Treatment With Angiotensin-Converting Enzyme Inhibitors Is Associated With a Reduction in Short-Term Mortality in Older Patients With Acute Ischemic Stroke

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Background. Stroke is the third cause of death in older people living in Western countries. We tested the hypothesis that angiotensin-converting enzyme inhibitors (A-I) might affect short-term (30 day) mortality in older persons with severe acute ischemic stroke.

Methods. We analyzed data from a retrospective study including 475 consecutive older patients hospitalized for acute ischemic stroke. Mean age was 78.4 ± 9.2 years; 58.2% were female. Stroke type was classified according to the Oxford Community Stroke Project (OCSP).

Results. Mortality rate was 28%. Thirty-two percent of patients were treated with A-I; mortality was 16.5% in patients treated compared with 33.3% in those not treated (χ² p = .001). The odds ratio for mortality in treated patients was: 0.47 (0.25–0.89) after full adjustment (age, sex, mean diastolic and systolic blood pressure, previous stroke and/or transient ischemic attack, congestive heart failure, atrial fibrillation, diabetes, hypertension, coronary heart disease, and previous treatment with A-I); 0.29 (0.09–0.89) in patients with altered level of consciousness after full adjustment; 0.60 (0.33–1.12) after adjustment for OCSP classification, age, and sex; and 0.30 (0.08–0.97) in total anterior circulation infarction stroke type after full adjustment.

Conclusions. Our data suggest that treatment with A-I might reduce short-term mortality in older patients with acute ischemic stroke. Randomized clinical trials should confirm this possible specific effect of A-I.

STROKE is the third cause of death in older persons living in Western countries (1). Despite general progress in the medical field, the therapy of stroke is still unsatisfactory, because it is based on very few effective drugs (e.g., antiplatelet drugs) (2). Angiotensin-converting enzyme inhibitors (A-I) are drugs commonly used in the therapy of hypertension and congestive heart failure (CHF) (3). The treatment with A-I has been associated with a reduction both in mortality after myocardial infarction (4) and in the number of new ischemic cerebrovascular events in secondary prevention trials (5). We have hypothesized that the treatment with A-I might also affect short-term mortality (30 days) in older patients with acute ischemic stroke.

METHODS
We analyzed data from a retrospective study including 475 consecutive patients aged ≥65 years with severe acute ischemic stroke admitted to hospital. Patients with transient ischemic attack (TIA) or minor stroke (Rankin scale <3) were excluded because short-term mortality is extremely low in these patients.

Stroke type was classified according to the Oxford Community Stroke Project (OCSP) as follows: TACI (total anterior circulation infarction), PACI (partial anterior circulation infarction), POCI (posterior circulation infarction), and LACI (lacunar infarction) (6). The data recorded included: 1) clinical features of stroke; 2) medical history, including vascular risk factors (arterial hypertension, diabetes mellitus, atrial fibrillation (AF), coronary heart disease (CHD), CHF, alcohol abuse, smoking, previous TIA and/or stroke); 3) 12-lead electrocardiogram; and 4) routine blood analysis.

Hypertension was defined as documented history of hypertension and/or current use of antihypertensive drugs and/or blood pressure >160/90 mmHg in two or more measurements. Diabetes mellitus was defined as documented history of diabetes or current use of antidiabetic drugs or insulin or documented fasting glycemia >126 mg/dL in two or more measurements. The prevalence of CHD, CHF, AF, and history of previous stroke or TIA was assessed by two investigators (GZ and AC) according to standardized criteria (clinical examination and chart review).

Statistical Analysis
Data were compared by unpaired Student’s t test or analysis of variance for continuous variables, and by chi-square
A-I compared with 33.3% (108/324) in untreated patients. The mortality ORs and 95% confidence intervals in different multivariate models of analysis are summarized in Figure 1. The OR for mortality in patients treated with A-I was 0.42 (95% CI = 0.25–0.70) after adjustment for age and sex, and 0.47 (95% CI = 0.25–0.89) after full adjustment (model 1).

To evaluate the possible influence of stroke severity on outcome, we considered two important prognostic factors: the presence of ALC and TACI type. Indeed, these conditions are known to be strongly associated with a worse prognosis.

The mortality OR was 0.55 (95% CI = 0.31–0.98) after adjustment for ALC, age, and sex (model 2), and 0.54 (95% CI = 0.28–1.03, \( p = .06 \)) after full adjustment including ALC (model 3). In patients with ALC, the OR for mortality was 0.29 (95% CI = 0.09–0.89) after full adjustment, including severity of ALC (model 4). In patients without ALC (\( n = 327 \); mortality: 9.7%) the treatment with A-I was not associated with a reduction in mortality (OR = 1.03, 95% CI = 0.41–2.52) after full adjustment (model 5). The OR for mortality was 0.60 (0.33–1.12) after adjustment for the OCSP classification, age, and sex (model 6).

In the TACI subgroup (\( n = 133 \)), the mortality rate was 39.1% (9/23) in patients treated with A-I, whereas it was 67.3% (74/110) in untreated patients (\( \chi^2 = 7.5; p = .01 \)). The mortality OR was 0.30 (95% CI = 0.08–0.97) after full adjustment (model 7). In the remaining patients (PACI, POCl, and LACI, \( n = 342 \); mortality: 12.5%), the treatment with A-I was not associated with a reduction in short-term mortality (OR = 1.09, 95% CI = 0.43–2.73) (model 8).

