Partial Aortic Occlusion for Cerebral Perfusion Augmentation
Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial

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Background and Purpose—Fewer than 5% of patients with acute ischemic stroke are currently treated, and there is need for additional treatment options. A novel catheter treatment (NeuroFlo) that increases cerebral blood flow was tested to 14 hours.

Methods—The Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke trial is a randomized trial of the safety and efficacy of NeuroFlo treatment in improving neurological outcome versus standard medical management. The primary safety end point was the incidence of serious adverse events through 90 days. The primary efficacy end point on a modified intent-to-treat population was a global disability end point at 90 days. Secondary end points included mortality, intracranial hemorrhage, modified Rankin scale score outcome of 0 to 2, and modified Rankin scale shift analysis.

Results—Between October 2005 and January 2010, 515 patients were enrolled at 68 centers in 9 countries. The primary efficacy end point did not reach statistical significance (OR, 1.17; CI, 0.81–1.67; P=0.407). The primary safety end point did not show a difference in serious adverse events (P=0.923). Ninety-day mortality was 11.3% (26/230) in treatment and 16.3% (42/257) in control (P=0.087). Post hoc analyses showed that patients presenting within 5 hours (OR, 3.33; CI, 1.31–8.48), with NIHSS score 8 to 14 (OR, 1.80; CI, 0.99–3.30), or older than age 70 years (OR, 2.02; CI, 1.02–4.03) had better modified Rankin scale score outcomes of 0 to 2; additionally, there were fewer stroke-related deaths in treatment compared to control groups (7.4% = 17/230; 14.4% = 37/257).

Conclusions—The trial met its primary safety end point but not its primary efficacy end point. Signals of treatment effect were suggested on all-cause mortality, in patients presenting early, older than age 70 years, or with moderate strokes, but these require confirmation.

Clinical Trial Registration Information—URL: http://clinicaltrials.gov. Unique identifier: NCT00119717.
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Key Words: aortic occlusion ■ cerebral perfusion augmentation ■ clinical trials ■ ischemic stroke ■ methodology

Worldwide, nearly 15 million people experience a stroke annually, making it the second most common cause of death and the leading cause of acquired major disability.1 Despite better attention and management of risk factors, each year >790 000 individuals experience an acute stroke in the United States2 and 1.1 million experience an acute stroke in Europe.3 Currently, the only approved treatment of acute ischemic stroke is the use of recombinant tissue plasminogen activator within 3 hours from the time of onset.4 A recent study indicated that this time window can be extended to 4.5 hours in selected patients.5 Treatment with recombinant tissue plasminogen activator has an increased risk of intracranial and systemic hemorrhage.5 In the 15 years since the therapy was approved in the United States, <5% of stroke patients in the United States and even fewer in other parts of the world are being offered the treatment.6 Clot retrieval and other

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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.609933/DC1.
Bo Norrving, MD, was the Consulting Editor for this paper.
One site, without the previous knowledge of the Steering Committee or CoAxia, published a trial-wide safety report on the initial 125 patients. The publication was retracted from the December 2008 Journal of Cardiovascular Surgery (Torino).
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1680
intra-arterial recanalization strategies also have been used, although randomized data are not yet available for these interventions.7,8 More than 100 neuroprotective medications have been investigated in animal models and in patients with acute ischemic or hemorrhagic stroke, but the results have been disappointing.9

Partial aortic occlusion of the abdominal aorta results in a prompt increase in blood volume above the occlusion, and it has been shown to specifically increase cerebral blood flow.10 Therapeutic titration of the blood flow in the descending aorta has been tested in a number of animal studies and enhances cerebral blood flow.11 Intra-aortic balloon counterpulsation has been demonstrated to improve cerebral blood flow in both animals12 and humans,13 but the complex algorithms required to achieve increases in cerebral blood flow have limited clinical adoption in patients with acute stroke. Complete aortic occlusion of either the descending thoracic aorta or the abdominal aorta above the renal arteries results in a prompt increase in blood volume above the occlusion14,15 and has been shown to specifically increase cerebral blood volume.14 Interestingly, the increase in blood flow persisted when the balloons were withdrawn.10 This led to the development of the NeuroFlo catheter (CoAxia; Figure 1). NeuroFlo was used in a study of 24 patients with symptomatic vasospasm after intracerebral aneurysm repair or coiling, which demonstrated increased blood flow velocities in the middle cerebral arteries and neurological improvement in 83% of the cases.16 Use of the NeuroFlo catheter was tested in a small number of patients with an acute ischemic stroke treated with tissue plasminogen activator17 and in a 24-hour time window with MRI mismatch-selected patients.18 The Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial is a prospective, randomized, multicenter trial that evaluated the safety and efficacy of cerebral blood flow augmentation in patients who experienced an acute ischemic stroke and are randomized within 14 hours from onset of symptoms.

