

# The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 336

APRIL 3, 1997

NUMBER 14



## INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, Ph.D.,  
AND CHARLES H. HENNEKENS, M.D.

### ABSTRACT

**Background** Inflammation may be important in the pathogenesis of atherothrombosis. We studied whether inflammation increases the risk of a first thrombotic event and whether treatment with aspirin decreases the risk.

**Methods** We measured plasma C-reactive protein, a marker for systemic inflammation, in 543 apparently healthy men participating in the Physicians' Health Study in whom myocardial infarction, stroke, or venous thrombosis subsequently developed, and in 543 study participants who did not report vascular disease during a follow-up period exceeding eight years. Subjects were randomly assigned to receive aspirin or placebo at the beginning of the trial.

**Results** Base-line plasma C-reactive protein concentrations were higher among men who went on to have myocardial infarction (1.51 vs. 1.13 mg per liter,  $P < 0.001$ ) or ischemic stroke (1.38 vs. 1.13 mg per liter,  $P = 0.02$ ), but not venous thrombosis (1.26 vs. 1.13 mg per liter,  $P = 0.34$ ), than among men without vascular events. The men in the quartile with the highest C-reactive protein values had three times the risk of myocardial infarction (relative risk, 2.9;  $P < 0.001$ ) and two times the risk of ischemic stroke (relative risk, 1.9;  $P = 0.02$ ) of the men in the lowest quartile. Risks were stable over long periods, were not modified by smoking, and were independent of other lipid-related and non-lipid-related risk factors. The use of aspirin was associated with significant reductions in the risk of myocardial infarction (55.7 percent reduction,  $P = 0.02$ ) among men in the highest quartile but with only small, nonsignificant reductions among those in the lowest quartile (13.9 percent,  $P = 0.77$ ).

**Conclusions** The base-line plasma concentration of C-reactive protein predicts the risk of future myocardial infarction and stroke. Moreover, the reduction associated with the use of aspirin in the risk of a first myocardial infarction appears to be directly related to the level of C-reactive protein, raising the possibility that antiinflammatory agents may have clinical benefits in preventing cardiovascular disease. (N Engl J Med 1997;336:973-9.)

©1997, Massachusetts Medical Society.

**T**HROMBUS formation is the proximate cause of myocardial infarction, but atherosclerosis, the chief underlying cause, is a chronic disease that progresses over decades of life.<sup>1</sup> Laboratory and pathological data support the idea that inflammation has a role in both the initiation and the progression of atherosclerosis, and antiinflammatory agents may have a role in the prevention of cardiovascular disease.<sup>2-5</sup> However, there are few data to indicate whether inflammation increases the risk of first myocardial infarction, stroke, and venous thrombosis or whether antiinflammatory therapy decreases that risk.

C-reactive protein is an acute-phase reactant that is a marker for underlying systemic inflammation. Elevated plasma concentrations of C-reactive protein have been reported in patients with acute ischemia<sup>6</sup> or myocardial infarction<sup>7,8</sup> and have been found to predict recurrent ischemia among those hospitalized with unstable angina.<sup>9</sup> C-reactive protein is also associated with a risk of myocardial infarction among patients with angina pectoris<sup>10</sup> and with a risk of fatal coronary disease among smokers with multiple risk factors for atherosclerosis.<sup>11</sup> However, since concentrations of C-reactive protein and other acute-phase reactants increase after acute ischemia<sup>6</sup> and are directly related to cigarette smoking,<sup>11,12</sup> it has been uncertain whether associations observed in previous studies of acutely ill patients<sup>9</sup> or high-risk popula-

From the Divisions of Preventive Medicine (P.M.R., C.H.H.) and Cardiovascular Disease (P.M.R.) and the Channing Laboratory (M.J.S.), Department of Medicine, Brigham and Women's Hospital; the Department of Ambulatory Care and Prevention, Harvard Medical School (C.H.H.); and the Departments of Epidemiology (M.J.S., C.H.H.) and Nutrition (M.J.S.), Harvard School of Public Health — all in Boston; and the Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington (M.C., R.P.T.). Address reprint requests to Dr. Ridker at the Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. E., Boston, MA 02215-1204.

tions<sup>10,11</sup> are causal or are due to short-term inflammatory changes or to interrelations with other risk factors, in particular smoking and hyperlipidemia.

