Inflammation, Hemostatic Markers, and Antithrombotic Agents in Relation to Long-Term Risk of New Cardiovascular Events in First-Ever Ischemic Stroke Patients

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Background and Purpose—The measurement of markers of inflammation or thrombosis has been proposed as a method to improve the prediction of risk in patients with vascular disease. We evaluated the usefulness of these markers as predictors of cardiovascular events in ischemic stroke patients.

Methods—We analyzed levels of C-reactive protein (CRP), fibrinogen, and D-dimer within the first 24 hours after stroke onset in 473 first-ever ischemic stroke patients and determined the cumulative survival curves free of cardiovascular events in relation to the level of each of these markers according to the Kaplan-Meier method. We adjusted for possible confounding variables using a multivariate Cox proportional-hazards model.

Results—Patients in the highest tertiles of D-dimer, fibrinogen, and CRP were associated with an excess risk of new cardiovascular events of 36% \((P=0.0134)\), 63\% \((P<0.0001)\), and 72\% \((P<0.0001)\), respectively, compared with patients in the lowest tertile. The patients in the highest tertile of CRP had 4 times the risk (hazard ratio, 4.04; \(P<0.0001)\) of a new cardiovascular event. Smoking, age, sex, and body mass index did not modify risk, and risk was independent of other confounding variables and of D-dimer and fibrinogen levels. The use of ticlopidine was associated with a significant risk reduction among patients with lower (86\%, \(P=0.0159)\) and middle (69\%, \(P<0.0001)\) levels of CRP, whereas a nonsignificant excess risk (27\%, \(P=0.3896)\) was evident among those with the highest levels.

Conclusions—Elevated levels of CRP, more than of D-dimer and fibrinogen, are related to the risk of new cardiovascular events after ischemic stroke. The efficacy of antiplatelet therapy in secondary prevention appears to be directly related to level of inflammatory and thrombotic markers. (Stroke. 2002;33:1763-1771.)

Key Words: C-reactive protein ■ fibrin D-dimers ■ inflammation ■ stroke, ischemic ■ ticlopidine

Strokes kill \(\approx\) 5 million people each year.\(^1\) Among those who survive a stroke, the risk of further stroke is very high: at least 1 in 6 suffers another stroke within 5 years.\(^2\) Although the risk of death and new vascular events after first-ever stroke is high, prediction of recurrent events or death is difficult. Increasing age, cardiovascular comorbidities, atrial fibrillation, arterial hypertension, diabetes mellitus, carotid stenosis, and stroke severity are all associated with death and new vascular events, but the sensitivity and specificity of these risk factors are low.\(^3\)-\(^6\)

Accumulated data demonstrate that inflammation plays an important role in the pathophysiology of ischemic stroke.\(^7\),\(^8\) Elevated blood levels of inflammatory and hemostatic markers are associated with increased cardiovascular risk in healthy subjects and in patients with coronary heart disease (CHD) and ischemic stroke.\(^9\)-\(^11\) Previous studies have also shown the brisk activation of fibrin formation and platelet activation in the acute phase after stroke.\(^12\) Local fibrin formation and lysis are also part of the inflammatory response, and fibrin degradation products, including D-dimer,\(^13\) have been shown to have different effects on acute-phase responses, including hepatic synthesis of acute-phase proteins such as fibrinogen and C-reactive protein (CRP).\(^14\)-\(^17\) Furthermore, high D-dimer levels double the risk of acute myocardial infarction in healthy subjects\(^18\)-\(^20\) and predict the risk of new events in subjects with CHD.\(^19\),\(^21\) Fibrinogen increases in patients with cardiovascular disease in association with inflammatory reactions,\(^5\),\(^10\) and elevated levels of CRP are associated with an increased risk of cardiac events in patients with unstable coronary artery disease and ischemic stroke, as well as in apparently healthy persons.\(^22\)-\(^26\) Only very limited information is available concerning the relationship between the acute-phase response and fibrin turnover and prognosis in patients with first-ever ischemic stroke. Therefore, we extended the follow-up period in the Villa Pini Stroke Data Bank Study\(^25\),\(^26\) to a mean of 2 years to further analyze this relationship. We evaluated and compared the usefulness of D-dimer, CRP, and fibrinogen levels and other indicators of risk, including neuroradiological findings, as predictors of the long-term risk of fatal and nonfatal cardiovascular recurrent events.
Methods

