Association of Carotid Artery Intima-Media Thickness, Plaques, and C-Reactive Protein With Future Cardiovascular Disease and All-Cause Mortality: The Cardiovascular Health Study

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Association of Carotid Artery Intima-Media Thickness, Plaques, and C-Reactive Protein With Future Cardiovascular Disease and All-Cause Mortality

The Cardiovascular Health Study

Jie J. Cao, MD, MPH; Alice M. Arnold, PhD; Teri A. Manolio, MD, PhD; Joseph F. Polak, MD, MPH; Bruce M. Psaty, MD, PhD; Calvin H. Hirsch, MD; Lewis H. Kuller, MD, PhD; Mary Cushman, MD, MSc

Background—Carotid atherosclerosis, measured as carotid intima-media thickness or as characteristics of plaques, has been linked to cardiovascular disease (CVD) and to C-reactive protein (CRP) levels. We investigated the relationship between carotid atherosclerosis and CRP and their joint roles in CVD prediction.

Methods and Results—Of 5888 participants in the Cardiovascular Health Study, an observational study of adults aged ≥65 years, 5020 without baseline CVD were included in the analysis. They were followed up for as long as 12 years for CVD incidence and all-cause mortality after baseline ultrasound and CRP measurement. When CRP was elevated (>3 mg/L) among those with detectable atherosclerosis on ultrasound, there was a 72% (95% CI, 1.46 to 2.01) increased risk for CVD death and a 52% (95% CI, 1.37 to 1.68) increased risk for all-cause mortality. Elevated CRP in the absence of atherosclerosis did not increase CVD or all-cause mortality risk. The proportion of excess risk attributable to the interaction of high CRP and atherosclerosis was 54% for CVD death and 79% for all-cause mortality. Addition of CRP or carotid atherosclerosis to conventional risk factors modestly increased in the ability to predict CVD, as measured by the c statistic.

Conclusions—In older adults, elevated CRP was associated with increased risk for CVD and all-cause mortality only in those with detectable atherosclerosis based on carotid ultrasound. Despite the significant associations of CRP and carotid atherosclerosis with CVD, these measures modestly improve the prediction of CVD outcomes after one accounts for the conventional risk factors. (Circulation. 2007;116:32-38.)

Key Words: aging ■ arteriosclerosis ■ atherosclerosis ■ cardiovascular diseases ■ carotid arteries ■ inflammation

Both carotid intima-media thickness (IMT) and plaques are measures of carotid atherosclerosis. Carotid IMT has been linked to many cardiovascular outcomes, including cerebral and coronary events. Characteristics of carotid plaque have been associated with stroke risk and coronary events in prospective studies. With the growing interest in cardiovascular disease (CVD) risk stratification by combining vascular imaging with conventional risk factors, it is essential to understand the relationship between carotid IMT and plaque and their independent and combined contribution to the risk of coronary as well cerebrovascular events.

In addition to ultrasonographic measures of atherosclerosis, C-reactive protein (CRP) has been shown to be a risk factor for CVD. Although higher CRP is associated with atherosclerosis measures such as higher carotid IMT and complex plaque, we have shown that the association of CRP with stroke is more apparent in the presence of a higher carotid IMT. Whether the association of CRP with CVD risk is modified by the presence of carotid atherosclerosis has not been explored fully.

In the present study, we evaluated the hypothesis that CRP is less predictive of CVD outcomes in the absence of atherosclerosis by investigating the associations of carotid IMT, carotid plaque, and CRP, alone and in combination, with incident myocardial infarction, stroke, CVD death, and all-cause mortality. We also examined the roles of CRP and carotid atherosclerosis in CVD prediction.
Methods
We studied participants of the Cardiovascular Health Study (CHS), a population-based, prospective study of men and women aged ≥65 years. Between 1989 and 1990, 5201 participants were enrolled from Medicare eligibility lists in 4 counties: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Allegheny County, Pennsylvania. To increase their representation, a second cohort of 687 black participants was enrolled between 1992 and 1993 with the use of similar methods. Details of the study design have been published.14-15 The study was approved by the institutional review boards at each participating center. All participants gave informed consent.

