Association of C-Reactive Protein With Carotid Atherosclerosis in Men and Women: The Framingham Heart Study


Objective—The objective of this study was to examine the relationship between C-reactive protein (CRP) and carotid atherosclerosis.

Background—Levels of CRP, a nonspecific marker of inflammation, predict risk for cardiovascular events. However, the association between CRP and direct measures of atherosclerosis is not well established.

Methods and Results—Subjects (n=3173, 52% women, mean age 55) in the offspring cohort of the Framingham Heart Study received a CRP measurement and then underwent carotid ultrasonography 4 years later. Carotid stenosis (≥25%) was present in 24% of men and 14% of women. Age-adjusted odds ratios for carotid stenosis were 1.62 (95% CI 1.12 to 2.36) for men and 3.90 (CI 2.44 to 6.44) for women in the fourth quartile of CRP compared with those in the lowest quartile. After further adjustment for traditional cardiovascular disease risk factors, the odds ratio remained significant for women (2.97, CI 1.72 to 5.25) but not for men. Similarly, after multivariable adjustment, women in the fourth CRP quartile had a higher mean internal carotid intima-media thickness than those in the lowest CRP quartile (P=0.001). There was no association between common carotid intima-media thickness and CRP.

Conclusions—There is a graded association between CRP and carotid atherosclerosis in women but not in men. The significance of this difference between sexes merits further investigation.

Key Words: C-reactive protein ■ carotid arteries ■ carotid stenosis ■ risk factors ■ atherosclerosis

High levels of C-reactive protein (CRP) have been shown to predict incident cardiovascular and cerebrovascular events. Medications with anti-inflammatory properties may reduce this risk in patients with high CRP levels. However, the mechanism underlying the importance of CRP, a nonspecific serum marker of inflammation, remains unclear. Elevated CRP levels may reflect a higher atherosclerotic burden, a higher tendency for plaque rupture and thrombosis, or both. An association between CRP and direct measures of atherosclerosis has not been firmly established.

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A better understanding of this link may clarify the mechanism by which CRP levels predict future cardiovascular events and have implications for screening potential candidates for anti-inflammatory treatments.

High-resolution B-mode ultrasonography has been used as a noninvasive measure of atherosclerosis. In particular, carotid plaque and intimal medial thickness (IMT) by ultrasound have been shown to correlate with prevalent cardiovascular disease, atherosclerosis in other vascular beds, and incident myocardial infarction and stroke. Risk factors for carotid atherosclerosis are generally similar to those for coronary heart disease.

The association of carotid disease with CRP has been examined primarily in referral samples or disease cohorts, with some studies reporting a positive association. A few studies have been performed in broader samples, and these have not found an association. Previous reports have assessed atherosclerosis at different sites within the carotid, and it is unclear to what extent the choice of site has influenced the results. In addition, there are conflicting data regarding the influence of sex on the relationship between CRP and atherosclerosis.

The Framingham Heart Study is a community-based cohort in which both CRP measurements and carotid ultrasound tests were performed.

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were obtained in 3173 men and women. We examined the association between CRP and carotid atherosclerosis and investigated whether this association varied by sex or by site of measurement.

Methods

Subjects and Measurements of Risk Factors

The selection criteria and study design of the Framingham Heart Study have been detailed previously.20 Subjects considered for this investigation were participants in the offspring cohort of the Framingham Heart Study, which began in 1971 with the recruitment of 5124 men and women who were offspring and spouses of offspring of the original Framingham Heart Study cohort and ranged in age from 5 to 70 years. There were 3798 participants in offspring study examination cycle 5 (1991 to 1995), and 3696 (97%) received CRP testing. A total of 3173 (86%) of these participants also underwent B-mode carotid ultrasonography during the sixth examination cycle (1995 to 1999); this group formed the main cohort for the analyses.

The medical history and physical examination conducted during the fifth examination cycle was the source of the cardiovascular risk factor data. Persons were classified as current cigarette smokers if they reported having smoked cigarettes during the previous year. Systolic and diastolic blood pressure values were the means of two physician-obtained measurements. Diabetes was defined by history of a fasting glucose ≥140 mg/dL or use of insulin or hypoglycemic medication. The protocol was approved by the Institutional Review Board of Boston Medical Center.

C-Reactive Protein Measurements

Blood samples were collected from an antecubital vein between 8:00 and 9:00 AM, with subjects supine after an overnight fast. CRP levels were determined by enzyme immunoassay (Hemagen Diagnostics, Inc). Details of the assay have been described previously.3 The correlation coefficient for replicate CRP measurements on 36 subjects was 0.86. Because CRP was used as a categorical predictor in our analyses, we also calculated a kappa statistic to assess between-assay agreement. The kappa value was 0.75 for CRP values in the fourth quartile compared with the first through third quartiles.

