ORIGINAL ARTICLE

C-reactive Protein Level and Traditional Vascular Risk Factors in the Prediction of Carotid Stenosis

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Hypothesis: There is no relationship between C-reactive protein (CRP) level and the presence and degree of carotid stenosis (null hypothesis).

Design: Institutional review board–approved cohort study.

Setting: Tertiary care regional medical center.

Patients: Patients (N=146) referred to a vascular surgery clinic for possible carotid stenosis.

Interventions: Baseline serum high-sensitivity CRP level, low-density lipoprotein cholesterol (LDL-C) level, and other traditionally used vascular risk factors were assessed in all patients. All underwent vascular surgery clinical examination, including bilateral duplex ultrasonography of their carotid bifurcations.

Main Outcome Measures: The potential relationship between serum CRP level and the presence and degree of carotid stenosis, as well as the strength of this association with traditionally established demographic, historical, and laboratory risk factors such as age, hypertension, and LDL-C level.

Results: In unadjusted analysis, CRP level, coronary artery disease (CAD), and lower extremity peripheral vascular disease (PVD) positively correlated with carotid stenosis (Pearson product moment correlation $r < 0.02$ for all). Low-density lipoprotein cholesterol level and other risk factors, including age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, and neurologic history, did not. The mean±SD CRP level was higher among 72 patients with carotid stenosis compared with that among 74 patients without carotid stenosis (3.7±6.1 vs 1.9±2.1 mg/L [to convert to nanomoles per liter, multiply by 9.524], $P=.02$), as were the baseline prevalences of CAD (49% vs 29%), PVD (27% vs 11%), and (84% vs 61%) ($P<.03$ for all). The mean±SD LDL-C levels were similar between the groups (92.3±28.6 vs 95.8±29.0 mg/dL [to convert to millimoles per liter, multiply by 0.0259], $P=.8$), and differences in the prevalences of other risk factors were not statistically significant. In multivariate regression analysis adjusting for age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), CAD, PVD, myocardial infarction, stroke or transient ischemic attack, hypercholesterolemia, aspirin or nonsteroidal anti-inflammatory drug use, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) use, CRP level was independently associated with carotid stenosis (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1-1.5; $P=.04$), and LDL-C level was not (OR, 1.0; 95% CI, 0.98-1.01; $P=.8$). Several risk factors had larger ORs for carotid stenosis than CRP level; however, none were statistically significant. C-reactive protein level and CAD were independently associated with the actual degree of carotid stenosis in multivariate analysis. No corresponding associations for LDL-C level or other risk factors were observed.

Conclusion: C-reactive protein level is a moderate but statistically significant marker of carotid stenosis and may be a useful adjunct to accurate global vascular risk assessment.

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C-REACTIVE PROTEIN (CRP) is a serum protein that is produced in increasing quantities by the liver in the context of acute or chronic systemic inflammation.[1,2] Interest in CRP level has intensified with (1) the development of a highly sensitive and reproducible assay (high-sensitivity CRP) and (2) new clinical guidelines from the Centers for Disease Control and Prevention and the American Heart Association[3] regarding the usefulness of CRP level as an adjunct to global coronary risk assessment. Elevated CRP levels have variously been associated with an increased risk of stroke, future acute coronary syndromes, and peripheral vascular disease (PVD).[4-6] C-reactive protein level may be more predictive of a first adverse coronary event than low-density lipoprotein cholesterol (LDL-C) level and seems to be independently additive to the Framingham Risk Score.[4,7]

See Invited Critique at end of article

The first objective of this study was to prospectively evaluate the potential rela-

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tionship between serum CRP level and the presence and degree of carotid stenosis. We hypothesized that similar inflammatory processes involved in coronary disease might manifest in atherosclerotic carotid arteries, perhaps making CRP level useful in this context as well. Second, we wanted to compare the strength of this association, if any, against that of traditionally established vascular risk factors in an attempt to characterize the additive potential of CRP level to established risk management strategies.

METHODS

DESIGN

This is an institutional review board–approved, Health Insurance Portability and Accountability Act of 1996–compliant prospective cohort study designed (1) to evaluate the potential relationship between serum CRP level and the presence and degree of carotid stenosis and (2) to compare the strength of this association with traditionally established demographic, historical, and laboratory risk factors such as age, hypertension, and LDL-C level. The protocol has 2 arms, a study cohort with carotid stenosis and a control group without disease as defined by bilateral carotid duplex ultrasonography velocity criteria.

