The ACCESS Study
Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors
Joachim Schrader, MD; Stephan Lüders, MD; Anke Kulschewski, MD; Jürgen Berger, PhD; Walter Zidek, MD; Johannes Treib, MD; Karl Einhäupl, MD; Hans Christoph Diener, MD; Peter Dominiak, MD; on behalf of the ACCESS Study Group

Background and Purpose—The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study was designed to assess the safety of modest blood pressure reduction by candesartan cilexetil in the early treatment of stroke. The study was also designed to provide an estimate of the number of cases required to perform a larger phase III efficacy study.

Methods—Five hundred patients were recruited in a prospective, double-blind, placebo-controlled, randomized, multicenter phase II study.

Results—This safety trial was stopped prematurely when 342 patients (339 valid) had been randomized because of an imbalance in endpoints. Demographic data, cardiovascular risk factors, and blood pressure on admission, on study onset, and within the whole study period were not significantly different between the 2 groups. However, the cumulative 12-month mortality and the number of vascular events differed significantly in favor of the candesartan cilexetil group (odds ratio, 0.475; 95% CI, 0.252 to 0.895). There were no significant differences in concomitant medication and in number or type of side effects.

Conclusions—Although the mechanisms by which angiotensin type 1 (AT1) receptor blockade affects cardiovascular morbidity and mortality are still unresolved, the present study shows that early neurohumoral inhibition has similar beneficial effects in cerebral and in myocardial ischemia. The fact that no cardiovascular or cerebrovascular event occurred as a result of hypotension is of significant clinical importance. When there is need for or no contraindication against early antihypertensive therapy, candesartan cilexetil is a safe therapeutic option according to the ACCESS results. (Stroke. 2003;34:1699-1703.)

Key Words: antihypertensive therapy ■ benzimidazoles ■ blood pressure ■ stroke, acute

Antihypertensive therapy in acute cerebral ischemia has been a matter of debate for several years.1–4 The current recommendation to tolerate acute hypertension in cerebral ischemia is based on the concept of disturbed autoregulation of cerebral blood flow in the penumbra surrounding the zone of necrosis. Given a pressure-dependent perfusion in the penumbra, any decrease in blood pressure is expected to impair tissue perfusion.5 Despite the well-founded theoretical basis of current practice, evidence-based data are lacking. In the Intravenous Nimodipine West European Stroke Trial (INWEST), the rapid hypotensive action of intravenous nimodipine was shown to involve the risk of neurological deterioration.6 In contrast, experimental and clinical studies demonstrated that a cautious reduction of blood pressure may even improve the prognosis in acute cerebral ischemia.7,8 Thus, we are clearly in need of more detailed data on how antihypertensive treatment affects outcome in acute stroke.

Recent literature on antihypertensive treatment in coronary and renal vascular disease indicates an emerging conceptual shift from lowering blood pressure to specific organ-protective effects. Whereas numerous earlier studies confirmed a benefit of antihypertensive treatment per se, there is now increasing evidence indicating that inhibition of neurohumoral activation confers clinical benefit beyond the effects of blood pressure reduction.9 On the basis of these studies, angiotensin-converting enzyme (ACE) inhibition is well established not only in the long-term treatment but also in the early management of myocardial infarction.10–12 Likewise, ACE inhibition and angiotensin type 1 (AT1) receptor blockade appear to be renoprotective independent of their hypo-
tensive effects.\textsuperscript{13,14} Moreover, there is emerging evidence indicating that AT\textsubscript{1} receptor blockade is also protective against stroke. The convincing data supporting the favorable effects of neurohumoral inhibition beyond any hemodynamic effects in renal and coronary vasculature provided a basis for studying the effects of AT\textsubscript{1} receptor blockade in the setting of acute cerebral ischemia.

The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study was designed to assess the safety of modest blood pressure reduction in the early treatment of stroke. The study was also designed to provide an estimate of the number of cases required to perform a larger phase III efficacy study.\textsuperscript{15} ACCESS is an investigator-initiated study with support by an unrestricted grant from ASTRA Zeneca, Germany.