Carotid Ultrasonography

Ultrasound studies were acquired and images analyzed according to a standard protocol.10,12 Imaging was conducted using a high-resolution 7.5 MHz transducer for the common carotid artery and a 5.0 MHz transducer for the carotid bulb and internal carotid artery (Toshiba Medical Systems). Two images were obtained at the level of the distal common carotid artery, 2 at the carotid artery bulb, and 2 in the proximal 2 cm of the internal carotid artery. A single trained sonographer who was blinded to all clinical information made measurements and was over-read by one of the investigators (J.F.P.). Ultrasound studies were conducted on nearly all examination cycle 6 participants (3407 of 3532; 96%).

A subjective estimate was made by the sonographer of the internal carotid artery narrowing, graded as 0%, 1 to 24%, and 25 to 49% when Doppler-derived peak systolic velocities in the internal carotid artery were <150 cm/s. Internal carotid narrowing of hemodynamic significance (≥50%) was defined as present when peak-systolic velocities in the internal carotid artery were ≥150 cm/s. For this article, the degree of stenosis was based on the more diseased artery.

Measurements of IMT were made at each of the 3 sites on both sides. The maximal IMT in each site was defined as the mean of the maximal IMT measurements of the near and far walls. The maximal IMT measurement has been shown to correlate well with cardiovascular risk in other studies.6 The internal carotid/bulb IMT was defined as the mean of the 4 maximal IMT measurements for the carotid artery bulb and the internal carotid artery on both sides. The common carotid IMT was defined as the mean of the maximal IMT measurements for the right and left common carotid arteries. All IMT images were gated to diastole.

| TABLE 1. Age-Adjusted Baseline Characteristics, According to Degree of Carotid Stenosis |
|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
| Men (n=1508)                            | Women (n=1665)                           |
| <25% Stenosis                           | ≥25% Stenosis                           | <25% Stenosis                           | ≥25% Stenosis                           |
| Mean age, y                             | 52.6                                    | 61.2                                    | 53.6                                    | 61.1                                    |
| Mean SBP, mm Hg                         | 127.3                                   | 132.1                                   | 122.8                                   | 129.5                                   |
| Current smoking, %                      | 16.2                                    | 25.9                                    | 16.1                                    | 35.1                                    |
| Diabetes, %                             | 5.7                                     | 14.8                                    | 4.1                                     | 10.1                                    |
| Mean BMI, kg/m²                         | 28.1                                    | 28.8                                    | 26.7                                    | 27.6                                    |
| Total cholesterol, mg/dL                | 200.5                                   | 203.1                                   | 206.9                                   | 217.0                                   |
| HDL cholesterol, mg/dL                  | 43.3                                    | 41.6                                    | 56.7                                    | 52.0                                    |
| Hypertension therapy, %                 | 17.6                                    | 25.5                                    | 14.8                                    | 31.7                                    |
| CVD, %                                  | 7.9                                     | 19.6                                    | 4.0                                     | 17.6                                    |
| Mean CRP, mg/L                          | 3.6                                     | 4.8                                     | 4.6                                     | 7.3                                     |
| Estrogen replacement, %                 | –                                       | –                                       | 17.8                                    | 11.9                                    |
| Postmenopausal, %                       | –                                       | –                                       | 65.5                                    | 64.3                                    |

SBP indicates systolic blood pressure; BMI, body mass index; CVD, cardiovascular disease, defined as a history of myocardial infarction; stable or unstable angina; congestive heart failure; intermittent claudication, or stroke or transient ischemic attack.

Statistical Methods

Bivariate analyses were performed comparing the prevalence of coronary heart disease, risk factors for coronary heart disease, and mean CRP in subjects with and without carotid stenosis (assessed at the subsequent examination cycle) using t tests or chi-square tests where appropriate. Comparisons were made between those with 0 to 24% carotid stenosis and those with 25 to 100% carotid stenosis. This cut point has been used in previous carotid ultrasound studies in Framingham and other cohorts.22,23 The kappa value (intra-reader) for 25% carotid stenosis from 158 paired readings on 79 studies was 0.69. Secondary analyses were performed (1) using a cut point of 50% carotid stenosis and (2) comparing subjects with 0% stenosis to those with ≥25% stenosis.