To evaluate the possible influence of stroke severity on the likelihood of prescribing antihypertensive drugs, as well

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Table 1. Principal Characteristics of the Sample of 475 Consecutive Older Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yes (( N = 151 ))</th>
<th>No (( N = 324 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female), %</td>
<td>60.3</td>
<td>57.7</td>
<td>.30</td>
</tr>
<tr>
<td>Age, y</td>
<td>77.1 ± 8.5</td>
<td>78.9 ± 9.4</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean ± standard deviation</td>
<td>87 ± 9</td>
<td>82 ± 11</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mean ± standard deviation</td>
<td>155 ± 19</td>
<td>146 ± 20</td>
<td>.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>82</td>
<td>65.5</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>24</td>
<td>.10</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>36.5</td>
<td>46.5</td>
<td>.02</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>10.2</td>
<td>10.1</td>
<td>.60</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>27.5</td>
<td>37.6</td>
<td>.02</td>
</tr>
<tr>
<td>Previous stroke and/or transient ischemic attack, %</td>
<td>21.5</td>
<td>28</td>
<td>.09</td>
</tr>
<tr>
<td>Altered level of consciousness, %</td>
<td>19</td>
<td>37</td>
<td>.01</td>
</tr>
</tbody>
</table>

**Oxfordshire Community Stroke Project classification**

- Total anterior circulation infarction, % 17 34
- Partial anterior circulation infarction, % 32 28
- Posterior circulation infarction, % 5 7
- Lacunar infarction, % 46 31 .01

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**RESULTS**

The mean age of the sample was 78.4 ± 9.2 years; 58.2% of patients were female. One hundred thirty-three patients died within 30 days from stroke onset (total mortality: 28%). On the whole, 151 patients (32%) were treated with A-I, mainly enalapril (10–20 mg/day), lisinopril (10–20 mg/day), and ramipril (2.5–5 mg/day); 48% of these patients were already on treatment with A-I at home. In all the patients, the A-I therapy was started within 24–48 hours of admission and continued through the entire period that the patient was in the hospital.

The principal characteristics of the sample are reported in Table 1. A-I-treated patients were more likely than those not treated to suffer from hypertension and diabetes, and were less likely to be affected by CHD, AF, history of stroke and/or TIA, and to have altered level of consciousness (ALC) or TACI stroke type. Both mean diastolic and mean systolic blood pressure were significantly higher in patients treated with A-I than in untreated patients.

Mortality rate was 16.5% (25/151) in patients treated with...
as the possible specificity of A-I effect on mortality, we also evaluated the relationship between in-hospital calcium-antagonists treatment and the risk of death. Mortality was not affected by this class of drugs: death rate was 25.2% (45/178) in treated patients and 30.0% (89/297) in untreated patients ($\chi^2 p = .16$). After exclusion of patients treated with A-I, the OR for mortality in treated patients was 0.80 (95% CI = 0.44–1.45) after full adjustment.

**DISCUSSION**

In this study, we found that treatment with A-I seems to be associated with a reduction in short-term mortality in a large sample of older patients hospitalized for acute ischemic stroke. In particular, our data suggest that A-I might be effective in severe types of strokes. To the best of our knowledge, this is the first time that this protective effect has been reported.

A-I are antihypertensive agents; they block the activation of the renin–angiotensin system, thus reducing the production of angiotensin II, which has vasoconstrictor, procoagulant, proinflammatory, and remodeling effects on blood vessels. Moreover, angiotensin II increases free radical generation, and hence counteracts the activity of nitric oxide. Randomized controlled trials have already demonstrated that A-I can reduce significantly the risk of first stroke and recurrent stroke (7,8).

The possible mechanisms linking A-I and the reduction of short-term mortality after acute ischemic stroke are not known, but several data might support the biological plausibility of our results. In hypertensive patients, these drugs reduce blood pressure and shift the autoregulation curve of cerebral blood flow back to normal. Moreover, A-I have been shown to reduce blood pressure without affecting cerebral blood flow in patients with recent ischemic stroke (9) and carotid artery stenosis (10). In animal models, A-I increases endothelium-dependent vasodilation (11), attenuates cerebral artery remodeling (12), and improves neurological outcome after cerebral ischemia. Furthermore, it has been shown that short-term treatment with these drugs significantly reduces fibrinogen (13) and plasminogen activator inhibitor I levels (14), thus improving fibrinolysis. Another potential mechanism of A-I in reducing mortality in older individuals with ischemic stroke might be a protective effect against the development or worsening of CHF during the acute phase of the disease.

The most important limitation of this study should be finally acknowledged. Despite our effort to take into account a number of potential confounders, because this is not a randomized clinical trial we cannot rule out the presence of a residual confounding effect. Nevertheless, in view of the high mortality associated with stroke, and of the availability of few effective treatments, we suggest that future randomized clinical trials should focus on the possible effect of A-I on short-term mortality in older patients with acute ischemic stroke.

**ACKNOWLEDGMENTS**

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Received December 3, 2003
Accepted December 10, 2003
Decision Editor: John E. Morley, MB, BCh