To address these issues, we measured base-line plasma C-reactive protein concentrations in 1086 apparently healthy men participating in the Physicians' Health Study<sup>13,14</sup>; myocardial infarction, stroke, or venous thrombosis subsequently developed in 543. We hypothesized a priori that levels of C-reactive protein would predict the risk of myocardial infarction and stroke but not of venous thrombosis — an occlusive vascular disease generally not associated with chronic atherosclerosis. After providing base-line blood samples, study participants were randomly assigned to receive aspirin or placebo. Thus, we had the unique opportunity to evaluate directly whether aspirin, an agent with both antiplatelet and anti-inflammatory properties, might modify any relation between C-reactive protein and the risk of first myocardial infarction.

## METHODS

### Study Population and Collection of Plasma Samples

The Physicians' Health Study was a randomized, double-blind, placebo-controlled two-by-two factorial trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. A total of 22,071 U.S. male physicians 40 to 84 years of age in 1982, with no history of myocardial infarction, stroke, transient ischemic attack, or cancer, were assigned to one of four treatments: 325 mg of aspirin on alternate days (Bufferin, provided by Bristol-Myers), 50 mg of beta carotene on alternate days (Lurotin, provided by BASF Corporation), both, or neither. The aspirin component of the study was terminated early, on January 25, 1988, primarily because of a statistically extreme 44 percent reduction in the risk of a first infarction in the aspirin group.<sup>13</sup> The beta carotene component continued until the study's scheduled termination on December 31, 1995.<sup>14</sup>

Before randomization, between August 1982 and December 1984, potential participants were asked to provide base-line blood samples during a 16-week run-in period during which all subjects were given aspirin and none received placebo. Blood-collection kits, including EDTA Vacutainer tubes, were sent to participants with instructions for taking blood. Participants were asked to have their blood drawn into the EDTA tubes, centrifuge the tubes, and return the plasma (accompanied by a cold pack provided to participants) by overnight courier. The specimens were then divided into aliquots and stored at  $-80^{\circ}\text{C}$ . Of the 22,071 participants in the Physicians' Health Study, 14,916 (68 percent) provided base-line plasma samples. Over the 14 years of the trial, no specimen inadvertently thawed during storage.

### Confirmation of End Points and Selection of Controls

We requested hospital records (and for fatal events, death certificates and autopsy reports) for all reported cases of myocardial infarction, stroke, and venous thrombosis. The records were reviewed by a committee of physicians using standardized criteria to confirm or refute reported events. Reviewers of end points were unaware of treatment assignments.

Reported myocardial infarction was confirmed if its symptoms met World Health Organization (WHO) criteria and it was associated with either elevated plasma concentrations of enzymes or characteristic electrocardiographic changes. Silent myocardial infarctions were not included, since they could not be dated accurately. Deaths due to coronary disease were confirmed on the basis of autopsy reports, symptoms, circumstances of death, and a his-

tory of coronary disease. Reported stroke was confirmed on the basis of medical records showing a neurologic deficit of sudden or rapid onset that persisted for more than 24 hours or until death. Strokes were classified as ischemic or hemorrhagic. Computed tomographic scans were available for more than 95 percent of the confirmed strokes. Reported deep venous thrombosis was confirmed by the documentation of a positive venography study or a positive ultrasound study; deep venous thromboses documented only by impedance plethysmography or Doppler examination without ultrasound were not considered confirmed. Reported pulmonary embolism was confirmed by a positive angiogram or a completed ventilation-perfusion scan demonstrating at least two segmental perfusion defects with normal ventilation.

Each participant who provided an adequate base-line plasma sample and had a confirmed myocardial infarction, stroke, or venous thrombosis after randomization was matched with one control. Controls were participating physicians who provided base-line plasma samples and reported no cardiovascular disease at the time the patient reported his event. Controls were selected randomly from among study participants who met the matching criteria of age ( $\pm 1$  year), smoking status (smoking currently, smoked in the past, or never smoked), and length of time since randomization (in 6-month intervals). Using these methods, we evaluated 543 patients and 543 controls in this prospective, nested, case-control study.

