C-Reactive Protein as a Predictor of Incident Ischemic Stroke Among Patients With Preexisting Cardiovascular Disease

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Background and Purpose—C-reactive protein (CRP) has emerged as an important predictor of cardiovascular disease, but there are few prospective data on its association with risk of ischemic stroke in patients at high risk.

Methods—We examined the association between CRP levels and subsequent risk of incident ischemic stroke among 2979 patients with stable coronary heart disease included in a controlled clinical trial (Bezafibrate Infarction Prevention) that assessed the efficacy of bezafibrate, a fibric acid derivative, versus placebo for secondary prevention. CRP was measured by a high-sensitivity assay in plasma samples collected before randomization and again at the second follow-up year of an overall mean follow-up of 6.2 years.

Results—Risk of ischemic stroke per 1000 person-years increased from 4.1% for baseline CRP in the lowest tertile (<2.3 mg/L; n = 982) to 5.9% for levels at the middle tertile (2.3 to 5.4 mg/L; n = 1013) and 10.5% for CRP levels at the upper tertile (>5.4 mg/L; n = 984; P<0.001). With adjustment for potential confounders, baseline CRP levels in the top versus bottom tertile were associated with a 2.16-fold increased hazard (95% CI, 1.32 to 3.53) for ischemic stroke, and CRP levels measured after 2 years were associated with a hazard ratio of 2.43 (95% CI, 1.30 to 4.57). The risk of an incident ischemic stroke did not differ between the bezafibrate group compared with the placebo group regardless of baseline CRP levels.

Conclusions—These findings, based on a large prospective study, demonstrate the risk prediction for incident ischemic stroke conferred by CRP levels in patients at high risk. (Stroke. 2006;37:1720-1724.)

Key Words: epidemiology ■ inflammation ■ risk factors ■ stroke

Inflammatory and hemostatic biomarkers have become well established in the risk prediction of atherothrombosis.1–4 C-reactive protein (CRP) and fibrinogen are the most studied biomarkers.1,4–7 CRP is an acute-phase reactant that has been shown in prospective cohort studies to be a reliable measure of underlying systemic inflammation, and levels in the high-normal range were found to predict future cardiovascular events. Several prospective studies examined the association between CRP and incident ischemic stroke, primarily among apparently healthy adults.8–12

Chronic disease, including coronary heart disease (CHD), is often accompanied by low-grade inflammation reflected by slightly elevated CRP levels.13 The Bezafibrate Infarction Prevention (BIP) study was a large multicenter, placebo-controlled randomized clinical trial investigating the efficacy of bezafibrate, a fibric acid derivative, in secondary prevention among patients with established stable CHD.14,15 We have previously found that plasma fibrinogen is a strong risk predictor for incident ischemic stroke in these patients.16 Our aim in the present study was to investigate the risk prediction of ischemic stroke conferred by CRP levels among patients at increased risk because of preexisting cardiovascular disease.

Subjects and Methods
The BIP study included patients with stable CHD (n = 3122), aged 45 to 74 years, who were recruited at 18 medical centers in Israel to a secondary prevention randomized placebo-controlled trial that compared the effect of bezafibrate 400 mg once daily versus placebo.14,15 In brief, the main inclusion criteria for men and women comprised history of myocardial infarction at least 6 months and no longer than 5 years before enrollment and/or stable angina pectoris confirmed by coronary angiography, and/or radionuclear studies or standard exercise tests during the 2 years preceding enrollment. In addition, serum total cholesterol had to be in the range of 180 to 250 mg/dL, LDL cholesterol ≤180 mg/dL (≤160 for patients aged ≤50 years), HDL cholesterol ≥45 mg/dL, and triglycerides ≤300 mg/dL.

