C-Reactive Protein Predicts Further Ischemic Events in First-Ever Transient Ischemic Attack or Stroke Patients With Intracranial Large-Artery Occlusive Disease

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Background and Purpose—The role of inflammation in intracranial large-artery occlusive disease is unclear. We sought to investigate the relationship between high-sensitivity C-reactive protein (CRP) levels and the risk of further ischemic events in first-ever transient ischemic attack (TIA) or stroke patients with intracranial large-artery occlusive disease.

Methods—Of a total of 127 consecutive first-ever TIA or ischemic stroke patients with intracranial stenoses detected by transcranial Doppler ultrasonography, 71 fulfilled all inclusion criteria, which included angiographic confirmation. Serum high-sensitivity CRP level was determined a minimum of 3 months after the qualifying event. Patients were followed up during 1 year after blood sampling.

Results—Thirteen patients (18.3%) with intracranial large-artery occlusive disease experienced an end point event: 9 cerebral ischemic events, 7 of which were attributable to intracranial large-artery occlusive disease, and 4 myocardial infarctions. Patients in the highest quintile of high-sensitivity CRP level had a significantly higher adjusted odds ratio for new events compared with those in the first quintile (odds ratio, 8.66; 95% CI, 1.39 to 53.84; \( P = 0.01 \)). A high-sensitivity CRP level above the receiver operating characteristic curve cutoff value of 1.41 mg/dL emerged as an independent predictor of new end point events (hazard ratio, 7.14; 95% CI, 1.77 to 28.73; \( P = 0.005 \)) and of further intracranial large-artery occlusive disease–related ischemic events (hazard ratio, 30.67; 95% CI, 3.6 to 255.5; \( P = 0.0015 \)), after adjustment for age, sex, and risk factors. Kaplan-Meier curves showed that a significantly lower proportion of patients with a high-sensitivity CRP level above the receiver operating characteristic curve cutoff value of 1.41 mg/dL remained free of a new ischemic event (\( P < 0.0001 \)).

Conclusions—High-sensitivity CRP serum level predicts further intracranial large-artery occlusive disease–related and any major ischemic events in patients with first-ever TIA or stroke with intracranial large-artery occlusive disease. These findings are consistent with the hypothesis that inflammation may be involved in the progression and complication of intracranial large-artery occlusive disease. (Stroke. 2003;34:2463-2470.)

Key Words: atherosclerosis ■ C-reactive protein ■ outcome ■ stenosis ■ stroke

Intracranial large-artery occlusive disease represents an important cause of stroke worldwide,\(^1\) and patients affected by this condition are at high risk of suffering recurrent ischemic events and vascular death.\(^2\)–\(^5\) However, there is uncertainty regarding the most effective preventive therapy for this disease, and scientific evidence to determine the selection of patients at higher risk is limited.\(^6\)

C-reactive protein (CRP), a sensitive indicator of systemic inflammation, has been shown to be a powerful predictor of future first-ever\(^7\)–\(^9\) and recurrent\(^10\)–\(^13\) coronary and cerebral ischemic events, a novel marker of atherothrombotic disease that may reflect the amount of inflammatory activity within the atherosclerotic plaque,\(^14\) and a direct mediator of atherogenesis.\(^15\)–\(^17\) Although inflammation is considered to play a major role in all stages of atherothrombosis at extracranial arterial territories,\(^18\) its relative contribution to the initiation, progression, and eventual destabilization of atherosclerotic lesions in intracranial large arteries remains largely unknown.

We conducted a prospective study to evaluate the relationship between CRP level determined several months after first-ever transient ischemic attack (TIA) or stroke in patients with intracranial large-artery occlusive disease and the risk of further ischemic events.

Subjects and Methods

Patient Selection

Our study group consisted of first-ever TIA or ischemic stroke patients with intracranial stenoses detected by transcranial Doppler ultrasound.
Baseline Vascular Risk Factors and Clinical Variables

Cigarette smoking was defined as present if the patient reported at least 10 cigarettes per day during the past 5 years. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medications. Hypercholesterolemia was defined as a total cholesterol concentration ≥220 mg/dL or the current use of cholesterol-lowering agents. Diabetes mellitus was defined by history of fasting glucose ≥140 mg/dL or use of hypoglycemic medication. History of diagnosed coronary artery disease and intermittent claudication was also recorded.

