

C-Reactive Protein, Carotid Intima-Media Thickness, and Incidence of Ischemic Stroke in the Elderly

The Cardiovascular Health Study

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Background—Increased carotid artery intima-media thickness (IMT) and elevated C-reactive protein (CRP) are both associated with the occurrence of stroke. We investigated whether elevated CRP is a risk factor for ischemic stroke independent of carotid IMT and studied the interaction between CRP and IMT.

Methods and Results—We studied 5417 participants aged 65 years or older without preexisting stroke or chronic atrial fibrillation who were participants in the Cardiovascular Health Study. The hazard ratio of incident ischemic stroke was estimated by Cox proportional hazards regression. During 10.2 years of follow-up, 469 incident ischemic strokes occurred. The adjusted hazard ratios for ischemic stroke in the 2nd to 4th quartiles of baseline CRP, relative to the 1st quartile, were 1.19 (95% CI 0.92 to 1.53), 1.05 (95% CI 0.81 to 1.37), and 1.60 (95% CI 1.23 to 2.08), respectively. With additional adjustment for carotid IMT, there was little confounding. The association of CRP with stroke was significantly different depending on IMT ($P < 0.02$), with no association of CRP with stroke among those in the lowest IMT tertile and a significant association among those with higher levels of IMT.

Conclusions—We conclude that elevated CRP is a risk factor for ischemic stroke, independent of atherosclerosis severity as measured by carotid IMT. The association of CRP with stroke is more apparent in the presence of a higher carotid IMT. CRP and carotid IMT may each be independent integrals in determining the risk of ischemic stroke. (*Circulation*. 2003;108:166-170.)

Key Words: inflammation ■ atherosclerosis ■ carotid arteries ■ stroke ■ risk factors

Elevated C-reactive protein (CRP) and increased carotid artery intima-media thickness (IMT) are both associated with the occurrence of stroke.¹⁻⁴ Higher CRP is also associated with higher IMT,^{5,6} although this has not been confirmed in all studies.^{7,8} It is not clear whether CRP and carotid IMT each play an independent role in the pathogenesis of stroke.

Inflammation mediates a key role in the pathogenesis of atherosclerosis.^{9,10} Various cytokines, growth factors, and inflammatory cells are abundant in atheromatous plaques.^{9,10} The atherosclerotic vessel wall is the source of soluble adhesion molecules that mark inflammation.^{11,12} Endarterectomy specimens from symptomatic patients compared with asymptomatic patients and those in areas with more extensive plaques have higher expression of adhesion molecules.¹³ Thus, the extent of inflammation may reflect in part the

propensity of atherosclerotic lesions to lead to clinical disease.

It appears that among inflammation-sensitive proteins studied to date in relation to cardiovascular disease risk, higher CRP concentration is most consistently and strongly related to risk.^{14,15} Higher CRP might be a marker of destabilizing plaques, and CRP itself might also participate in plaque destabilization.¹⁶ It has been proposed that CRP reflects the overall inflammatory burden of atherosclerotic disease.¹⁷ However, there is also evidence for possible direct roles of CRP in the pathogenesis of atherosclerosis, such as induction of endothelial cell adhesion molecules,¹⁸ opsonization of native LDL to form foam cells,¹⁹ induction of monocyte tissue factor production,²⁰ and recruitment of monocytes by receptor-mediated chemotaxis.²¹

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We hypothesize here that CRP is a risk factor for stroke independent of carotid IMT and, because it might be a marker of plaque severity and instability, that CRP would be more strongly related to stroke among those with higher carotid IMT. We investigated the hypothesis in adults who were 65 years of age or older without preexisting stroke and who were participants in the Cardiovascular Health Study (CHS).

Methods

Study Subjects

The study subjects were the participants in CHS, a longitudinal, observational study of men and women 65 years of age or older.²² The study was designed to investigate risk factors for cardiovascular disease in this age group. 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 by similar methods. The study design has been published previously.²² The study was approved by the institutional review boards at each participating center. All the participants provided informed consent.

All participants underwent baseline clinical examinations, which included medical history, physical examination, carotid ultrasound, ECG, and ankle-brachial blood pressure index.²³ The diagnoses of diabetes mellitus and impaired fasting glucose were based on American Diabetes Association criteria.²⁴ Blood was drawn in the morning after an overnight fast.²⁵ Samples were promptly centrifuged at 3000g for 10 minutes at 4°C. Aliquots of plasma were stored in a central laboratory at -70°C. In 1997, CRP was measured in all stored baseline plasma samples by a high-sensitivity immunoassay, with an interassay coefficient of variation of 6.25%.²⁶