Study Design

The study is part of a prospective hospital-based, first-ever ischemic stroke data bank. We evaluated all 790 patients included between March 1998 and October 1999 with complete data on D-dimer, CRP, and fibrinogen levels. The original inclusion criterion was a diagnosis of first-ever ischemic stroke within 24 hours before enrollment. Exclusion criteria were related mainly to conditions associated with increased levels of inflammation markers. All therapeutic decisions were made without knowledge of the patient’s D-dimer, CRP, and fibrinogen levels. All patients provided witnessed informed consent, and the ethics committee of our institution approved the study. We have previously described diagnostic criteria, study protocol, data collection, and follow-up methods, along with the preliminary results.

Blood Sampling and Laboratory Methods

Venous blood samples were obtained at enrollment within 24 hours after index stroke. D-dimer levels were determined by turbidimetric determination of cross-linked fibrin degradation products (Dade Behring). Levels of CRP were determined with a commercially available, high-sensitivity, immunonephelometric, latex-enhanced assay (Dade Behring). Fibrinogen levels were determined by immunonephelometry (Dade Behring) and according to the Clauss method. Details of the analytic procedures have been described elsewhere. The coefficient of variation within each of these assays was 1.3% to 5%; the variation between assays was ~0.8% to 5.7%.

Neuroradiological Findings

CT scan of the brain was performed at enrollment within 24 hours after stroke onset to confirm the diagnosis of ischemic stroke. A second CT or MRI scan was usually performed within 1 week to determine cerebral infarct size. Neuroradiological findings were classified according to type of lesion: large or small infarcts, cortical involvement (>50%), leukoaraiosis, and single or multiple infarcts. Details of the neuroradiological criteria have been given elsewhere. Brain swelling (sulcal effacement, midline shift, or ventricular compression) was also registered.

Evaluation of End Points

We monitored all patients during hospitalization; thereafter, they were followed up regularly as outpatients for 2 years. The primary end point considered in this analysis was the combination of vascular death (sudden death or death resulting from myocardial infarction, congestive heart failure, systemic embolism, and other cardiovascu-

Statistical Analysis

Differences in proportions were evaluated by the Pearson and Mantel-Haenszel χ² tests as appropriate. The Mann-Whitney U test was used to test the equality of distributions in independent groups. Spearman correlation coefficients were calculated to explore the relationship between D-dimer, fibrinogen, and CRP. The cumulative survival curves in relation to D-dimer, CRP, and fibrinogen levels were determined according to the Kaplan-Meier method with the use of log-rank tests for statistical assessment. On the basis of previous reports, we evaluated the following cutoff levels: <5 mg/L, 5 to 33 mg/L, and >33 mg/L CRP; <3.78 mg/L, 3.78 to 6.17 mg/L, and >6.17 mg/L fibrinogen; and <312 mg/L, 312 to 1327 mg/L, and >1327 mg/L D-dimer.

We used Cox regression analysis to calculate the unadjusted and adjusted relative risk ratios and 95% confidence intervals (CIs) for cardiovascular events after 1 year and for the total 2-year follow-up period in relation to D-dimer, CRP, and fibrinogen levels. To identify independent predictors of fatal or nonfatal cardiovascular events, we used multivariate Cox regression analyses with forward, stepwise selection in 3 models. All clinical and neuroradiological variables associated with the primary end point in the univariate analysis that had a value of P<0.05 were included in the first model. D-dimer and fibrinogen levels were added to the second model, and CRP levels were added to the third model. Variables with a value of P<0.05 were included in the model, and variables with a value of P>0.10 were removed. We calculated the hazard ratio and 95% CI when appropriate.