Qualifying strokes and TIAs were considered potentially attributable to intracranial large-artery occlusive disease if the ischemic lesion was located within the territory supplied by a stenosed artery or if the symptoms could be explained by cerebral ischemia within a region perfused by a diseased vessel, in the absence of any other potential causes. Stroke severity was assessed with the maximum National Institutes of Health Stroke Scale (NIHSS) score obtained during admission. The use of the following drugs at inclusion visit was registered: acenocoumarol, aspirin, clopidogrel, triflusal, statins, and angiotensin-converting enzyme inhibitors.

Ultrasound Protocol

TCD recordings were performed with the use of a Multi-Dop-X/TCD (DWL Elektronische Systeme GmbH) device, with a hand-held transducer, in a range-gated, pulsed-wave mode at a frequency of 2 MHz. We used a standard method of insonation without compression testing. According to validated criteria, intracranial stenoses were diagnosed if the mean blood flow velocity at a circumscribed insonation depth was >80 cm/s, with side-to-side differences >30 cm/s and signs of disturbed flow. TCD examinations were performed on admission and repeated at the inclusion visit.

Baseline cervical internal carotid artery (ICA) atherosclerosis was categorized as follows: absent, mild, if 1 or both ICAs had a mild <50% stenosis; moderate, when any of the ICAs presented a moderate <70% stenosis; and severe, if any ICA had a severe stenosis or there was a history of carotid surgery or angioplasty.

MRA and CTA

MRA was performed with a 1.5-T whole-body imager system with 24-mT/m gradient strength, 300-ms rise time, and an echo-planar–capable receiver equipped with a gradient override (Magnetom Vision Plus, Siemens Medical Systems). We used a 3-dimensional time-of-flight sequence with magnetization transfer suppression and tilted optimized nonsaturating excitation, using 1.5-mm-thick sections, 200-mm field of view, 200×512 matrix, and acquisition time that ranged from 7 to 11 minutes. Maximal intensity projection (MIP) reconstructions were performed at the time of imaging. Data were reconstructed around the head-to-foot axis and right-to-left axis. If necessary, target MIP reconstructions were performed.

CTA was performed on a Multislice MX8000 Philips spiral CT scanner with 4 rows of detectors. Ninety milliliters of iodinated contrast medium (320 mg/mL) was administered intravenously at a rate of 3 mL/s with a 13-second prescan delay. Scanning began at the cranial base and continued cranially for 80 mm. Total acquisition time average was 22 seconds. Raw data were transferred to a workstation, and MIP reconstructions were obtained.

The number of angiographically confirmed stenoses in every patient was used to assess the extent of intracranial large-artery occlusive disease.

Blood Sampling and High-Sensitivity CRP Level Determination

Blood samples were drawn a median of 8 months after the qualifying event. Acute infections, surgery, trauma, ischemic events during the previous 3 months, and incident neoplasm or inflammatory conditions were ruled out by careful medical history and physical examination previous to sampling. After centrifugation at 3500 rpm and 4°C for 15 minutes, serum was blinded coded and stored at −80°C until used. High-sensitivity CRP levels were obtained with a Behring Nephelometer Analyzer and expressed in milligrams per deciliter. All determinations were done by duplicate. The mean intra-assay coefficients of variation were <10% for all cases.

Clinical End Points

Clinical interviews were performed every 6 months during 1 year after blood sampling. End point events included the following: certainly diagnosed ischemic stroke or TIA attributable to intracranial stenoses; intracranial large-artery occlusive disease–unrelated stroke or TIA; and coronary ischemic events and sudden death.