All participants underwent baseline clinical examinations, which included medical history, physical examination, and carotid ultrasound. Blood was drawn in the morning after an overnight fast. Samples were promptly centrifuged at 3000g for 10 minutes at 4°C. Aliquots of plasma were stored in a central laboratory at −70°C. CRP was measured in all stored baseline plasma samples by a high-sensitivity immunoassay, with an interassay coefficient of variation of 6.25%.16 The diagnosis of diabetes mellitus was made following American Diabetes Association criteria as fasting glucose ≥126 mg/dL or use of insulin or oral glucose-lowering agents. Impaired fasting glucose was defined as fasting glucose >110 and <126 mg/dL.

The carotid arteries were evaluated at baseline with high-resolution B-mode ultrasonography (model SSA-270A; Toshiba America Medical Systems, Tustin, Calif). One longitudinal image of the common carotid artery and 3 longitudinal images of the internal carotid artery were acquired. The maximal IMT of the common carotid artery and of the internal carotid artery was defined as the mean of the maximal IMT of the near and far walls on both the left and right sides. Focal plaques, when present, were included in the maximum IMT measurement. Carotid IMT was defined as a composite measure that combined the maximum common and internal carotid wall thickness of the left and right carotid arteries after standardization (subtraction of the mean and division by the standard deviation).17 The ultrasound reading center located in Boston, Mass, was responsible for developing standardized protocols for both scanning and interpretation of carotid sonographic images. The ultrasound protocol, including measurement and reading methods, has been published.18 The interreader variability defined by Spearman correlation coefficients on maximum wall thickness of the common carotid artery was 0.91 and of the internal carotid artery was 0.92.20 The interreader and interobserver agreement were 0.69 and 0.58 for the common carotid artery and 0.91 and of the internal carotid artery.

Lesion texture was classified as homogeneous or heterogeneous. In the following American Diabetes Association criteria as fasting glucose ≥126 mg/dL or use of insulin or oral glucose-lowering agents. Impaired fasting glucose was defined as fasting glucose >110 and <126 mg/dL.

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Carotid plaque, defined by the appearance of the largest focal lesion, was classified by surface characteristics, echogenicity, and texture. Surface characteristics were classified as smooth, mildly irregular (height variations of 0.4 mm), markedly irregular (height variations of >0.4 mm), and ulcerated (a discrete depression of >2 mm in width extended into the media). Lesion echogenicity was characterized as hypoechoic, isoechoic, hyperechoic, or calcified. Lesion texture was classified as homogeneous or heterogeneous. In case of multiple focal lesions, the largest lesion on each side was measured.20 Participants were then classified as having no plaque, intermediate-risk plaque, and high-risk plaque. Those with no plaque were defined as having a smooth intimal surface with no focal thickening. High-risk plaque was defined as presence of markedly irregular or ulcerated surface or hypodense or heterogeneous plaques that occupied >50% of the total plaque volume, those features reportedly associated with clinical CVD.2,3,5,20,21 The remaining plaques, including hyperdense, calcified, or homogenous plaques or those with mildly irregular surface, were defined as intermediate risk. When >1 type of plaque was detected in an individual, the plaque risk was determined by the more severe type. In some analyses, we grouped carotid findings into binary variables: detectable and minimal atherosclerosis. Detectable atherosclerosis was defined as present for participants in the upper 2 tertiles of carotid wall thickness or in the intermediate- or high-risk plaque groups.

Minimal atherosclerosis was defined as having the lowest tertile of IMT and no plaque.

The methods of ascertainment and classification of incident stroke and myocardial infarction have been reported.21 Participants were examined annually at each clinical site. In addition, telephone interviews were alternated with clinic visits so that contacts were every 6 months. Follow-up was complete through June 30, 2001. Potential vascular events were validated through medical record review by committees. Myocardial infarction and stroke included incident fatal and nonfatal events. Composite CVD was defined to include any incident myocardial infarction, stroke, or CVD death.