Finally, to address the clinical need for improvement in secondary prevention among persons with ischemic stroke, we also performed a subgroup analysis to evaluate directly whether antiplatelet therapy might modify any relation between D-dimer, fibrinogen, and CRP and the risk of fatal or nonfatal cardiovascular events in ischemic stroke patients. To evaluate whether antiplatelet therapy affected these relations, analyses were also repeated, including an interaction term for antiplatelet therapy, and the considered parameters were treated as log-transformed continuous variables. For all statistical analyses, a value of P<0.05 was considered to indicate significant difference.

Results

Patient Enrollment and Baseline Characteristics

Between March 1998 and October 1999, 790 potential first-ever ischemic strokes were registered: 317 (40.1%) were subsequently found to be ineligible because they did not fulfill the inclusion criteria for the present study (Figure 1). The median age of the study population was relatively old (74 years), and 42% (n=197) had ≥3 associated atherogenic risk factors. Approximately 39% (n=185) had a previous diagnosis of CHD, and 25% (n=118) had atrial fibrillation. In addition to the primary preventive treatment with aspirin (n=252), ticlopidine (n=65), or warfarin (n=22). The median time from symptom onset to blood sample was 12 hours; the median time to CT scan was 15 hours. At entry, 257 patients exhibited a single infarct, 194 had multiple infarcts, and 22 had no pathological changes in support of infarct. The index event was atherothrombotic in 194, embolic in 156, and lacunar in 82; in 41, the diagnosis was other or uncertain. The median (25% to 75% interquartile ranges) CRP, fibrinogen, and D-dimer values within 24 hours were 12 mg/L (6 to 28 mg/L), 4.55 g/L (3.53 to 5.67 g/L), and 692 µg/L (259 to 1249 µg/L), respectively. The concentrations of CRP and D-dimer were correlated, but the correlation was weak.
The median CRP level (25 mg/L [9 to 69 mg/L], P<0.0001) and median fibrinogen level (5.24 g/L [4.00 to 6.34 g/L], P<0.0001) were both significantly higher at enrollment among patients who had a cardiovascular event than in patients who survived free of cardiovascular events (9 mg/L [5 to 19 mg/L] and 4.22 g/L [3.19 to 5.36 g/L], respectively) and in patients who died of cardiovascular causes during follow-up (37 mg/L [10 to 96 mg/L], P<0.0001, and 5.55 g/L [4.02 to 7.57 g/L], P<0.0001). The median CRP level at enrollment was also higher among patients who died of nonvascular causes than among those who survived (21 mg/L [12 to 23 mg/L], P=0.0062), whereas there was no corresponding significant difference in fibrinogen levels (4.84 g/L [2.74 to 6.10 g/L], P=0.4545). Higher median levels of CRP and fibrinogen were also significant predictors of recurrent stroke (16 mg/L [6 to 38 mg/L], P=0.0062, and 5.10 g/L [3.79 to 5.67 g/L], P=0.0077) and cardiac event (24 mg/L [9 to 65 mg/L], P<0.0001, and 4.96 g/L [4.33 to 6.25 g/L], P=0.0032). Kaplan-Meier analysis showed that patients with the highest levels of CRP at enrollment (>33 mg/L) had a significantly higher probability of a primary end point during the entire follow-up period than did patients with levels of 5 to 33 mg/L or those with levels <5 mg/L (χ² for trend=59.05, P<0.0001; Figure 2B). This difference was more evident in the first months after stroke. The risk of patients in the highest tertile increased further but slowly after the first months. The probability of a fatal or nonfatal cardiovascular event was also higher for patients with the highest fibrinogen levels (≥6.17 g/L) than for those with the lower (3.78 to 6.17 g/L) and lowest (<3.78 g/L) levels (χ² for trend=30.42, P<0.0001; Figure 2C) but with a clear increase only after the first month after stroke. The rates of fatal and nonfatal cardiovascular events and unadjusted and adjusted relative risks at 1 year and for the total 2-year follow-up period are shown in Table 2 according to CRP and fibrinogen levels at enrollment. Although relative risk was substantially stable over time and after adjustment for confounding factors for D-dimer and fibrinogen, the relative risk for fatal or nonfatal cardiovascular events fell from 8.80 (95% CI, 4.33 to 17.90) at 1 year to 5.76 (95% CI, 3.34 to 10.00) at 2 years in patients in the top third compared with those in the bottom third of CRP concentrations at admission, suggesting a time-to-event dependency.