Statistical Analysis

Analyses were performed with the SPSS statistical package, version 9.0. Statistical significance for intergroup differences was assessed by the χ² test for categorical variables and the Student t and Mann-Whitney U tests for continuous variables. High-sensitivity CRP concentration was not normally distributed (Kolmogorov-Smirnov test). Using multivariate logistic regression analysis, we computed age-, sex-, and vascular risk factor–adjusted odds ratios (ORs) for new ischemic events associated with increasing quintiles of the population distribution of high-sensitivity CRP, with the lowest quintile as the reference. Univariate analyses were performed to detect variables associated with the occurrence of any major vascular event and of an intracranial large-artery occlusive disease–related cerebral ischemic event. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of high-sensitivity CRP levels that optimally predicted the occurrence of end point events. Cox proportional hazards multivariate analyses were used to identify predictors of further intracranial large-artery occlusive disease–related cerebral ischemic event.
patients was 67.4 ± 10.3 years. Fifty-four patients (76.1%) were hypertensive, and 39 (55%) were diabetic. The qualifying ischemic event was a stroke in 54 cases (76.1%) and a TIA in the remaining 17 (23.9%). Forty-one (76%) of the qualifying event stroke/TIA demonstrated the persistence of intracranial large-artery occlusive disease. Median high-sensitivity CRP concentration was 0.36 (0.14–1.07) mg/dL. In univariate analysis, shown in Table 3, high-sensitivity CRP concentration (P = 0.009) was significantly associated with a higher recurrence rate, whereas presence of > 2 risk factors (P = 0.06), total/HDL cholesterol (P = 0.09), and antiaggregation (P = 0.07) showed a trend toward significance. A ROC curve detected a cutoff point of high-sensitivity CRP level of 1.41 mg/dL (61.5% sensitivity, 89.7% specificity), which was used to include the variable into the multivariate model. After adjustment for age, sex, and vascular risk factors, a Cox regression model identified elevated high-sensitivity CRP level as an independent predictor of further major vascular events (HR, 7.14; 95% CI, 1.77 to 28.73; P = 0.005). Kaplan-Meier curves in Figure 1 show that a significantly lower proportion of patients with a high-sensitivity CRP > 1.41 mg/dL remained free of a new ischemic event (P < 0.0001).

CRP Predicts Further Cerebral Ischemic Events Attributable to Intracranial Large-Artery Occlusive Disease
Seven intracranial large-artery occlusive disease–related cerebral ischemic events (4 strokes and 3 TIAs) were recorded. Ischemic events were attributable to previously symptomatic stenoses in 3 of the 7 cases, to confirmed but initially asymptomatic stenoses in 2 cases, and to newly developed MRA-confirmed stenoses in the remaining 2 patients. The responsible stenoses were located in the MCA in 5 cases and in the intracranial ICA in 2. In univariate analysis, shown in Table 3, high-sensitivity CRP concentration (P = 0.0004) was significantly associated with a higher recurrence rate. Presence of a single stenosis showed a trend toward significance (P = 0.09). A ROC curve provided a cutoff point of high-sensitivity CRP level of 1.41 mg/dL (sensitivity 85.7%, specificity 87.5%). High-sensitivity CRP concentration above this point was the only independent predictor of new intracranial large-artery occlusive disease–related ischemic events.
CRP determination several months after stroke may better reflect the dynamics of the subjacent atherosclerotic disease.

Unstable atherosclerotic plaques with a rich inflammatory component have been found infrequently in intracranial large vessels, and it has been suggested that the atherosclerotic process in intracranial arteries may have differential characteristics. However, in our series elevated CRP levels predicted the occurrence of new cerebral ischemic events potentially caused by intracranial large-artery occlusive disease, paralleling the findings reported in coronary patients. Furthermore, intracranial stenoses are known to be dynamic lesions whose progression may determine an increased risk of recurrent ischemic events. Since CRP level may be a marker of the inflammatory activity of the underlying atherosclerotic disease, our observation supports an important role for inflammation in the progression and destabilization of intracranial large-artery occlusive disease.

