Angiotensin-Converting Enzyme Inhibitor Use Is Associated With Reduced Plasma Concentration of C-Reactive Protein in Patients With First-Ever Ischemic Stroke

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Background and Purpose—High levels of C-reactive protein (CRP) are associated with an increased risk of future cardiovascular events in ischemic stroke. It has been hypothesized that the benefit of angiotensin-converting enzyme (ACE) inhibitors in patients at high vascular risk may also result from their anti-inflammatory action. Data evaluating this hypothesis are limited in ischemic stroke.

Methods—We conducted a prospective observational study in 507 patients with first-ever ischemic stroke to analyze the effect of ACE inhibitor treatment at the time of stroke onset on CRP levels within the first 24 hours and the relationship to outcome. Risk estimates were calculated according to Cox regression analysis controlled for blood pressure (BP) levels, clinical and neuroradiological confounding variables, and log-normalized CRP levels at entry.

Results—ACE inhibitor treatment was associated with lower (2.6-fold; \( P < 0.0001 \)) median CRP levels and with a reduced 2-year cardiovascular risk (hazard ratio, 0.39; 95% CI, 0.29 to 0.53; \( P < 0.0001 \)) compared with a different BP-lowering regimen. The relationship between ACE inhibitor status and log-normalized CRP levels remained significant (\( P < 0.0001 \)) after we controlled for important confounding variables and concomitant treatments. The reduced risk was also evident in multivariable analysis when ACE inhibitor treatment was controlled for BP, associated risk factors, neuroradiological findings, and concomitant treatments (hazard ratio, 0.43; 95% CI, 0.30 to 0.62; \( P < 0.0001 \)). This risk reduction was greatly attenuated and not more significant when log-normalized CRP levels were included (hazard ratio, 0.67; 95% CI, 0.43 to 1.04; \( P = 0.0721 \)) in the model.

Conclusions—Concomitant treatment with ACE inhibitor at the time of an acute stroke is associated with lower inflammatory response and better long-term outcomes, apparently apart from the effects on BP. (*Stroke*, 2003;34:2922-2929.)

Key Words: angiotensin-converting enzyme inhibitors ■ C-reactive protein ■ inflammation ■ stroke, ischemic

Epidemiological evidence suggests that blood pressure (BP) levels are directly and continuously associated with the occurrence of ischemic stroke and cerebral hemorrhage.\(^1\) BP is recognized as an important determinant of the risk of first-ever stroke in nonhypertensive individuals, as well as in those with hypertension.\(^2,3\) Arterial hypertension has been associated with an increased risk of stroke recurrence in some\(^4,5\) but not other\(^6\) community studies of outcome after first stroke.

Furthermore, prospective data demonstrate that inflammation appears to predict the risk of cardiovascular events among healthy subjects\(^7,8\) and among patients with high vascular risk,\(^9,10\) stable and unstable angina,\(^11-13\) and ischemic stroke.\(^14-16\) Because arterial hypertension is an important determinant of cardiovascular risk in subjects with and without vascular disease and elevated levels of C-reactive protein (CRP) are a risk factor for future cardiovascular events in both healthy subjects and patients with high vascular risk, the intriguing possibility exists that there is a definite link between inflammation and arterial hypertension.\(^17-22\)

Finally, experimental data suggest that the renin-angiotensin system may modulate the atherosclerotic process. Recent work has shown that angiotensin II has significant proinflammatory actions in the vascular wall, inducing the production of reactive oxygen species, inflammatory cytokines, and adhesion molecules.\(^23\) Angiotensin-converting enzyme (ACE) inhibitors lower BP but have other potentially protective actions on left ventricular hypertrophy, endothelial function, smooth muscle growth, and anti-inflammatory and probably neuroprotective actions.\(^23-26\) Specifically, ACE inhibitor treatment is associated with a reduction in interleukin-6 response to coronary artery bypass graft surgery, suggesting a direct anti-inflammatory effect, which could explain some of its clinical benefit.\(^27\)

From this standpoint, it is possible that ACE inhibitor therapy may have clinically relevant anti-inflammatory effects that may reduce the inflammatory response after stroke independently of BP reduction. Although the effects of
antiplatelet agents and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may be modified by the levels of inflammation after ischemic stroke, it is unknown whether other preventive agents, such as ACE inhibitors, may also have differential effects among those with and without evidence of inflammation. We evaluated directly whether any association between markers of inflammation and risk of recurrent fatal or nonfatal cardiovascular events might be affected by the use of ACE inhibitors in a long-term prospective observational study.

