

# Effects of Blood Pressure–Lowering Treatment in Different Subtypes of Acute Ischemic Stroke

Else Charlotte Sandset, MD, PhD; Mirza Jusufovic, MD; Per Morten Sandset, MD, PhD; Philip M.W. Bath, FRCP, FESO; Eivind Berge, MD, PhD; on behalf of the SCAST Study Group

**Background and Purpose**—The Scandinavian Candesartan Acute Stroke Trial (SCAST) found no benefits of blood pressure–lowering treatment with candesartan in acute stroke. We have investigated whether the effect of treatment is different in different subtypes of ischemic stroke.

**Methods**—SCAST was a randomized- and placebo-controlled trial of candesartan in 2029 patients presenting within 30 hours of ischemic or hemorrhagic stroke and systolic blood pressure  $\geq 140$  mm Hg. Ischemic stroke subtype was categorized by the Oxfordshire Community Stroke Project classification. There were 2 primary effect variables: the composite vascular end point of vascular death, myocardial infarction, or stroke during the first 6 months and functional outcome at 6 months.

**Results**—A total of 1733 patients with ischemic stroke were included: total anterior circulation infarcts in 129, partial anterior in 850, posterior in 236, and lacunar in 510 patients. For functional outcome there was a significant trend toward a better effect of candesartan in patients with larger infarcts (total anterior circulation or partial anterior circulation) than in patients with smaller infarcts (lacunar infarction;  $P=0.02$ ). For the composite vascular end point, there were no differences in treatment effect.

**Conclusions**—The results suggest that the effect of blood pressure–lowering treatment with candesartan may differ according to different types of acute ischemic stroke, but this needs to be confirmed in future trials.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00120003.

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**Key Words:** angiotension II receptor blocker ■ blood pressure ■ candesartan ■ clinical trial ■ ischemic stroke

Blood pressure is commonly elevated in patients with acute stroke, and a spontaneous fall to normal levels is usually seen within the first 10 to 14 days.<sup>1,2</sup> A recent study has strongly suggested that blood pressure should be actively lowered during the first hours of hemorrhagic stroke,<sup>3</sup> but overall no benefits have been found in ischemic stroke.

The Scandinavian Candesartan Acute Stroke Trial (SCAST) found no beneficial effects of blood pressure lowering with candesartan during the first week of stroke.<sup>4</sup> In this prespecified analysis, we assessed the effect of blood pressure lowering according to different subtypes of ischemic stroke, particularly whether there is a difference in the effect of treatment in patients with large infarctions of presumed atherothrombotic or cardioembolic pathogenesis, than in patients with smaller infarcts of presumed lacunar type.

## Materials and Methods

SCAST was a randomized- and placebo-controlled, double-masked trial of the angiotensin receptor blocker candesartan in 2029 patients presenting within 30 hours of acute ischemic or hemorrhagic stroke

and with systolic blood pressure  $\geq 140$  mm Hg. Patients were allocated to treatment with candesartan or placebo for 7 days, and doses were increased from 4 to 16 mg during the first 3 days. The follow-up period was 6 months. Full details on study design and participants have been reported previously.<sup>4,5</sup>

The analysis of the patients with different types of ischemic stroke was prespecified in the protocol and the statistical analysis plan. SCAST was designed before advanced imaging techniques were widely available and stroke subtype was classified based on clinical data using the Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation [TACI], partial anterior circulation [PACI], posterior circulation, and lacunar infarction [LACI]).<sup>6</sup>

The trial had 2 coprimary effect variables: the composite end point of vascular death, stroke, or myocardial infarction during 6 months and functional outcome as measured by the modified Rankin Scale at 6 months. The composite vascular end point was analyzed using Cox proportional hazard models, and functional outcome was analyzed using binary logistic regression. We adjusted for age and systolic blood pressure at baseline. Heterogeneity of treatment effect was assessed by including an interaction term in the model. We also did analyses based on an assumption of linear trends. All analyses were performed using SPSS version 18.0 (SPSS Statistics, Chicago, IL).

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From the Department of Neurology (E.C.S., M.J.), Department of Haematology (P.M.S.), and Department of Internal Medicine (E.B.), Oslo University Hospital, Oslo, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway (P.M.S.); and Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom (P.M.W.B.).