PATIENTS

The study was available to any male or female patient 40 years or older who was referred to, or followed up by, the vascular surgery service for possible, known, unilateral, bilateral, symptomatic, or asymptomatic carotid stenosis. Referral patients in general were evaluated in outpatient consultation for a recent stroke, amaurosis fugax, syncopic episode, asymptomatic bruit, or transient ischemic attack (TIA). Patients with known disease were offered enrollment at a regularly scheduled surveillance visit or during an evaluation for new symptoms such as recent stroke or TIA. Patients younger than 40 years, pregnant, or with documented active infection, untreated malignant neoplasms, or a chronic autoimmune condition, or those using a corticosteroid were excluded. There were no other exclusions. Of approximately 160 consecutive eligible patients, 149 were interested, enrolled, and studied. Subsequently, 3 patients requested disenrollment or were lost to follow-up before all study procedures were completed, leaving 146 patients available for analysis.

PROCEDURES

All interested eligible patients provided informed consent and were enrolled by the study research nurse. A standardized historical questionnaire was completed, risks and benefits of the study and of evaluation for carotid stenosis were discussed, and scheduled study visits were arranged. Baseline fasting serum high-sensitivity CRP and LDL-C levels were evaluated for all patients. All patients then underwent a vascular clinical evaluation by a staff vascular surgeon with supervised resident assistance, including a complete medical history and physical examination. Formal bilateral carotid duplex ultrasonography was performed on all patients by a registered vascular technologist in an Intersocietal Commission for the Accreditation of Vascular Laboratories–certified vascular laboratory.

On the basis of duplex velocities, patients were placed in the experimental (disease) study cohort or the control (no disease) group. The experimental cohort included any patient found to have carotid stenosis in 1 or both carotid arteries as defined by bilateral carotid duplex ultrasonography demonstrating internal carotid artery or bulb velocity measurements of 125 cm/s or greater in either artery. A corresponding control group without carotid stenosis demonstrated internal carotid artery or bulb velocity measurements of less than 125 cm/s in both arteries.

STATISTICAL ANALYSIS

Continuous data were compared using independent *t* tests and categorical proportions using χ^2 analysis or the Fisher exact test as appropriate. Prevalence data, Pearson product moment *r* correlations, and odds ratios (ORs) were calculated using the standard equations.[8] Logistic regression analysis was used to examine the independent associations of high-sensitivity CRP level against LDL-C level and various other traditional vascular risk (TVR) factors, with the binary categorical outcome measure being the confirmed presence of 125 cm/s or greater carotid stenosis in either carotid artery by duplex ultrasonography.[9,10] A corresponding linear regression analysis was performed using the same covariates but with the continuous outcome of actual velocity in centimeters per second to evaluate the relationship of the study variables with the degree of measured carotid stenosis.

Regression equations took the following form: outcome variable = $b_0 + b_1(\mathrm{TVR_a}) + b_2(\mathrm{TVR_b}) + b_3(\mathrm{TVR_c}) + b_n(\mathrm{TVR_i})$[11,12] (where *b* indicates the regression coefficient representing the amount the dependent variable changes when a corresponding independent variable changes 1 U, and the subscript indicates that that coefficient corresponds to that specific variable). The TVR factors studied included age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), coronary artery disease (CAD), lower extremity PVD, myocardial infarction, stroke or TIA, hypercholesterolemia, and LDL-C level. Potential confounders such as aspirin or nonsteroidal anti-inflammatory drug use or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) use were also included in the models to minimize this potential source of bias because these drugs are known to affect CRP levels. Comparative receiver operating characteristic (ROC) curves were prepared for all study variables with the categorical outcome of carotid stenosis (velocity, ≥125 cm/s). Each area under the ROC curve was calculated and compared against a null line. Statistical significance was set at $P < .05$ and reflected 2-tailed distributions in all cases. Statistical analysis was performed using commercially available software (SPSS Windows version 11; SPSS Inc, Chicago, Illinois).