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Laboratory Methods
Blood samples, drawn after at least 12 hours of fasting, were collected with the use of standardized equipment and procedures and transferred to a central study laboratory. Laboratory measurements were performed with the use of standard automated procedures with commercially available kits (Roche Diagnostics). For the purpose of the present study we measured CRP concentration in samples of citrated plasma stored at −70°C for 12 years. These samples were taken from each study participant before randomization (baseline) and at the 2-year follow-up visit. After plasma samples were thawed, high-sensitivity CRP levels were measured in plasma citrate on an IMMULITE 2000 analyzer from Diagnostics Products Corporation with the manufacturer’s reagents solid-phase, chemiluminescent immunometric assay. The validity of using plasma citrate compared with serum was tested by analysis of samples from 30 randomly selected individuals. CRP levels in plasma citrate were 68% of the serum levels (coefficient of variation = 3.0; range, 65% to 74%). The correlation between plasma and serum levels was $r=0.998$. CRP measurements were available from 2979 patients (95%; 1486 allocated to placebo, 1493 to bezafibrate) at baseline and from 2762 patients (92%; 1369 allocated to placebo, 1393 to bezafibrate) at the 2-year follow-up visit.

Follow-Up and Outcome Assessment
Routine follow-up clinical evaluations by study physicians were scheduled every 4 months for a mean follow-up period of 6.2 years (range, 4.7 to 7.6 years). Stroke was defined according to World Health Organization criteria. Stroke type was differentiated by results of CT scan into ischemic stroke and intracerebral hemorrhage. Cases in which brain imaging was not available were regarded as stroke of undetermined origin. Ischemic stroke subtypes were determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and were categorized as cardioembolic, noncardioembolic, and of undetermined origin. A stroke neurologist (D.T.) reviewed all data on cerebrovascular events. Study physicians assessed functional outcome after stroke during follow-up, and severity was defined as minor for cases in which the modified Rankin Scale score was 0 or 1, major for score of 2, and fatal for 30-day case fatality.

Statistical Analysis
SAS software was used for statistical analyses. To account for the skewed distribution of CRP and triglycerides, geometric means are presented with 95% CIs. Multivariable analysis was performed with the Cox proportional hazard model with adjustment for age, sex, history of myocardial infarction, smoking status at entry, body mass index, hypertension, baseline HDL cholesterol, diabetes mellitus, history of stroke, angina pectoris, and, for models including the entire group of patients, for allocation to bezafibrate versus placebo. CRP as a continuous variable was log-transformed to account for its skewed distribution. Estimates of hazard ratio (HR) and 95% CI are presented. We compared the cumulative incidence of ischemic stroke (Kaplan-Meier curves) by tertiles of baseline CRP. Comparisons were conducted by the log-rank test. The statistical power of detecting the difference between crude rates in the top versus bottom tertile was 97% for $n=0.1$. To evaluate the combined role of CRP and fibrinogen concentrations as predictors of the risk of subsequent ischemic stroke, we divided the patients into 9 groups according to tertiles of both CRP and fibrinogen concentrations. A Cox proportional hazard model was used to evaluate the HR of ischemic stroke in each of the 9 groups, with the group of patients at the bottom tertile of both CRP and of fibrinogen considered the reference group.

Results
During a mean follow-up of 6.2 years, 173 of 2979 patients with baseline CRP measurements developed a cerebrovascular event, of which 138 were strokes (118 ischemic, 10 hemorrhagic, 10 of undetermined origin) and an additional 36 were transient ischemic attacks. Patients with elevated baseline CRP levels included a higher proportion of women, patients with diabetes mellitus, previous stroke, history of angina pectoris, and family history of CHD. Patients with high CRP levels had higher body mass index and higher systolic and diastolic blood pressure. Total and LDL cholesterol levels were not related to CRP levels, but fasting triglycerides, fasting glucose, and fibrinogen levels were directly related and HDL inversely related to CRP level (Table 1). CRP and fibrinogen were highly correlated (Spearman correlation 0.52). Geometric mean of baseline CRP levels was higher in patients subsequently experiencing a cerebrovascular event than in those who did not (3.5; 95% CI, 3.4 to 3.6 versus 4.8; 95% CI, 4.2 to 5.5; $P<0.0001$). Baseline CRP levels did not differ significantly, however, by type of cerebrovascular event or by etiology, severity, or vascular distribution among patients with ischemic strokes.