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Correspondence to Else C. Sandset, MD, PhD, Department of Neurology, Oslo University Hospital, Postboks 4956 Nydalen, 0424 Oslo, Norway. E-mail [else@sandset.net](mailto:else@sandset.net)

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## Results

Of the 1733 patients with ischemic stroke, 1725 (99%) could be classified according to the OCSF classification. Baseline characteristics of the different subtypes are presented in the Table. Within each subtype baseline characteristics were well balanced between the treatment groups.

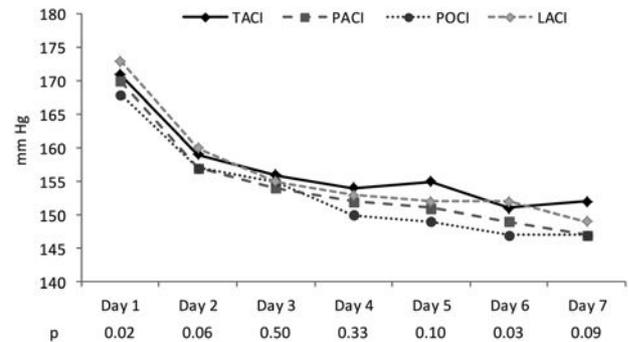
The greatest drop in systolic blood pressure occurred in the LACI and PACI patients; however, there was no significant difference in systolic blood pressure between the subtypes on day 7 ( $P=0.09$ ; Figure 1).

There was a significant trend toward a better functional outcome with candesartan in patients with TACI and PACIs, than in patients with LACI ( $P$  value for trend=0.02; Figure 2). In the unadjusted analysis, treatment with candesartan was associated with a better functional outcome in the patients with TACI (odds ratio, 0.47; 95% confidence interval, 0.22–1.01;  $P=0.05$ ). The difference was no longer significant in the adjusted analysis, and, overall, there was no heterogeneity of treatment effect between the subgroups ( $P=0.11$ ). For the

**Table. Baseline Characteristics**

	TACI (n=129)	PACI (n=850)	POCI (n=236)	LACI (n=510)	PValue
Female sex	73 (57)	370 (44)	101 (43)	211 (41)	0.02
Age, y	75.2±11.6	71.0±11.0	73.2±9.6	70.3±10.8	<0.001
Systolic blood pressure, mmHg	171.4±19.8	170.4±18.8	168.4±18.3	172.7±19.4	0.023
Diastolic blood pressure, mmHg	88.6±14.7	89.7±13.6	86.6±13.6	91.5±13.6	<0.001
SSS score	22 (13–33)	46 (36–53)	35 (24–46)	46 (40–51)	<0.001
Duration of symptoms, h	17.6±8.1	18.0±8.1	17.7±8.1	18.5±7.8	0.47
Treatment with candesartan	63 (49)	425 (50)	126 (53)	244 (48)	0.56
Medical history					
Hypertension	83 (66)	587 (72)	159 (70)	329 (67)	0.35
Diabetes mellitus	20 (16)	149 (18)	30 (13)	89 (18)	0.33
Current or previous atrial fibrillation	43 (35)	167 (20)	69 (30)	67 (13)	<0.001
Previous stroke or TIA	40 (33)	202 (24)	57 (25)	105 (21)	0.03
Current use of an ACE inhibitor	35 (28)	227 (27)	62 (26)	143 (28)	0.93
Thrombolytic treatment before randomization	12 (11)	71 (10)	29 (15)	34 (8)	0.05

Data presented are n (%), mean±SD, or median (interquartile range). Percentages are proportion of valid data entries, which might be lower than the number of patients in each group. ACE indicates angiotensin-converting enzyme; LACI, lacunar infarct; PACI, partial anterior circulation; POCI, posterior circulation; SSS, Scandinavian Stroke Scale; TACI, total anterior circulation infarct; and TIA, transient ischemic attack.



**Figure 1.** Blood pressure in the treatment period according to stroke subtype.  $P$  value derived from ANOVA. LACI indicates lacunar infarction; PACI, partial anterior circulation; POCI, posterior circulation; and TACI, total anterior circulation.