**Discussion**

The present study demonstrates that elevated high-sensitivity CRP concentration identifies intracranial large-artery occlusive disease patients at a higher risk of suffering new ischemic events after their first-ever stroke or TIA. This finding is in agreement with a growing body of evidence that implicates CRP as a strong predictor of future vascular events. CRP concentration during admission may in part constitute a response to cerebral ischemia or stroke secondary complications. Therefore, our high-sensitivity CRP determination several months after stroke may better

**Table 3. Univariate Analyses of Variables Associated With Further ILOD-Related Cerebral Ischemic and Other Major Vascular Events**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ILOD-Related Cerebral Ischemic Event</th>
<th>Any Ischemic Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=7)</td>
<td>No (n=64)</td>
</tr>
<tr>
<td>Age, y</td>
<td>67.8±12.4</td>
<td>67.4±10.2</td>
</tr>
<tr>
<td>Sex (M), n (%)</td>
<td>3 (42.9)</td>
<td>39 (60.9)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (42.9)</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>6 (85.7)</td>
<td>47 (73.4)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>4 (57.1)</td>
<td>35 (54.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>4 (57.1)</td>
<td>49 (76.6)</td>
</tr>
<tr>
<td>&gt;2 risk factors, n (%)</td>
<td>4 (57.1)</td>
<td>29 (45.3)</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>0 (0)</td>
<td>9 (14.1)</td>
</tr>
<tr>
<td>Intermittent claudication, n (%)</td>
<td>0 (0)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Qualifying stroke, n (%)</td>
<td>5 (71.4)</td>
<td>49 (76.6)</td>
</tr>
<tr>
<td>NIHSS, median (Q1–Q3)</td>
<td>1 (0–9)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Normal cervical ICAs, n (%)</td>
<td>6 (85.7)</td>
<td>45 (70.3)</td>
</tr>
<tr>
<td>Multiple stenoses, n (%)</td>
<td>2 (28.6)</td>
<td>43 (67.2)</td>
</tr>
<tr>
<td>Antiaggregation (vs AC), n (%)</td>
<td>6 (85.7)</td>
<td>39 (60.9)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>3 (42.9)</td>
<td>29 (45.3)</td>
</tr>
<tr>
<td>Time to sampling, median, mo</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>4.63±1.3</td>
<td>4.25±1.2</td>
</tr>
</tbody>
</table>

Hs-CRP, median (Q1–Q3), mg/dL 3.85 (1.42–6.9) 0.34 (0.14–0.88) 0.0004 1.94 (0.26–3.92) 0.34 (0.15–0.75) 0.009

ILOD indicates intracranial large-artery occlusive disease; AC, anticoagulation. On the left half, univariate analysis of potential predictors of a new ILOD-related event. On the right half, univariate analysis of potential predictors of any ischemic event during follow-up. Results of the multivariate analyses are shown in text.
response and an increased propensity to plaque progression and complication. In addition, the relative frequency of incident coronary ischemic events in patients with raised CRP levels emphasizes the conception of atherosclerosis as an inflammatory systemic disease and reinforces the need to treat atherosclerotic patients globally. Finally, further research is required to understand the causes of persistent inflammation in these high-risk intracranial large-artery occlusive disease patients.

This study has limitations. First, a greater cohort would be desirable to improve the power of the study, which is 85% for the prediction of any ischemic event and 80% for the prediction of new intracranial large-artery occlusive disease–related events. Second, we relied on clinical data to rule out infection and other inflammatory diseases before sampling, but we cannot exclude that some patients had unrecognized conditions responsible for the elevated high-sensitivity CRP levels observed. In this context, a second high-sensitivity CRP determination would have been appropriate. Third, although an extensive workup was done to exclude nonatherosclerotic intracranial stenoses, neither TCD nor MRA nor CTA provides information regarding the histopathological nature of the lesions responsible for vessel narrowing, and we may have included patients with stenoses caused by different underlying vascular pathologies. This fact may explain in part the differences in the prognostic value of the extent of intravascular pathologies. This fact may explain in part the reasons why the extent of intravascular pathologies have been associated with a significant increase in the risk of ischemic events in patients with intracranial large-artery occlusive disease.

In conclusion, increased high-sensitivity CRP levels strongly predict the risk for new intracranial large-artery occlusive disease–related and other ischemic events in first-ever TIA or stroke patients with intracranial stenoses. Elevated high-sensitivity CRP concentration may identify high-risk intracranial large-artery occlusive disease patients, in whom strict vigilance regarding vascular risk factors and therapy combining antithrombotic and anti-inflammatory strategies may be indicated.