Of the 5888 CHS participants, 868 were excluded from analysis because of prebaseline myocardial infarction or stroke (n=765), missing CRP value (n=72), or missing carotid ultrasound (n=31).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analysis
Analyses were done with the use of SPSS for Windows, version 11.0.1 (SPSS, Inc, Chicago, Ill) and STATA, version 9.2 (College Station, Tex). Incidence rates of CVD were calculated by dividing the total number of events by the total person-years at risk over the follow-up time within groups defined by the carotid IMT tertile, plaque risk group, and CRP level. Pearson correlation coefficients were computed to assess the linear relationships among carotid IMT, CRP, and plaque. CRP was log-transformed when modeled continuously. Hazard ratios (HRs) from multivariable Cox proportional hazards models were used to estimate the relative risks (RRs) associated with high CRP, carotid IMT tertile, and plaque characteristics for CVD outcomes and all-cause mortality. The proportional hazards assumption was assessed for the 3 measures of interest (IMT, plaque risk group, and high CRP) by testing each with an interaction for time in a Cox model. No significant interactions with time were found. In addition, we examined Kaplan-Meier plots visually to look for inconsistent effects over time. Participants who died or were lost to follow-up before the event of interest or June 30, 2001, were censored at the time of death or last follow-up. Multivariable models were adjusted for age and sex and then further adjusted for race, systolic and diastolic blood pressure, use of antihypertensive medications, body mass index, smoking (never, former, current), and amount smoked (ln[pack-years]), high-density lipoprotein and low-density lipoprotein cholesterol, and diabetes (none, impaired fasting glucose, diabetes). All conventional risk factors were measured at the baseline examination and were imputed if missing, as previously described.23 The maximum percentage missing and imputed for any variable was 3.2% for pack-years of smoking. All other variables were imputed for <0.3% of participants. Categorical measures were modeled with the use of indicator variables for each level compared with the lowest level, and continuous measures were modeled linearly, per unit. We examined multiplicative and additive interactions of CRP with measures of atherosclerosis from ultrasound.

We tested our hypothesis that CRP confers excess risk only in the presence of atherosclerosis by stratifying on presence of atherosclerosis and by computing the relative excess risk, based on an additive model,24 using the following 4-level variable: minimal atherosclerosis and CRP ≤3 mg/L, detectable atherosclerosis and CRP ≤3 mg/L, minimal atherosclerosis and CRP >3 mg/L, and detectable atherosclerosis and CRP >3 mg/L. On the basis of an additive model, Rothman defined no interaction if the difference in risk between having both risk factors and having neither is equal to the sum of the differences in risk between each risk factor alone and neither, arguing that this presents the interaction in terms of the number of excess cases, which is an appropriate scale for epidemiological studies. Dividing by the risk when both risk factors are absent produces an equality in terms of RR when there is no relative excess risk due to CRP and atherosclerosis: RR(both)−1=RR(high CRP)−1+RR(high atherosclerosis)−1. We used Cox proportional hazards models to estimate the RR due to both risk factors and each one singly and computed the relative excess risk due to interaction (RERI), defined by RR(both)−RR(high CRP)−RR(atherosclerosis)−1.
sis)+1 for each outcome. Probability values and 95% CIs were computed by the delta method.25 The proportion of the disease related to high CRP and atherosclerosis, either singly or in combination, attributable to their interaction was calculated24 as

\[
\text{RERI\%} = \frac{\text{RERI}}{\text{RR(both)}/100}.
\]

We assessed the ability of carotid atherosclerosis and CRP to predict CVD and all-cause mortality by receiver-operating characteristic (ROC) curves and by the \(c\) statistic,26 a measure equivalent to the area under the ROC curve, but allowing for time to event analysis. The Hosmer-Lemeshow goodness-of-fit test, which compares observed and predicted probabilities,27 was used to assess model fit. Because the probabilities were derived from a logistic regression analysis, we used occurrence of events through 8 years of follow-up, which was available for both cohorts.

### Results

Among 5020 individuals in the analysis, the mean age was 72.6±5.5 years, and 60.2% were women. Other demographic data are shown in Table 1. A total of 593 myocardial infarctions, 613 strokes, 696 CVD deaths, and 1844 all-cause deaths occurred during a median follow-up time of 11 years (range, 5 days to 12 years).