Further analyses were restricted to risk prediction of ischemic stroke, the main stroke type. Ischemic stroke rates per 1000 person-years rose in a dose-dependent manner, from 4.1% for CRP levels in the bottom tertile to 5.9% in the middle tertile and 10.5% in the top tertile ($P<0.001$). Rates of ischemic stroke nearly doubled between those with CRP levels $>10$ mg/L and those with levels 3 to 10 mg/L, providing further support for the predictive value of CRP levels $>10$ mg/L. Similar trends were observed in both the placebo group and the bezafibrate group. Kaplan-Meier curves for the cumulative incidence of ischemic stroke by tertiles of baseline CRP are depicted in Figure 1.

Models assessing prediction of ischemic stroke by plasma CRP levels in the entire study group and separately in the placebo and bezafibrate arms are presented in Table 2. HR of ischemic stroke increased with higher CRP levels. Baseline CRP in the top tertile was associated with an adjusted hazard for having an ischemic stroke relative to the bottom tertile of 2.16 (95% CI, 1.32 to 3.53). Each 1 natural log unit increase in the concentration of baseline CRP was associated with 35% excess risk of ischemic stroke (adjusted HR, 1.35; 95% CI, 1.11 to 1.64). For comparison, HR associated with diabetes mellitus was 2.3, with current smoking 1.7 and high blood pressure 1.4.

Additional models were performed, with adjustment additionally for plasma fibrinogen, a well-studied hemostatic and inflammatory biomarker. When we compared the top versus bottom tertile, CRP was associated with an adjusted hazard for developing an ischemic stroke of 1.62 (95% CI, 0.95 to 2.76), and fibrinogen was associated with a HR of 2.38 (95% CI, 1.34 to 4.20). Each 1 natural log unit increase in the concentration of baseline CRP was associated with an adjusted HR for an incident ischemic stroke of 1.14 (95% CI, 0.90 to 1.45), and each 1 SD in fibrinogen levels was associated with a HR of 1.31 (95% CI, 1.06 to 1.61). The HR associated with an interaction term defined as $\text{CRP} \times \text{fibrinogen}$ was 1.00, indicating that there is no interaction between the 2 markers. Figure 2 depicts the HR for experiencing an ischemic stroke according to tertiles of baseline concentrations of both CRP and fibrinogen. HR increased with increasing tertiles of either CRP or fibrinogen. Patients with both CRP and fibrinogen levels in the top tertiles exhibited a 2.3-fold increased HR (95% CI, 1.54 to 3.56) compared with counterparts with both biomarkers in the bottom tertile.
Mean CRP levels increased after 2 years of follow-up from 3.49 to 3.62 mg/L in the placebo group (mean change of 0.13 mg/L) and from 3.44 to 3.55 mg/L in bezafibrate-treated patients (mean change of 0.11 mg/L). The correlation between initial CRP values and values after 2 years was 0.60. CRP level after 2-year follow-up remained an independent predictor for subsequent incident ischemic stroke with an adjusted HR associated with CRP in the top versus bottom tertile of 2.43 (95% CI, 1.30 to 4.57). Each 1 natural log unit increase in the concentration of CRP level after 2 years was associated with 37% excess risk of ischemic stroke (adjusted HR, 1.37; 95% CI, 1.07 to 1.77).

The risk of an incident ischemic stroke did not differ between the bezafibrate group compared with the placebo group regardless of baseline CRP levels, with adjusted hazards associated with bezafibrate versus placebo of 1.09 (95% CI, 0.48 to 2.46) for CRP in the lower tertile, 0.81 (95% CI, 0.42 to 1.59) for CRP in the middle tertile, and 0.97 (95% CI, 0.58 to 1.63) for CRP in the upper tertile.

**Discussion**

Our main findings are that high CRP levels represent a strong risk predictor for subsequent ischemic stroke among patients with preexisting atherothrombotic disease, with a >2-fold increased risk observed after adjustment for potential confounders for the top versus bottom tertile. Patients with high levels of both CRP and fibrinogen exhibited additive risk.