RESULTS

In unadjusted analysis, CRP level, CAD, and lower extremity PVD positively correlated with carotid stenosis (Pearson product moment correlation $r < 0.02$ for all). Low-density lipoprotein cholesterol level and other risk factors, including age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, and neurologic history, did not. Among the subset of patients with confirmed carotid stenosis (n = 72), 11 patients (15.3%) endorsed documented ipsilateral neurologic symptoms within 120 days of study enrollment, and the remaining 61 patients (84.7%) were asymptomatic. The mean ± SD CRP level was higher among symptomatic compared with asymptomatic patients with carotid stenosis (5.1 ± 7.1 vs 2.8 ± 3.7 mg/L [to convert to nanomoles per liter, multiply by 9.524]), but this difference was not statistically significant ($P = .11$). The mean ± SD CRP levels were higher among 72 patients with carotid stenosis compared with those among 74 patients without carotid ste-

Table 1. High-Sensitivity C-reactive Protein (CRP) Level, Low-density Lipoprotein Cholesterol (LDL-C) Level, and Age Stratified by the Presence or Absence of Confirmed Carotid Stenosis by Duplex Ultrasonography[a]

Continuous Study Variable	No Carotid Stenosis (n=74)	Carotid Stenosis (n=72)
CRP level, mg/L	1.9±2.1	3.7±6.1[b]
LDL-C level, mg/dL	95.8±29.0	92.3±28.6
Age, y	68.7±8.3	71.3±8.3

SI conversion factor: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; cholesterol to millimoles per liter, multiply by 0.0259.
[a] Data are given as mean±SD and are unadjusted comparisons for outcome peak systolic velocity of 125 cm/s or greater using *t* test.
[b] $P<.05$.

Table 2. Comparative Proportions Stratified by the Presence or Absence of Confirmed Carotid Stenosis by Duplex Ultrasonography[a]

Categorical Study Variable	No Carotid Stenosis (n=74)	Carotid Stenosis (n=72)
Male sex	53	56
White race/ethnicity	58	93
Smoking history	46	54
Hypertension	70	82
Hypercholesterolemia	61	84
Diabetes mellitus	29	30
Coronary artery disease or myocardial infarction	29	49
Stroke or transient ischemic attack	26	36
Symptoms	8	16
Lower extremity peripheral vascular disease	11	27
Aspirin or nonsteroidal anti-inflammatory drug use	77	81

[a] Data are given as baseline percentages and are unadjusted comparisons for outcome peak systolic velocity of 125 cm/s or greater using χ^2 test or Fisher exact test as appropriate.

nosis (3.7±6.1 vs 1.9±2.1 mg/dL, $P=.02$), as were the baseline prevalences of CAD (49% vs 29%), PVD (27% vs 11%), and hypercholesterolemia (84% vs 61%) ($P<.03$ for all). The mean±SD LDL-C levels were similar between the groups (92.3±28.6 vs 95.8±29.0 mg/dL [to convert to millimoles per liter, multiply by 0.0259], $P=.8$), and differences in the prevalences of other risk factors were not statistically significant (**Table 1** and **Table 2**).

In multivariate regression analysis adjusting for age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), CAD, PVD, myocardial infarction, stroke or TIA, hypercholesterolemia, aspirin or nonsteroidal anti-inflammatory drug use, and statin use, CRP level was independently associated with carotid stenosis (OR, 1.2; 95% CI, 1.1-1.5; $P=.04$), and LDL-C level was not (OR, 1.0; 95% CI, 0.98-1.01; $P=.8$). Several risk factors had larger ORs for carotid stenosis than CRP level; however, none were statistically significant (**Table 3**).

Table 3. Comparative Odds Ratios (ORs) of Study Variables for the Presence of Confirmed Carotid Stenosis by Duplex Ultrasonography[a]

Study Variable	OR (95% Confidence Interval)	*P* Value
Coronary artery disease	3.2 (1.0-10.4)	.06
Lower extremity peripheral vascular disease	2.7 (0.9-8.3)	.09
Myocardial infarction	2.3 (0.6-8.6)	.2
Male sex	1.4 (0.5-3.6)	.5
Recent neurologic symptoms, <120 d	1.3 (0.4-5.1)	.7
Diabetes mellitus	1.3 (0.5-3.2)	.6
Hypertension	1.3 (0.5-3.5)	.7
CRP level	1.2 (1.1-1.5)	.04[b]
White race/ethnicity	1.2 (0.2-6.0)	.8
Stroke or transient ischemic attack	1.0 (0.4-2.8)	.9
Age	1.0 (0.98-1.01)	.2
Smoking history	1.0 (0.4-2.4)	.9
LDL-C level	1.0 (0.98-1.01)	.8

Abbreviations: CRP, C-reactive protein; LDL-C, low-density lipoprotein.
[a] Logistic regression analysis for outcome peak systolic velocity of 125 cm/s or greater, adjusting for age, sex, race/ethnicity, smoking history, LDL-C level, CRP level, aspirin or nonsteroidal anti-inflammatory drug use, and statin use.
[b] $P<.05$.