### Correlation of Carotid IMT Category, Plaque Groups, and CRP

The frequencies of no plaque, intermediate-risk plaques, and high-risk plaques were 23%, 21.4%, and 55.6%, respectively. Carotid IMT category was related to plaque risk group, with no plaque being more frequent in persons in the lowest IMT tertile and high-risk plaque more frequent in the highest IMT
ter
tile (Figure 1). The majority (80.9%) of persons in the highest IMT tertile had high-risk plaques, with only 1.5% having no plaque. In contrast, among those in the lowest third of IMT, 27.4% had high-risk plaque, and 54.3% had no plaques. The Pearson correlation coefficient between plaque risk group and carotid IMT was 0.51 \((P<0.001)\).

The linear correlation between (ln)CRP level and carotid IMT was 0.12 and between (ln)CRP and plaque group was 0.08 (both \(P<0.001\)). Within each plaque group, higher CRP was correlated with higher IMT (Figure 2). For example, in the intermediate-risk plaque group, the geometric mean CRP ranged from 1.58 to 1.85 to 2.20 mg/L across increasing tertiles of IMT. When the comparison was made across the plaque groups, the difference in CRP level again varied by IMT tertile.

### Risk of CVD Related to Carotid IMT, Plaque Group, and CRP

HRs increased from the lowest to the highest tertile of carotid IMT for every CVD outcome and for all-cause mortality (Table 2) after adjustment for the conventional risk factors, carotid plaque groups, and CRP. The highest tertile was associated with an 84% increased risk of composite CVD events, 54% increased risk of all-cause mortality, and doubling of risk for CVD death.

Compared with those with no plaque, participants with intermediate- or high-risk plaque were at increased risk of every CVD outcome and of all-cause mortality after adjustment for
CVD risk factors, carotid IMT, and CRP (Table 2). Compared with those with no plaque, the HRs (95% CI) of composite CVD were 1.86 (1.55 to 2.23) and 2.09 (1.78 to 2.46) for intermediate- and high-risk plaques, respectively, after adjustment for age and gender only but fell to 1.46 (1.21 to 1.77) and 1.42 (1.20 to 1.70), respectively, after further adjustment for carotid IMT. Additional adjustment for conventional risk factors and CRP only slightly attenuated the association, with HRs of 1.41 (1.15 to 1.72) and 1.38 (1.14 to 1.67), respectively. Results were similar for individual CVD outcomes and for all-cause mortality (Table 2).

Elevated CRP (≥3 mg/L) was associated with increased risk of every outcome compared with CRP <3 mg/L in the multivariable-adjusted model. The magnitude of association ranged from a 26% to a 50% increased risk (Table 2).

Cardiovascular Risk Assessment by Detectable Carotid Atherosclerosis and CRP

In multivariable Cox models stratified by amount of atherosclerosis (detectable versus minimally detectable), elevated CRP conferred no increased hazard of composite CVD events, CVD death, or all-cause mortality in individuals with minimally detectable atherosclerosis, with HRs of 1.05 (95% CI, 0.70 to 1.56), 1.14 (0.60 to 2.14), and 0.87 (0.62 to 1.23), respectively. In contrast, the HRs for elevated CRP were significant in those with detectable atherosclerosis: 1.45 (1.29 to 1.62) for composite CVD events, 1.72 (1.46 to 2.01) for CVD death, and 1.52 (1.37 to 1.68) for all-cause mortality. A significant multiplicative interaction between CRP and presence of atherosclerosis was observed for all-cause mortality.

The cumulative event rates for composite CVD and all-cause mortality are shown in Figure 3. The increased rates associated with CRP in the presence of atherosclerosis indicated the possibility of an additive interaction. This finding was consistent in individual CVD outcome (data not shown). For example, the incidence of composite CVD in participants with minimal atherosclerosis and CRP ≤3 mg/L was 13.7/1000 person-years. Among participants with detectable atherosclerosis and CRP ≤3 mg/L, it was 32.9/1000 person-years (19.2/1000 person-years higher than the baseline rate), and with minimal atherosclerosis and CRP >3 mg/L, it was 14.4/1000 person-years (0.7 person-years higher than the baseline rate). If an additive model held, we would expect the incidence rate for participants with both risk factors to be 33.6/1000 person-years (the baseline rate of 13.7 plus 19.9 for the combination of atherosclerosis and high CRP). The observed incidence rate for participants with both risk factors was 46.5/1000 person-years, suggestive of an excess additive risk due to the interaction of CRP and atherosclerosis. The total excess additive risk due to CRP, atherosclerosis, and their interaction was 32.8/1000 person-years, and 39% of that excess risk [(32.8−19.9)/32.8] was due to the interaction of CRP and atherosclerosis. This excess risk rose to

