Effects of Candesartan in Acute Stroke on Cognitive Function and Quality of Life
Results From the Scandinavian Candesartan Acute Stroke Trial

Astrid G. Hornslien, MD; Else C. Sandset, MD; Philip M. Bath, FRCP; Torgeir B. Wyller, MD; Eivind Berge, MD; on Behalf of the Scandinavian Candesartan Acute Stroke Trial Study Group

Background and Purpose—High blood pressure is common in the acute phase of stroke and is associated with poor outcome. We examined whether blood pressure–lowering treatment with candesartan in the acute phase affects long-term cognitive function and quality of life.

Methods—Scandinavian Candesartan Acute Stroke Trial was a randomized-controlled and placebo-controlled trial of candesartan in 2029 patients with acute stroke and raised blood pressure. At 6 months, cognitive function was assessed by the Mini Mental State Examination and quality of life by the EuroQol instrument. We used ordinal logistic and multiple linear regression for statistical analysis, adjusting for predefined key variables.

Results—Median Mini Mental State Examination score was 28 in both groups, and there was no significant difference between the distribution of Mini Mental State Examination scores in the 2 groups (common odds ratio, 1.11; 95% confidence interval, 0.91–1.34; P=0.32). Median EuroQol-5D index were 0.74 and 0.78 (P=0.034), and the mean EuroQol-visual analogue scale scores were 66.0 and 67.3 in the candesartan and placebo groups, respectively (P=0.11).

Conclusions—Candesartan did not improve cognitive function or quality of life. Rather, there were signs of harmful effects.


Key Words: Acute stroke ■ Candesartan ■ Cognition ■ Hypertension ■ Quality of life

High blood pressure is common in the acute phase of stroke and is associated with poor outcome. In the Scandinavian Candesartan Acute Stroke Trial (SCAST), we tested whether blood pressure–lowering treatment in the acute phase confers clinical benefits using the angiotensin receptor blocker candesartan. However, for the primary effect variables, vascular events, and functional outcome at 6 months, there were no signs of benefit from treatment.1

Cognitive impairment and reduced quality of life are 2 other common and clinically important outcomes after stroke.2–5 Blood pressure–lowering treatment with angiotensin–converting enzyme inhibitors or angiotensin receptor blockers administered for secondary prevention after stroke has been shown to prevent cognitive impairment6–8 and low quality of life.9 We therefore wanted to examine whether similar effects can be seen from treatment with the angiotensin receptor blocker candesartan in the acute phase of stroke.

Materials and Methods
SCAST was a North European, multicenter, randomized-controlled, placebo-controlled, double-masked trial of candesartan in patients with acute stroke and raised blood pressure. Study design and participants have been described elsewhere.10 The study recruited 2029 patients presenting within 30 hours of acute ischemic or hemorrhagic stroke and with systolic blood pressure ≥140 mm Hg, and patients were randomized to treatment with candesartan or placebo for 7 days. The trial complied with Good Clinical Practice standards and with the Declaration of Helsinki.10 Cognitive function at 6 months was assessed by the Mini Mental State Examination (MMSE),11 and quality of life was measured by the EuroQol (EQ) instrument,12 which includes 5 dimensions of functioning (EQ-5D: mobility, self care, usual activities, pain/discomfort, and anxiety/depression), a summary index, and a summary visual analogue scale (EQ-VAS). As a secondary analysis, we examined the effects among patients who had a recurrent stroke in the follow-up period.

MMSE scores were categorized as definite (≤23 points), possible (24–27), or no cognitive impairment (≥28 points)13 and were analyzed using ordinal logistic regression. The levels of functioning in the individual EQ-5D dimensions also were analyzed using ordinal logistic
regression, whereas the EQ-5D indices and the EQ-VAS scores were analyzed with multiple linear regression. The subgroup analyses and the analysis of the subset of patients who had a recurrent stroke were performed using binary logistic regression. All multivariable analyses were adjusted for the following predefined key variables: age, sex, cause of stroke (ischemic versus all other), systolic blood pressure, and Scandinavian Stroke Scale score at baseline. All analyses were performed using SPSS version 18.0.

**Results**

Of the 2029 patients included in the trial, data on MMSE scores, EQ-5D indices, and EQ-VAS scores were available for 1644 (81%), 1734 (85%), and 1697 patients (84%), respectively. The Table shows the baseline characteristics of all patients included in the analyses.

Figure 1 shows the effect of candesartan on the MMSE scores at 6 months. The median score was 28 (interquartile range 25–29) in both groups. The ordinal regression analysis showed a small, nonsignificant difference between the distribution of MMSE scores in the 2 groups in disfavor of candesartan (common adjusted odds ratio, 1.11; 95% confidence interval, 0.91–1.34; *P* =0.32). The median EQ-5D index score was 0.74 (interquartile range, 0.59–0.88) in the candesartan group and 0.78 (interquartile range, 0.62–0.88) in the placebo group; and in the multiple linear regression analysis, the difference was statistically significant (*P* =0.034). For the 5 individual EQ-5D domains, there were also small differences in disfavor of candesartan (Figure 2). The mean EQ-VAS score was 66.0 (SD, 20) for the candesartan group and 67.3 (SD, 19) for the placebo group (*P* =0.11). We tested for heterogeneity of effect between the prespecified subgroups, but the *P* values for interaction were nonsignificant. We also assessed the effect of candesartan on the MMSE score and EQ-5D index among patients who had a recurrent stroke in the follow-up period. Five percent of patients had a new stroke during follow-up, and there was no evidence of any better effect of candesartan in these patients than in patients without recurrent stroke (*P* =0.78). The same result was found for the EQ-5D index.

### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th>Candesartan (n=870)</th>
<th>Placebo (n=882)</th>
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<tbody>
<tr>
<td>Female 343 (39%) 377 (43%)</td>
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<tr>
<td>Age, y 70 (11.2) 70 (10.9)</td>
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<tr>
<td>Systolic blood pressure, mm Hg 171.1 (18.9) 171.5 (19.3)</td>
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<tr>
<td>Diastolic blood pressure, mm Hg 90.6 (13.7) 90.7 (13.9)</td>
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<tr>
<td>Ischemic stroke 744 (86%) 758 (86%)</td>
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<tr>
<td>Hemorrhagic stroke 116 (13%) 114 (13%)</td>
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<tr>
<td>Other 8 (1%) 10 (1%)</td>
<td></td>
</tr>
<tr>
<td>Unknown 2 (&lt;1%) 0</td>
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<tr>
<td>SSS score 42.0 (11.2) 42.0 (11.6)</td>
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<tr>
<td>Total anterior 52 (6%) 47 (5%)</td>
<td></td>
</tr>
<tr>
<td>Partial anterior 429 (49%) 437 (50%)</td>
<td></td>
</tr>
<tr>
<td>Posterior 125 (14%) 111 (13%)</td>
<td></td>
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<tr>
<td>Lacunar 260 (30%) 282 (32%)</td>
<td></td>
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<tr>
<td>Other 4 (0.5%) 5 (0.6%)</td>
<td></td>
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<tr>
<td>Duration of symptoms, h 17.8 (8.1) 18.1 (8.0)</td>
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<tr>
<td>Premorbid mRS score 0 (0-0) 0 (0-0)</td>
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<tr>
<td>Hypertension 565 (67%) 583 (70%)</td>
<td></td>
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<tr>
<td>Diabetes mellitus 134 (16%) 141 (16%)</td>
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<tr>
<td>Current or previous atrial fibrillation 158 (19%) 148 (17%)</td>
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<tr>
<td>Previous stroke or TIA 207 (24%) 167 (19%)</td>
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<tr>
<td>Current use of an ACE inhibitor 226 (26%) 226 (26%)</td>
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<tr>
<td>Thrombolytic treatment before randomization 50 (8%) 69 (11%)</td>
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</table>

Data represent numbers (%), mean (SD), or median (interquartile range). Percentages are proportions of valid data entries, which might be lower than the number of patients in each group.

ACE indicates angiotensin-converting enzyme; mRS, modified Rankin Scale; OCSP, Oxfordshire Community Stroke Project (both ischemic and hemorrhagic strokes); SSS, Scandinavian Stroke Scale; and TIA, transient ischemic attack.

**Discussion**

Long-term treatment with inhibitors of the renin–angiotensin system has been shown to reduce the risks of cognitive impairment and low quality of life after stroke, but we found no such effects from treatment in the acute phase of stroke. One explanation may be that treatment in our trial was too short for candesartan to have any protective effect on cognitive function and quality of life. Alternatively, treatment with candesartan in the acute phase actually may be detrimental, as suggested by our previous analysis of functional outcome.

<table>
<thead>
<tr>
<th>Common OR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mobility 1.16 (0.96-1.42) 0.13</td>
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<tr>
<td>Selfcare 1.28 (1.03-1.60) 0.025</td>
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<tr>
<td>Activity 1.20 (0.99-1.46) 0.062</td>
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<tr>
<td>Pain/discomfort 1.12 (0.92-1.35) 0.28</td>
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<tr>
<td>Anxiety/depression 1.13 (0.92-1.38) 0.24</td>
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**Figure 1.** Effect of candesartan on cognitive status (Mini Mental State Examination scores) at 6 months.

**Figure 2.** Effect of candesartan on the individual EuroQol (EQ)-5D domains at 6 months. Analysis by ordinal logistic regression. CI indicates confidence interval; and OR, odds ratio.
The Perindopril Protection Against Recurrent Stroke (PROGRESS) Study found that perindopril reduced the risk of cognitive impairment associated with recurrent stroke in the follow-up period. Our trial showed no effect on the risk of recurrent stroke. If the benefits of treatment come through prevention of stroke, as suggested by PROGRESS, it is therefore no surprise that candesartan had no effect on cognitive function in our trial.

One limitation of this analysis is that we did not have complete data for cognitive function and quality of life for all patients, but data were equally complete in the 2 groups; therefore, attrition bias is not likely to have played a role. Also, the study was not powered to reliably detect differences in these outcomes. The strength of the analysis is the randomization of a large number of patients and the blinded assessment of secondary outcomes. The results are consistent with the results of the main analysis of vascular events and functional outcome, and support the conclusion in our previous report that there is no indication for routine blood pressure–lowering treatment with candesartan in the acute phase of stroke.

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Disclosures
Dr Bath received travel support from AstraZeneca to attend meetings in the trial steering committee. Drs Wyller and Berge have received payment for lectures given at meetings arranged by AstraZeneca.

References
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