means are back-transformed to the original scale by taking antilogs, thus representing geometric means. The probability value is the significance level obtained for testing the simultaneous equality of all group means in a 1-way ANOVA. All tests are significant at the 5% level except that for HDL cholesterol, but the tests for alcohol consumption, education, and work activity are only very slightly significant. Of the other variables, total cholesterol shows a U-shaped relation; age, BMI, and smoking exhibit a graded positive association, and diabetes showed a positive association. Blood pressure also is positively related, with the

TABLE 1. CRP Means and SEs (Antilogs) in Subgroups of Categorical Covariables, Including Probability Value for Testing the Simultaneous Equality of the Means: MONICA Augsburg Cohort Study, 1984–1992

Variable	Mean (Antilog), mg/L	SE (Antilog), mg/L	*P* (Equality of Means)
Age, y			
45–49	1.26	1.07	0.000
50–54	1.49	1.08	
55–59	1.96	1.08	
60–64	1.97	1.08	
BMI, kg/m^2			
<25	1.06	1.08	0.000
25–30	1.71	1.05	
≥30	2.11	1.08	
TC, mmol/L			
<5.17	1.70	1.10	0.006
5.17–6.21	1.37	1.07	
≥6.21	1.78	1.05	
HDL, mmol/L			
<0.91	1.93	1.12	0.089
≥0.91	1.59	1.04	
Smoking			
Never	1.24	1.07	0.000
Ex	1.37	1.06	
Current	2.44	1.06	
Alcohol consumption, g/d			
None	1.73	1.11	0.049
<40	1.47	1.06	
≥40	1.77	1.06	
BP, mm Hg			
<140/90	1.52	1.05	0.004
Other	1.53	1.08	
≥160/95	2.07	1.09	
Education, years of schooling			
8	1.91	1.11	0.042
10	1.63	1.05	
11	1.82	1.16	
12	1.75	1.13	
13	1.66	1.19	
15	1.39	1.24	
17	1.12	1.13	
WLTPA, h/wk			
None	1.82	1.05	0.001
<1	1.38	1.11	
1–2	1.72	1.09	
>2	1.23	1.09	
SLTPA, h/wk			
None	1.81	1.06	0.008
<1	1.61	1.10	
1–2	1.79	1.09	
>2	1.35	1.07	
WA, h/wk			
None	1.52	1.08	0.023
<1	1.47	1.07	
1–2	1.66	1.07	
>2	2.09	1.10	
Diabetes			
No	1.58	1.04	0.001
Yes	2.84	1.19	

TC indicates total cholesterol; BP, blood pressure; WLTPA, winter LTPA; SLTPA, summer LTPA; and WA, work activity. n=936 men 45 to 64 years of age.

TABLE 2. CRP Regression Coefficients From Cox Regressions of CHD Incidence on CRP in Various Degrees of Adjustment: MONICA Augsburg Cohort Study, 1984–1992

Adjustment	Regression Coefficient (b), mg/L	SE	Lower 95% Confidence Limit (l)	Upper 95% Confidence Limit (u)	*P*
None	0.4517	0.1152	0.2259	0.6775	0.000
Age	0.4111	0.1168	0.1821	0.6401	0.000
Age, smoking	0.3557	0.1218	0.1169	0.5945	0.004

For 2 CRP values, $CRP1_1$ and $CRP2_2$, the HRRs and 95% confidence limits (L and U) can be calculated as

$$HRR=\left(\frac{CRP_1}{CRP_2}\right)^b, \qquad L=\left(\frac{CRP_1}{CRP_2}\right)^l, \qquad U=\left(\frac{CRP_1}{CRP_2}\right)^u$$

with b, l, and u taken from the table.

n=936 men 45 to 64 years of age.

first 2 categories having essentially the same CRP levels. The 2 LTPA variables show nonmonotonic behavior, perhaps with a slight downward linear trend.

Analysis

Modeling the crude association of CRP concentration and CHD by means of a Cox regression resulted in a linear relationship of log hazards and CRP. There was no indication of a nonlinear relation not accounted for by the linear CRP term; no observation showed unusual behavior in the model; and the proportional hazard assumption appeared to be tenable throughout the observation period. The procedure for prechecking the covariables for nonlinearities, as outlined in the Statistical Analysis section, did not indicate the need to abandon the linear terms. The variable selection procedure chosen, forcing age into the model, resulted in 1 variable, namely smoking, changing the HRR, ignoring the sign, by >5% (−5.4%). The next variable would have been BMI, entering with a change of 2.3%, then total cholesterol (1.9%), and eventually HDL cholesterol (−1.7%). The remaining variables produced changes <1%.

Table 2 presents selected regression statistics for the crude model, age-adjusted model, and 5%-change model, with adjustment for age and smoking. The table includes the regression coefficients of the linear log-transformed CRP variable and their 95% confidence limits. It also gives formulas for computing the HRRs for 2 arbitrary CRP values. For instance, for the 90th percentile of the CRP distribution (6.5 mg/L, read from Figure 1) and the 10th percentile (0.4 mg/L), the fully adjusted HRR was $(6.5/0.4)^{0.3557}=2.69$ [lower 95% confidence limit, $(6.5/0.4)^{0.1169}=1.39$; upper limit, $(6.5/0.4)^{0.5945}=5.25$].

Table 3 presents HRRs for an increase in CRP concentration of 1 SD of the log-transformed values (1.142 ln mg/L) and corresponding 95% confidence limits for the fully adjusted model.