The carotid arteries were evaluated at baseline with high-resolution B-mode ultrasonography (model SSA-270A; Toshiba America Medical Systems). The maximum IMT of the common carotid artery and of the internal carotid artery was defined as the mean of multiple measures of the maximum IMT of the near and far wall on both the left and right sides. Methods of measurement and quality control have been published previously.²⁷ A composite measure that combined the maximum common carotid artery IMT and maximum internal IMT was obtained by averaging these 2 measurements after standardization (subtraction of the mean and division by the standard deviation for the measurement).²⁸

The method of ascertainment and classification of incident stroke has been reported previously.²⁹ Participants were examined annually at each clinical site. In addition, telephone interviews were alternated with clinic visits so that contacts occurred every 6 months. Follow-up was complete through June 30, 2000. Incident stroke was ascertained by self-report or from the Health Care Financing Administration hospitalized patient database of International Classification of Diseases, 9th Revision (ICD-9) codes. For confirmation and classification of stroke type, hospital records, including cranial computed tomography and cerebral magnetic resonance images, were reviewed by a committee that included neurologists and a neuroradiologist. Only ischemic cerebral infarction was included as stroke in this analysis. Those participants who suffered primarily from hemorrhagic stroke were not included in this analysis.

Statistical Analysis

All analyses were performed with SAS version 6.12 software. Differences between CRP medians were tested with the Kruskal-Wallis test for factors with more than 2 groups. Differences in means of risk factor levels between the stroke group and the no-stroke group were tested with *t* tests. For variables with skewed distributions, the Wilcoxon rank-sum test was used to test for differences in medians. The χ^2 test was used to assess associations among categorical variables. To equalize the power across quartiles, quartiles were

TABLE 1. Baseline Characteristics

Characteristic*	No Ischemic Stroke (n=4948)	Incident Ischemic Stroke (n=469)	P
Age, y	72.5 (5.5)	74.2 (5.6)	<0.001
Male gender, %	41.4	42.4	0.68
Black, %	15.2	12.6	0.13
Hypertension, %	41.9	58.2	<0.001
Congestive heart failure, %	3.6	5.3	0.06
Transient ischemic attack, %	1.5	3.6	0.001
Diabetes status, %			
Impaired fasting glucose	13.2	16.3	<0.001
Diabetes	15.1	21.6	
Smoking, %			
Current	12.1	11.7	0.21
Former	41.7	38.0	
Pack-years smoking	17.7 (26.3)	16.5 (27.0)	0.38
Hormone replacement therapy, %	11.6	9.3	0.27
Body mass index, kg/m ²	26.7 (4.7)	26.7 (4.4)	0.87
Cholesterol, mg/dL	211.6 (38.8)	215.3 (40.9)	0.06
HDL, mg/dL	54.6 (15.6)	53.5 (17.1)	0.17
LDL, mg/dL	130.2 (35.4)	132.3 (36.2)	0.23
Systolic blood pressure, mm Hg*	135.6 (21.4)	143.6 (23.6)	<0.001
Diastolic blood pressure, mm Hg*	70.5 (11.2)	72.3 (12.2)	0.003
Internal carotid IMT, mm*	1.41 (0.56)	1.59 (0.60)	<0.001
Common carotid IMT, mm*	1.05 (0.21)	1.12 (0.25)	<0.001
CRP, mg/L	1.87 (2.38)	2.07 (3.28)	0.006

*Values for continuous variables except CRP are mean (SD). Values for CRP are median (interquartile range). Values for hormone replacement therapy include women only.

defined on the basis of the distribution of CRP among those with events.

Cox proportional hazards regression was used to calculate hazard ratios (HRs) of stroke for elevated CRP in multivariate models that included adjustment for age, gender, race, diabetes status (normal, fasting glucose intolerance, and diabetes mellitus), hypertension, systolic blood pressure, smoking status (never, current, or past), and total cholesterol. Factors not associated with stroke were not included in these models. The interaction between CRP and carotid IMT as continuous variables and as categorical variables was tested. A probability value of less than 0.05 was considered statistically significant.

Results

Of the total 5888 participants, 471 were excluded because of the presence of prebaseline stroke (n=249), chronic atrial fibrillation (n=148), or missing CRP measurement (n=74). Thus, 5417 participants were considered for this analysis. During a median follow-up time of 10.2 years, 469 incident ischemic strokes occurred, with an incidence of 9.7 and 11.1 per 1000 person-years for women and men, respectively.