Multivariate Analyses
Multivariate analysis of the relation among clinical data, findings on the CT scan obtained at admission, and risk of fatal or nonfatal cardiovascular event (model 1) showed that during the first month, patients with intermediate levels of D-dimer (312 to 1327 μg/L) had a probability of a fatal or nonfatal cardiovascular event that was similar to that in the group with the lowest levels, but thereafter the risk gradually approached that in the group with the highest levels. The rates of cardiovascular events and unadjusted and adjusted relative risks of fatal or nonfatal cardiovascular events at 1 year and for the entire 2-year follow-up period are presented in Table 2 according to the D-dimer levels.

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(r=0.20, P<0.0001, Spearman’s rank correlation). However, the correlations between CRP and fibrinogen levels and between D-dimer and fibrinogen levels were modest (r=0.56, P<0.0001 and r=0.46, P<0.0001, respectively).

**Clinical Outcome**
All patients received a secondary preventive treatment with aspirin (dose range, 100 to 400 mg/d; 41.6%), ticlopidine (dose range, 250 to 500 mg/d; 35.1%), or warfarin (attempted international normalized ratio range, 2.5 to 3.5; 19.9%) with strict control of recognized vascular risk factors. After 1 month, 65 of the 473 patients (19.2%) had a fatal (n=20) or nonfatal (n=45) cardiovascular event; after 1 year, 139 patients had a fatal (n=55) or nonfatal (n=84) cardiovascular event; and 6 died of nonvascular causes. During the entire 2-year follow-up period, 182 patients (38.5%) had a fatal (n=64) or nonfatal (n=104) cardiovascular event or died of nonvascular causes (n=14). Of these, 61 were men and 121 were women; 136 (74.7%) were >70 years of age; 46 experienced a recurrent stroke; and 58 had a cardiac event. At the end of follow-up, 104 patients (22%) were functionally independent, and 281 (59.4%) were functionally dependent; 149 of them resided in nursing homes or needed assistance to live at home.

**Clinical Variables and Neuroradiological Findings**
As shown in Table 1, there were many significant differences between patients who survived free of new cardiovascular events and those who had a fatal or nonfatal cardiovascular event in both clinical and neuroradiological findings at enrollment. No differences were found between primary prevention therapies used before admission (P=0.6456), whereas significant differences were found in hospital treatment and during follow-up. Patients with a cardiovascular event were more frequently treated with intravenous heparin during their in-hospital stay (15.5% versus 4.8%, P=0.0001), whereas patients treated early with ticlopidine (20.8% versus 36.1%, P=0.0001) and during follow-up (25.7% versus 40.2%, P=0.0004) had significantly fewer fatal and nonfatal cardiovascular events. Aspirin and warfarin were used equally in the 2 groups without any significant difference in outcome.

**D-Dimer**
The median (25% and 75% interquartile range) D-dimer level within the first 24 hours after stroke was higher in patients who had a cardiovascular event during follow-up (692 μg/L [225 to 1214 μg/L], P=0.0914) and in patients who died of vascular causes (852 μg/L [398 to 1978 μg/L], P=0.0201) than in those who survived free of cardiovascular events (634 μg/L [370 to 1424 μg/L]), but there were no significant differences in levels between survivors and those who died of nonvascular causes (594 μg/L [242 to 1268 μg/L], P=0.9876) or patients who had a recurrent stroke (659 μg/L [215 to 1103 μg/L], P=0.8346) or a cardiac event (544 μg/L [425 to 1521 μg/L], P=0.1748). Kaplan-Meier analysis showed an increased probability of vascular death or new cardiovascular events during follow-up with increasing levels of D-dimer (χ² for trend=6.11, P=0.0134; Figure 2A).
9 variables were significant: age >70 years, Canadian Neurological Stroke Scale score, the presence of CHD, mitral or aortic valve disease, hypertriglyceridemia, and atrial fibrillation, together with the presence of brain swelling and larger infarcts on CT scan at admission and therapy with ticlopidine at discharge. In model 2, highest fibrinogen levels but not D-dimer levels were independently associated with prognosis, as were a number of other variables. Finally, in model 3, in which the CRP levels at enrollment were added to the other variables, the highest CRP level was an independent predictor of fatal or nonfatal cardiovascular events, whereas fibrinogen levels were not more significant. The hazard ratios and 95% CIs for the independent prognostic variables in models 1 through 3 are given in Table 3.