Subjects and Methods

Study Design
The study is part of a prospective, hospital-based first-ever ischemic stroke data bank. We evaluated all 881 patients included between March 1998 and March 2000 with complete follow-up data. The original inclusion criterion was a diagnosis of first-ever ischemic stroke within 24 hours before enrollment. To avoid possible confounding factors, we excluded patients with history of recent clinical infection, concurrent major renal or hepatic disease or cancer, surgery or major trauma in the previous month, and obvious signs and clinical evidence of acquired infection. We have previously described diagnostic criteria, exclusion criteria, study protocol, data collection, and follow-up methods with the preliminary intervention consent obtained from all patients included or their legal representative. The study was approved by our institutional committee.

Blood Pressure
BP was measured at entry and during the hospital stay until discharge and thereafter at each programmed follow-up visit. Two measurements were taken on each arm after the patient had been supine for 5 minutes. The lowest measurements on each arm were averaged to obtain the systolic and diastolic values that were recorded. Information on current use of BP-lowering medications and concomitant treatments was also obtained.

Blood Samples and CRP Assay
All routine biochemistry, hematology, and coagulation data were collected at entry, within 24 hours after stroke onset. Blood samples collected in EDTA were also assayed for CRP by use of a high-sensitivity assay with a coefficient of variation according to the method described by the manufacturer (Dade Behring).

Study Variables
Variables considered in this study were as follows: age, sex, body mass index, cerebrovascular risk factors (cigarette smoking status, alcohol abuse, hypercholesterolemia [>200 mg/dL], hypertglycemia [>180 mg/dL], diabetes mellitus), cardiovascular comorbidity (arrhythmias and impulse conduction disorders, valvulopathies, left ventricular hypertrophy, coronary heart disease, symptomatic internal carotid stenosis, peripheral arterial disease), stroke subtypes (atherothrombotic, cardioembolic, small-vessel occlusive [lacunar], or undetermined cause), and neuroradiological findings (leukoaraiosis, ischemic lesions [none/single/multiple infarcts], large/small infarcts, brain edema, hemorrhagic transformation). The Canadian Neurological Stroke Scale and Barthel Index assessed initial stroke severity and disability, respectively.

Outcome Measures
The primary end point considered in this analysis was the combination of vascular death (sudden death or death from myocardial infarction, congestive heart failure, systemic embolism, and other cardiovascular causes or as consequence of the qualifying stroke or of a new fatal stroke in absence of other intervening causes) and any new nonfatal vascular event, cardiac (myocardial infarction or unstable angina, requiring admission to the hospital) or cerebral (recurrent ischemic stroke), whichever came first, during the follow-up and defined as cardiovascular event. We monitored all patients during hospitalization, and thereafter they were followed up regularly as outpatients for 2 years. The evaluators were blinded to information regarding CRP levels that were not used to modify current treatment both during in-hospital and follow-up periods. The BP-lowering therapy during the follow-up period was prescribed by a referring physician who was in charge of the patients and who did not participate in the study.

Statistical Analysis
We used the Student t test and the χ2 test to compare differences in baseline cardiovascular risk factors among study participants. Because distributions of CRP are skewed, differences in median levels according to ACE inhibitor treatment status were tested with the Mann-Whitney U test or the Kruskal-Wallis test for multiple comparisons. Mean concentrations of CRP were also computed after log transformation that resulted in nearly normal distribution. Pearson’s correlation analysis was performed to assess any relationship between log-normalized levels of CRP and BP at entry. For statistical analysis, BP values were also categorized with the following cutoff levels: ≥160, 140 to 159, and <140 mm Hg for systolic BP and ≥95, 85 to 94, and <85 mm Hg for diastolic BP.

We used the test for trend to assess any relation between increasing CRP values and risk of recurrent cardiovascular events after dividing the study sample into prespecified quintiles defined by the distribution of CRP values in the population of patients not treated with ACE inhibitor, considered control subjects. The cumulative survival curves free of cardiovascular events in relation to ACE inhibitor treatment status were determined according to the Kaplan-Meier method with the use of the log-rank test for statistical assessment.