Several prospective studies assessed specifically the association between CRP and incident of ischemic stroke, mainly among apparently healthy adults.3,8–11,18 Most studies,8,9,11,12 although not all,10 found a significant independent association between CRP and the risk of incident stroke. A meta-analysis of studies with long-term follow-up showed that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 1.7-fold compared with those with the lowest quartile.18 In a nested case-control study among patients after a cerebrovascular event included in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) clinical trial, odds ratios for a recurrent event

### Table 1. Baseline Characteristics According to Baseline CRP Tertiles

<table>
<thead>
<tr>
<th>CRP Levels, mg/L</th>
<th>(n=982)</th>
<th>(n=1013)</th>
<th>(n=984)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP,* mg/L</td>
<td>1.26 (1.22–1.30)</td>
<td>3.55 (3.50–3.60)</td>
<td>10.10 (9.77–10.45)</td>
<td>–</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±7</td>
<td>60±7</td>
<td>60±7</td>
<td>0.30</td>
</tr>
<tr>
<td>Men</td>
<td>920 (94)</td>
<td>932 (92)</td>
<td>871 (88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>764 (78)</td>
<td>776 (77)</td>
<td>785 (80)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68 (7)</td>
<td>109 (11)</td>
<td>120 (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>303 (31)</td>
<td>329 (33)</td>
<td>331 (34)</td>
<td>0.40</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3 (0.3)</td>
<td>11 (1.1)</td>
<td>21 (2.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>536 (55)</td>
<td>562 (55)</td>
<td>608 (62)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New York Heart Association class ≥2</td>
<td>191 (20)</td>
<td>250 (25)</td>
<td>274 (28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>27 (3)</td>
<td>37 (4)</td>
<td>39 (4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Current smoking</td>
<td>62 (6)</td>
<td>112 (11)</td>
<td>178 (18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous smoking</td>
<td>574 (58)</td>
<td>596 (59)</td>
<td>578 (58)</td>
<td>0.99</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±3</td>
<td>27±3</td>
<td>27±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131±17</td>
<td>134±18</td>
<td>135±18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80±9</td>
<td>81±9</td>
<td>81±9</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212±17</td>
<td>212±18</td>
<td>213±17</td>
<td>0.50</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>35.4±5.4</td>
<td>34.5±5.5</td>
<td>33.7±5.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>149±16</td>
<td>149±17</td>
<td>149±16</td>
<td>0.95</td>
</tr>
<tr>
<td>Triglycerides,* mg/dL</td>
<td>130 (127–133)</td>
<td>138 (135–142)</td>
<td>141 (138–144)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>312±53</td>
<td>341±58</td>
<td>398±78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>98±15</td>
<td>101±18</td>
<td>102±18</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SD for continuous variables and n (%) for categorical variables.

*Geometric mean (95% CI).

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Kaplan-Meier curves for cumulative incidence of ischemic stroke by tertiles of baseline CRP.
associated with the top versus bottom tertile were 1.34 for plasma fibrinogen and 1.39 for CRP.\textsuperscript{19} We found stronger risk prediction estimates in our study cohort, characterized by the presence of chronic atherosclerotic cardiovascular disease. These strong associations identified are likely applicable, therefore, to populations at high risk because of preexisting atherothrombosis. When both fibrinogen and CRP were entered into the same multivariable model, although highly correlated, fibrinogen lessened the association of CRP while remaining a strong independent biomarker. Comparable findings were observed in the prediction of incident CHD and in a recent individual participant meta-analysis of plasma fibrinogen.\textsuperscript{4,20}

Elevated circulating concentrations of acute-phase proteins, cytokines, and cell adhesion molecules suggest that inflammatory processes are occurring systemically, and the role of multiple biomarkers has been shown in the prediction of stroke.\textsuperscript{21–23} Inflammation contributes to stroke risk via various interrelated mechanisms. There is evidence that CRP may play a direct role in the pathogenesis of atherosclerosis. The protein is markedly upregulated in atheromatous plaques,\textsuperscript{24} where it may promote LDL cholesterol uptake by macrophages, a key step in atherogenesis. Stroke is a syndrome of multiple etiologies. Higher CRP levels were found to be associated with the presence and progression of white matter cerebral lesions,\textsuperscript{25} as well as with large-vessel atherosclerotic disease.\textsuperscript{26}

