ACCESS Study: Blood Pressure Effect?

To the Editor:

In order to know whether the apparently striking effects of early treatment with an angiotensin receptor blocker after ischemic stroke were due to the timing of treatment, the drug class, or confounding variables, important information is missing in the article. We note that blood pressure values were similar in the treatment and the study population, in both the acute and the follow-up period. Furthermore, the curves of cumulative event rates started to diverge only after the phase during which the treatments differed. Explanations for the observed effects may therefore be (1) an influence of candesartan treatment on vascular events following the acute phase, (2) chance, (3) a difference of candesartan doses in the treatment and placebo groups in the follow-up period, where nearly all control patients also received candesartan, or (4) another confounding factor. As the first 2 possibilities are highly unlikely, it is crucial to know the mean dose of candesartan in each group during the follow-up period (beyond 7 days) as it is stated only that there was “no significant difference of concomitant medication . . . during follow-up.” If the candesartan group received more of this medication during the follow-up period, an important non-antihypertensive effect of candesartan during chronic treatment can be postulated. This possibility is discussed by the authors and suggested by another secondary prevention study showing an advantage in stroke prevention of an angiotensin receptor blocker over a beta-blocker despite similar blood pressure reduction. If there was no difference of candesartan doses during the follow-up, an influence of the candesartan treatment during the acute phase on the following 12 months must be postulated, which seems highly unlikely, given that the curves of event rates begin to diverge only after the acute phase and continue to do so over 12 months. Alternatively, a confounding factor may be present; in this regard it would be important to know whether partial unblinding took place after day 7. Before additional information and confirmation by other trials, it seems premature to change current guidelines about the timing or type of antihypertensive treatment after ischemic stroke.

Regarding the statement that “no cerebrovascular event occurred as a result of hypotension,” it should be noted that a potential deleterious effect of blood pressure–lowering during the acute phase may manifest clinically by progressive worsening or by less complete recovery due to impaired salvage of the penumbra, and not necessarily by a new ischemic event. This may not be of concern in this study, however, because hypertension was treated according to existing international guidelines, significant carotid stenosis was excluded before treatment, and blood pressure was not significantly reduced in the acute phase by the intervention. The effect of blood pressure–lowering on neurological function might be more adequately assessed in future studies by repeat neurological scoring (eg, NIHSS) at prespecified time points during the acute phase and by another functional measure than the Barthel Index at 3 to 12 months, as mentioned by the authors.

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Re: Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors

To the Editor:

Dr Schrader and his colleagues have published their account of a clinical trial to test the safety of 7 days of blood pressure reduction with candesartan, compared with placebo, among patients with an acute ischemic stroke. They describe their primary outcome as a combination of case-fatality and disability as assessed 3 months after randomization.

Although the investigators describe their study as double-blinded, the written account of their trial seems to indicate that the blind was broken 7 days after randomization. They report that after blood pressure was measured at day 7, hypertensive patients in the candesartan group were treated with increased dosage of their medication or addition of others. Hypertensive patients in the placebo group were placed on candesartan. How were these management decisions instituted without unblinding patients and investigators to the randomized treatment assignment? This technical issue is important because outcome events occurring between 7 days and 12 months after randomization (as well as earlier events) were included in the analyses for the primary and secondary outcome.

Blinding in the assessment of these outcome events would protect against an important source of research bias.

The authors begin their discussion section with the statement that “a 7-day course of candesartan after an acute ischemic stroke significantly improves cardiovascular morbidity and mortality.” This statement seems to be based on analysis of secondary outcomes, including all-cause mortality and vascular events. The combined primary and secondary outcomes were analyzed in the meta-analysis. The authors state that the combined primary end point of disability or case fatality was abandoned after the research began. Among the components of that primary end point, only findings for disability are reported; case fatality (ascertained at 3 months) is neither defined nor reported.

A second claim in the discussion section, that “the same favorable effect is not achieved when candesartan is started 7 days after an acute stroke has occurred” was not supported by data.

Finally, authors state that sample size was based on estimated reductions in case fatality and disability. The criteria for case fatality and disability, however, are not described.

The article by Schrader and colleagues may highlight the need for clinical trial investigators to describe masking procedures, provide operational definitions for planned outcomes, specify assumptions in sample size calculations, report findings for planned primary outcomes (however problematic they may be), and provide data to support major claims.

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Response

P. Michel, J. Bogousslavsky, and W. Kernan have asked some very interesting questions that have been discussed by the ACCESS authors as well:

1. As there are certain limits concerning number of words, figures and tables for Stroke articles, we had to be limited to the substantial aspects. Further details can be found in the study protocol, which is in agreement with GCP guidelines.
2. It is true that in accordance with the protocol, the double-blinded phase ended after 1 week. However, all events were assessed by independent specialists unaware of the patients’ initial treatment, so the end point evaluation was of course blinded. This procedure was chosen to exclude observer bias due to open label therapy during follow-up. For all 339 patients the vital status could be evaluated (no selection bias concerning

initial therapy groups; death is an objective criterion). It is not impossible but very unlikely that the results are due to observer bias.

3. There was no significant difference of mean treatment doses of candesartan during follow-up: candesartan group/placebo group 11.7/11.3 mg 3 months, 12.3/12.4 mg 6 months, 12.4/12.5 mg 12 months.

4. Therefore, from the statistical point of view, the results are unlikely due to chance ($P=0.026$); the chance to observe such or more extreme outcome between the 2 groups if there is no real difference is $<1:38$.

5. Authors never postulated to change current guidelines worldwide but ACCESS is the first study that could show advantages of early AT1-inhibitor treatment in acute cerebral ischemia. It has to be stressed that no patient in this study showed a blood pressure decrease with clinically relevant symptoms. It can be concluded thus far that the early treatment with AT1-inhibitor candesartan cilexetil is safe and that this therapeutic option should be considered until further data from large trials are available.

6. Progressive worsening of neurological deficits were defined as “adverse events” by study protocol and were queried and documented by standardized CRF every day during the placebo-controlled first week.

7. Criteria for case fatality and disability are described already in the article (assessment of outcomes); case fatality during follow-up is shown in the article (in Figure 4).