Analyses were designed to assess (1) the association of ACE inhibitor treatment with CRP levels after adjustment for the other study variables and (2) the hypothesis that ACE inhibitors exert their therapeutic effect in part through anti-inflammatory mechanisms. In the first analysis, the CRP levels and other study factors were independent variables, and ACE inhibitor treatment was the dependent variable. We analyzed CRP as a continuous variable after log transformation in logistic regression models. The regression analysis was performed as follows. The explanatory variables were first tested 1 against the dependent variable for the presence of a significant association (P<0.05). Variables for which no significant association was found were removed. The systolic and diastolic BP components were entered as continuous, linear variables (per 10-mm Hg increase). Age (per 10-year increase) and Canadian Neurological Stroke Scale score (per 1.0-point increase) were entered into the logistic models as continuous variables. All the other variables were included as categorical dichotomized variables according to the categories described previously. To evaluate the hypothesis that ACE inhibitors exert their therapeutic effect in part through an anti-inflammatory mechanism, we used multivariable forward stepwise Cox regression analyses in 3 models. In the first model, ACE inhibitor treatment status was controlled for systolic and diastolic BP levels at entry and for variables associated with ACE inhibitor treatment in the univariate analysis that had a value of P≤0.05. Log-normalized CRP levels at entry were added to the second model. Finally, in the third model we also formally tested for treatment interaction between quintiles of CRP levels and ACE inhibitor treatment regimen. Variables with a value of P≤0.05 were entered into the model, and variables with a value of P>0.10 were removed.

For the variables that met the statistical significance criterion included between P>0.05 and P<0.10 values, we verified that the final adjusted hazard ratio was not altered by their exclusion before the final adjustment.

In all analyses, participants were grouped according to their original treatment, irrespective of whether treatment was continued. For all statistical analyses, a value of P<0.05 was considered to indicate a significant difference.
Results

Enrollment of Patients and Baseline Characteristics of Ischemic Stroke Cohort
Between March 1998 and March 2000, 881 potential first-ever ischemic stroke patients were registered, and 507 (57.5%) were subsequently found to be eligible because they fulfilled the inclusion criteria for the present study (Figure 1). The exclusion criteria were mainly related to conditions associated with increased levels of inflammation markers or an unconfirmed diagnosis of first-ever ischemic stroke. The mean age of the cohort was relatively old (72.5 ± 9.1 years), and 303 (59.8%) were women. The median time from onset of symptoms was 12 hours to blood sample and 15 hours to CT scan. Table 1 shows baseline characteristics of the patients according to ACE inhibitor treatment status. Two hundred sixty-six patients (52.5%) were taking ACE inhibitor [ACE-I(−)] alone or in combination with other BP-lowering agents (n = 141). Two hundred forty-one patients did not undergo therapy (n = 32) or had a different BP-lowering regimen [ACE-I(+) group], alone or in combination (n = 104; 43.2%). Details on different BP-lowering drugs are given in Figure 1.

BP and Different BP-Lowering Regimens
At entry, mean systolic BP was 160 ± 16 mm Hg, and mean diastolic BP was 94 ± 13 mm Hg. Patients with a history of arterial hypertension had a significantly higher mean systolic (164 ± 9 versus 148 ± 24 mm Hg; P < 0.0001) and diastolic (96 ± 8 versus 86 ± 19 mm Hg; P < 0.0001) BP than patients without. No difference in mean systolic BP levels was found between patients in the ACE-I(−) group compared with those treated with a different BP-lowering regimen in the ACE-I(+) group. A small, significant difference of 3 mm Hg (P = 0.0083) was found in diastolic BP. BP decreased on average by 11 mm Hg (systolic) and 14 mm Hg (diastolic) during in-hospital stay, with a more evident reduction in both mean systolic (−18 mm Hg; P < 0.0001) and mean diastolic (−15 mm Hg; P < 0.0001) measurements in the ACE-I(+) group.

The BP-lowering treatment regimen was substantially stable during the follow-up period in all patients (approximately 95%): only 25 patients changed their original BP-lowering regimen at the discretion of their referring physician. At the end of the 2-year follow-up period, the mean systolic BP was 158 ± 18 mm Hg, and the mean diastolic BP was 79 ± 13 mm Hg. The 2 different BP-lowering regimens resulted in similar BP control; only a small reduction of diastolic BP was found in the ACE-I(+) group (78 ± 14 versus 81 ± 10 mm Hg; P = 0.0301).