### Laboratory Analysis

For each patient and control, plasma collected and stored at base line was thawed and assayed for C-reactive protein by enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem).<sup>15</sup> Antibodies were used to coat microtiter-plate wells, and biotinylated C-reactive protein, together with the patient's plasma, was diluted 1:700 in assay buffer (phosphate-buffered saline with 0.1 percent Tween 20 and 1 percent bovine serum albumin). The excess was then washed off and the amount of biotinylated protein estimated by the addition of avidin-peroxidase (Vectastain, Vector Laboratories). Purified C-reactive protein was used as the standard, with protein concentrations as determined by the manufacturer. The C-reactive protein assay was standardized according to the WHO First International Reference Standard and had a sensitivity of  $0.08 \mu\text{g}$  per microliter, with a standard reference range of between 0.5 and 2.5 mg per liter. Methods used to measure plasma total and high-density lipoprotein (HDL) cholesterol, triglyceride, lipoprotein(a), total homocysteine, fibrinogen, D-dimer, and endogenous tissue plasminogen activator (t-PA) antigen have been described elsewhere.<sup>16-20</sup>

Blood specimens were analyzed in blinded pairs, with the position of the patient's specimen varied at random within the pairs to reduce the possibility of systematic bias and decrease interassay variability. The mean coefficient of variation for C-reactive protein across assay runs was 4.2 percent.

### Statistical Analysis

Means or proportions for base-line risk factors were calculated for patients and controls. The significance of any difference in means was tested by using Student's t-test, and the significance of any differences in proportions was tested by using the chi-square statistic. Because C-reactive protein values are skewed, median concentrations were computed and the significance of any differences in median values between patients and controls was assessed by using Wilcoxon's rank-sum test. Geometric mean concentrations of C-reactive protein were also computed after log transformation that resulted in nearly normal distribution. We used tests for trend to assess any relation of increasing C-reactive protein values with the risk of future vascular disease after dividing the sample into quartiles defined by the distribution of the control values. We obtained adjusted estimates by using conditional logistic-regression models that accounted for the matching variables and controlled for the random treatment assignment,

body-mass index, diabetes, history of hypertension, and parental history of coronary artery disease. Similar models were employed to adjust for measured base-line plasma concentrations of total and HDL cholesterol, triglyceride, lipoprotein(a), t-PA antigen, fibrinogen, D-dimer, and homocysteine. To evaluate whether aspirin affected these relations, analyses were repeated for all cases of myocardial infarction occurring on or before January 25, 1988 — the date when randomized aspirin assignment was terminated. All P values are two-tailed, and confidence intervals were calculated at the 95 percent level.

**RESULTS**

Table 1 shows the base-line characteristics of the study participants. As expected, those in whom myocardial infarction subsequently developed were more likely than those who remained free of vascular disease to have a history of hypertension or hyperlipidemia or a parental history of coronary artery disease. Similarly, those in whom stroke subsequently developed were more likely to be hypertensive. Because of the matching, patients and controls were similar in age and history of smoking.

Geometric mean and median plasma concentrations of C-reactive protein at base line were significantly higher among those in whom any vascular event subsequently developed than among those who remained free of vascular disease (P<0.001). The difference between patients and controls was greatest for those in whom myocardial infarction subsequently developed (1.51 vs. 1.13 mg per liter, P<0.001), although differences were also significant for stroke (P=0.03), particularly ischemic stroke (P=0.02). In contrast, concentrations of C-reactive protein were not significantly higher among those in whom venous thrombosis subsequently developed (P=0.34) (Table 2).

The relative risk of first myocardial infarction increased significantly with each increasing quartile of

base-line concentrations of C-reactive protein (P for trend across quartiles, <0.001), in such a way that the men in the highest quartile had a risk of future myocardial infarction almost three times that among those in the lowest quartile (relative risk, 2.9; 95 percent confidence interval, 1.8 to 4.6; P<0.001) (Table 3). Similarly, men with the highest base-line C-reactive protein values had twice the risk of future ischemic stroke (relative risk, 1.9; 95 percent confidence interval, 1.1 to 3.3; P=0.02). No significant associations were observed for venous thrombosis. The findings were similar in analyses limited to non-fatal events.