C-reactive protein level and CAD were independently associated with the actual degree of carotid stenosis in multivariate analysis. In this model, each additional 1 mg/dL of measured baseline serum CRP level corresponded with a 5.2-cm/s (95% CI, 1.3-9.2 cm/s) increase in observed carotid duplex velocity magnitude ($P<.01$). Similarly, the presence of CAD was associated with a 35.4-cm/s (95% CI, 1.8-70.7 cm/s) increase in measured velocity ($P<.05$). No corresponding associations for LDL-C level or other risk factors were observed.

Finally, an analysis of comparative areas under the ROC curves demonstrated a larger measured area for CRP level than for LDL-C level (0.6 vs 0.5), suggesting that CRP level was more predictive of confirmed carotid stenosis in these patients (**Figure**). The curve for CRP level was statistically significant compared with a null line, whereas that for LDL-C level was not. Similar analysis of the remaining study variables revealed that age, CRP level, and CAD produced the largest integral areas under the ROC curve. However, age and CRP level were the only variables studied found to be statistically significant when compared with a null line (**Table 4**).

COMMENT

The first objective of this study was to examine the relationship between CRP level and the presence and degree of carotid stenosis. In this regard, we found that baseline CRP level was prospectively associated with both outcomes in these 146 patients and that this relationship was independent of other statistically significant historical covariates, including CAD, lower extremity PVD, myocardial infarction, and hypercholesterolemia. Second, we wanted to compare the strength of this associa-

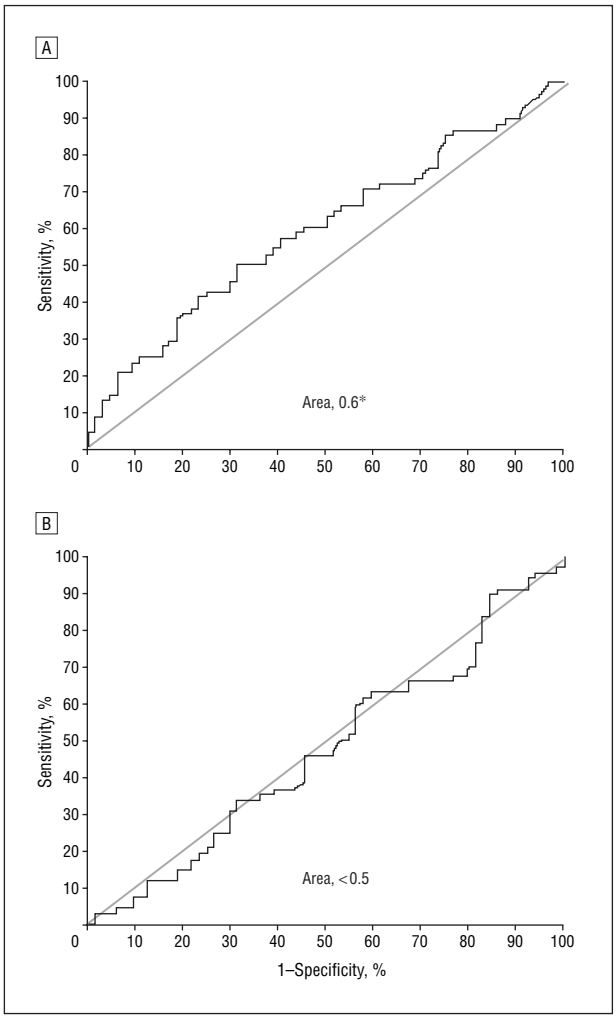

Figure. Receiver operating curve for high-sensitivity C-reactive protein level (A) compared with that for low-density lipoprotein cholesterol level (B) in the prediction of carotid stenosis. *$P<.05$ vs null line.

tion with that of established risk factors for carotid disease. Herein, we found that the magnitude of independent association of baseline CRP level with carotid stenosis was moderate, with an observed OR of 1.2. Nevertheless, CRP level was the only variable among 15 studied that was statistically significantly associated with both primary outcomes of this study, namely, the presence and degree of carotid stenosis.