Arterial Hypertension and CRP Levels
Log-normalized concentration of CRP within 24 hours after stroke was significantly but modestly correlated with both
systolic \((r=0.47; \ P<0.0001)\) and diastolic \((r=0.50; \ P<0.0001)\) BP at entry. Patients without a history of arterial hypertension had significantly higher levels of CRP (median [25th to 75th interquartile ranges]) at entry than patients with a documented history (2.0 [1.0 to 3.4] versus 1.0 [0.5 to 2.75] mg/dL; \(P<0.0001)\). To better evaluate the apparent paradox between BP levels, CRP levels, and history of arterial hypertension, we computed the median CRP levels for each BP cut point according to the history of arterial hypertension (Table 2). Higher median levels of CRP were found in patients with higher levels
of systolic or diastolic BP irrespective of the history of arterial hypertension.

**ACE Inhibitor Treatment Status and CRP Levels**

Overall, median CRP levels were 2.6-fold higher among ACE-I(-) patients than among ACE-I(+) patients (2.1 versus 0.8 mg/dL; P<0.0001). This difference was present in all high-risk subgroups evaluated, including those with a history of hypercholesterolemia (P=0.0005), arterial hypertension, coronary heart disease, peripheral artery disease, cigarette consumption, diabetes, or obesity and in the presence of multiple risk factor association (all P<0.0001). To evaluate the potential impact of ACE inhibitor treatment on CRP distributions in patients with arterial hypertension, we computed cut points for each increasing quintile of CRP for patients with and without a history of arterial hypertension according to their ACE inhibitor status. Furthermore, quintile cut points for ACE-I(-) patients were higher in normotensives than in hypertensives; however, for ACE-I(+) patients, the cut points determining each successive quintile of CRP were lower, particularly at the upper end of the distribution, irrespective of the history of arterial hypertension (Table 3). In multivariable analysis, the relationship between ACE inhibitor status at the time of stroke onset and log-normalized levels of CRP remained significant (P<0.0001) after we controlled for age, sex, cardiovascular risk factors, stroke severity, and concomitant treatments, including statins.

**Clinical Outcome**

The mean duration of the follow-up was 38.4±6.8 months. No relevant differences were found in both groups in in-hospital treatment. All patients received a secondary preventive treatment with aspirin (dose range, 100 to 400 mg/d; 42%), ticlopidine (dose range, 250 to 500 mg/d; 35%), or warfarin (attempted normalized ratio range, 2.5 to 3.5; 20%) with a strict control of recognized vascular risk factors. After 1 month, 71 of the 507 patients (14%) had a fatal (n=22) or nonfatal (n=49) cardiovascular event; after 1 year, 165 patients had a fatal (n=59) or nonfatal (n=106) cardiovascular event, and 6 died of nonvascular causes. During the 2-year follow-up period, 206 (40.6%) had a fatal (n=68) or nonfatal (n=138) cardiovascular event or died of nonvascular causes (n=14). Figure 2 shows Kaplan-Meier estimates according to ACE inhibitor treatment status. ACE-I(+) patients had a significantly reduced risk of new fatal or nonfatal cardiovascular events (n=67; 25.2%) compared with those in the ACE-I(-) group (n=125; 51.9%; P<0.0001, log-rank test). The relative risk of developing a new cardiovascular

<p>| TABLE 2. Median and 25th to 75th CIs of C-Reactive Protein Values (mg/dL) According to Systolic and Diastolic Blood Pressure Levels and History of Arterial Hypertension |</p>
<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median, mg/dL</th>
<th>25th-75th CI</th>
<th>No. of Patients</th>
<th>Median, mg/dL</th>
<th>25th-75th CI</th>
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</thead>
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<td>Diastolic blood pressure, mm Hg</td>
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<tr>
<td>≤85</td>
<td>58</td>
<td>1.0</td>
<td>0.6–2.5</td>
<td>26</td>
<td>0.4</td>
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<tr>
<td>86–94</td>
<td>43</td>
<td>1.1</td>
<td>1.0–1.9</td>
<td>108</td>
<td>0.3</td>
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<tr>
<td>≥95</td>
<td>25</td>
<td>5.4</td>
<td>3.4–6.0</td>
<td>247</td>
<td>2.1</td>
</tr>
<tr>
<td>P*</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≤140</td>
<td>74</td>
<td>1.0</td>
<td>0.6–1.7</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>141–159</td>
<td>26</td>
<td>0.6</td>
<td>0.3–2.4</td>
<td>34</td>
<td>0.3</td>
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<tr>
<td>≥160</td>
<td>26</td>
<td>5.4</td>
<td>3.5–6.0</td>
<td>335</td>
<td>1.2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
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</tr>
</tbody>
</table>

*Kruskal-Wallis test for multiple comparisons. CRP indicates C-reactive protein.