Both pooled and sex-specific analyses were conducted. Age- and sex-adjusted odds ratios for carotid stenosis were calculated using multivariable logistic regression. Quartiles of CRP were included as categorical predictor variables in the regression analyses. We further adjusted for the effect of traditional risk factors by including the following variables as covariates: smoking, systolic blood pressure, use of antihypertensive therapy, diabetes, body mass index, total/HDL cholesterol ratio, menopausal status, and use of hormone replacement therapy. Secondary analyses were performed after excluding subjects who were using cholesterol-lowering medications because recent evidence suggests that statin medications may reduce CRP levels.4 In similar fashion, we analyzed the adjusted association between CRP quartile and carotid IMT using analysis of covariance. The effect of CRP on internal carotid/bulb IMT and common carotid IMT was analyzed separately.

The SAS System (SAS Institute Inc) was used to perform all statistical analyses. All statistical tests were two-sided and P<0.05 was considered significant.

Results

The mean age of the 3173 subjects was 55 years at examination cycle 5, and 52% of subjects were women. Twenty-four percent of men and 14% of women had carotid stenosis of 25% or greater on ultrasound at examination cycle 6. Age-adjusted baseline characteristics, stratified by the presence of carotid stenosis (≥25%), are shown in Table 1. Subjects with carotid stenosis had a higher age-adjusted mean
We found that elevated CRP levels were associated with measures of carotid atherosclerosis. This finding persisted,

**TABLE 2. Age-Adjusted and Multivariable-Adjusted Odds Ratios for Carotid Stenosis (≥25%), by Quartile of CRP**

<table>
<thead>
<tr>
<th>CRP quartile*</th>
<th>Pooled</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.45 (1.07, 1.97)</td>
<td>1.30 (0.88, 1.92)</td>
<td>1.61 (0.95, 2.78)</td>
</tr>
<tr>
<td>3</td>
<td>1.66 (1.24, 2.25)</td>
<td>1.39 (0.95, 2.04)</td>
<td>2.55 (1.57, 4.26)</td>
</tr>
<tr>
<td>4</td>
<td>2.37 (1.78, 3.18)</td>
<td>1.62 (1.12, 2.36)</td>
<td>3.90 (2.44, 6.44)</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for age (and for sex in pooled analyses).
†Odds ratios adjusted for age, sex (in pooled analyses), smoking, systolic blood pressure, diabetes, total to HDL cholesterol ratio, body mass index, hypertension therapy, menopausal status (for women), and use of estrogen replacement therapy (for women).

CRP (men: 4.81 versus 3.56 mg/L, women: 7.26 versus 4.55 mg/L, P<0.005 for both sexes) and a higher prevalence of cardiovascular disease (Table 1).

Overall mean CRP levels were 3.87 and 4.93 mg/L for men and women, respectively. Ten percent of men and 14% of women had CRP levels of 10 mg/L or greater. The quartile ranges for CRP (in mg/L) in men were 0 to 0.34, 0.35 to 1.45, 1.46 to 4.32, and 4.33 to 51 and in women, 0 to 0.28, 0.29 to 1.71, 1.72 to 5.59, and 5.60 to 333.4.

Age-adjusted odds ratios for carotid stenosis by CRP quartile are shown in Table 2. Subjects in the highest quartile of CRP had a significantly greater prevalence of carotid stenosis compared with those in the first quartile (odds ratio, men: 1.62, 95% CI 1.12 to 2.36, women: 3.90, 95% CI 2.44 to 6.44). After multivariable adjustment, the association remained significant in women, with an odds ratio for the fourth quartile of 2.97 (95% CI 1.72 to 5.25), but not in men.

We repeated these analyses after excluding subjects with clinically apparent cardiovascular disease at examination cycle 5, when CRP levels were obtained, and the results were similar (Table 3). These results also were similar after the exclusion of subjects who used cholesterol-lowering medications at either examination cycle (odds ratio for women in the fourth CRP quartile 3.24, 95% CI 1.74 to 6.25). Additional analyses were performed using a cut point of 50% carotid stenosis and comparing subjects with 0% versus ≥25% stenosis. We found odds ratios of similar magnitude but with wider confidence intervals when a cut point of 50% stenosis was used (data not shown).

