No Benefit From BP-Lowering in Acute Stroke

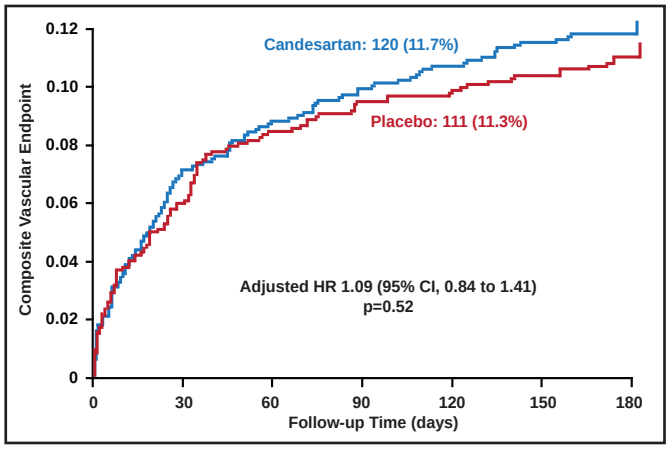
Else C. Sandset, MD, Oslo University Hospital, Ullevål, Oslo, Norway, presented the results of the Scandinavian Candesartan Acute Stroke Trial (SCAST; NCT00120003), which showed that routine blood pressure (BP)-lowering treatment in patients with acute stroke and elevated BP had no benefit and could have a potentially harmful effect.

SCAST was a multicenter, double-blind, randomized, placebo-controlled trial of candesartan in patients (n=2029) with acute stroke and elevated BP. The objective was to assess whether BP-lowering with candesartan was beneficial in the setting of acute stroke. Adult patients with a clinical diagnosis of stroke (ischemic or hemorrhagic) and systolic BP ≥140 mm Hg for whom treatment was possible within 30 hours of the onset of symptoms were eligible for inclusion.

Subjects were randomly assigned to candesartan (n=1017) or placebo (n=1012) for 7 days. The dose of candesartan increased from 4 mg on Day 1 to 16 mg on Days 3 to 7. Treatment during the follow-up period was at the discretion of the clinician. BP was monitored daily during the treatment phase and during the follow-up visits at 1, 3, and 6 months. The coprimary endpoints were: a composite vascular endpoint, comprising vascular death, myocardial infarction (MI), and stroke during the first 6 months; and functional outcome at 6 months, as measured by modified Rankin Scale. To adjust for the use of two coprimary effect variables, a p-value of 0.025 or 0.05 was required for one or both variables, respectively, for the results to be considered significant.

Subjects had a mean age of 71 years and a mean BP at baseline of 171/90 mm Hg. Mean duration of symptoms prior to inclusion was 18 hours. Ischemic stroke was present in 85% of subjects; hemorrhagic stroke was present in 14%. Over the 7-day treatment period, BP was significantly lower among patients who received candesartan, with a mean BP of 147/82 mm Hg, versus 152/84 mm Hg in the placebo group (p<0.001). BP reduction was observed as early as Day 2.

Figure 1. Composite Vascular Endpoint: Vascular Death, MI, or Stroke.



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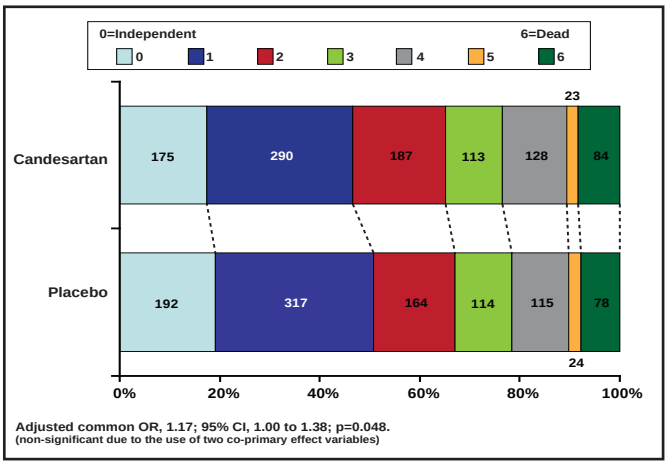
There was no difference in the composite vascular endpoint of vascular death, MI, and stroke (Figure 1). There was also no difference in the coprimary endpoint of functional outcome, although there was a consistent shift in all categories of the modified Rankin Scale in favor of placebo (adjusted common OR, 1.17; 95% CI, 1.00 to 1.38; p=0.048; Figure 2). Across all secondary endpoints, there was a nonsignificant increased risk in the candesartan-treated group. For stroke progression (6% of subjects in the candesartan group and 4% of placebo subjects), the relative risk was 1.47 (95% CI, 1.01 to 2.13; p=0.04).