| TABLE 3. Range of CRP Values (mg/dL) According to Quintiles of CRP Distribution Patients With and Without a History of Arterial Hypertension Not Using Angiotensin-Converting Enzyme Inhibitors and Using Angiotensin-Converting Enzyme Inhibitors |
|-----------------|-------------|
| Study Group     | Quintiles of CRP, mg/dL |
|                 | 1           | 2            | 3            | 4            | 5            |
| No HTN/ACE-I(-) (n=92) | <0.6       | 0.6–1.6     | 1.7–2.5     | 2.6–6.0     | >6.0         |
| No HTN/ACE-I(+) (n=34) | <1.0       | 1.0–1.1     | 1.2–2.1     | 2.2–2.4     | >2.4         |
| HTN/ACE-I(-) (n=149) | <0.6       | 0.6–1.4     | 1.5–3.8     | 3.9–9.4     | >9.4         |
| HTN/ACE-I(+) (n=232) | <0.3       | 0.3–0.6     | 0.7–1.0     | 1.1–1.8     | >1.8         |

CRP indicates C-reactive protein; HTN, hypertension; ACE-I(-), not using and ACE-I(+), using angiotensin-converting enzyme inhibitors.
event in the ACE-I(+) group was 0.39 (95% CI, 0.29 to 0.53; P<0.0001).

**CRP Levels, ACE Inhibitor Treatment Status, and Outcome**

The CRP value within 24 hours was 1.2 (0.6 to 2.9) mg/dL. Median plasma concentration of CRP at the entry was significantly higher among those in whom cardiovascular events subsequently developed than among those who remained free of new cardiovascular events (2.6 [0.9 to 7.5] versus 0.9 [0.5 to 1.8] mg/dL; P<0.0001). In analysis evaluating the association between increasing levels of CRP and recurrent cardiovascular events, a statistically significant trend was observed across quintiles of CRP (χ² for trend=57.46; P<0.0001). A significantly increased risk was evident only for the patient in the fourth (relative risk=2.45; 95% CI, 1.49 to 4.04; P=0.0004) and in the highest quintile (relative risk=5.68; 95% CI, 3.57 to 9.03; P<0.0001). Although those with levels of CRP at entry in the highest quintile had a risk of developing a recurrent cardiovascular event that was 6-fold higher than among those in the lowest quintile, there was no statistically significant evidence of increased risk among those with levels of CRP at entry in the first through third quintiles (all P>0.05; Table 4). These risk estimates were strongly altered in analyses controlling for age, sex, cardiovascular risk factors, stroke severity, neurological findings, and concomitant treatments, showing a dramatic fall in risk. Only the highest level of CRP remained an independent predictor of risk of recurrent cardiovascular events. After further adjustment for systolic and diastolic BP values at entry and ACE inhibitor treatment, the association between CRP levels and risk of new cardiovascular events persisted at the highest CRP levels, with only a reduced impact on these risk estimates (Table 4).

**Multivariable Analyses**

To better investigate these effects, we analyzed in details the effect of ACE inhibitor treatment status on the risk of new cardiovascular events in 3 multivariable models. ACE inhibitor treatment reduced the risk of cardiovascular events compared with other BP-lowering regimens, irrespective of BP control, associated risk factors, neuroradiological findings, and concomitant treatments (hazard ratio, 0.43; 95% CI, 0.30 to 0.62; P<0.0001; model 1). This risk reduction was greatly attenuated when log-normalized CRP level was included in the model (hazard ratio, 0.67; 95% CI, 0.43 to 1.04; P=0.0721; model 2). When a term representing the interaction between CRP levels and ACE inhibitor status was included in model 3, it was found not to be significant (P=0.2711), and the risk reduction remained substantially stable (hazard ratio, 0.66; 95% CI, 0.42 to 1.05; P=0.0789).

**Discussion**

These results provide some support for the hypothesis that the individual acute-phase response after an acute ischemic stroke is an important independent prognostic predictor. This inflammatory response can be modified by preventive agents (antiplatelet agents and HMG-CoA reductase inhibitors) and now perhaps by ACE inhibitors as well.