Bezafibrate is a potent nonselective ligand/activator for peroxisome proliferator–activated receptor \( \alpha \). Post hoc analysis from the BIP study has suggested that bezafibrate may reduce recurrent coronary events among patients with high triglycerides or with the metabolic syndrome.\textsuperscript{14,27} Bezafibrate did not reduce CRP levels after 2 years of treatment compared with placebo, and CRP levels could not assist in identifying a subgroup that may benefit from bezafibrate for the prevention of stroke. We have previously shown that although bezafibrate reduced fibrinogen levels in our cohort, it nevertheless did not prevent subsequent incident stroke.\textsuperscript{16}

The main strengths of our study include its large size and prospective follow-up. CRP levels were measured in >2500 patients both at baseline and after 2 years, with comparable risk estimates obtained. Because of the prospective design of the study, our findings could not be affected by changes in CRP levels that may occur after a cerebrovascular event. Indeed, unstable angina, prior stroke, and acute myocardial infarction in the 6 months preceding enrollment constituted exclusion criteria for the BIP study. Healthy lifestyle modifications advocated to patients, including dietary pattern, smoking cessation, weight loss, and exercise training, not only affect levels of traditional risk factors but also reduce levels of fibrinogen and CRP.\textsuperscript{28,29} Clinical trials are needed, however, to determine whether these biomarkers might represent valid targets for interventions to decrease the risk of stroke.

Disclosures

None.

### Table 2. Rate (per 1000 Person-Years) and Adjusted HRs of Ischemic Stroke According to CRP Tertiles

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=2979)</th>
<th>Placebo (n=1486)</th>
<th>Bezafibrate (n=1493)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRP at baseline, mg/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.3</td>
<td>4.1 (1.0–1.7)</td>
<td>3.8 (1.0–1.7)</td>
<td>4.4 (1.0–1.7)</td>
</tr>
<tr>
<td>2.3–5.4</td>
<td>5.9 (1.3–1.6)</td>
<td>6.5 (1.3–1.6)</td>
<td>5.3 (1.0–1.6)</td>
</tr>
<tr>
<td>&gt;5.4</td>
<td>10.5 (2.1–2.4)</td>
<td>10.8 (2.1–2.4)</td>
<td>10.1 (2.1–2.4)</td>
</tr>
<tr>
<td>Ln CRP (per 1 SD)</td>
<td>– 1.35 (1.1–1.6)</td>
<td>– 1.31 (1.0–1.6)</td>
<td>– 1.41 (1.0–1.9)</td>
</tr>
<tr>
<td><strong>CRP after 2-year follow-up, mg/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.3</td>
<td>4.0 (1.0–1.7)</td>
<td>4.6 (1.0–1.7)</td>
<td>3.4 (1.0–1.7)</td>
</tr>
<tr>
<td>2.3–5.4</td>
<td>7.7 (1.6–4.1)</td>
<td>6.5 (1.6–4.1)</td>
<td>6.9 (2.0–5.5)</td>
</tr>
<tr>
<td>&gt;5.4</td>
<td>10.4 (2.4–4.5)</td>
<td>10.6 (2.4–4.5)</td>
<td>10.2 (3.0–8.0)</td>
</tr>
<tr>
<td>Ln CRP (per 1 SD)</td>
<td>– 1.37 (1.0–1.7)</td>
<td>– 1.27 (1.0–1.7)</td>
<td>– 1.50 (1.0–2.1)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, history of myocardial infarction, angina pectoris severity, prior stroke, smoking status at entry, body mass index, hypertension, diabetes, HDL cholesterol, and, for models including the entire group of patients, allocation to bezafibrate vs placebo.

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**Figure 2.** HRs of ischemic stroke according to tertiles of baseline concentrations of CRP and fibrinogen. The bottom tertile of CRP and fibrinogen is the reference group.
References


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