Secondary Prevention Therapy
Finally, we analyzed the effect of antiplatelet therapy on the risk of cardiovascular events varied according to the baseline level of...
Figure 2. Cumulative probability of fatal or nonfatal cardiovascular events (primary end point) in relation to D-dimer (A), C-reactive protein (B), and fibrinogen (C) levels at enrollment.
CRP, fibrinogen, and D-dimer. The rates of fatal or nonfatal cardiovascular events were significantly lower in the ticlopidine compared with the aspirin group (25.9% versus 38.1%; \( P=0.0144 \)). However, the magnitude of the beneficial effect of ticlopidine in preventing new cardiovascular events was different in the different tertiles of CRP (\( \chi^2=12.79, P=0.0003 \), Mantel-Haenszel \( \chi^2 \) test), fibrinogen (\( \chi^2=4.28, P=0.0383 \)), and D-dimer (\( \chi^2=4.02, P=0.0449 \)). Specifically, ticlopidine treatment was associated with a significant reduction in the risk of new cardiovascular events among patients with baseline levels of CRP and fibrinogen in the lowest and middle tertiles (Table 4). However, among those with fibrinogen and CRP levels in the highest tertile, the reduction in risk associated with ticlopidine was far smaller and no longer significant (risk reduction, 21.1%; \( P=0.2513 \)), showing a nonsignificant excess risk as a possible better effect of aspirin in the subgroup of patients in the highest tertile of CRP (excess risk, 26.8%; \( P=0.3896 \)). Notably, ticlopidine was also associated with a large and statistically significant reduction in the risk of new cardiovascular events among patients with baseline levels of D-dimer in the highest tertile (risk reduction, 61.3%; \( P=0.0048 \)). These effects were exponential across tertiles, so the apparent benefit of ticlopidine therapy diminished markedly after a threshold of CRP or fibrinogen. However, a similar threshold effect was not evident for D-dimer. The benefit of ticlopidine remained essentially unchanged after adjustment for other confounding factors, and the interaction between ticlopidine therapy and baseline levels of CRP (treated as a continuous log-transformed variable) was statistically significant (\( P<0.0001 \)), but this interaction was not evident for fibrinogen or D-dimer.

**Discussion**

As expected, we found that several baseline variables were important predictors of a higher risk of fatal or nonfatal cardiovascular event during the 2-year follow-up. In this prospective study, CRP, fibrinogen, and D-dimer were found to be significant predictors of the risk of future cardiovascular events. However, only CRP was independent of other clinical, laboratory, and neuroradiological prognostic factors in predicting the risk of recurrent cardiovascular events with a time-to-event dependency. Finally, the benefit of antiplatelet therapy was variable in reducing the risk of new cardiovascular events according to levels of CRP, fibrinogen, and D-dimer at enrollment, an intriguing finding given that aspirin and ticlopidine have different antiplatelet effects.

Several studies have found that an increased concentration of hemostatic or inflammation markers is associated with worse prognosis in vascular disease.\(^9\)\(^-\)\(^12\) However, there are no head-to-head comparisons between acute-phase reactants and D-dimer considered jointly. The inflammatory and thrombotic components in ischemic stroke are of current interest, and there is some experimental evidence that they may be linked.\(^7\)\(^,\)\(^11\)\(^,\)\(^12\)\(^,\)\(^14\)\(^-\)\(^17\) CRP, fibrinogen, and D-dimer levels showed a weak to moderate correlation. This correlation supports the hypothesis that there may be a link between these markers of inflammation, hypercoagulability, and fibrin turnover, respectively, in ischemic stroke patients, which may be associated with an unstable atherosclerotic condition that can increase the risk of future cardiovascular events. However, the correlation is not strong, which suggests that other factors have different effects on the levels of these variables.

