Blood Pressure Management in Acute Stroke

Does the Scandinavian Candesartan Acute Stroke Trial (SCAST) Resolve All of the Unanswered Questions?

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Whether raised blood pressure in patients with acute stroke should be treated is one of the major unresolved issues in acute stroke management, due mainly to a paucity of reliable data from sufficiently powered randomized controlled trials. However, the Scandinavian Candesartan Acute Stroke Trial (SCAST), recently published in The Lancet, adds important new information about the risks and benefits of treatment of poststroke hypertension.1 Else Sandset and colleagues assessed whether careful blood pressure-lowering treatment with candesartan is beneficial in a wide range of patients with acute ischemic and hemorrhagic stroke and raised blood pressure.

Rationale for Blood Pressure-Lowering in Acute Stroke

Blood pressure is increased in up to 75% to 80% of patients with acute stroke and usually decreases spontaneously over the next few days.2–4 The cause of this transient rise in blood pressure (ie, poststroke hypertension) is unknown. A specific physiological reaction to the stroke itself is often postulated, possibly due to disturbed cerebral autoregulation,5 damage or compression of brain regions that regulate the autonomic nervous system,6 or neuroendocrine factors.7,8 However, nonstroke-specific mechanisms such as headache,6 urine retention,6 infection,9 and psychological stress of admission to hospital10,11 have also been postulated.

Data from observational studies have consistently shown that raised blood pressure after stroke is associated with poor short- and long-term outcomes.12–14 In patients with acute ischemic stroke, raised blood pressure is potentially harmful because it increases the risk of cerebral edema and hemorrhagic transformation in the freshly infarcted brain tissue.6 In patients with hemorrhagic stroke, high blood pressure increases the risk of hematoma expansion, growth of the perihematomal edema, and early rebleeding into the brain.15 However, optimum management of poststroke hypertension remains controversial, particularly in ischemic stroke, in which there are concerns that lowering blood pressure reduces blood flow from collateral vessels to the ischemic penumbra and increases the size of the brain infarction or perihematomal ischemia.16 A Cochrane review of 12 randomized trials of blood pressure lowering in acute stroke in a total of 1153 patients within 1 week of acute ischemic or hemorrhagic stroke concluded that there is insufficient evidence to reliably assess effects on functional outcome or death.17 Therefore, the current guidelines do not recommend blood pressure-lowering in patients with acute stroke unless levels are extremely high or thrombolysis is being considered.18,19

The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study randomized 342 patients with high blood pressure to candesartan versus placebo during the first week after stroke and reported a reduced risk of vascular events and deaths during the next 12 months (OR, 0.48; 95% CI, 0.25 to 0.90). However, there was no effect on the primary end point of functional outcome and most of the vascular events that were prevented were transient ischemic attacks.20 Nevertheless, these results encouraged the investigators of the SCAST trial to assess the effect on moderate blood pressure-lowering drugs on outcome in a larger randomized controlled trial.

Results of the SCAST Trial

SCAST was a large, multicenter, randomized placebo-controlled, double-blind trial that enrolled patients with acute ischemic (85%) or hemorrhagic (14%) stroke and systolic blood pressure of ≥140 mm Hg. A total of 2029 patients were randomly assigned within 30 hours of symptom onset (average 18 hours) to either candesartan cilexetil (1017 patients) or placebo (1012 patients) for 7 days with doses increasing from 4 mg on Day 1 to 16 mg on Days 3 to 7. Demographic and clinical characteristics at baseline were well balanced between treatment groups. Mean blood pressure was 171/90 mm Hg on admission but was significantly lower in patients allocated to candesartan than in those on placebo (P≤0.001) during the 7-day treatment period with a mean difference in systolic blood pressure on Day 7 of 5 mm Hg (95% CI, 3 to 7; P<0.0001) and the mean difference in diastolic blood pressure of 2 mm Hg (1 to 3; P=0.001). At 6 months, mean blood pressure was 143/81 mm Hg in both groups. Follow-up was 99% complete at 6