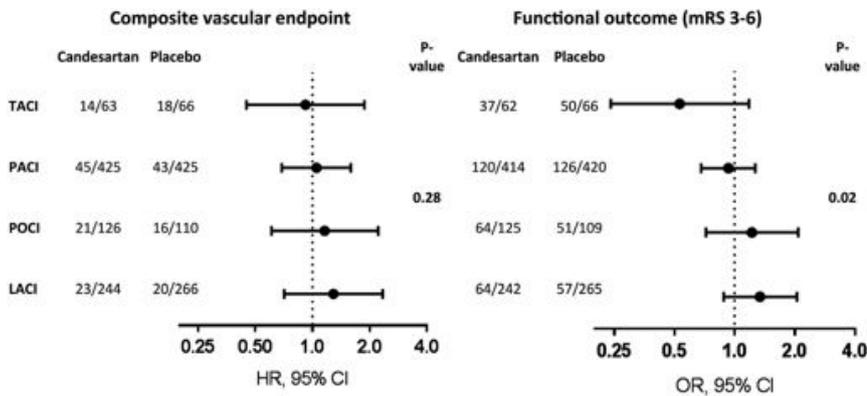
composite vascular end point there were no differences in treatment effect for either subgroup (Figure 2).

## Discussion

We used the OCSF classification to differentiate patients with larger infarcts of presumed atherothrombotic or cardioembolic pathogenesis (TACI or PACI) from patients with smaller infarcts, mostly of lacunar type (LACI) and found a trend indicating a better effect of treatment in patients with TACI or PACI than in patients with LACI. Similar results were found in a study of intravenous nimodipine, where blood pressure lowering was associated with a better effect in patients with TACI than in patients with non-TACI.<sup>7</sup> If there is a true difference in treatment according to stroke subtype this can possibly be explained by 2 mechanisms. First, most patients with lacunar infarcts have long-standing hypertension resulting in a rightward shift of the autoregulatory curve, which means that lowering to blood pressure to normal values can lead to larger perfusion deficits.<sup>8</sup> Second, in patients with lacunar infarcts there are data suggesting that cerebral autoregulation is impaired not only in the affected hemisphere but also in the opposite hemisphere, which means that a fall in blood pressure can lead to disproportionate fall in cerebral perfusion.<sup>9</sup> On the other side of the spectrum, larger infarcts (TACI and PACI) more often have an atherothrombotic or a cardioembolic pathogenesis, which was supported by the finding of a higher prevalence of atrial fibrillation in patients with these infarct subtypes. Such infarcts are usually larger and more prone to edema development or hemorrhagic transformation, and it is plausible that moderate blood pressure reduction is beneficial, by avoiding such complications.<sup>10</sup>

The present analyses were prespecified analyses of a large, randomized-controlled trial with blinded outcome assessment and near complete follow-up. One important limitation is that we do not have information about the size, location of the infarct, presence of penumbra, or precise pathogenic subtype. For example, we have previously found indications that outcome is worse if treatment is given to patients with carotid artery stenosis.<sup>11</sup> Another limitation is that this is a subgroup analysis of a trial with a neutral outcome, with the inherent risk of spurious findings, because of chance alone.

In conclusion, these results suggest that the effect of acute blood pressure lowering treatment may be different in the



**Figure 2.** Risk of the composite vascular end point and poor functional outcome according to stroke subtype. CI indicates confidence interval; HR, hazards ratio; LACI, lacunar infarction; mRS, modified Rankin Scale; PACI, partial anterior circulation; POCI, posterior circulation; and TACI, total anterior circulation.

different subtypes of ischemic stroke. Future trials will hopefully be able to show whether this is really the case.

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Dr E.C. Sandset collected the data, performed the statistical analyses, and wrote the first draft of the article. Dr Jusufovic contributed to the statistical analyses and commented on the article. Drs P.M. Sandset and Bath participated in the planning and conduction of the study and commented on the article. Dr Berge was the coordinating investigator of Scandinavian Candesartan Acute Stroke Trial and commented on the article.

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### Disclosures

Dr Berge has received payment for lectures given at meetings arranged by AstraZeneca. Dr Bath received travel support from AstraZeneca to attend meetings in the trial steering committee. The other authors report no conflicts.

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