C-Reactive Protein in Ischemic Stroke
An Independent Prognostic Factor

Mario Di Napoli, MD; Francesca Papa, MD; Vittorio Bocola, MD

Background and Purpose—There is growing evidence of the prognostic importance of C-reactive protein (CRP) in ischemic stroke. However, the independent value of CRP at different stages after stroke has not been established. Therefore, we assessed the prognostic values of CRP in ischemic stroke. We also compared the relation of CRP at admission and discharge with 1-year outcome.

Methods—One hundred ninety-three patients were included in a derivation set (n=128) and a validation set (n=65). Serum CRP was measured, within 24 hours after index ischemic stroke, within 48 to 72 hours, and at hospital discharge. We examined the association between the level of CRP at different stages after stroke and outcome. We adjusted for the possible confounding effect using a multivariate Cox proportional hazard model.

Results—A cutoff point of 1.5 mg/dL for CRP at discharge provided optimum sensitivity and specificity for adverse outcome, based on the receiver operator curves. CRP at admission (hazard ratio [HR] 2.78, 95% CI 1.45 to 5.33; \( P=0.0021 \)) and discharge (HR 9.42, 95% CI 4.27 to 19.05; \( P<0.0001 \)) were predictors of the combined end point of new vascular events or death at 1 year. CRP at hospital discharge was the strongest independent marker of adverse outcome (HR 7.42, 95% CI 2.75 to 20.03; \( P=0.0001 \)). These results were confirmed in the validation set (HR 15.66, 95% CI 3.36 to 72.97; \( P=0.0005 \)).

Conclusions—CRP is a marker of increased 1-year risk in ischemic stroke. CRP at discharge is better related to later outcome and could be of greater utility for risk stratification. These findings are consistent with the hypothesis that elevated CRP may predict future cardiovascular events or death. (Stroke. 2001;32:917-924.)

Key Words: inflammation ■ prognosis ■ proteins ■ stroke outcome ■ stroke, ischemic

Several case-control studies with ischemic stroke patients have indicated that recent infections are a possible risk factor for ischemic stroke.\(^1\)\(^-\)\(^3\) In particular, there is increasing evidence that inflammatory processes are involved in cerebral ischemia.\(^4\)\(^-\)\(^6\) Ischemic brain injury secondary to an arterial occlusion is characterized by acute local inflammation and changes in levels of inflammatory cytokines in body fluids of human patients.\(^7\)\(^,\)\(^8\) In addition, several prospective studies have been indicated that elevated levels of inflammation markers, notably C-reactive protein (CRP), are present among individuals at risk for future first-ever myocardial infarction (MI) or stroke.\(^9\)\(^-\)\(^13\) Elevated CRP also predicts mortality in MI patients and is more reliable predictor of outcome than peak creatine kinase if thrombolytic drugs have been given.\(^14\)

Clinical data relating CRP to prognosis after ischemic stroke are sparse; many patients with elevated CRP levels within 72 hours of stroke have an increased risk of death, with an excess of cardiovascular mortality.\(^15\)\(^,\)\(^16\) However, there is no complete information regarding the independent value of this finding or the meaning of CRP determinations carried out at different times after stroke. Therefore, we performed a prospective study in patients with first-ever ischemic stroke to further analyze the relationship between CRP values measured immediately and at different times after stroke, and the 1-year outcome.

Subjects and Methods

Study Design

We studied all patients who were admitted to the Villa Pini d’Abruzzo Care Center (Chieti, Italy) with a diagnosis of ischemic stroke and included in the Villa Pini Stroke Data Bank between March 1, 1998, and March 31, 1999. The Villa Pini d’Abruzzo Care Center is an acute, rehabilitation, and long-term care center. This center has no specific selection criteria for the admission of stroke patients. The Villa Pini Data Bank is an ongoing hospital-based stroke data bank started on March 1, 1998, in the Department of Neurology and Neurorehabilitation to continue for at least 5 years. Informed consent was obtained from all patients included or their legal representative. Our institutional committee approved the study.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients, documented by a brain CT or an MRI indicating the presence of infarction or the absence of hemorrhage.\(^17\)

All patients were included in a derivation and validation set to validate our results and to be confident that our findings can be
generalized. Temporal criteria were adopted to include the patients in the derivation or validation set; all patients recruited between March 1, 1998, and December 31, 1998, were included in the derivation set; all patients recruited between January 1, 1999, and March 31, 1999, in the validation set.