Subjects and Methods

Patient Population
In this prospective, double-blind, placebo-controlled, randomized, multicenter phase II study, 500 patients were recruited. The sample size of 250 patients per group was chosen to provide information about the reduction in case fatality and disability rate by treating patients immediately with candesartan cilexetil. This sample size was large enough to detect a reduction in the event rate by 6\% to 12\% compared with the placebo group, with an assumed event rate between 15\% and 40\% and with a statistical power of 80\% and a 1-tailed Fisher test at the 5\% level (\(\alpha = 0.05\)). The study was performed in agreement with the basic principles of the Declaration of Helsinki and after permission was given by the ethical committee of the State Medical Board of Lower Saxony and all local ethical committees. This was an investigator-initiated study.

Inclusion criteria were a motor deficit, a cerebral CT scan excluding intracranial hemorrhage, and the necessity to treat hypertension according to current recommendations.\textsuperscript{1} This was assumed when the mean of at least 2 blood pressure measurements was \(\geq 200\ \text{mm Hg}\) systolic and/or \(\geq 110\ \text{mm Hg}\) diastolic 6 to 24 hours after admission or \(\geq 180\ \text{mm Hg}\) systolic and/or \(\geq 105\ \text{mm Hg}\) diastolic 24 to 36 hours after admission.

Exclusion criteria were age \(>85\) years, disorders in consciousness potentially preventing acquisition of consent, occlusion or \(>70\%\) stenosis of the internal carotid artery, malignant hypertension, manifest cardiac failure (New York Heart Association class III and IV), high-grade aortic or mitral stenosis, unstable angina pectoris, or contraindications against candesartan cilexetil.

All patients received carotid ultrasound examination before randomization. The vital status of all patients was ascertained. All patients received a clinical examination on admission. A full neurological examination was performed with recording of neurological deficits and state of consciousness.

Further diagnostic measures included assessment by Rankin Scale and Barthel Index (BI) (on admission and discharge), ECG, echocardiography (optional), laboratory investigations, and tests according to clinical requirements.

The following laboratory values were determined before randomization and before discharge: electrolytes, creatinine, urea, aspartate aminotransferase, alanine aminotransferase, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, hemoglobin, platelet count, blood glucose, coagulation rate (prothrombin time, thrombin time, fibrinogen), and urinalysis (blood, glucose, protein, microalbuminuria) (once during stay in hospital). Creatinine and electrolytes were checked within the first 3 days of when the investigational medication was started again.

Blood Pressure Control
The target reduction in blood pressure was 10\% to 15\% within 24 hours. The reduction in blood pressure was taken as the mean value of 2 measurements within 30 minutes. In the first 3 days, occasional measurements of blood pressure were performed by nurses or automatically throughout the day at 1- to 2-hour intervals and during the night at 2- to 3-hour intervals. On day 7 an automatic 24-hour recording of blood pressure was performed.

Treatment Design
Treatment was started with 4 mg candesartan cilexetil daily or placebo on day 1. On day 2, dosage was increased to 8 or 16 mg candesartan cilexetil or placebo if blood pressure exceeded 160 mm Hg systolic or 100 mm Hg diastolic. Treatment was targeted to a 10\% to 15\% blood pressure reduction within 24 hours. When blood pressure was \(>230\ \text{mm Hg systolic or } >115\ \text{mm Hg diastolic}\) for \(>30\) minutes on day 1 or 2 or on the following days \(>200\ \text{mm Hg systolic or } >110\ \text{mm Hg diastolic}\) for \(>30\) minutes, an acute intervention (urapidil) was allowed.