### Table 2. Hazard Ratios (95% CIs)* of CVD and All-Cause Mortality by CRP, Carotid IMT, and Plaque Groups

<table>
<thead>
<tr>
<th>Event</th>
<th>No.</th>
<th>CRP &gt;3 mg/L†</th>
<th>Carotid IMT in Tertiles</th>
<th>Plaque Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=1433)</td>
<td>1 (n=1673)</td>
<td>2 (n=1674)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
<td>-------------</td>
<td>-------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>595</td>
<td>1.33 (1.11 to 1.60)</td>
<td>1.00</td>
<td>1.41 (1.08 to 1.83)</td>
</tr>
<tr>
<td>Stroke</td>
<td>613</td>
<td>1.26 (1.05 to 1.51)</td>
<td>1.00</td>
<td>1.18 (0.92 to 1.51)</td>
</tr>
<tr>
<td>CVD death</td>
<td>696</td>
<td>1.50 (1.28 to 1.77)</td>
<td>1.00</td>
<td>1.23 (0.95 to 1.59)</td>
</tr>
<tr>
<td>Composite CVD</td>
<td>1904</td>
<td>1.33 (1.18 to 1.50)</td>
<td>1.00</td>
<td>1.28 (1.08 to 1.52)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1844</td>
<td>1.38 (1.25 to 1.53)</td>
<td>1.00</td>
<td>1.16 (1.01 to 1.35)</td>
</tr>
</tbody>
</table>

*From a model that included age, sex, race, systolic and diastolic blood pressure, use of antihypertensive medications, body mass index, smoking (never, former, current), and amount smoked (in pack-years), high-density lipoprotein and low-density lipoprotein cholesterol, diabetes (none, impaired fasting glucose, diabetes), CRP, plaque risk group, and carotid wall thickness.
†Compared with CRP <3 mg/L.

Figure 3. Kaplan-Meier plots of cumulative cardiovascular events (A) and all-cause mortality (B) over 12-year follow-up stratified by carotid atherosclerosis and CRP level (low level ≤3 mg/L vs high level >3 mg/L). athero indicates atherosclerosis.
50% after adjustment for CVD risk factors (Table 3). The adjusted excess risk attributable to interaction was 54% for CVD death and 79% for all-cause mortality.

### CVD Risk Prediction by Carotid Atherosclerosis and CRP

CVD risk prediction was compared with the use of c statistics based on models with conventional risk factors alone and with the sequential addition of CRP >3 mg/L, carotid IMT, and carotid plaque (Table 4). c Statistics increased only modestly with each additional risk factor. This observation was consistent for every CVD outcome and for all-cause mortality. The final models had excellent fit on the basis of the Hosmer-Lemeshow goodness-of-fit test (P = 0.28) except for the stroke outcome (P = 0.001). As shown in Figure 4, ROC curves for composite CVD (Figure 4A) and all-cause mortality (Figure 4B) overlapped for models with conventional risk factors alone and with the addition of CRP >3 mg/L and the further addition of detectable atherosclerosis.

### Discussion

In the present large cohort study, we demonstrated that elevated CRP, carotid IMT, and carotid plaque were all correlated with one another, yet each remained a significant risk factor for CVD outcomes and all-cause mortality in the presence of the others. Furthermore, elevated CRP was associated with increased CVD and all-cause mortality risk only in those with detectable atherosclerosis. Addition of CRP or carotid atherosclerosis to conventional risk factors resulted in a modest increase in the ability to predict CVD, as measured by the c statistic.