**Study Protocol, Data Collection and Follow-Up**

All patients were screened according to a strict protocol consisting of a complete medical history, a full neurological examination, standardized blood tests, at least 1 and usually 2 CT scans of the brain or MRI, duplex scanning of the carotid arteries, and a cardiac analysis that included standard 12-lead ECG and thoracic echocardiography and, if indicated, 24-hour ECG monitoring and transesophageal echocardiography. The nature and time course of symptoms were recorded by means of detailed checklist. The Canadian Neurological Stroke Scale (CNSS) and Barthel Index (BI) assessed initial stroke severity and disability, respectively.

Finally, patients were classified into 4 subgroups of different presumed etiology: atherothrombotic, cardioembolic, small-vessel occlusive (lacunar), or undetermined cause, as previously described based on standard criteria. Neuroradiological findings were also classified to type: 1) infarcts; 2) large/small infarcts, with cortical involvement (>50%), leukoaraiosis (diffuse or patchy lucencies of the white matter or centrum ovale), and single/multiple infarcts. By definition, large infarcts were so designated when the sum of the largest transverse and sagittal diameter divided by 2 was >1.5 cm; small infarcts, when the sum of the largest transverse and sagittal diameter divided by 2 was <1.5 cm.

Cerebrovascular risk factors such as never, current, or previous cigarette smoking; alcohol abuse (>100 g/d); hypercholesterolemia (history of hypercholesterolemia and/or fasting total cholesterol level >200 mg/dL); hypertriglyceridemia (history of hypertriglyceridemia and/or fasting triglycerides level >180 mg/dL); arterial hypertension (history of hypertension and/or systolic blood pressure >150 mm Hg and/or diastolic pressure >90 mm Hg, out of the acute phase, treated or not); and diabetes mellitus (diagnosis according to the criteria of the National Diabetes Data Group23) were screened together with associated medical diseases. A special effort was made to assess the presence of cardiovascular comorbidity such as arrhythmias and impulse conduction disorders (as present when documented by standard 12-lead ECG), mitral and/or aortic valve disease (diagnosed by echocardiography), left ventricular hypertrophy (as present when documented by standard 12-lead ECG), coronary heart disease (CHD; angina pectoris or previous Q and non-Q MI diagnosed by history and chart review), and peripheral arterial disease (PAD; in the presence of a history of intermittent claudication or previous arterial intervention or Doppler ultrasonography documentation). For statistical analysis, carotid ultrasonography measurements were grouped into 2 categories: stenosis 0% to 50% and 51% to occlusion. Routine laboratory investigations included a complete blood count, erythrocyte sedimentation rate, blood urea, creatinine, total cholesterol and HDL subfraction, triglycerides, glucose, electrolytes, liver enzymes, serological tests for syphilis, ferritin, transferrin, and plasma fibrinogen. To avoid confounding factors, we excluded patients with history of recent clinical infection; concurrent major renal, hepatic, and cancerous disease; surgery or major trauma in the previous month; and obvious signs and clinical evidence of acquired in-hospital infection. Previous infections were monitored with an exhaustive medical history focusing on signs and symptoms of potentially clinical infection during the last 4 weeks before stroke, together with the review of patient’s hospital access schedule.