To evaluate whether increased base-line C-reactive protein values were associated with early rather than late thrombosis, we stratified the analysis of myocardial infarction according to the number of years of follow-up. The relative risk of future myocardial infarction that was associated with the highest quartile of C-reactive protein (as compared with the lowest quartile) ranged from 2.4 for events occurring in the first two years of follow-up to 3.2 for events occurring six or more years into follow-up (Table 4). Similarly, the relative risk of future myocardial infarction that was associated with a one-quartile change in the C-reactive protein concentration was stable over long periods (Fig. 1).

Smokers had significantly higher median concentrations of C-reactive protein than nonsmokers (2.20 vs. 1.19 mg per liter, P<0.001). By matching patients and controls for smoking status, we minimized the potential for confounding by smoking. To assess for effect modification, however, we repeated the analyses, limiting the cohort to nonsmokers. As Table 3 also shows, the relative risk of future myocardial infarction among nonsmokers increased sig-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PARTICIPANTS.**

CHARACTERISTIC	CARDIOVASCULAR DISEASE DURING FOLLOW-UP*				
	NONE (N=543)	ANY (N=543)	MYOCARDIAL INFARCTION (N=246)	STROKE (N=196)	VENOUS THROMBOSIS (N=101)
Age (yr)	59±9.1	59±9.2	58±8.6	62±9.1	57±9.4
Smoking status (%)					
Never smoked	44	44	45	42	50
Smoked in the past	41	41	40	40	44
Currently a smoker	15	15	15	18	6
Diabetes (%)	4	7	5	12	2
Body-mass index†	25±2.8	26±3.2	26±3.3	25±3.2	26±2.9
History of high plasma cholesterol (%)	9	13	17	10	7
History of hypertension (%)	16	29	27	35	20
Parental history of coronary artery disease (%)	10	13	17	11	8

\*Plus-minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

**TABLE 2.** BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN IN STUDY PARTICIPANTS WHO REMAINED FREE OF VASCULAR DISEASE DURING FOLLOW-UP (CONTROLS) AND IN THOSE IN WHOM MYOCARDIAL INFARCTION, STROKE, OR VENOUS THROMBOSIS DEVELOPED (PATIENTS).

CARDIOVASCULAR DISEASE DURING FOLLOW-UP	PLASMA C-REACTIVE PROTEIN			
	GEOMETRIC MEAN	P VALUE	MEDIAN	P VALUE
	mg/liter		mg/liter	
None (n = 543)	1.10	—	1.13	—
Any vascular event (n = 543)	1.37	<0.001	1.40	<0.001
Myocardial infarction (n = 246)	1.48	<0.001	1.51	<0.001
Any stroke (n = 196)	1.30	0.03	1.36	0.03
Ischemic stroke (n = 154)	1.36	0.01	1.38	0.02
Venous thrombosis (n = 101)	1.24	0.22	1.26	0.34

**TABLE 3.** RELATIVE RISK OF FUTURE MYOCARDIAL INFARCTION, STROKE, AND VENOUS THROMBOSIS ACCORDING TO BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN.

VASCULAR EVENT*	QUARTILE OF C-REACTIVE PROTEIN CONCENTRATION (mg/liter)				P FOR TREND
	≤0.55	0.56–1.14	1.15–2.10	≥2.11	
Myocardial infarction (total cohort)					
Relative risk	1.0	1.7	2.6	2.9	<0.001
95% CI	—	1.1–2.9	1.6–4.3	1.8–4.6	
P value	—	0.03	<0.001	<0.001	
Myocardial infarction (nonsmokers)					
Relative risk	1.0	1.7	2.5	2.8	<0.001
95% CI	—	1.0–2.8	1.5–4.1	1.7–4.7	
P value	—	0.06	<0.001	<0.001	
Ischemic stroke					
Relative risk	1.0	1.7	1.9	1.9	0.03
95% CI	—	0.9–2.9	1.1–3.2	1.1–3.3	
P value	—	0.07	0.02	0.02	
Venous thrombosis					
Relative risk	1.0	1.1	1.2	1.3	0.38
95% CI	—	0.6–2.0	0.7–2.3	0.7–2.4	
P value	—	0.78	0.51	0.42	

\*CI denotes confidence interval.

**TABLE 4.** RELATIVE RISK OF FIRST MYOCARDIAL INFARCTION ASSOCIATED WITH THE HIGHEST QUARTILE OF BASE-LINE PLASMA C-REACTIVE PROTEIN CONCENTRATIONS AS COMPARED WITH THE LOWEST QUARTILE, ACCORDING TO THE YEAR OF STUDY FOLLOW-UP.