The baseline characteristics of the study cohort are shown in Table 1. Those with incident stroke were more likely to have baseline hypertension, diabetes or impaired fasting glucose, higher total cholesterol, and higher systolic and diastolic blood pressure. Compared with the control group, the stroke group had higher internal carotid thickness and

TABLE 2. Baseline CRP and Risk of Ischemic Stroke, With and Without Adjustment for Other Risk Factors and Carotid IMT

Risk Factors Included in the Model	HR (95% CI) of Stroke by CRP Concentration				P†
	Quartile 1 (<1.12 mg/L)	Quartile 2 (1.12–2.05 mg/L)	Quartile 3 (2.05–4.30 mg/L)	Quartile 4 (≥4.30 mg/L)	
Unadjusted	1.00 (Reference)	1.27 (0.99–1.65)	1.18 (0.92–1.53)	1.83 (1.41–2.36)	<0.001
Adjusted*	1.00 (Reference)	1.19 (0.92–1.53)	1.05 (0.81–1.37)	1.60 (1.23–2.08)	0.002
Adjusted* + internal carotid IMT	1.00 (Reference)	1.17 (0.90–1.51)	1.02 (0.78–1.32)	1.52 (1.16–1.98)	0.007
Adjusted* + common carotid IMT	1.00 (Reference)	1.17 (0.90–1.51)	1.02 (0.79–1.33)	1.53 (1.17–1.99)	0.006
Adjusted* + combined carotid IMT	1.00 (Reference)	1.16 (0.89–1.50)	1.01 (0.78–1.31)	1.49 (1.14–1.94)	0.01

*Adjusted for baseline age, gender, race, diabetes, hypertension, systolic blood pressure, total cholesterol, and smoking status.

†P value from test of equality in hazards.

higher common carotid thickness (both $P < 0.001$). Median baseline CRP was significantly higher in the stroke group than in the control group ($P < 0.01$).

CRP concentration was closely correlated with carotid IMT measures. For each 1 SD higher of common or internal carotid IMT, CRP was 0.37 and 0.40 mg/L higher, respectively ($P < 0.001$ for Spearman correlation). Although they were highly statistically significant for both men and women, the correlations were larger among men. For example, for each 1 SD higher of internal carotid IMT, CRP was 0.60 mg/L higher for men and 0.26 mg/L higher for women.

In the first to fourth quartiles of baseline CRP, the respective stroke incidence rates were 8.2, 10.4, 9.6, and 14.8 strokes per 1000 person-years. In Table 2, multivariate analysis of the HR of stroke for CRP categories was based on a model that adjusted for age, gender, race, hypertension, diabetes, systolic blood pressure, total cholesterol, and smoking status. Compared with the first quartile of CRP, the adjusted HRs of stroke for the second, third, and fourth quartiles were 1.19 (95% CI 0.92 to 1.53), 1.05 (95% CI 0.81 to 1.37), and 1.60 (95% CI 1.23 to 2.08), respectively. With additional adjustment for internal carotid IMT, common carotid IMT, or combined carotid IMT, there was little confounding, with the HR comparing the fourth to the first quartile being 1.5 for each adjusted model (Table 2).

In gender-stratified analyses, the unadjusted risk of stroke in the fourth compared with the first quartile of CRP was 2.21 (95% CI 1.50 to 3.25) in men and 1.64 (95% CI 1.17 to 2.31) in women. This difference was not statistically significant (P for interaction of CRP and sex, 0.07). In both men and women, the risk was attenuated with adjustment for other risk factors (OR 1.88 [95% CI 1.25 to 2.81] and 1.38 [95% CI 0.97 to 1.97], respectively). With further adjustment for combined carotid IMT, these ORs changed trivially (1.69 [95% CI 1.13 to 2.54] for men; 1.33 [95% CI 0.93 to 1.91] for women). In this final model, the interaction term P value for sex and CRP was 0.36.

As reported previously, the risk of ischemic stroke was significantly increased with increasing common, internal, and combined carotid IMT (data not shown).² To address whether the CRP-related stroke risk differed within categories of IMT, we expressed the HR of stroke per interquartile range (2.38 mg/L) higher CRP. Overall, the adjusted HR of stroke per interquartile range of CRP was 1.05 (1.02 to 1.07). With stratification by tertiles of IMT, the interquartile range HRs are shown in Table 3. CRP was significantly associated with stroke risk in the second and third tertiles of each IMT measurement. However, among those in the first tertile of IMT, the association of CRP with stroke risk was weak or not present. As an example, considering combined carotid IMT, the risk of stroke was increased 7% for each interquartile range of higher CRP concentration among those in the second or third tertile of combined IMT. The risk of stroke was increased only 3% per interquartile range of higher CRP

TABLE 3. Baseline CRP, Carotid IMT, and Risk of Stroke

Carotid IMT Tertile	Unadjusted HR (95% CI)*	P	Adjusted HR (95% CI)†	P
Internal carotid IMT				
Tertile 1	1.03 (0.97–1.08)	0.33	1.01 (0.96–1.08)	0.65
Tertile 2	1.06 (1.02–1.09)	0.001	1.04 (1.01–1.08)	0.01
Tertile 3	1.06 (1.02–1.11)	0.006	1.07 (1.02–1.12)	0.004
Common carotid IMT				
Tertile 1	1.05 (1.01–1.09)	0.02	1.03 (0.99–1.07)	0.20
Tertile 2	1.05 (1.01–1.09)	0.01	1.05 (1.01–1.10)	0.01
Tertile 3	1.08 (1.03–1.13)	0.003	1.08 (1.03–1.13)	0.003
Combined IMT				
Tertile 1	1.04 (1.00–1.08)	0.09	1.03 (0.98–1.08)	0.21
Tertile 2	1.08 (1.03–1.12)	0.001	1.07 (1.02–1.12)	0.005
Tertile 3	1.06 (1.01–1.11)	0.013	1.07 (1.02–1.12)	0.007

*HR for each interquartile range (2.38 mg/L) higher CRP.