months and showed no significant difference in the coprimary outcome measures. The composite end point of stroke, myocardial infarction, or vascular death occurred in 120 events in the candesartan group and in 111 events in the placebo group (adjusted hazard ratio, 1.09; 95% CI, 0.84 to 1.41; \( P=0.52 \)). Analyses of functional outcome suggested a trend toward higher risk of poor outcome in the candesartan group (modified Rankin Scale: adjusted OR, 1.17; 95% CI, 1.00 to 1.38; \( P=0.048 \) [not significant at \( P\leq 0.025 \) level because of 2 coprimary effect variables]). The observed effects were similar for all prespecified secondary end points (including death from any cause, vascular death, ischemic stroke, hemorrhagic stroke, myocardial infarction, stroke progression, symptomatic hypotension, and renal failure) and outcomes (stroke severity at 7 days and Barthel Index at 6 months), and there was no evidence of a differential effect in any of the prespecified subgroups.

The SCAST investigators finally added their results to a meta-analysis of all 10 randomized controlled trials of blood pressure-lowering drugs within the first week of acute stroke; overall, there was no evidence of a beneficial effect on functional outcome (relative risk, 1.04; 95% CI, 0.97 to 1.12; \( P=0.30 \)). The authors concluded that “there was no evidence that careful blood pressure lowering with the angiotensin blocker candesartan is beneficial in patients with acute stroke and raised blood pressure. If anything the evidence suggested a harmful effect.” The accompanying commentary concluded that clinicians should not prescribe blood pressure-lowering drugs within the first week of acute stroke.21

**Comments on SCAST**

SCAST was a well-performed trial and appears to have very good internal validity. The fact that it was stopped slightly short of the originally planned target of recruitment (target population 2500) is unlikely to have resulted in any bias. Furthermore, the pragmatic design of the trial suggests that it is likely to have good external validity and the results of the meta-analysis strengthen the overall conclusions. However, although SCAST adds important new information on the risks and benefits of blood pressure-lowering in patients with acute stroke, several questions inevitably remain.

**Was Treatment Acute Enough?**

The average time to treatment in SCAST was 17.6 hours (SD 8.1) in the candesartan group and 17.9 hours (SD 8.1) in the placebo arm. However, blood pressure appears to be highest immediately after stroke and many of the adverse consequences of severe hypertension might be expected to occur within the first few hours after onset.2–4 Interestingly, in patients in SCAST treated within 6 hours, candesartan was of statistically benefit in terms of the composite vascular end point, although statistical power was limited and the subgroup–treatment effect interaction was not statistically significant (\( P=0.08 \)). However, the reported interaction was based on a test for heterogeneity in effect over 4 timing subgroups rather than a test for any trend in effect. Although it is clearly data-dependent, there was a smooth trend toward less benefit with increasing time to treatment, which would be statistically significant by test for trend. It must be said, however, that there was no such trend in benefit for the functional outcome.

Patients with intracerebral hemorrhage might be expected to benefit most from early antihypertensive therapy. Growth of intracerebral hematoma and rebleeding occur mainly within the first hours after symptom onset. However, SCAST showed no benefit in patients with hemorrhagic stroke in any primary or secondary outcome measure. The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) showed that aggressive blood pressure-lowering reduced hematoma growth in patients with intracerebral hemorrhage when started within 6 hours of symptom onset.22 Whether early and aggressive therapy is also beneficial in terms of eventual clinical outcome in this patient group is currently assessed in the INTERACT 2 study.23

**Can We Say That Blood Pressure-Lowering in Acute Stroke Is at Least Safe?**

Early progression of stroke after treatment of hypertension has always been the primary worry of those who have been concerned about lowering blood pressure early after stroke, especially in patients with hypoperfused but still salvageable brain tissue, that is, the penumbra. Stroke severity in SCAST, measured with the Scandinavian Stroke Scale, was similar in both treatment groups at 7 days; stroke progression was observed in 6% of patients treated with candesartan and 4% in the placebo arm (relative risk, 1.47; 95% CI, 1.01 to 2.13; \( P=0.04 \)). This finding is a cause for concern, especially because early stroke progression is a potentially more sensitive outcome measurement than functional status averaged across all types of stroke. It would be important to know whether the effect of treatment on early stroke progression varied with stroke subtype (ischemic or hemorrhagic), stroke etiology (large artery versus small artery versus cardioembolic stroke), the presence of intra- and extracranial stenoses, and the extent of the fall in blood pressure within the first hours after the event.