Carotid IMT and plaques are both measures of atherosclerosis, perhaps having different attributes or risk associations but still closely related.28,29 Common and internal carotid IMT can be viewed as an estimate of atherosclerosis quantity. Sonographic characterization of carotid plaque can be considered a measure of atherosclerosis quality. Both indices are associated with CVD risk factors and outcomes. High-risk plaques as defined here were more common in those with thicker IMT, thus linking atherosclerosis quantity with quality. The high-risk plaque group had a higher risk of CVD outcomes in age- and gender-adjusted analyses than the intermediate-risk plaque group, but this was significantly attenuated after carotid IMT was taken into account. The definition of high-risk plaque in the present study was based on features previously demonstrated to be associated with stroke risk, and high-risk plaque was common in this older cohort. That the RR of CVD associated with high-risk plaque was comparable to that of intermediate-risk plaque after accounting for wall thickness suggests that ultrasound definition of high-risk or vulnerable plaque can be challenging. We suggest that future research on plaque quality should evaluate atherosclerosis quantity when assessing risk of CVD.

CRP-related risk of CVD and all-cause mortality differed by the severity of atherosclerosis in this cohort of older adults. Elevated CRP was not associated with increased risk of CVD or all-cause mortality in the group with minimal atherosclerosis, an observation that was consistent with our previous report on stroke risk from the present study.18 However, there was signif-

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**TABLE 3. Hazard Ratios and Relative Excess Risk of Cardiovascular Outcomes With and Without Detectable Atherosclerosis and Elevated CRP**

<table>
<thead>
<tr>
<th>Event</th>
<th>No.</th>
<th>CRP ≤3 mg/L (n=686)</th>
<th>CRP &gt;3 mg/L (n=223)</th>
<th>CRP ≤3 mg/L (n=2901)</th>
<th>CRP &gt;3 mg/L (n=1210)</th>
<th>Adjusted Relative Excess Risk (95% CI)*</th>
<th>% Attributable to Interaction†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>595</td>
<td>1.00</td>
<td>1.16</td>
<td>2.24</td>
<td>3.52</td>
<td>0.65 (0.14 to 1.43)</td>
<td>39%</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke</td>
<td>613</td>
<td>1.00</td>
<td>1.04</td>
<td>1.80</td>
<td>2.43</td>
<td>0.51 (−0.10 to 1.12)</td>
<td>49%</td>
<td>0.10</td>
</tr>
<tr>
<td>CVD death</td>
<td>696</td>
<td>1.00</td>
<td>1.16</td>
<td>2.22</td>
<td>4.06</td>
<td>1.14 (0.42 to 1.86)</td>
<td>54%</td>
<td>0.002</td>
</tr>
<tr>
<td>Composite CVD</td>
<td>1904</td>
<td>1.00</td>
<td>1.08</td>
<td>1.99</td>
<td>3.06</td>
<td>0.70 (0.26 to 1.14)</td>
<td>50%</td>
<td>0.002</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1844</td>
<td>1.00</td>
<td>0.88</td>
<td>1.47</td>
<td>2.36</td>
<td>0.79 (0.47 to 1.12)</td>
<td>79%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*From a model that included age, sex, race, systolic and diastolic blood pressure, use of antihypertensive medications, body mass index, smoking (never, former, current), and amount smoked (in pack-years), high-density lipoprotein and low-density lipoprotein cholesterol, diabetes (none, impaired fasting glucose, diabetes), CRP, plaque risk group, and carotid wall thickness.
†Proportion of disease related to high CRP and atherosclerosis, either singly or together, that is attributable to their interaction, from the multivariable models.

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**TABLE 4. c Statistics for Models of Cardiovascular Outcomes and All-Cause Mortality With Conventional Risk Factors and Additionally With Elevated CRP, Carotid IMT, and Carotid Plaque**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Covariates*</th>
<th>With CRP ≤3 mg/L</th>
<th>With Carotid Tertile</th>
<th>With Plaque Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>0.6799</td>
<td>0.6289</td>
<td>0.6971</td>
<td>0.6961</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6856</td>
<td>0.6869</td>
<td>0.6984</td>
<td>0.6994</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.7424</td>
<td>0.7485</td>
<td>0.7626</td>
<td>0.7632</td>
</tr>
<tr>
<td>Composite CVD</td>
<td>0.6840</td>
<td>0.6867</td>
<td>0.7009</td>
<td>0.7017</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.7151</td>
<td>0.7188</td>
<td>0.7247</td>
<td>0.7252</td>
</tr>
</tbody>
</table>

