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 stroke1 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.2 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,3 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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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).
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