**Acknowledgments**

This study was supported in part by a research grant from the Cerebrovascular Diseases Study Group of the Spanish Society of Neurology to Dr Arenillas. The authors wish to thank Teresa Benito, Anna Penalba, Mercè Badia, and Emy Edo for their excellent technical assistance.

**References**


**Figure 1.** Kaplan-Meier estimates of the proportion of patients remaining free of any ischemic event (P<0.0001, log-rank test). Dashed line indicates CRP >1.41 mg/dL; solid line indicates CRP ≤1.41 mg/dL.

**Figure 2.** Kaplan-Meier curves show that a significantly lower proportion of patients with a high-sensitivity CRP >1.41 mg/dL (dashed line) remained free of new intracranial large-artery occlusive disease (ILOD)–related events (P<0.0001, log-rank test). Solid line indicates CRP ≤1.41 mg/dL.
C-Reactive Protein and Vascular Risk in Stroke Patients: Potential Use for the Future

In the accompanying article, Arenillas and colleagues1 furnish new evidence that a persistently elevated level of CRP after a first cerebrovascular event (ischemic stroke or TIA) is associated with an increased risk of vascular events (both cerebral and cardiac) in a population of patients with documented intracranial large-artery occlusive disease. The evolving concept of using a high-sensitivity CRP assay as a marker of cerebrovascular risk is enticing, and the message suggested by the results of this study is both provocative and in accord with the increasing body of literature rapidly accumulating in the exciting field of stroke preventive medicine. The theory behind this association is fascinating: patients with high-risk lesions may be expected to manifest signs of increased inflammatory activity. Such inflammation appears to occur not only locally (in the affected vessel wall) but also systemically, as suggested by increased circulating levels of CRP. The use of an easily measurable systemic marker of inflammation (such as high-sensitivity CRP) may hold the key for determining which patients with intracranial large-artery occlusive disease are most at risk. In fact, the patients at highest risk manifest evidence of surprisingly widespread inflammatory response. Although the full relation between CRP elevation and cardiovascular risk is not yet completely known, the inflammatory status may be a marker for individuals with an exaggerated inflammatory response that may in turn accelerate atheroma progression and facilitate thrombogenesis.

Studying the effect that a general inflammatory marker, such as CRP, has on cerebrovascular risk prediction is far from a simple task. Methodological problems are inherent in design, implementation, and analysis of any such study. The role of elevated high-sensitivity CRP as a risk marker for cardiovascular diseases, including coronary heart disease, stroke, and peripheral arterial disease, is well established through consistent results from a number of prospective studies. CRP also conveys important prognostic information after stroke, but additional well-designed epidemiological studies are needed to validate the findings. Subjects with ischemic stroke and increased levels of high-sensitivity CRP are candidates for a worse outcome with a variety of adverse events, such as vascular deaths, recurrent strokes, and cardiovascular events. Even in the presence of the results of clinical and neuroradiological outcome predictors, high-sensitivity CRP adds relevant prognostic information. Moreover, persistent elevation of high-sensitivity CRP levels after standard treatment of ischemic stroke according to current strategies, measured at the time of hospital discharge, is predictive of recurrent events. Thus, from the clinical point of view, high-sensitivity CRP testing represents a valuable additional diagnostic tool. The available data suggest the utility of a sample taken at admission, within 12 to 24 hours after stroke onset. However, when samples were also taken at discharge, CRP levels were better predictors of the mid- to long-term prognosis than those at admission. This is probably due to the fact that discharge levels more closely reflect the baseline inflammatory status of the patients and thus their intrinsic risk as a result of inflammatory activity. It is reasonable to assess CRP levels at entry and when possible at discharge; assessment 1 to 3 months later may be useful because it is likely that the highest risk of future events is confined to patients with persistently elevated levels of CRP.