Figure 2. Functional Outcome (mRS).



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There was no evidence of a differential effect in any of the subgroup analyses (eg, stroke subtype, systolic BP, duration of symptoms, history of hypertension), with the exception of a trend that favored candesartan in subjects with a symptom duration <6 hours for the composite vascular endpoint.

The results of SCAST were confirmed by a meta-analysis of clinical trials of BP-lowering in acute stroke, comprising more than 100 subjects.

No Added Benefit From EC-IC Bypass Surgery When Added to Standard Medical Therapy in Preventing Recurrence of Ipsilateral Stroke

Results from the Carotid Occlusion Surgery Study (COSS; NCT00029146), presented by William Powers, MD, University of North Carolina, Chapel Hill, North Carolina, failed to show an overall benefit on 2-year stroke recurrence when extracranial-intracranial (EC-IC) bypass surgery was added to standard medical therapy.

The COSS study was a prospective, randomized, blinded endpoint, controlled trial in which subjects with a recent (≤120 days) symptomatic, ipsilateral hemisphere carotid territory transient ischemic attack or mild-to-moderate ischemic stroke (Barthel index >12/20) were randomly assigned to standard medical treatment plus EC-IC (n=97) or medical treatment only (n=98). All subjects were required to have occlusion of an internal carotid artery, as detected by contrast arteriography; vessels that were suitable for anastomosis; and a PET $O^{15}O/H_2{}^{15}O$ count-based ratio image with an ipsilateral-to-contralateral oxygen extraction fraction (OEF) ratio >1.130. The primary study endpoint was a combination of all stroke and death at 30 days from randomization for the medical-only group or from the day of surgery for the surgical group plus ipsilateral ischemic stroke within 2 years.

For the medical-only group, the investigators projected a 40% rate of ipsilateral stroke, based on data from medically treated patients with high OEF in the St. Louis Carotid Occlusion Study [Grubb RL et al. *JAMA* 1998]. For the combined group, the investigators projected a 24% rate of ipsilateral stroke, based on surgical morbidity and mortality from the EC-IC Bypass Trial [EC-IC Bypass Group. *N Engl J Med* 1985] and medically treated patients with normal OEF in the St. Louis Carotid Occlusion Study.

The first subject was enrolled in July 2002. Of the 4967 subjects who were screened, 705 were enrolled for PET and 195 were randomized to treatment. COSS was stopped in June 2010 for two reasons: the prespecified boundary for futility to determine a clinically meaningful difference had been reached, and there was an unexpectedly low rate of observed primary endpoints in the medically treated group. Dr. Powers presented the results of the intent-to-treat analysis, which was based on all 195 randomized patients.

With the exception of systolic blood pressure, which was significantly (p=0.02) higher in the medical treatment-only group (139±20 mm Hg vs 133±20 mm Hg in the combined treatment group), the baseline characteristics for the two groups were similar.

A total of 93 subjects (93/98; 95%) received surgery. The mean time from randomization to surgery was 10±13 (SD) days. Thirty-day graft patency was 98%, and patency at last follow-up was 96%. Mean ipsilateral-contralateral OEF ratio improved from 1.258 at baseline to 1.109 at 30 days in the surgical group (data for 87 of 93 subjects). Fourteen subjects in the surgical group experienced the primary endpoint of ipsilateral ischemic stroke in the 30-day postoperative period (one fatal). None occurred between randomization and surgery. This perioperative stroke rate of 15% was not significantly different from the EC-IC Bypass Trial. Six additional surgical patients experienced an endpoint ipsilateral stroke, yielding a 2-year primary endpoint rate in the surgical group of 21%. In the nonsurgical group, the 2-year primary endpoint rate was 23%. This difference was not statistically significant (p=0.7279; 95% CI [for the true difference],- 0.104 to 0.141).

In 1985, the EC-IC Bypass Trial demonstrated no benefit of bypass surgery to prevent recurrent stroke in a study of 1377 patients, including the subgroup of 808 with symptomatic carotid artery occlusion. At the time this