The Villa Pini clinical laboratory, blind to the status of patients, measured CRP concentrations using a monoclonal antibody coated to polystyrene particles and fixed-time kinetic nephelometric measurements (Behering Institute S.p.A.). The nephelometer (Dade/Behring Marburg GmbH) makes a 1:400 dilution to measure CRP concentrations between 0.35 and 21.0 mg/dL and a 1:20 dilution and any new vascular event (transient ischemic attack [TIA], recurrent stroke, unstable angina, or acute MI), whichever came first, during the 1-year follow-up. Vascular and other nonvascular death, and nonfatal vascular event (TIA, stroke, unstable angina, and MI) were considered separately in a secondary analysis. TIA was defined as an episode of focal cerebral dysfunction, presumably ischemic in origin, lasting <24 hours and followed by a return to normal. Recurrent stroke was defined as any new fatal or nonfatal event, ischemic or hemorrhagic, subsequent to the initial one, with a new neurological deficit or an increased impairment of the previous deficit, persisting beyond 24 hours. Unstable angina was defined as the appearance of ischemic chest pain at rest, documented with typical ischemic changes on ECG, that required admission to hospital. Acute MI was diagnosed in the presence of chest pain lasting >20 minutes, characteristic ECG alterations, and plasma CK-MB elevation greater than twice the normal or previous elevated value. Vascular death included sudden death or death from MI, congestive heart failure, systemic embolism, and other cardiovascular causes (including pulmonary embolism, aneurysm rupture, and acute intestinal ischemia) or as a consequence of the qualifying stroke or of a new fatal stroke in the absence of other intervening causes. Nonvascular death included cancer, pneumonia, sepsis, and other less-frequent causes of death not included in the vascular death.

**Statistical Analysis**

The degree of univariate association between each clinical or laboratory datum and the main and secondary end points were examined by use of the χ²-test with Yates’ correction and Fisher’s exact test when appropriate, by unpaired t test for continuous normally distributed variables, and the Mann-Whitney test for non-normally distributed variables. The Kaplan-Meier technique (log-rank test) was applied to survival analysis. To establish a cutoff point between low and high levels, centiles of CRP values and the corresponding rates of the primary combined end point at 1 year were related via a receiver operator characteristic (ROC) curve. This procedure was repeated with the use of the values obtained at admission, within 24 hours after stroke, within 48 to 72 hours, and at discharge. The CRP value showing the maximum likelihood ratio χ² test in the curve with the largest area was established as the cutoff point between normal and elevated CRP. This cutoff point was prospectively tested in the validation set.

Cox proportional hazards analysis was performed to evaluate the independent contribution of CRP levels to the risk of new event. Univariate predictors of potential significance and CRP values were included in a forward stepwise selection. The model included age (cutoff point 70 years), stroke subtypes, C-reactive protein score, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, fibrinogen level >400 mg/dL, and history of smoking, coronary heart disease, atrial fibrillation, and arterial hypertension. Two models (considering the CRP values on admission and at discharge separately) were tested. In the latter model, patients who had an end point before the third CRP measurement were excluded.

Spearman correlation coefficients were calculated to explore the relationships between the variables selected for the model. Candidate markers were tested with the likelihood ratio χ² test. A prognostic score was calculated for each patient as the sum of the weights.
assigned to the variables in the multivariate analysis. The overall predictive ability of the final model was assessed with the area under the ROC curve in both sets, and its sensitivity and specificity to predict the 1-year outcome were calculated. To define the incremental value of elevated CRP when added in a stepwise fashion to a statistical model that contained the clinical variables without the CRP values, we created a prognostic model by using all clinical variables and determined the area under the ROC curve. Subsequently, we added the CRP data to this model and determined the ROC curve to determine whether this improved the ROC area of the previous model.

### Results

Between March 1, 1998, and March 31, 1999, 307 patients with clinical signs attributable to ischemic stroke were identified. After comprehensive evaluation, 193 patients were included. One hundred fourteen patients (37.1%) were excluded because they did not fulfill the inclusion criteria for the present study: hemorrhagic stroke (n=5); recurrent stroke (n=10); vasculitis (n=3); concurrent major renal (n=4); hepatic (n=7), and cancerous diseases (n=5); surgery (n=3); or major trauma in the previous month (n=2). History of recent clinical infection and obvious signs and clinical evidence of inhospital acquired infection after index stroke were registered in 19.2% of patients (n=59). Seventy-two percent of patients (n=42) with recent clinical infection had a relevant comorbidity that was also capable of increasing acute reactants. In this prospective study, 128 patients were included in the derivation set and 65 in the validation set.