Another clinical concern about lowering blood pressure in acute stroke is the potential to increase the risk of early recurrent stroke as well as progression of the initial event. We know from randomized controlled trials that secondary prevention with blood pressure-lowering after a few weeks is safe and effective.24 SCAST provided information on stroke recurrence at 6 months, but it would be helpful to have more information about early recurrent stroke at 1 week or at 1 month. Although 2 previous studies on blood pressure-lowering and continuing prior antihypertensive medication in patients with acute stroke (Control of Hypertension and Hypotension Immediately Post-Stroke [CHHIPS] and Continue or Stop post-Stroke Antihypertensives Collaborative Study [COSSACS]) did not show any increase in early adverse events, both trials were rather small and were definitely underpowered for early recurrent events.25,26

**Other Issues of External Validity?**

SCAST included patients with all types of stroke. Although analyses were adjusted for age, cause of stroke (ischemic versus hemorrhagic), stroke severity, and systolic blood pressure levels, and results were consistent across these prespecified subgroup, the trial was inevitably not powered to
look at effects of treatment in different etiologic subtypes or all other relevant clinical subgroups. The pathophysiological mechanism of poststroke hypertension is still poorly understood. Data from population-based studies have shown that levels of poststroke hypertension are not only related to stroke severity, but also to stroke etiology. Therefore, the mechanism of poststroke hypertension may differ between subtypes of stroke, which might influence therapeutic approaches. In addition to patients with intracerebral hemorrhage, subgroups of interest include patients with strokes due to small vessel disease, patients with longstanding prior hypertension, and patients with increased variability in blood pressure, which has shown to be a risk factor for stroke independent of mean blood pressure. Furthermore, patients with transient ischemic attack were excluded from SCAST and therefore we do not know whether these patients benefit from early blood pressure-lowering therapy, although antihypertensive therapy in these patients is often started early in daily clinical practice.

Patients in SCAST were treated with the oral angiotensin receptor blocker candesartan and previous trials have been too small to allow reliable assessment of potential drug class effects. Previous studies have shown that there are drug class effects on interindividual and intraindividual variation in blood pressure, which appear to account for differences in effects of antihypertensive drugs on the risk of stroke independently of effects on mean blood pressure. Compared with other drugs, variation in systolic blood pressure is reduced by calcium channel blockers and nonloop diuretics and increased by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers. It is possible, at least in theory, that the results of SCAST were determined in part by effects of candesartan on variability of blood pressure. Further research is required on whether variability in blood pressure is related to outcome in acute stroke. If so, other drugs might need to be studied in future randomized trials.

**Blood Pressure Management and Thrombolysis**

The SCAST trial suggested that there might be an adverse effect of treatment with candesartan on functional outcome and stroke progression. However, in patients with acute stroke undergoing thrombolysis, it is common practice to avoid systolic blood pressures >185 mm Hg. Results from SCAST should probably not stop clinicians from lowering blood pressure in candidates for thrombolysis. Recanalization is the most important modifiable predictor of outcome in patients with acute stroke, and observational data suggest that blood pressure-lowering before intravenous tissue plasminogen activator therapy, even using aggressive measures, may not be associated with a poor outcome. However, further trials are required to address this question more reliably. In the meantime, thrombolysis should probably not be withheld due to high blood pressure, if it can be lowered to 185 mm Hg, because the potential damage of a moderate blood pressure reduction is probably smaller than to withheld thrombolysis.

In conclusion, the results of the SCAST trial indicate that there does not seem to be any benefit from starting oral blood pressure-lowering therapy with candesartan within the first week of stroke. Whether particular subgroups of patients with stroke might benefit from early treatment and whether other drugs are effective has yet to be determined.

**Implications for Future Research**

Given the many unanswered questions regarding antihypertensive therapy despite SCAST and at the same time as awaiting the results of the ongoing randomized trials (INTERACT 2, Efficacy of Nitric Oxide in Stroke [ENOS]), more research is required on the mechanisms of poststroke hypertension. In an ideal world, future randomized controlled trials assessing the impact of blood pressure-lowering on outcome in patients with acute stroke would take into consideration stroke severity, stroke etiology, premorbid blood pressure levels, and findings of imaging such as the presence of a penumbra and intra- and extracranial stenoses, although statistical power will always be limited in some subgroups. Whether different classes of antihypertensives drugs should be investigated is also open to question.

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