GROUP*	FOLLOW-UP (YR)			
	0–2	2–4	4–6	≥6
Total cohort				
Relative risk	2.4	2.9	2.8	3.2
95% CI	0.9–6.8	1.1–7.6	1.1–6.9	1.2–8.5
P value	0.09	0.03	0.03	0.02
Nonsmokers				
Relative risk	2.8	2.9	2.7	2.9
95% CI	0.9–8.7	1.0–8.3	1.0–7.0	1.1–8.2
P value	0.07	0.05	0.05	0.04

\*CI denotes confidence interval.

nificantly with each increasing quartile of C-reactive protein (P for trend, <0.001). Similarly, the long-term effects of the concentration of C-reactive protein on the risk of myocardial infarction were virtually identical among nonsmokers (Table 4). Moreover, the relation between the concentration of C-reactive protein and myocardial infarction was not significantly altered in analyses that adjusted for body-mass index; the presence or absence of diabetes, hypertension, or a family history of premature coronary artery disease; and the plasma concentrations of total cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), t-PA antigen, D-dimer, fibrinogen, or homocysteine (Table 5).

Finally, to assess whether the beneficial effect of aspirin on the risk of myocardial infarction varied according to the base-line level of C-reactive protein, we repeated these analyses for events occurring before January 25, 1988, the date when randomized aspirin treatment was terminated.

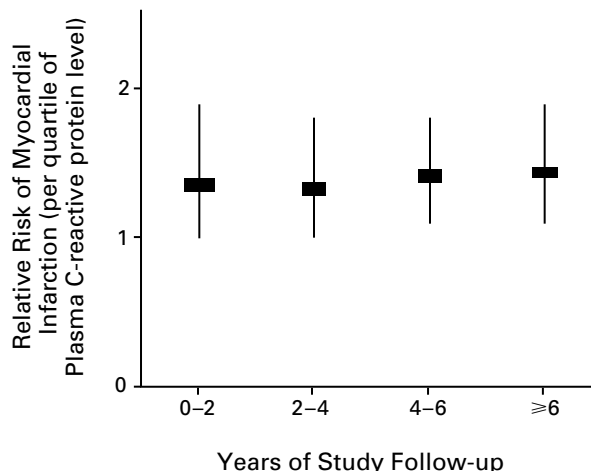
The risk of future myocardial infarction increased with each increasing quartile of C-reactive protein values for men randomly assigned to either aspirin or placebo, and the rates of myocardial infarction were lower in the aspirin group for all quartiles of C-reactive protein (Fig. 2). However, the magnitude of the beneficial effect of aspirin in preventing myocardial infarction was directly related to base-line levels of C-reactive protein. Specifically, randomized aspirin assignment was associated with a large and statistically significant reduction in the risk of myocardial infarction among men with base-line levels of C-reactive protein in the highest quartile (risk reduction, 55.7 percent; P = 0.02). Among those with base-line levels of C-reactive protein in the lowest quartile, however, the reduction in risk associated with aspirin was far smaller and no longer statistically significant (risk reduction, 13.9 percent; P = 0.77). These effects were linear across quartiles, so that the apparent benefit of aspirin diminished in magnitude with each decreasing quartile of inflammatory risk (Fig. 2). This finding remained essentially unchanged after further adjustment for other coronary risk factors, and the interaction between assignment to the aspirin group and base-line levels of C-reactive protein (treated as a log-transformed continuous variable) was statistically significant (P = 0.048).

## DISCUSSION

These prospective data indicate that the base-line plasma concentration of C-reactive protein in apparently healthy men can predict the risk of first myocardial infarction and ischemic stroke. In addition, the risk of arterial thrombosis associated with the level of C-reactive protein was stable over long periods and was not modified by other factors, including smoking status, body-mass index, blood pressure, or the plasma concentration of total or HDL cholesterol, tri-

glyceride, lipoprotein(a), t-PA antigen, D-dimer, fibrinogen, or homocysteine. In contrast, the benefits of aspirin in reducing the risk of a first myocardial infarction diminished significantly with decreasing concentrations of C-reactive protein — an intriguing finding, since this substance has antiinflammatory as well as antiplatelet properties. Finally, there was no significant association for venous thromboembolism, suggesting that the relation of inflammation to vascular risk may be limited to the arterial circulation.