### Derivation Set

Among 128 patients included in the derivation set, there were 53 men and 75 women (male-to-female ratio, 0.7). The mean±SD age was 73.10±9.17 years. CT was performed in 113 patients (88.3%) and MRI or both in all remaining. The CRP values (median and 25% to 75% interquartile ranges) within 24 hours, between 48 to 72 hours, and at hospital discharge (or at the occurrence of inhospital end point) were 1.3 (0.5 to 3.3), 1.0 (0.5 to 2.3), and 0.6 (0.3 to 2.2) mg/dL, respectively (normal value <0.5 mg/dL). The levels of CRP changed (P=0.0002, \( \chi^2 \) test) between admission and discharge. Among 95 patients (74.2%) with CRP levels >0.5 mg/dL on admission, values remained elevated until discharge in 59 and dropped to normal in 36 patients. In the group of 33 patients with normal CRP on admission, CRP levels persisted at >0.5 mg/dL in 25 and were abnormally elevated at discharge in the remaining 8 patients (Figure 1).

No difference was found in the length of hospital stay between the different patterns of CRP (P=0.5945). The area of the ROC curves relating CRP levels to 1-year outcome, at baseline, 48 to 72 hours, and discharge were 0.65±0.03, 0.77±0.07, and 0.81±0.07, respectively. The highest likelihood ratio corresponded to a value of 1.5 mg/dL in the discharge CRP ROC curve (likelihood ratio \( \chi^2 \) test=42.05; df=1, P<0.0001).

Baseline characteristics of patients according to CRP level at admission (above or below 1.5 mg/dL) are compared in Table 1. A greater prevalence of fibrinogen level >400 mg/dL (47.9% versus 89.5%; P<0.0001) and male sex (32.4% versus 52.6%; P=0.0209) and a lower prevalence of arterial hypertension (83.1 versus 57.9%; P=0.0016), mitral/aortic valve disease (50.7% versus 31.6%; P=0.0294), and hypercholesterolemia >200 mg/dL (50.7% versus 29.8%; P=0.0171) were noted in patients with elevated CRP, together with more severe neurological deficit and relevant disability as judged by the CNSS score (P=0.0003) and BI (P=0.0001), respectively. There were no differences regarding treatment with aspirin (dose range 100 to 300 mg/d), ticlopidine, warfarin, and intravenous heparin between patients with CRP levels at admission above or below 1.5 mg/dL (Table 1). During the follow-up period, all patients received a secondary preventive treatment with aspirin (50%), ticlopidine (22%), or warfarin (28%), with a strict control of recognized vascular risk factors.

Fifty-one patients had cardioembolic stroke, 46 atherothrombotic stroke, 22 small-vessel occlusive stroke, and in 9 patients the diagnosis was other/uncertain. No significant differences were found between stroke type and level of CRP at admission. Seventy-two patients (56.3%) exhibited a single infarct, 48 (37.4%) multiple infarcts, and 8 (6.3%) had no pathological changes in support of infarct. Fifty-five patients (50.8%) had a large infarct and 58 patients (45.3%) had an infarct with cortical involvement. Thirty-eight patients (29.7%) displayed leukoaraisia. CRP levels above normal value (>0.5 mg/dL) at entry were significantly associated with larger infarcts (87.7% versus 60.3%; P=0.0004) and cortical involvement (91.4% versus 60.0%; P=0.0001). At discharge, higher CRP levels were also associated with larger infarcts (64.6% versus 39.7%; P=0.0047). No associations were found between CRP level and the presence of multiple infarcts and leukoaraisia.