†Adjusted for baseline age, gender, race, diabetes, hypertension, systolic blood pressure, total cholesterol, and smoking status.

among those in the first tertile of combined carotid IMT ($P=0.21$). The interaction term of CRP and IMT to predict stroke was statistically significant, which supports multiplicative interaction ($P=0.002$, 0.02 , and 0.003 for internal, common, and combined carotid IMT, respectively). The overall results were unaltered if women were excluded from the analyses.

Discussion

We have demonstrated that elevated CRP concentration was an independent risk factor for future ischemic stroke over 10 years of follow-up in an elderly population without preexisting stroke. To the best of our knowledge, this is the first prospective study to explore the joint associations of CRP and carotid IMT in incidence of ischemic stroke, although a case-control study published by CHS investigators demonstrated the interrelation of subclinical atherosclerosis and CRP in relation to coronary artery disease.¹⁷ We confirmed prior observations that higher CRP is associated with future stroke¹⁻⁴ and extended prior findings to examine the independent roles of CRP and carotid atherosclerosis in relation to ischemic stroke. An independent association of CRP from carotid IMT in the risk of stroke suggests a hypothesis of an additional pathophysiological role for CRP to that of measurable atherosclerosis in relation to stroke.

We confirm here that CRP and IMT are closely associated; the higher the CRP, the greater the carotid atherosclerosis as measured by carotid IMT, as also reported by others.^{5,6} The atherosclerotic vessel wall is a likely source of measurable systemic inflammation. Therefore, elevated CRP in part reflects the burden of atherosclerosis. It appears, however, that CRP may not simply represent the extent of atherosclerosis severity, because CRP remained an independent risk factor for ischemic stroke even when atherosclerosis was advanced, as defined by IMT. A recent report by Park et al³⁰ demonstrated that coronary calcium score and CRP provided independent and complementary prediction of cardiovascular events. Further study on the interrelations of inflammation markers and subclinical atherosclerosis in relation to clinical outcomes is required.

In the present study, the association of CRP with stroke was significant not only in the highest tertile of IMT but also in the second tertile of IMT. In fact, the stroke risks for higher CRP within the second and third tertiles of IMT were comparable. Several hypotheses requiring further evaluation may be raised based on these findings. The CRP concentration might be related to the composition of the carotid atherosclerotic plaque, such that higher CRP is associated with a more active or unstable plaque, with greater propensity to stroke.^{5,16} Therefore, CRP-associated stroke risk is more significant when there is greater measurable plaque burden that is subject to rupture. It is possible that an elevated CRP is causally related to onset of stroke, primarily among those with atherosclerosis. Proposed biological activities of CRP within plaques, such as complement activation,³¹ induction of leukocyte chemotaxis²¹ and adhesion molecules,¹⁸ opsonization of LDL,¹⁹ and induction of monocyte tissue factor production,²⁰ would support these hypotheses.

Strengths of the present study include the prospectively collected data from a large sample of older, community-based individuals and the availability of carefully performed measures of subclinical atherosclerosis before the onset of stroke. The limitations include the relatively low incidence of ischemic stroke in this healthy elderly cohort. Although this lower incidence is likely due to selection and survival of a healthier cohort,³² one would not expect these biases to affect prospective associations within the cohort in important ways. However, these findings should be further explored in studies with higher prevalences of carotid disease and stroke risk factors, including other population-based cohorts. Other limitations include the determination of IMT and CRP by a single measure, which could result in imprecision or residual confounding due to measurement error. We believe this would bias our findings toward the null hypothesis, yielding underestimates of the actual risk associated with these measures.

We conclude that elevated CRP is related to the future occurrence of ischemic stroke in this elderly cohort, an association that is largely independent of atherosclerosis severity as measured by carotid IMT. The association of CRP with stroke was less apparent among those with less advanced compared with more advanced carotid atherosclerosis. Although CRP and carotid IMT are closely correlated, each factor may be an independent integral in the risk of ischemic stroke. There is a trend to suggest that the association of CRP and stroke might be stronger in men than in women. These findings should be further explored both in the laboratory and in ongoing observational and interventional studies.

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