Because blood samples were collected at base line, we can exclude the possibility that acute ischemia affected levels of C-reactive protein. Furthermore, the statistically significant associations observed were present among nonsmokers, indicating that the effect of C-reactive protein on vascular risk is not simply the result of cigarette smoking.<sup>11,12</sup> Thus, our prospective data relating base-line levels of C-reactive protein to future risks of myocardial infarction and stroke among apparently healthy men greatly

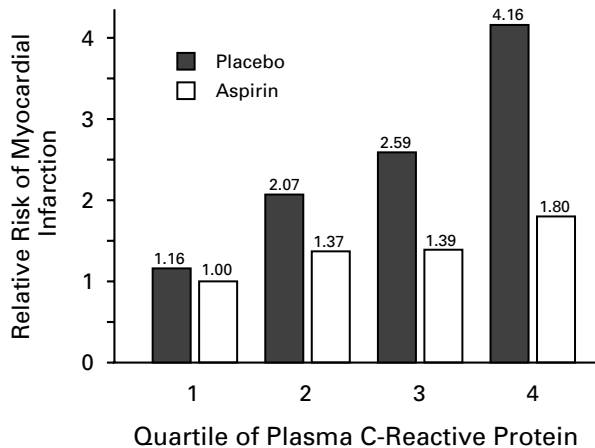


**Figure 1.** Relative Risk (and 95 Percent Confidence Intervals) of a First Myocardial Infarction Associated with Each Increasing Quartile of Base-Line C-Reactive Protein Values, According to the Year of Study Follow-up.

**TABLE 5.** RELATIVE RISK OF FUTURE MYOCARDIAL INFARCTION, ACCORDING TO BASE-LINE PLASMA CONCENTRATIONS OF C-REACTIVE PROTEIN, ADJUSTED FOR LIPID AND NONLIPID VARIABLES.\*

VARIABLES ADJUSTED FOR	QUARTILE OF C-REACTIVE PROTEIN CONCENTRATION (mg/liter)				P FOR TREND
	≤0.55	0.56-1.14	1.15-2.10	≥2.11	
Total and HDL cholesterol					
Adjusted relative risk	1.0	1.8	2.2	2.3	0.002
95% CI	—	1.0-3.1	1.3-3.7	1.4-3.9	
P value	—	0.05	0.004	0.002	
Triglycerides					
Adjusted relative risk	1.0	1.8	2.1	2.8	<0.001
95% CI	—	1.0-3.2	1.2-3.7	1.6-4.9	
P value	—	0.06	0.008	<0.001	
Lipoprotein(a)					
Adjusted relative risk	1.0	2.0	2.5	2.5	<0.001
95% CI	—	1.2-3.4	1.5-4.2	1.5-4.2	
P value	—	0.01	<0.001	<0.001	
t-PA antigen					
Adjusted relative risk	1.0	1.7	1.9	2.9	0.002
95% CI	—	0.9-3.4	1.0-3.6	1.5-5.6	
P value	—	0.13	0.06	0.002	
Total homocysteine					
Adjusted relative risk	1.0	1.8	2.9	3.6	<0.001
95% CI	—	1.1-3.1	1.7-4.8	2.1-5.9	
P value	—	0.02	<0.001	<0.001	
D-Dimer					
Adjusted relative risk	1.0	2.2	2.4	2.7	0.001
95% CI	—	1.2-4.1	1.3-4.2	1.5-4.7	
P value	—	0.007	0.003	<0.001	
Fibrinogen					
Adjusted relative risk	1.0	2.2	2.2	2.9	0.01
95% CI	—	1.1-4.7	1.0-4.4	1.4-5.9	
P value	—	0.04	0.04	0.005	
Body-mass index, diabetes, history of hypertension, and family history of coronary artery disease					
Adjusted relative risk	1.0	1.5	2.4	2.6	<0.001
95% CI	—	0.9-2.5	1.5-4.0	1.6-4.4	
P value	—	0.14	<0.001	<0.001	

\*All models were further adjusted for random assignment of patients to receive aspirin and beta carotene. CI denotes confidence interval.