As a whole, 40 patients (31.3%; 18 men and 22 women) had a primary end point within 1 year of stroke onset; 32 (80%) were aged >70 years. Twenty patients died, 16 (80%) of vascular causes. Twenty patients experienced a new vascular event (TIA in 1, MI in 3, recurrent stroke in 7, and...
occurrence of unstable angina requiring new admission to hospital in 9). The distribution of primary end point events according to CRP level at discharge is shown in Table 2.

At the end of the first year of follow-up, the median CNSS score was 8.0 (6.0 to 10.0) and the median BI score 60 (40 to 75); 33 patients (25.8%) were functionally independent and 50% (58.6%) functionally dependent. The functional status was significantly worse in the subgroup of patients with CRP levels at discharge above and below 1.5 mg/dL: only 3 patients were functionally independent at 1 year (6.5% versus 36.6%; P<0.0001).

As shown in Table 3, the occurrence of combined end point at 1-year follow-up was related to CRP level at admission (hazard ratio [HR] 2.78, 95% CI 1.45 to 5.33; P=0.0021) and discharge (HR 9.42, 95% CI 4.27 to 19.05; P<0.0001). Kaplan-Meier survival curves of patients with CRP at admission and at discharge above and below 1.5 mg/dL are shown in Figure 2. Univariate markers of worse prognosis were also the presence of CHD (HR 2.31, 95% CI 1.23 to 4.32; P=0.0092), PAD (HR 2.96, 95% CI 1.31 to 6.69; P=0.0094), age >70 years (HR 2.18, 95% CI 1.01 to 4.74; P=0.0486), and lower CNSS score at entry (per 1.0 point increase, HR 0.81, 95% CI 0.75 to 0.88; P<0.0001). CRP level at hospital discharge (HR 7.42, 95% CI 2.75 to 20.03; P=0.0001) showed the strongest independent association with the combined end point at 1 year, followed by the CNSS score (HR 0.88, 95% CI 0.80 to 0.97; P=0.0069).

In the analysis of secondary end points, univariate predictors of death were cholesterol level (HR 0.14, 95% CI 0.03 to 0.59; P=0.0077), CHD (HR 3.87, 95% CI 1.49 to 10.08; P=0.0056), atrial fibrillation (HR 3.55, 95% CI 1.47 to 8.58; P=0.0048), PAD (HR 6.18, 95% CI 2.37 to 16.14; P=0.0002), CNSS score (HR 0.75, 95% CI 0.66 to 0.84; P<0.0001), and CRP at discharge (HR 12.33, 95% CI 3.61 to 42.13; P<0.0001). There was not a significant association between CRP on admission and death (HR 2.03, 95% CI 0.83 to 4.96; P=0.1220). In the multivariate analysis, CNSS score (HR 0.75, 95% CI 0.64 to 0.88; P=0.0004), cholesterol level (HR 0.21, 95% CI 0.03 to 0.95; P=0.0397), and CRP at discharge (HR 11.73, 95% CI 1.30 to 19.66; P=0.0030) were independent predictors of death, while CRP levels at admission (HR 3.71, 95% CI 1.11 to 12.35; P=0.0330) and at discharge (HR 5.82, 95% CI 1.60 to 21.13; P=0.0074) were the only independent predictors of the occurrence of new vascular events.

The area under the ROC curve of the prognostic model increased from 0.72±0.05 to 0.82±0.07 (P=0.0185) when CRP values at discharge were added to the model including clinical variables. On the contrary, the addition of the clinical model to the CRP data did not significantly improve the ROC area (0.80±0.07 and 0.81±0.08; P=0.9260).
Validation Set