Furthermore, CRP level was 1 of only 2 variables with statistically significant areas under the ROC curve, the traditional statistical yardstick against which diagnostic tests are compared against one another. In addition, CRP level generated the second largest area under the ROC curve of any variable studied. These findings are compelling given that included among 14 other variables to which CRP level was compared were several classic, widely used, and well-established risk factors of carotid stenosis (entities such as hypertension, diabetes mellitus, CAD, and LDL-C level). In aggregate, these results suggest that baseline CRP level may be independently contributive, albeit moderately so, to traditional global vascular risk assessment.

Our results reinforce published research linking CRP level with carotid stenosis and with the risk of future stroke.

Table 4. Comparative Areas Under the Receiver Operating Characteristic Curve for the Presence of Confirmed Carotid Stenosis by Duplex Ultrasonography

Study Variable	Area Under Curve	*P* Value
Age	0.61	.03[a]
CRP level	0.60	<.05[a]
Coronary artery disease	0.60	.06
Lower extremity peripheral vascular disease	0.59	.07
Hypertension	0.54	.5
Stroke or transient ischemic attack	0.54	.4
Recent neurologic symptoms, <120 d	0.53	.4
White race/ethnicity	0.53	.5
Smoking history	0.53	.5
Male sex	0.52	.7
Myocardial infarction	0.51	.9
Diabetes mellitus	0.49	.9
LDL-C level	0.47	.6

Abbreviations: CRP, C-reactive protein; LDL-C, low-density lipoprotein.
[a] $P<.05$ vs null line.

C-reactive protein level has been demonstrated to be a marker of carotid stenosis, plaque instability, thrombosis, ulceration, and rupture; to relate to the presence of subintimal macrophages and T lymphocytes; and to correlate with the presence of symptoms, the occurrence of future ipsilateral neurologic clinical events, and the risk of death following stroke.[13-17] With respect to postneurologic event CRP levels, Canova et al[18] demonstrated that the protein elevates in similar quantities regardless of the nature of the neurologic injury incurred. They observed no statistically significant differences in postevent CRP elevations across the spectrum of TIA, completed ischemic stroke without deficit, or hemorrhagic stroke with residua. This observation, along with our present finding that CRP level is independently associated with carotid stenosis even among patients with no prior neurologic history, suggests that an elevated CRP level in these patients is more likely due to smoldering endovascular activity than global postischemic cerebral inflammation.

There are several limitations of this study. First, its sample size is small compared with the large population-based studies that have been published regarding CRP level and CAD. Although the number of patients was adequate to demonstrate several statistically significant differences relevant to our study question, the potential for type I and type II errors is not inconsequential in a project of this size. For example, given the absolute magnitude of difference we observed among the mean ± SD CRP levels for symptomatic vs asymptomatic patients with carotid stenosis (5.1 ± 7.1 vs 2.8 ± 3.7 mg/dL, $P=.11$), it seems possible that this comparison might have achieved statistical significance with a larger sample size and greater statistical power. Indeed, the potential usefulness of CRP level to differentiate symptomatic vs asymptomatic patients with surgically significant carotid disease was well described in a larger study by Rerkasem et al.[19] Another potentially confounding issue regarding this patient population is that it may be heterogeneous in that it includes new referrals and follow-up patients. Therefore, any in-

nate differences that might exist in the biology of carotid lesions in these 2 types of vascular clinic patients would theoretically represent unmeasured variance in this study and a potential source of bias.

Second, the definition of carotid stenosis in our study at the low-grade velocity of 125 cm/s has unclear clinical significance in terms of future stroke morbidity.[20,21] Depending on the context, this velocity might correlate with a degree of luminal carotid stenosis ranging from a mild 15% to a moderate 50%. Factors affecting this interpretation include the ultrasonography equipment used, the local laboratory duplex criteria, the anatomic location of the measurement within the artery, the associated echogenicity and morphologic structure of the plaque, and the presence or absence of spectral broadening and other descriptors. Many of these factors represent unmeasured variance in our study. We selected this velocity because we were interested in evaluating the predictive value of CRP level in part as a possible screening tool, whereby identification of disease at the earliest possible juncture might theoretically be most advantageous for optimal future management. Furthermore, this threshold provided an appropriate early baseline measurement so that we might follow the progression of carotid stenosis, CRP values, and symptoms in these patients longitudinally over time.