The present torrent of studies of CRP in cardiovascular disease and associated conditions is facilitated by the ready
commercial availability of automated CRP assays and of CRP itself as a research reagent. The current enthusiasm over CRP in cardiovascular disease is widely characterized by failure to recognize appropriately the nonspecific nature of the acute-phase response and by lack of critical biological judgment. Hardly a week passes without report of a new potential association between CRP values and some commonly encountered medical condition, physiological state, or vascular risk factor. Examples include cardiac arrhythmias, renal insufficiency, type 2 diabetes mellitus, obstructive sleep apnea, arterial hypertension, obesity, insulin resistance syndrome, estrogen use, frequent physical activity, and moderate alcohol consumption. In contrast, the positive association of CRP values with other classic cardiovascular disease risk factors, such as periodontal disease and smoking, seems more clearly related to local nonarterial vascular disease risk factors, such as atherosclerosis. The current enthusiasm over CRP ascribed is also often ignored. However, it is critically important to recognize that the CRP response is nonspecific and is triggered by many disorders unrelated to cardiovascular disease. Specificity of CRP for inflammation is clearly not infallible, with noninflammatory states such as chronic fatigue, high-protein diet, depression, and aging all associated with increased likelihood of CRP. When CRP is used for assessment of cardiovascular risk, it is therefore essential to clearly establish true baseline CRP values that are not distorted by either trivial or serious intercurrent pathologies. Not surprisingly, then, these concerns can be raised in regard to the study by Arenillas et al. If the CRP value persistently remains >1.0 mg/dL, indicating the presence of a significant acute-phase response, a single measurement is not sufficient; ≥2 serial samples taken at intervals of ≥1 week should be retested until a stable baseline value is seen. Furthermore, when patients with ischemic stroke are studied, no value should be discharged as too high a priori because after stimulation, CRP levels can increase 1000-fold, and there is evidence that in some patients constitutional hyperresponsiveness may lead to very high CRP levels even in the first hours after stroke and for longer periods. While adequate data are now available to document an overall increase in relative risk for cardiovascular events in patients with CRP elevation, data are still lacking with respect to absolute risk and the positive predictive value that CRP elevation might have in patients with acute and less acute ischemic stroke. Data are also lacking to show that interventions aimed at reducing CRP levels will lower the risk of subsequent cardiovascular events. Without this information, use of high-sensitivity CRP assay either acutely or as a screening modality will be limited. In particular, routine inclusion of high-sensitivity CRP assay in risk factor profiling of ischemic stroke patients could result in a disproportionate number of patients with false-positive CRP elevations that are unrelated to prediction of future cardiovascular events. The following guidelines may be reasonable: risk factor assessment with attention to optimizing primary and secondary preventive measures for cardiovascular disease should remain the essential objective of clinicians; interventions aimed at enacting healthy lifestyle changes should benefit all patients; cardiovascular risk may be further reduced by interventions aimed at correcting additional risk factors (ie, enhancing control of diabetes, lipid abnormalities, and blood pressure); and potential preventive measures, such as aspirin, clopidogrel, and angiotensin-converting enzyme inhibitors, should be actively considered and encouraged when appropriate. However, the demonstration that statins are probably effective in the presence of high CRP levels and that the efficacy of antiplatelet therapy in secondary prevention appears to be directly related to the level of inflammatory markers is already a first response.

Finally, inflammation appears an important and common but not a necessary or a sufficient condition, and hence the predictive accuracy of CRP measurement can only be limited, as it is in the case of isolated traditional prognostic factors. Moreover, it is likely that the prevalence of an inflammatory component in acute ischemic stroke may vary according to age, sex, environmental conditions, and different ethnic groups. Variations in baseline plasma CRP of individuals may also reflect differences in CRP responses caused, for example, by genetic differences in the CRP gene yielding high and low responders, with the former being at risk for cardiovascular disease. Multicenter, carefully controlled studies in ischemic stroke patients that include information on stroke severity and other important prognostic factors are needed to determine whether CRP evaluation has utility in the secondary prevention of ischemic stroke before its use is recommended in common clinical practice. From this standpoint, CRP measurements should be included according to standardized protocols and reported on appropriate registries together with patient outcome. These registries will provide the presently lacking information and will gradually improve the prognostic information obtainable from CRP measurements according to age, sex, population, clinical variables, and selected clinical end points. Once these data are available, the profile of patients will be drawn; the causes, genetic or acquired, of the hyperresponsiveness can be sought; and new insights will be provided in ischemic stroke medicine.

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References


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*Stroke*. 2003;34:2463-2468; originally published online September 18, 2003;
doi: 10.1161/01.STR.0000089920.93927.A7
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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