**Figure 2.** Relative Risk of a First Myocardial Infarction Associated with Base-Line Plasma Concentrations of C-Reactive Protein, Stratified According to Randomized Assignment to Aspirin or Placebo Therapy.

Analyses are limited to events occurring before the unblinding of the aspirin component of the Physicians' Health Study. The reduction in the risk of myocardial infarction associated with the use of aspirin was 13.9 percent in the first (lowest) quartile of C-reactive protein values, 33.4 percent in the second quartile, 46.3 percent in the third quartile, and 55.7 percent in the fourth (highest) quartile.

extend previous observations from studies of acutely ill patients,<sup>9</sup> patients with symptomatic coronary disease,<sup>10</sup> or those at high risk partly because of cigarette smoking.<sup>11</sup> Moreover, in these data, the effects of C-reactive protein were independent of a large number of lipid-related and non-lipid-related risk factors.

The mechanism that relates the level of C-reactive protein to atherothrombosis is unclear. Previous infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus, or cytomegalovirus may be a source of the chronic inflammation detected by C-reactive protein.<sup>21-27</sup> It is also possible that C-reactive protein is a surrogate for interleukin-6,<sup>28</sup> a cellular cytokine associated with the recruitment of macrophages and monocytes into atherosclerotic plaques.<sup>29</sup> In addition, C-reactive protein can induce monocytes to express tissue factor, a membrane glycoprotein important in initiating coagulation.<sup>30</sup> Finally, it had been hypothesized that bronchial inflammation due to smoking was responsible for associations seen in previous studies relating C-reactive protein to vascular risk.<sup>11</sup> In this regard, our observation that the effect of C-reactive protein is present among nonsmokers makes bronchial inflammation a less likely mechanism. Furthermore, the finding that the effects are stable over long periods suggests that short-term effects on clotting are unlikely.

Our data regarding the interrelation of C-reactive protein and aspirin merit careful consideration. In

the Physicians' Health Study, aspirin reduced the risk of a first myocardial infarction by 44 percent.<sup>13</sup> The present findings indicate that the effect of aspirin in preventing a first myocardial infarction was greatest among the men with the highest base-line C-reactive protein concentrations and that the benefit diminished significantly with decreasing concentrations of this inflammatory marker. Thus, although the antiplatelet effects of aspirin may be modified by underlying inflammation, these data also suggest the possibility that the benefit of aspirin may have been due, at least in part, to antiinflammatory effects.<sup>31</sup> Alternatively, patients with large inflammatory burdens may have a distinct vascular mechanism leading to thrombosis that is affected differently by aspirin therapy. For example, the protective effect of aspirin may differ in the setting of plaque rupture as compared with focal endothelial erosion.<sup>32,33</sup>

The potential limitations of these data also merit consideration. First, our analyses are based on a single base-line determination that may not accurately reflect inflammatory status over long periods. Furthermore, although coefficients of variation were low, misclassification due to laboratory error cannot be ruled out. It is important to note, however, that neither of these sources of variability can account for the observed associations, since any random misclassification would bias results toward the null hypothesis. Since our study was limited to measures of C-reactive protein, other prospective studies evaluating specific cytokines, cellular adhesion molecules, and chronic infectious agents will be required to further elucidate the role of inflammation in the initiation and progression of atherosclerosis.

We draw four main conclusions from these data. First, among apparently healthy men, the base-line level of inflammation as assessed by the plasma concentration of C-reactive protein predicts the risk of a first myocardial infarction and ischemic stroke, independently of other risk factors. Second, the base-line concentration of C-reactive protein is not associated with the risk of venous thrombosis, a vascular event generally not associated with atherosclerosis. Third, C-reactive protein is not simply a short-term marker of risk, as has previously been demonstrated in patients with unstable angina,<sup>9</sup> but is also a long-term marker of risk, even for events occurring six or more years later. This observation suggests that the effects of inflammation are probably mediated through a chronic process and excludes the possibility that undetected acute illness at base line is responsible for the observed effects. Finally, the benefits of aspirin appear to be modified by underlying inflammation — an observation that raises the possibility of antiinflammatory as well as antiplatelet effects of this agent. The latter observation also suggests the possibility that other antiinflammatory agents may have a role in preventing cardiovascular

disease. Moreover, these data suggest that inflammatory markers such as C-reactive protein may provide a method of identifying people for whom aspirin is likely to be more or less effective — a hypothesis requiring direct testing in randomized trials.