In all patients a 24-hour blood pressure profile was obtained on day 7. In patients in the candesartan cilexetil group who showed a hypertensive profile (mean daytime blood pressure \(>135/85\ \text{mm Hg}\)), candesartan cilexetil was increased or an additional antihypertensive drug (hydrochlorothiazide, felodipine, metoprolol) was added. In placebo-treated patients showing a hypertensive profile, candesartan cilexetil was started and was adjusted to lower blood pressure to \(<140/90\ \text{mm Hg}\) (office blood pressure) or \(<135/85\ \text{mm Hg}\) (mean daytime blood pressure, automatic blood pressure monitoring). Patients who showed a normotensive profile on placebo (\(n = 2\)) did not receive antihypertensive medication.

Follow-up examinations (blood pressure, neurological index/status, adverse events, medication) were performed after 3, 6, and 12 months (Figure 1).

Assessment of Outcomes
The primary end point was defined to include case fatality and disability, measured as functional status with the use of the BI\textsuperscript{16} 3 months after the end of a placebo-controlled 7-day phase. Cerebral complications are hemorrhages, recurrent stroke, reduction in state of consciousness, and development of cerebral edema. Cardiac complications are any cardiovascular event (including myocardial infarction) and heart failure. BI was excluded post hoc for analysis of a combined end point because new data show that BI is not useful for assessing minor deficits at a high functional level. Because of its U-shaped distribution, the BI is an inappropriate outcome measure for this sample size.\textsuperscript{17} The combined secondary end point included overall mortality and cerebrovascular and cardiovascular events occurring within the study period. The secondary end point was assessed 12 months after hospital discharge. Terminating events for analysis were all “first events” after randomization. End points were confirmed by hospital discharge reports. All end points were evaluated during on-site monitoring by independent physicians who were familiar with stroke therapy.
Baseline Characteristics on Admission, Barthel Index at 3 Months, Cumulative Mortality Until 12 Months, and Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>Candesartan Cilexetil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>173</td>
<td>166</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.3±9.3</td>
<td>67.8±9.4</td>
</tr>
<tr>
<td>Male, %</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>Blood pressure on admission, mm Hg</td>
<td>196±23.1</td>
<td>199±22.9</td>
</tr>
<tr>
<td>Systolic</td>
<td>196±23.1</td>
<td>199±22.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>103±14.0</td>
<td>102±14.9</td>
</tr>
<tr>
<td>Blood pressure on study onset, mm Hg</td>
<td>188±20.9</td>
<td>190±19.7</td>
</tr>
<tr>
<td>Systolic</td>
<td>188±20.9</td>
<td>190±19.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>99±14.9</td>
<td>99±13.0</td>
</tr>
<tr>
<td>Duration of symptoms until study onset, h</td>
<td>29.9</td>
<td>29.7</td>
</tr>
<tr>
<td>Barthel Index day 0</td>
<td>60.0±30.2</td>
<td>64.1±27.5</td>
</tr>
<tr>
<td>Barthel Index 3 mo</td>
<td>87.0±22.9</td>
<td>88.9±19.9</td>
</tr>
<tr>
<td>Cumulative 12-mo mortality</td>
<td>5 (2.9%)</td>
<td>12 (7.2%)</td>
</tr>
<tr>
<td>Vascular events*</td>
<td>17 (9.8%)*</td>
<td>31 (18.7%)*</td>
</tr>
<tr>
<td>Cardiovascular events (fetal and nonfatal)</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Cerebrovascular events (fatal and nonfatal)</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Noncardiovascular mortality</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*P=0.026

Candesartan cilexetil (candesartan cilexetil versus placebo: age, 68.3 versus 67.8 years; male sex, 50% versus 52%; diabetes mellitus in 39% versus 35%; coronary heart disease in 22% versus 19%; hyperlipidemia in 43% versus 45%, respectively) (Table and Figure 3). The study was initiated on average 29.9 versus 29.7 hours after recognition of the symptoms.

No significant differences in blood pressure were evident between the groups on hospital admission (candesartan cilexetil versus placebo: 196/103 versus 199/102 mm Hg) and on study onset (candesartan cilexetil versus placebo: 188/99 versus 190/99 mm Hg). During the placebo-controlled phase in the first 7 days, blood pressure levels were similar in both groups. Likewise, in the subsequent 12 months of follow-up, no significant differences in blood pressure were apparent (Figure 3). In 164 of 166 patients in the placebo group, candesartan cilexetil was started on day 7 because of a hypertensive 24-hour blood pressure profile and was continued throughout the study.