Table 1 describes the baseline characteristics of the derivation and validation sets. Median and 25th to 75th percentile baseline CRP values were similar in both sets (1.3 [0.5 to 3.3 mg/dL] versus 1.2 [0.6 to 3.1 mg/dL]; P=0.8881). In the ROC curve of the validation set, a CRP value of 1.5 mg/dL at discharge was also associated with the best likelihood ratio of major events at 1 year (likelihood ratio \( \chi^2 \) test=29.64; df=1, \( P<0.0001 \)). A CRP value \( \geq 1.5 \) mg/dL at admission was significantly associated with a worse prognosis at 1 year (39.3% versus 16.2%, \( P=0.0331 \)). A strong relationship was observed between CRP \( \geq 1.5 \) mg/dL at discharge and 1-year outcome (65.2% versus 48%; \( P<0.0001 \)), similar to that shown in the derivation set. In the validation set, CRP at discharge remained the strongest independent prognostic marker of 1-year outcome (HR 15.66, 95% CI 3.36 to 72.97; \( P=0.0005 \)).

The addition of CRP data to the non-CRP model significantly increased the area of the ROC curve from 0.79 ± 0.04 to 0.89 ± 0.08 (\( P=0.0116 \)). Conversely, no significant difference in ROC area was observed when the non-CRP model was added to CRP values (0.84 ± 0.09 to 0.85 ± 0.09; \( P=0.8529 \)).

Discussion

The aim of the study was to elucidate the relationship between CRP and prognosis after cerebral ischemia. We adopted strict enrollment criteria to have a homogeneous population: all patients were selected to avoid possible confounding factors capable of increasing inflammation markers. We found in our stroke population a high rate of cardioembolic stroke (40%), a low rate of stroke of unknown cause (7%), and a very high rate of primary end point within 1 year (31%). Although all patterns were largely due to the older age of our population, other reasons should be considered: diligent case ascertainment, complete screening procedures, and extensive use of cardiovascular examination, together with the progressive increase of cardioembolic stroke incidence in the general population, registered in the last decade, could explain the clinical characteristics of our stroke population.26,27 From this standpoint, the possible presence of a selection bias is less plausible. We have prospectively validated our findings in another sample of stroke patients to be confident that our findings could be generalized beyond the group that we studied. Our data indicate that patients with ischemic stroke who have CRP levels \( \geq 1.5 \) mg/dL at discharge have a significantly worse outcome. Another important finding of this study is that CRP adds independent prognostic information to that provided by known clinical variables. We also demonstrate that compared with CRP after stroke, CRP at discharge has the strongest association with 1-year outcome in a multivariate model.

Several prior studies have reported elevated CRP values in patients with unstable CHD, MI, and ischemic stroke.11–13,15,16,28–30 However, variations in CRP level in ischemic stroke were not previously analyzed in detail. According to our data, 2 distinctive patterns with a different prognostic message can be described: a benign pattern, consisting of either persistently normal or decreasing values from admission through to discharge, and an adverse pattern, represented by those patients with persistently elevated or increasing values from admission to discharge. These variations in CRP level cannot be explained by different methods of treatment, because the use of antithrombotic or anticoagulant medication was similar in patients with CRP levels above and below 1.5 mg/dL. Persistently elevated or crescendo patterns may represent either an ongoing inflammatory process or the extension of cerebral ischemia.15 A growing body of evidence from animal models and preliminary human studies indicates that inflammatory mechanisms contribute to secondary neuronal injury after cerebral ischemia.1–6,31 Mortality and new vascular events spread evenly over the duration of follow-up and are not concentrated shortly after stroke. Thus, the elevated levels of CRP do not appear to be linked only to an immediate process related to stroke, but also to a persistent inflammatory response in stroke survivors.13

The pathophysiological reason for an association between CRP and prognosis is uncertain. Elevated CRP levels may