Figure 2 shows a plot of HRRs for CRP quintiles relative to the first quintile. These HRRs were obtained by computing the median CRP value within each quintile and using the ratio of the 2 medians in the formula for HRR in Table 2. The unadjusted HRR, age-adjusted HRR, and fully adjusted HRR, together with 95% confidence limits for the fully adjusted HRR, are shown.

Discussion

These prospective data from a large random sample of initially healthy middle-aged men demonstrate a strong relationship between CRP and the future risk of a fatal or nonfatal coronary event. This relationship is linear in the log hazards and independent of a variety of potential confounders. A 1-SD increase in the log-transformed value of CRP was associated with a remarkable 50% increase in coronary risk, and subjects in the highest quintile of the CRP distribution thus showed a 2.6-fold increase in their risk of a future coronary event. These data confirm a recent nested case-control study in middle-aged US male physicians.[21] Case-control data from the Cardiovascular Health Study showed that CRP levels may be able to predict coronary risk in men and women >65 years of age with and without evidence of subclinical atherosclerotic disease,[22] and another case-control study among participants in MRFIT related CRP values to CHD mortality in healthy but high-risk individuals.[20] The prospective ECAT study in patients with angina pectoris showed that CRP levels also predict coronary events in symptomatic subjects over a 2-year period.[19] Interestingly, the distribution of CRP values was very similar in all these studies, with 55% to 80% of CRP values being <2 mg/L, which is well below the range seen in routine use of CRP measurement for monitoring acute or chronic active inflammatory, infective, or tissue-damaging disorders. The strength of the association between CRP and future coronary events was also remarkably consistent in these studies, with a relative risk of 2 to 3 in comparisons of the top and bottom quintiles or quartiles of the CRP distribution.

In our study, CRP was also related to several cardiovascular risk factors that had been reported earlier.[37] Particularly

TABLE 3. HRRs for a 1-SD CRP Increase on the Log-Transformed Scale for the Models of Table 2: MONICA Augsburg Cohort Study, 1984–1992

Adjustment	HRR	Lower 95% Confidence Limit	Upper 95% Confidence Limit
None	1.67	1.29	2.17
Age	1.60	1.23	2.08
Age, smoking	1.50	1.14	1.97

For a multiple of 1 SD, raise the numbers in the table to the power of that multiple.

n=936 men 45 to 64 years of age.

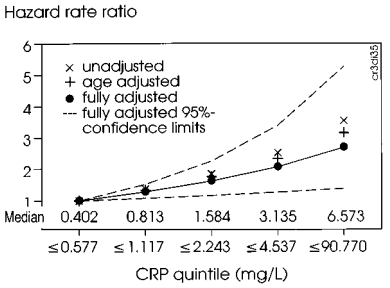

Figure 2. HRRs for CRP quintiles, relative to the first quintile, in various adjustments. HRRs were computed for quintile medians listed in graph by use of formulas given in footnote of Table 2.

strong unadjusted positive associations were found with age, BMI, smoking, and history of diabetes. Current smokers had CRP concentrations twice as high as nonsmokers, but interestingly, subjects who had never smoked had values similar to ex-smokers. Obese subjects (BMI $\geq$30 kg/m^2) also had CRP concentrations twice as high as those with BMI $<$25 kg/m^2. Despite these associations, multivariable analysis clearly showed an independent contribution of CRP in the prediction of future coronary events.

CRP is an extremely sensitive, nonspecific, acute-phase reactant produced in response to most forms of tissue injury, infection, and inflammation and regulated by cytokines, including interleukin-6, interleukin-1, and tumor necrosis factor-α.[38] Although reportedly expressed by some mononuclear populations, these cells do not secrete CRP, and circulating CRP is exclusively produced by hepatocytes.[39,40] The stimuli responsible for the generally modest elevations in plasma CRP predictively associated with coronary events are not known. They may arise in the atheromatous lesions themselves and reflect the extent of atherosclerosis and the local inflammation that predisposes to plaque instability, rupture, and occlusive thrombosis. On the other hand, increased CRP production may result from inflammation elsewhere in the body that is somehow proatherogenic and procoagulant. Chronic low-grade infections may be associated with increased risk of CHD,[41,42] as is the chronic inflammation of rheumatoid arthritis.[43] Many coagulation proteins, including fibrinogen, are acute-phase reactants; elevation of fibrinogen is a well-recognized risk factor for coronary events,[4] and increased CRP values may just be a signal of the acute-phase response in general.

However, there is substantial evidence that CRP may contribute directly to the pathogenesis of atherothrombosis. CRP is a ligand binding protein that binds to the plasma membranes of damaged cells.[44,45] Aggregated but not soluble native CRP selectively binds LDL and VLDL from whole plasma and, as we have previously proposed, could thereby participate in their atherogenic accumulation.[46] Complexed CRP also activates complement and can be proinflammatory,[47] whereas CRP has recently been found to be a potent stimulator of tissue factor production by macrophages in vitro.[48] Tissue factor is the main initiator of coagulation in vivo, and its local concentration in the arterial wall is clearly related to coronary thrombotic events.[49–51] There are conflicting reports about the presence of CRP in atheromatous lesions,[52–54] and claims that CRP affects platelet function are also controversial.[55] However, the capacity of CRP to enhance tissue factor production suggests a possible causative link between increased CRP values and coronary events.

Although the number of cases was relatively small, results of the present prospective study of a large cohort of initially healthy middle-aged men indicate that modest elevations in serum CRP concentration significantly predict future coronary events. These observations strengthen the association between low-grade inflammation and the progression and complications of atherosclerosis. Further work is required to clarify the underlying pathophysiological mechanisms, but modulation of the acute-phase response generally and/or the functions of specific acute-phase proteins specifically, especially CRP, already constitutes novel potential therapeutic targets in CHD.

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