Supported by grants (HL-26490, HL-34595, HL-46696, CA-34944, CA-42182, and CA-40360) from the National Institutes of Health. Dr. Ridker is supported by a Clinician Scientist Award from the American Heart Association.

## REFERENCES

- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242-50.
- Munro JM, Cotran RS. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Lab Invest* 1988;58:249-61.
- Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362:801-9.
- Alexander RW. Inflammation and coronary artery disease. *N Engl J Med* 1994;331:468-9.
- Nieminen MS, Mattila K, Valtonen V. Infection and inflammation as risk factors for myocardial infarction. *Eur Heart J* 1993;14:Suppl K:12-6.
- Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. *Am J Cardiol* 1990;65:168-72.
- de Beer FC, Hind CR, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischemia and infarction. *Br Heart J* 1982;47:239-43.
- Pietila K, Harmoinen A, Hermens W, Simoons ML, Van de Werf F, Verstraete M. Serum C-reactive protein and infarct size in myocardial infarction patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. *Eur Heart J* 1993;14:915-9.
- Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;331:417-24.
- Thompson SG, Kienast J, Pyke SDM, Haverkate F, van de Loo JCW. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med* 1995;332:635-41.
- Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol* 1996;144:537-47.
- Das I. Raised C-reactive protein levels in serum from smokers. *Clin Chim Acta* 1985;153:9-13.
- Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129-35.
- Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145-9.
- Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy adults: implications for reference interval and epidemiologic methods. *Clin Chem* 1997;43:52-8.
- Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373-81.
- Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 1993;270:2195-9.
- Ridker PM, Hennekens CH, Selhub J, Miletich JP, Malinow MR, Stampfer MJ. Interrelation of hyperhomocyst(e)inemia, factor V Leiden, and risks of future venous thromboembolism. *Circulation* (in press).
- Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. *Lancet* 1993;341:1165-8.
- Ridker PM, Hennekens CH, Cerskus A, Stampfer MJ. Plasma concentration of cross-linked fibrin degradation product (D-dimer) and the risk of future myocardial infarction among apparently healthy men. *Circulation* 1994;90:2236-40.
- Buja LM. Does atherosclerosis have an infectious etiology? *Circulation* 1996;94:872-3.
- Grayston JT. Chlamydia in atherosclerosis. *Circulation* 1993;87:1408-9.
- Saikkun P, Leinonen M, Tenkanen L, et al. Chronic *Chlamydia pneumoniae* infection as a risk factor for coronary heart disease in the Helsinki Heart Study. *Ann Intern Med* 1992;116:273-8.
- Thom DH, Grayston JT, Siscovick DS, Wang S-P, Weiss NS, Daling JR. Association of prior infection with *Chlamydia pneumoniae* and angiographically demonstrated coronary artery disease. *JAMA* 1992;268:68-72.
- Melnick JL, Adam E, DeBakey ME. Possible role of cytomegalovirus in atherogenesis. *JAMA* 1990;263:2204-7.
- Mendall MA, Goggin PM, Molineaux N, et al. Relation of *Helicobacter pylori* infection and coronary heart disease. *Br Heart J* 1994;71:437-9.
- Patel P, Mendall MA, Carrington D, et al. Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995;311:711-4. [Erratum, *BMJ* 1995;311:985.]
- Bataille R, Klein B. C-reactive protein levels as a direct indicator of interleukin-6 levels in humans in vivo. *Arthritis Rheum* 1992;35:982-4.
- Biasucci LM, Vitelli A, Liuzzo G, et al. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;94:874-7.
- Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993;82:513-20.
- Vane J. The evolution of non-steroidal anti-inflammatory drugs and their mechanisms of action. *Drugs* 1987;33:Suppl 1:18-27.
- van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation* 1994;89:36-44.
- Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996;93:1354-63.

**CORRECTION**

**Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men**

Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men . On page 974, the sentence that begins in line 13 under the heading "Laboratory Analysis" should have read, "The C-reactive protein assay was standardized according to the WHO First International Reference Standard and had a sensitivity of 0.08  $\mu\text{g}$  per *milliliter*," not "0.08  $\mu\text{g}$  per *microliter*," as printed.