<table>
<thead>
<tr>
<th>TABLE 2. One-Year Outcome Events in Relation to Levels of CRP at Discharge or at Inhospital End Point in 193 Patients With First-Ever Ischemic Stroke, by Derivation and Validation Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation Set (n=128)</strong></td>
</tr>
<tr>
<td>CRP &lt;1.5 mg/dL (n=71)</td>
</tr>
<tr>
<td>CRP &lt;1.5 mg/dL (n=57)</td>
</tr>
<tr>
<td>Combined end point (any vascular event + death)</td>
</tr>
<tr>
<td>Formal end point</td>
</tr>
<tr>
<td>Secondary end point</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
affect coagulation through the important role of tissue factor expression. Previous data showed that activation of coagulation factors in stroke patients increased mortality, and fibrinogen has a putative role. We simultaneously measured fibrinogen levels in our study, to assess the role of the coagulation system, so one explanation for our results might be that patients with higher baseline levels of CRP had higher levels of fibrinogen when the inflammation system was activated. It is likely; however, that the explanation is more complicated. In this study, we found a strong association between fibrinogen and CRP without any association between fibrinogen and outcome, suggesting that the effects of higher CRP levels are independent from fibrinogen. The mechanism that can lead to initiation of such inflammatory reaction may be multiple and to date are largely unexplained.

CRP is normally a trace protein that is regulated at the level of transcription, principally by IL-6, a pleiotropic cytokine with proinflammatory and anti-inflammatory effects. Increased levels of CRP in this study might identify patients with altered balance release of IL-6. These patients might be predisposed to intense activation of inflammation in response to a variety of stimuli such as infection or trauma. We speculate that stroke patients in whom the inflammation system reacts most intensely may be at greater risk for subsequent vascular events. CRP levels would identify those patients whose inflammation system responds most actively to stimuli. These might be the patients at highest risk for subsequent vascular events or death, in whom more aggressive therapy and clinical surveillance might be appropriate.

TABLE 3. Univariate Predictors of 1-Year Combined End Point in 128 First-Ever Ischemic Stroke Patients in the Derivation Set

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;=70 y</td>
<td>2.18</td>
<td>1.01–4.74</td>
<td>0.0486</td>
</tr>
<tr>
<td>Female</td>
<td>0.84</td>
<td>0.45–1.56</td>
<td>0.5718</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.66</td>
<td>0.34–1.26</td>
<td>0.2034</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.96</td>
<td>0.51–1.81</td>
<td>0.9053</td>
</tr>
<tr>
<td>Cholesterol level (&gt;200 mg/dL)</td>
<td>0.56</td>
<td>0.29–1.11</td>
<td>0.0978</td>
</tr>
<tr>
<td>Triglycerides level (&gt;180 mg/dL)</td>
<td>1.61</td>
<td>0.84–3.09</td>
<td>0.1489</td>
</tr>
<tr>
<td>Fibrinogen level (&gt;400 mg/dL)</td>
<td>1.35</td>
<td>0.66–2.63</td>
<td>0.4404</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.20</td>
<td>0.86–2.45</td>
<td>0.6231</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0.54</td>
<td>0.26–1.14</td>
<td>0.1081</td>
</tr>
<tr>
<td>CHD</td>
<td>2.31</td>
<td>1.23–4.32</td>
<td>0.0092</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.42</td>
<td>0.75–2.74</td>
<td>0.2827</td>
</tr>
<tr>
<td>Mitral/aortic valve disease</td>
<td>1.32</td>
<td>0.71–2.46</td>
<td>0.3763</td>
</tr>
<tr>
<td>PAD</td>
<td>2.96</td>
<td>1.31–6.69</td>
<td>0.0094</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1.50</td>
<td>0.72–3.15</td>
<td>0.2834</td>
</tr>
<tr>
<td>Symptomatic carotid stenosis (&gt;50%)</td>
<td>1.17</td>
<td>0.61–2.26</td>
<td>0.6335</td>
</tr>
<tr>
<td>CNSS score (per 1.0-point increase)</td>
<td>0.81</td>
<td>0.75–0.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke type*</td>
<td>1.32</td>
<td>0.66–2.63</td>
<td>0.4359</td>
</tr>
<tr>
<td>Stroke type†</td>
<td>0.53</td>
<td>0.77–1.60</td>
<td>0.2561</td>
</tr>
<tr>
<td>CRP &gt;1.5 mg/dL at admission</td>
<td>2.78</td>
<td>1.45–5.33</td>
<td>0.0021</td>
</tr>
<tr>
<td>CRP &gt;1.5 mg/dL at discharge</td>
<td>9.02</td>
<td>4.27–19.05</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Embolic vs atherothrombotic; †lacunar vs atherothrombotic.