Analyses of the association of CRP with internal carotid/bulb IMT and common carotid IMT are shown in Tables 4 and 5, respectively. In age-adjusted analyses, men and women in the highest CRP quartile had significantly higher mean internal carotid/bulb IMT (P<0.0001). After multivariable adjustment, this association remained significant in women (P=0.0001) but not in men (P=0.096; Table 4). In the multivariable analyses, total cholesterol was positively

**TABLE 3. Age-Adjusted and Multivariable-Adjusted Odds Ratios for Carotid Stenosis (≥25%) by Quartile of CRP, After Excluding Subjects With Prevalent CVD**

<table>
<thead>
<tr>
<th>CRP quartile*</th>
<th>Pooled</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.32 (0.95, 1.85)</td>
<td>1.13 (0.74, 1.74)</td>
<td>1.51 (0.85, 2.73)</td>
</tr>
<tr>
<td>3</td>
<td>1.50 (1.10, 2.08)</td>
<td>1.27 (0.84, 1.92)</td>
<td>2.17 (1.29, 3.79)</td>
</tr>
<tr>
<td>4</td>
<td>2.16 (1.59, 2.97)</td>
<td>1.54 (1.03, 2.30)</td>
<td>2.94 (1.76, 5.09)</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for age (and for sex in pooled analyses).
†Odds ratios adjusted for age, sex (in pooled analyses), smoking, systolic blood pressure, diabetes, total to HDL cholesterol ratio, body mass index, hypertension therapy, menopausal status (for women), and use of estrogen replacement therapy (for women).

Associated with internal carotid/bulb IMT in men (P=0.01) and women (P=0.001), and HDL cholesterol had a negative association with internal carotid/bulb IMT in women (P<0.001).

Similarly, in age-adjusted analyses, subjects in the highest CRP quartile had higher common carotid IMT (Table 5). However, after multivariable adjustment, there were no significant differences in common carotid IMT across quartiles of CRP for either sex.

**Discussion**

We found that elevated CRP levels were associated with measures of carotid atherosclerosis. This finding persisted,

**TABLE 4. Age-Adjusted and Multivariable-Adjusted Mean Internal Carotid IMT in mm (SE), by Quartile of CRP**

<table>
<thead>
<tr>
<th>CRP quartile*</th>
<th>Pooled</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.96 (0.018)</td>
<td>1.03 (0.025)</td>
<td>0.83 (0.021)</td>
</tr>
<tr>
<td>2</td>
<td>0.97 (0.018)</td>
<td>1.07 (0.025)</td>
<td>0.82 (0.021)</td>
</tr>
<tr>
<td>3</td>
<td>1.05 (0.018)†</td>
<td>1.12 (0.025)†</td>
<td>0.91 (0.021)†</td>
</tr>
<tr>
<td>4</td>
<td>1.15 (0.018)†</td>
<td>1.21 (0.025)†</td>
<td>1.03 (0.021)†</td>
</tr>
</tbody>
</table>

*IMT adjusted for age and sex (in pooled analyses).
†P<0.05, compared with first quartile.
‡IMT adjusted for age, sex (in pooled analyses), smoking, systolic blood pressure, diabetes, total to HDL cholesterol ratio, body mass index, hypertension therapy, use of estrogen replacement therapy (for women), and menopausal status (for women).
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TABLE 5. Age-Adjusted and Multivariable-Adjusted Mean Common Carotid IMT in mm (SE), by Quartile of CRP

<table>
<thead>
<tr>
<th>CRP quartile*</th>
<th>Pooled</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.72 (0.006)</td>
<td>0.75 (0.009)</td>
<td>0.69 (0.007)</td>
</tr>
<tr>
<td>2</td>
<td>0.73 (0.006)</td>
<td>0.76 (0.009)</td>
<td>0.69 (0.007)</td>
</tr>
<tr>
<td>3</td>
<td>0.73 (0.006)†</td>
<td>0.78 (0.009)†</td>
<td>0.70 (0.007)</td>
</tr>
<tr>
<td>4</td>
<td>0.77 (0.006)†</td>
<td>0.81 (0.009)†</td>
<td>0.74 (0.007)†</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex (in pooled analyses).
†P<0.05, compared with first quartile.
‡P<0.05, compared with first quartile.

near areas of hemodynamic stress.27 Furthermore, in the absence of plaque, common carotid IMT may be influenced by medial thickening rather than intimal thickening.28 Kiechl and Willeit27 have previously reported that risk factors for “focal stenotic disease” (more likely to form in the internal carotid artery) differ from those for nonstenotic atherosclerosis (diffuse predilection); in particular, procoagulant factors, including fibrinogen, which is also an inflammatory marker, were more likely to be associated with stenotic disease. Finally, prospective studies have found internal carotid IMT to be a better predictor of prevalent cardiovascular disease and risk for future cardiac events.6,9

We also analyzed both carotid stenosis and carotid IMT because the determinants of established atherosclerotic plaque may differ from the determinants of early, vascular thickening, even at the same site.25,29 Our findings for carotid stenosis (≥25%) were similar to those for internal carotid/bulb IMT. A similar pattern was also found when we substituted a more stringent threshold for carotid stenosis (≥50%), although the confidence intervals were wide because of the low prevalence of this degree of stenosis.