The BI revealed no significant differences on day 0 and after 3 months (candesartan cilexetil versus placebo: day 0, 60.0 [SD 30.24] versus 64.1 [SD 27.53]; 3 months, 87.0 [SD 22.91] versus 88.9 [SD 88.9]).

In contrast, the cumulative 12-month mortality (candesartan cilexetil versus placebo: 5 [2.9%] versus 12 [7.2%]; P=0.07) and the number of vascular events (candesartan cilexetil versus placebo: 17 [9.8%] versus 31 [18.7%];
effects of AT1 receptor blockade may be effective, while the structural kinases ERK1/2. It is conceivable that the structural growth and hence the role of angiotensin II in vascular remodeling are known to be mediated via a pathway starting with activation of the Src family of tyrosine kinases, stimulation of the small G protein Ras, activation of the serine/threonine kinase Raf-1, and subsequently the threonine/tyrosine kinase and the mitogen-activated protein kinases ERK1/2. It is conceivable that the structural effects of AT1 receptor blockade most likely do not play a role. However, it is known that angiotensin II principally affects vascular tone and structure via 2 different pathways: vasoconstriction is mainly mediated via G proteins activating phospholipase C, which in turn releases inositol triphosphate and diacylglycerol, inducing cellular Ca2+ release and transmembrane Ca2+ influx, respectively. On the other hand, vascular growth and hence the role of angiotensin II in vascular remodeling are known to be mediated via a pathway starting with activation of the Src family of tyrosine kinases, stimulation of the small G protein Ras, activation of the serine/threonine kinase Raf-1, and subsequently the threonine/tyrosine kinase and the mitogen-activated protein kinases ERK1/2. It is conceivable that the structural effects of AT1 receptor blockade may be effective, while the hemodynamic effects are counterbalanced by the complex interplay of blood pressure–regulating neurohumoral systems.

The favorable effects of early AT1 receptor blockade are mainly due to a lower incidence of myocardial ischemic events. However, recurrent cerebral ischemic events did not significantly contribute to the differences in cardiovascular morbidity and mortality. How can the modulation of cerebrovascular remodeling then be linked with improved cardiovascular survival? Indeed, there are sound data providing a link between incidence of cardiac death and central autonomic nervous function. Impaired central autonomic regulation was shown to be associated with increased mortality from myocardial infarction. It is conceivable that early local angiotensin II effects may affect not only early but also long-term autonomic function. Such a link is further suggested from studies dealing with other organ systems. The beneficial effect of early ACE inhibition on survival after myocardial infarction lends support to the view that early vascular remodeling profoundly affects cardiovascular survival. The fact that the benefit did not arise immediately, but instead appeared to increase during follow-up, is analogous with data acquired from cardiac intervention studies involving lysis therapy or ACE inhibitors. Although the mechanisms by which AT1 receptor blockade affects cardiovascular morbidity and mortality are still unresolved, the present study shows that early neurohumoral inhibition has similar beneficial effects in cerebral and in myocardial ischemia. The fact that no cardiovascular or cerebrovascular event occurred as a result of hypotension is of significant clinical importance. When there is need for or no contraindication against early antihypertensive therapy, candesartan cilexetil is a safe therapeutic option according to the ACCESS results.

Acknowledgment

This study was supported by ASTRA Zeneca Germany.

References


The ACCESS Study: Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors
Joachim Schrader, Stephan Lüders, Anke Kulschewski, Jürgen Berger, Walter Zidek, Johannes Treib, Karl Einhäupl, Hans Christoph Diener and Peter Dominiak on behalf of the ACCESS Study Group

Stroke. 2003;34:1699-1703; originally published online June 19, 2003; doi: 10.1161/01.STR.0000075777.18006.89
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/34/7/1699

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/