Precise knowledge of the possible triggers of inflammation and the determinants of its individual response may open novel therapeutic avenues.

Elevated levels of CRP can reflect the extent of brain infarction. In our study, patients with elevated CRP had significantly lower CNSS score and larger infarcts and cortical involvement. These findings support previous observations and are consistent with elevated CRP reflecting the extent of brain infarction. CRP may reflect inflammations related to pathobiology of ischemic stroke. However, many patients (26%) in our series had normal levels of CRP after stroke, implying that ischemic stroke itself does not induce a full-blown acute-phase response. Patients with persistently elevated CRP levels had a worse outcome, supporting the possibility that postischemic inflammation contributes to ischemic brain injury. Baird et al have suggested that the progression of ischemic damage is delayed in stroke patients. However, the initial neurological deficit reflects injury to the core as well as the penumbra. As collateral perfusion develops, brain function can be restored within the penumbra. In addition, the structural lesion solidifies over time and might recruit parts of the ischemic penumbra into infarction. Such delayed progression of brain damage might lead to neurolog-
CRP is elevated by underlying conditions other than acute stroke, such as infection, surgery, and cancer. We were careful to exclude from our study patients with any of these conditions. However, it is possible that some patients had unrecognized conditions that elevated their inflammation marker levels and also increased the risk of vascular events and death. Of the patients with higher CRP levels at discharge, 9 (15.8%) had a new coronary event. Patients who respond to a stroke with marked activation of the inflammation system may be those who are also at risk for more intense activation in response to coronary triggering events. 42

Taken together, our data suggest that it may be time to add a marker of inflammation to the list of cardiovascular risk factors commonly used to assess the risk in vascular patients. In general, we advocate a cautious approach for several reasons: (1) a diagnostic test with reproducible assay characteristics must be available; (2) there must be a consistent series of prospective studies which indicates that elevation of a given marker predicts future events; and (3) to be of clinical use, a marker of inflammation must be shown to add substantially to our ability to predict risk beyond that achievable by use of traditional risk factors. CRP might be a good candidate because its levels are affected by little other than inflammation, its risk prediction is independent of other known cardiovascular risk factors, and highly sensitive reproducible assays are becoming available. 32 For 2 main reasons, however, whether CRP is an independent outcome predictor after stroke remains uncertain. First, the hazard risk of elevated CRP levels at discharge was substantially reduced (from 9.02 to 7.42) in our study after baseline confounding factors were adjusted for. This substantial reduction suggests that more exact adjustment might produce a greater reduction. Second, although experimental studies suggest that CRP might directly contribute to vascular damage, no direct evidence exists for such involvement. 30,32,41

In conclusion, we believe that these data support 3 main conclusions. First, elevation of CRP is common in ischemic stroke. In patients who have overcome the acute phase, the finding of elevated CRP levels at hospital discharge is strongly related to the occurrence of subsequent vascular events or death. Second, CRP levels may provide a mechanism to stratify poststroke patients into relatively high-risk and low-risk groups: patients with CRP levels ≥1.5 mg/dL have a worse prognosis. Finally, these data also raise the intriguing possibility that stroke patients may be at greater risk of subsequent cardiovascular complications or death and severe neurological deficit and disability when the inflammation system reacts most strongly because of predisposition to an intense activation.

References


32. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood. 1993;82:513–520.


C-Reactive Protein in Ischemic Stroke: An Independent Prognostic Factor
Mario Di Napoli, Francesca Papa and Vittorio Bocola

Stroke. 2001;32:917-924
doi: 10.1161/01.STR.32.4.917

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/4/917

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/