Our investigation extends the results of previous studies by examining an unselected cohort of generally healthy middle-aged men and women with a sample size of more than 3000 subjects. Differences in the site and method of carotid measurement may also account for differences between studies. Some studies focused on the common carotid IMT;12,24 others on the internal carotid IMT;18 and still others on the average IMT in the common carotid artery, carotid bulb, and internal carotid artery.15,17 Thickening may progress at different rates in the common carotid and internal carotid arteries, and associations with risk factors may differ between these sites.9

In our study, a single experienced sonographer and over-reader (J.F.P.) were used and internal and common carotid IMT measures were analyzed separately using well-described methods.8,21 We found that CRP was more strongly associated with internal carotid/bulb IMT than with common carotid IMT. Internal carotid/bulb IMT may be a better marker of early, focal atherosclerosis compared with common carotid IMT because plaques have a greater tendency to form after we adjusted for traditional cardiovascular risk factors, in women but not in men. Even modest elevations of CRP in women predicted a 2- to 3-fold increase in the odds of having carotid stenosis ≥25%. Similar associations were noted between CRP levels and IMT assessed at the internal carotid artery and carotid bulb.

Previous studies relating CRP levels to carotid atherosclerosis have yielded conflicting results. A positive association has been reported in neurological inpatients,13 dyslipidemic men,14 and ever-smoking women.24 Other studies have found a weak or nonexistent association after adjustment for age and other cardiovascular disease risk factors.15–18,25,26 Differences in study populations may have contributed to the variability in these findings because the majority of studies have been based on patients with specific disease conditions, and some may have been limited by small sample sizes.12–16 Our investigation extends the results of previous studies by examining an unselected cohort of generally healthy middle-aged men and women with a sample size of more than 3000 subjects.

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CRP with a carotid ultrasound study 4 years later should probably be viewed as a “cross-sectional” association, a measurable degree of plaque progression may occur over this time interval.\cite{25,37} Thus, our findings may also reflect an association between CRP and incident atherosclerosis, in addition to prevalent atherosclerosis. Additional studies are needed to examine this temporal relationship in large cohorts using rigorous, reproducible measures of carotid atherosclerosis obtained at baseline and follow-up.

Although the intra-reader reproducibility in our study compared favorably with those of previous studies using ultrasound and conventional angiography,\cite{38} misclassification may have occurred in the subjective assessment of carotid stenosis. We performed additional analyses comparing the 0% to the 25 to 100% stenosis categories, reasoning that subjects with mild (1 to 24%) stenosis were at highest risk of being misclassified. Our findings did not differ from those in the main analyses. Because scans were read in a blinded fashion, we believe that misclassification of carotid stenosis would be random and lead to a conservative bias.

In contrast to most\cite{1} but not all\cite{2} previous studies, we used a commercially available assay rather than an in-house research assay for CRP. Commercial assays may not perform as well as research assays, particularly for the lower range of CRP values, although they may be more representative of assays available for clinical use.\cite{2} The kappa statistic of 0.75 suggests that this assay was adequate for separation of CRP values in the highest quartile from those in the lower quartiles, which corresponds to the use of CRP in our analyses. Any misclassification of CRP quartile would be expected to bias our results toward the null. Although it is possible that measurement variation systematically affected men more than women, we believe this is unlikely. As in other studies, few subjects had CRP levels of 10 mg/L or higher, a threshold commonly used to indicate clinically important inflammation.

Although we viewed carotid atherosclerosis as a marker for overall atherosclerotic burden, this disease may progress in other vascular territories, including the coronary circulation, at different rates. The results of this study may not be generalizable to atherosclerosis in other major vascular beds.

In summary, levels of CRP were associated with subsequent measures of carotid atherosclerosis in a large community-based cohort. An increased atherosclerotic burden may explain part of the increased risk of cardiovascular events in individuals, particularly women, with elevated CRP levels. The importance of the sex-related differences that we observed require confirmation in other studies but may have important implications for screening subjects at risk for cardiovascular disease and identifying candidates for anti-inflammatory therapy. In addition, further studies are warranted to determine whether carotid atherosclerosis progression is a useful marker of response to anti-inflammatory treatments.

Acknowledgments
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