First, elevated levels of systolic or diastolic BP in the acute phase after an ischemic stroke are associated with elevated CRP levels. An acute increase of BP more than a history of arterial hypertension apparently is associated with higher levels of CRP after stroke. It is probable that the BP level after an ischemic stroke is 1 of the underlying processes related to inflammation that are relevant in the inflammatory response in ischemic stroke patients. These data reproduce recent observations that high BP values are associated with the production of inflammation-sensitive plasma protein and radiological findings.
particularly CRP. Many speculative hypotheses have been formulated regarding the relationship between BP and the inflammatory mechanism in ischemic stroke. Thus, because higher CRP levels are an independent prognostic factor after stroke and high BP is apparently associated with CRP levels, new aspects may emerge regarding the pathophysiological role of acute hypertension and its treatment after stroke.

Second, these prospective data indicate that plasma concentrations of CRP are significantly lower among ischemic stroke patients who are currently treated with ACE inhibitor at the time of their first-ever ischemic stroke than among similar patients with a different BP-lowering regimen. This association was present in all subgroups of patients evaluated and remained significant after we controlled for age, sex, cardiovascular risk factors, stroke severity, and concomitant treatment including statins, all factors known to influence CRP levels.

Third, these prospective data reproduce in a larger cohort previous findings that plasma concentration of CRP, within 24 hours after ischemic stroke, predicts the risk of recurrent fatal or nonfatal cardiovascular events among first-ever ischemic stroke patients. The risk of recurrent cardiovascular events associated with elevations of CRP was independent of many clinical variables, although it was substantially reduced after we adjusted for baseline confounding factors and remained significant only for the highest CRP levels. This relationship between CRP and the risk of new cardiovascular events was also preserved in the presence of ACE inhibitor treatment status.

Fourth, in an observational cohort, ACE inhibitor treatment reduced the risk of new cardiovascular events in stroke patients, as previously shown. However, CRP levels modified ACE inhibitor therapeutic effects on the risk of new cardiovascular events, suggesting that changes in CRP levels are probably important to take into account, and the absence of a significant interaction between CRP levels and ACE inhibitor treatment suggests that ACE inhibitors reduce risk by reducing inflammation (and the markers of inflammation), not that they alter the association between the markers of inflammation and outcome. The finding that ACE inhibitors also perform their therapeutic effects probably through an anti-inflammatory effect, apart from the effect on BP, raises several intriguing issues. ACE inhibitors have multiple mechanisms, in addition to BP lowering, by which they could prevent atherosclerotic events. Furthermore, a recent analysis of the United Kingdom Prospective Diabetes Study showed that the benefits seen with an ACE inhibitor (and a β-blocker) were substantially larger than predicted from differences in BP alone. However, we advocate a cautious approach for 3 reasons. First, we do not have complete data to understand the anti-inflammatory effect of ACE inhibitors; no trial was designed to elucidate the mechanisms of cardiovascular protection. Second, we do not know whether these molecules have intrinsic anti-inflammatory properties in humans, as suggested by experimental models, or whether they reduce inflammation only by lowering high BP. Third, the present study was based on observational data, and confounding from factors that were not controlled for and/or residual confounding from factors that we did control for, but that were imperfectly measured, may be an alternative explanation for our results. The presence of a selection bias is also plausible because this is not a randomized controlled trial: both CRP level and better outcome may be a marker for something involved in the selection bias. One cannot definitively rule out chance as an explanation for the findings of this study; the large number of variables entered into the univariable analysis and a borderline modeling technique make this a possibility and suggest that without internal or external validation, our results should be considered hypotheses generating. Currently, we believe that speculations about the ancillary properties of BP-lowering drugs are counterproductive and detract from the main message that the arterial hypertension trial conveys. All BP-lowering drugs have similar long-term efficacy and safety if BP is controlled.

For these reasons, the clinical impact of these new data is uncertain but may have implications for considering ACE inhibitor therapy in patients initiating a BP-lowering regimen. Because elevated levels of CRP are associated with increased cardiovascular risk among otherwise healthy subjects, we can hypothesize that the initiation of ACE inhibitor therapy can reduce CRP levels and result in anti-inflammatory actions in the vascular wall, inducing the reduction of reactive oxygen species, inflammatory cytokines, and adhesion molecules.

In summary, these data raise the intriguing possibility that the efficacy of ACE inhibitors may result in part from anti-inflammatory as well as BP-lowering properties, and the effect of CRP on cardiovascular risk may be attenuated by ACE inhibitor therapy in stroke patients. Whether these observations have clinical relevance requires further investigation. We therefore believe that the potential impact of ACE inhibitor treatment on inflammatory parameters should be investigated directly in ongoing clinical trials, particularly those that can provide longitudinal data and differentiate between different ACE inhibitors.

References


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