*Covariates included age, gender, race, body mass index, smoking status, pack-years of smoking, diabetes, systolic and diastolic blood pressure, total cholesterol, and high-density lipoprotein and low-density lipoprotein cholesterol.
significant excess additive risk when CRP was elevated in individuals with detectable atherosclerosis. This finding supports a complex relationship among inflammation, subclinical atherosclerosis, and clinical CVD.\textsuperscript{30} Determining a patient’s risk for CVD events or all-cause mortality on the basis of the level of CRP may thus be clinically challenging if CRP is used in low-risk populations in whom atherosclerosis burden might be small. This conclusion is in accord with recent findings in a population of young women.\textsuperscript{31} Further research is needed in this area.

In the present study, the increased rates associated with CRP only in the presence of atherosclerosis indicated the possibility of an additive interaction. We demonstrated an excess risk of CVD and all-cause mortality as a result of the additive interaction of elevated CRP and detectable atherosclerosis. Although most atherosclerosis epidemiology studies use multiplicative interaction to test effect modification, there are times when additive effects may reflect the underlying mechanism, as evident by our data and the data of others.\textsuperscript{32,33}

Despite the significant association between CRP and CVD outcomes, only modest improvement is made in CVD risk prediction by adding CRP to the conventional risk factors, as shown recently by Bos et al\textsuperscript{34} and Wang et al.\textsuperscript{35} We expanded our observation to the detection of carotid atherosclerosis that identifies a population at risk for CVD outcomes but does not seem to significantly increase the ability to predict a CVD event for an individual patient, as demonstrated by the modest increment in \( c \) statistics over conventional CVD risk factors. Similar findings have been demonstrated previously,\textsuperscript{36,37} although it is still debatable whether ROC curve or \( c \) statistics is the best way to assess the power of risk prediction for a given risk factor.\textsuperscript{38}

We recognize the limitations of the present study. The definition of high-risk plaque was based on published data linking certain plaque characteristics with clinical events, and by this definition 53\% of participants had high-risk plaques. This classification was designed to provide a model to study the interaction of carotid IMT and plaque characteristics, and therefore we caution against the clinical use of this approach. In the CHS, reproducibility of assessing plaque characteristics by ultrasound was only moderate\textsuperscript{3} and would need improvement for routine clinical application. Finally, a single measure of CRP was used, which may be subject to error.

To summarize, carotid IMT, plaque, and elevated CRP each independently contributed to the risk of CVD and all-cause mortality in models that included all 3 measures. However, elevated CRP was associated with CVD events and all-cause mortality only in those with detectable atherosclerosis. Addition of CRP or carotid atherosclerosis to conventional risk factors resulted in a modest increase in the ability to predict CVD on the basis of ROC analysis.

**Acknowledgments**

A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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**Disclosures**

None.

**References**


10-year follow-up study (the CAFES-CAVE Study(1)). *Atherosclerosis.* 2001;156:379–387.

**CLINICAL PERSPECTIVE**

Ultrasound-determined carotid intima-media thickness and presence of plaques are measures of carotid atherosclerosis. Higher carotid intima-media thickness is a risk marker for future stroke and coronary heart disease. Characteristics of carotid plaque have also been associated with vascular risk. C-reactive protein (CRP) is also a risk factor for cardiovascular disease. In the present study we examined the relationship of carotid atherosclerosis and CRP and their joint roles in cardiovascular risk prediction in 5022 elderly individuals (≥65 years) who were the participants of the Cardiovascular Health Study. After up to 12 years of follow-up, we found that when CRP was elevated (>3 mg/L) among those with detectable atherosclerosis on ultrasound, there was a significantly increased risk for cardiovascular disease and all-cause mortality. Elevated CRP in the absence of atherosclerosis did not increase cardiovascular or all-cause mortality risk. We concluded that determining a patient’s risk for cardiovascular events or all-cause mortality on the basis of the level of CRP may be clinically challenging if CRP is used in low-risk populations in whom atherosclerosis burden might be small.