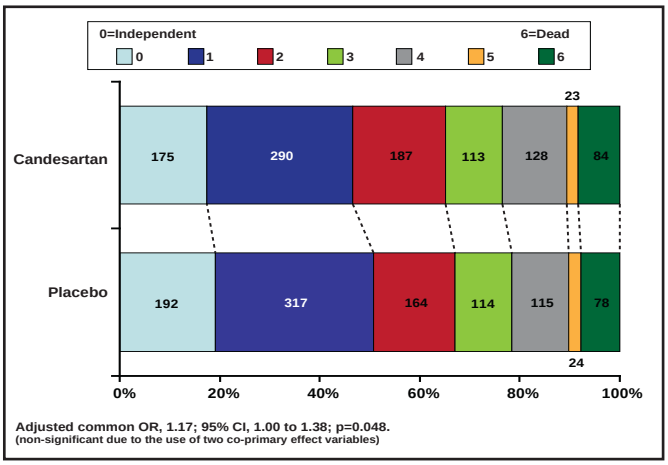
Figure 2. Functional Outcome (mRS).



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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

trial was designed, there was no proven method for identifying patients for whom hemodynamic factors were of primary importance in the pathogenesis of recurrent stroke. Since that time, advances in medical imaging have made it possible to identify patients who are at high risk of recurrent stroke due to hemodynamic factors. COSS was designed to determine if EC-IC bypass could reduce subsequent ipsilateral ischemic stroke in a select group of patients with symptomatic carotid artery occlusion who were at high risk due to poor effective collateral circulation (high OEF). Based on the results of this study and the original EC-IC Bypass Trial, EC-IC should not be employed as a treatment to prevent stroke recurrence in patients with presumed atherosclerotic carotid occlusion, even when imaging demonstrates poor cerebral perfusion.

Fluoxetine Improves Motor Function in Patients with Severe Motor Deficit When Given Early After Ischemic Stroke

François Chollet, MD, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, presented data from the Multicenter Randomized Double-Blind Placebo-Controlled Trial with Fluoxetine on Motor Rehabilitation After Acute Ischemic Stroke (FLAME; NCT00657163) trial, showing that in patients with severe motor deficit resulting from ischemic stroke, early use of fluoxetine in addition to physiotherapy enhances motor recovery after 3 months.

Animal studies indicate that serotonergic neurons can modulate motor output [Jacobs BL and Fornal CA. *Curr Opin Neurobiol* 1997], exert a neuroprotective effect in the postischemic brain [Lim CM et al. *J Neurosci Res* 2009], and promote hippocampal neurogenesis after stroke [Li WL et al. *J Neurosci Res* 2009]. Similar results have been reported in a few small clinical trials [Pariente J et al. *Ann Neurol* 2001; Dam M et al. *Stroke* 1996; Zittel S et al. *Neurorehabil Neural Repair* 2008; Gerdelat-Mas A et al. *Neuroimage* 2005].

FLAME was a double-blind, placebo-controlled trial of 118 patients with hemiparesia or hemiplegia that resulted from ischemic stroke and a Fugl-Meyer motor scale score (FMMS; a validated scale exclusively testing motricity in an analytical and global manner) ≤55 from nine stroke centers in France. Subjects were randomly assigned to once-daily treatment with fluoxetine 20 mg (n=59) or placebo (n=59), starting 5 to 10 days after stroke onset and continuing for 3 months. All subjects also received physiotherapy and standard care. The primary study endpoint was change in FMMS score between baseline and Day 90. Secondary outcomes included score changes in the National Institutes of Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), and the Montgomery-Åsberg Depression Rating Scale (MADRS) between baseline and Day 90.

Subjects in the fluoxetine group were slightly older than those in the placebo group (mean age 66.4 years vs 62.9 years) and more likely to have had a prior stroke (16.9% vs 6.8% of placebo subjects). Baseline mean FMMS score was 13.4 (±8.8) and 17.1 (±11.7) in the placebo and fluoxetine groups, respectively, a significant difference that was adjusted for in the analysis.

FMMS score progression at Day 90 was significantly (p=0.003) greater in the fluoxetine group (+34.0; 95% CI, 29.7 to 38.4) than in the placebo group (+24.3; 95% CI, 19.9 to 28.7), with the majority of benefit being seen for the upper limb part of the scale (+22.9 for fluoxetine; +13.1 for placebo; p=0.002; Table 1). Overall, there was no difference in NIHSS or MADRS score between the two groups; however, when only the motor portion of the NIHSS was considered, there was a significant (p=0.012) improvement, favoring fluoxetine. The number of independent patients (mRS score of 1–2) was significantly higher in the fluoxetine group at Day 90 than in the placebo group (26.3% [n=15] vs 8.9% [n=5]; p=0.015; Table1). Fluoxetine was well tolerated; a slight, positive effect on mood was detected, as indicated by a reduction in mean adjusted MADRS score (-0.1 [SD= –2.1 to 1.9]).

Table 1. Primary Outcome: Change in FMMS Score Baseline to Day 90.

	Placebo* n=56	Fluoxetine* n=57	p value
FMMS	+24.3 [19.9-28.7]	+34.0 [29.7-38.4]	0.003
FMMS upper limb	+13.1 [8.9-17.4]	+22.9 [18.6-27.1]	0.002
FMMS lower limb	+9.5 [7.8-11.2]	+12.8 [11.1-14.5]	0.010

*Adjusted mean [95% CI]; FMMS=Fugl-Meyer motor scale.

Prof. Chollet noted that although the FLAME trial was limited by its small size, the short-term nature of the trial and the fact that it was conducted in a group of patients who were specifically selected for having a severe motor deficit render the study treatment a new and promising therapeutic approach. The treatment target is neural plasticity, for which the only existing validated treatment is arterial deocclusion with IV thrombolytic agents. Fluoxetine is well tolerated and can potentially be given to a large cohort of patients at a reasonable cost and without the need for advanced treatment facilities.