The results of the present study have several implications. First, the findings confirm that in patients with ischemic stroke, CRP is an important predictor of the risk of recurrent cardiovascular events. Thus, from a pathophysiological perspective, the current data support the hypothesis that patients who respond to stroke with marked activation of the inflammatory system may be at risk for more intense activation of coronary triggering events.\(^28\)\(^,\)\(^29\) Second, we used commercially available assays. The commercial assays are inexpensive and can be used with standard laboratory equipment; thus, screening for these predictors of vascular risk would be
practical in many clinical settings. Third, our observation can significantly improve the prediction of vascular risk in patients with ischemic stroke and may lead to better clinical identification of patients who might benefit from new strategies of secondary prevention. Thus, our observation can be relevant to patients identified in clinical practice who may benefit from an aggressive secondary prevention and for whom the cost-to-benefit ratio for long-term use of new antiplatelets agents would be improved with public health implications. This issue is particularly intriguing because recent data from the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study indicate that clopidogrel was significantly more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, and vascular death in patients with atherosclerotic vascular disease. However, the large number of patients who would need to be treated and the high cost of this approach have limited the application of those findings in a clinical practical setting. Thus, our observation that CRP, fibrinogen, and D-dimer levels can significantly improve the prediction of vascular risk may lead to better clinical identification of patients who might benefit from new strategies of secondary prevention.

Finally, the present findings indicate that the effects of aspirin and ticlopidine after an ischemic stroke are variable. The effect of ticlopidine in preventing recurrent cardiovascular events was greater among patients with lower CRP or fibrinogen concentrations, and the benefit diminished significantly after a threshold. After this threshold, aspirin is probably more effective. However, our study does not have sufficient statistical power to confirm this hypothesis. Patients with large inflammatory burdens may have a distinct vascular mechanism leading to thrombosis that is affected differently by aspirin and ticlopidine therapy. There is greater activation of the coagulation system in patients with acute ischemic stroke with elevated CRP levels,9 which inhibits platelet aggregation through irreversible inhibition of the binding of ADP, could not produce sufficient clinical relevant inhibition of platelet aggregation.44 From this standpoint, aspirin could be more effective because it inhibits platelet aggregation by irreversibly blocking the prostaglandin G/H synthase 1.
Different factors may influence the levels of CRP, fibrinogen, and D-dimer and thereby act as confounders. However, together with strict enrollment criteria to avoid possible confounding factors capable of increasing inflammation markers, there were no major changes in the relative risk of cardiovascular event after adjustment for age, smoking status, body mass index, and sex (Table 2). Furthermore, we also validated the consistency of our ischemic stroke cohort.26

We draw 3 main conclusions. First, CRP proved to be the strongest and most significant predictor of the risk of future cardiovascular events in ischemic stroke patients, independently of other risk factors. Fibrinogen and D-dimer, when CRP levels are taken into account, do not show the prognostic value that was previously reported.11–13 Second, these data raise the possibility that the addition of CRP to standard initial screening will generate an improved method for identifying persons at high risk of future cardiovascular events. Finally, the benefits of antithrombotic therapy appear to be modified by underlying inflammation. The latter observation also suggests the possibility that inflammatory markers such as CRP may provide a method of identifying people for whom a specific antithrombotic agent is likely to be more or less effective, a hypothesis requiring direct testing in randomized clinical trials.

### References


### Table 4. Cumulative Probability of Fatal or Nonfatal Cardiovascular Events Associated With Baseline Plasma Concentrations of D-Dimer, Fibrinogen, and CRP According to Aspirin or Ticlopidine Therapy During Follow-up Period

<table>
<thead>
<tr>
<th>Prognostic variables</th>
<th>Aspirin (n=197)</th>
<th>Ticlopidine (n=166)</th>
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<tr>
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<td>Events/ Patients</td>
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<td>D-dimer, µg/L</td>
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Stroke. 2002;33:1763-1771
doi: 10.1161/01.STR.000019124.54361.08
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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