Even with the clear association of CRP elevation and carotid stenosis in our patients, how this marker might be used in the future remains uncertain. Future studies will be needed to demonstrate the potential of CRP level to identify asymptomatic patients with occult disease and to differentiate vulnerable plaques from stable lesions in patients with known disease. Population norms would need to be determined that might guide the interpretation of CRP level as an index of disease severity, target for intervention, or therapeutic end point. Finally, management of elevated CRP levels pharmacologically or otherwise must be ultimately demonstrated prospectively to actually prevent future adverse neurologic events. All of these questions remain open at this time.

Our results suggest implications for future therapy. As has been promulgated for CAD, surveillance and management of elevated CRP level with established drugs such as antiplatelets and statins may have a role in carotid stenosis. Aspirin and statin agents have been shown to reduce CRP levels and future stroke incidence. These drugs seem to affect this risk reduction independent of their respective antiplatelet and lipid-lowering effects. Statin agents in particular have numerous anti-inflammatory properties and have recently been shown to reduce interleukin 6 synthesis, inhibit vascular smooth muscle cell proliferation, prevent complement activation, and favorably modulate nitric oxide–derived oxidants.[22-25] At least for CAD, the magnitude of benefit of antiplatelet and statin therapy correlates quantitatively with the degree of baseline CRP elevation. This suggests that even patients with normal thrombotic risk factors and normal LDL-C levels might benefit from these agents if they demonstrate elevated CRP levels in the context of documented carotid stenosis. Another major area of therapeutic investigation that might someday favorably exploit the inflammatory pathogenesis of carotid stenosis includes emerging anti-inflammatory drug–eluting stent technology.[26] The immunosuppressive agent rapamycin, for example, inhibits T-cell proliferation, vascular smooth muscle cell migration, and proliferative changes in the arterial wall, without destroying cells or causing vessel injury.[27] The demonstrated capability of rapamycin-impregnated stents to dramatically reduce carotid restenosis rates in the coronary artery context is compelling and suggests at least the potential for similar future usefulness in carotid disease.[27-29]

In summary, we performed a prospective comparative cohort study evaluating the potential relationship between serum CRP level and the presence and degree of carotid stenosis in 146 vascular clinic outpatients. We found that CRP level was independently associated with confirmed disease to a moderate degree (OR, 1.2), while LDL-C level and a large group of established demographic and historical risk factors for carotid stenosis were not. Furthermore, CRP level was independently correlated with the actual degree of carotid stenosis and generated a moderate but statistically significant area under the ROC curve for the presence of disease that compared favorably against the other variables. Together, these results suggest that the predictive value of CRP level, while modest, was additive to the traditionally used vascular risk factors currently considered in the management of carotid stenosis. Therefore, CRP level may be a useful adjunct to accurate global vascular risk assessment.

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INVITED CRITIQUE

Mullenix et al, in an accompanying article, measured high-sensitivity CRP levels along with a host of other traditional risk factors in a group of 146 patients undergoing duplex ultrasonography for possible carotid stenosis. They found that CRP levels were higher in patients with than in those without stenoses, and that CRP levels were stronger predictors of stenosis than anything else they measured (including smoking and LDL levels), even when corrected for statin use.

C-reactive protein is today's "hot" molecule. Atherosclerosis is increasingly viewed as an inflammatory process, and CRP seems to be a strong marker of systemic inflammation—the American Heart Association's position that anyone with a CRP level of greater than 3.0 mg/L is in a "high-risk" category for cardiovascular events.[1]

What can we make of these data? Can we simply measure CRP levels and forgo duplex ultrasonography? Of course not, and this is not the authors' objective. The use of this article lies elsewhere. First, it adds another brick in the wall of information regarding the roles of this molecule and inflammation in general in atherosclerotic disease, specifically with regard to carotid stenosis. I believe these results are valid, and I do believe that CRP levels are higher in those with increasing levels of atherosclerosis. Second, it adds support to the growing realization that CRP levels may, in fact, be one of the strongest markers for atherosclerotic-associated risk. Third, this work and others like it help bring this concept closer to the surgeon. Cardiologists and primary care physicians are not the only ones who care about reducing risk, but unless we dive into their literature, we may miss this boat if we do not study this ourselves.

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1. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for health-care professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107(3): 499-511.