**Materials and Methods**

**Design**

The SENTIS trial is a prospective, randomized, blinded outcome observer, multicenter, international trial of the safety and efficacy of NeuroFlo treatment plus standard medical management in improving neurological outcome versus standard medical management alone.

**Patient Population**

Patients 18 years or older who presented with clinical evidence of cortical ischemic stroke and in whom NeuroFlo treatment could begin within 14 hours of symptom onset (defined as the last time known normal) were screened for enrollment. The inclusion and exclusion criteria are presented in the Supplemental Appendix Table I (http://stroke.ahajournals.org).

**Randomization**

Patients who met all of the enrollment criteria and provided written consent were allocated to treatment (NeuroFlo plus standard medical management) or control (standard medical management alone) groups using a 1:1 randomization scheme, stratified by site, the National Institutes of Health Stroke Scale (NIHSS) score at baseline (stratified ≤10 or 11 to 18), and the time from symptom onset (stratified <5 hours or ≥5 hours).
Intervention and Follow-Up
Control patients received standard medical care, as based on current American Stroke Association Guidelines (United States)\textsuperscript{19} and appropriate local or national guidelines for the management of stroke (international). Treatment patients received standard medical management and underwent an abdominal aortogram to verify appropriateness for NeuroFlo treatment. Once confirmed, the dual-balloon NeuroFlo catheter was placed in the abdominal aorta via femoral introduction (Figure 1). Cerebral flow augmentation was accomplished with an optimized protocol derived from preclinical animal studies. Specifically, 2 balloons are independently inflated to occupy \( \geq 70\% \) of the aortic lumen 6 cm above and below the renal arteries. During sequential inflation (infrarenal first), suprarenal and infrarenal pressures were monitored. Balloons were inflated until a total incremental pressure decrease of 10 to 15 mm Hg was detected across both balloons. Balloons were left inflated for 45 minutes and then slowly deflated and the catheter was removed. Use of heparin was left to the discretion of the treating interventionalist. All patients were to be followed-up for safety and efficacy through 90 days. Formal clinical assessments were timed from pretreatment NIHSS examinations; they occurred at 6 and 24 hours, 4 days (or hospital discharge if earlier), and 30 and 90 days (final, blinded assessment). All patients had repeated 24-hour cranial CT performed. Cranial CT scans were also repeated in case of neurological worsening at anytime up to 90 days.

Primary Outcomes
The primary safety end point for this trial was a comparison between the treatment and control groups in incidence of serious adverse events (SAE) from time of enrollment through 90 days of follow-up. The primary efficacy end point for this trial was the global disability end point measured at 90 days as defined by Tilley et al.,\textsuperscript{20} and by the NINDS recombinant tissue plasminogen activator stroke study group.\textsuperscript{4} A certified assessor blinded to the patient’s treatment allocation completed the 90-day assessments. For those patients with missing 90-day data, their 30-day values were carried forward for all efficacy analyses; if 30-day data were not available, then the subjects were considered nonevaluable. The components and definitions of favorable outcomes for the global end point were the same as in the 2 NINDS trials: NIHSS score 0 or 1; modified Rankin scale (mRS) score 0 or 1; Barthel Index 95 to 100; and Glasgow Outcome scale equal to 5 (good recovery).

Additional Prespecified Analyses
To provide corroborative evidence in support of the primary efficacy and safety end points, additional prespecified analyses were conducted. Additional safety analyses included: mortality/survival; index stroke-related SAE; all new intracranial hemorrhage (classified in a blinded fashion by the University of California San Francisco Imaging Core Laboratory, including the classification of all hemorrhagic transformation into the 4 categories as specified in the European Cooperative Acute Stroke Study;\textsuperscript{21} and symptomatic intracerebral hemorrhage (defined as local or remote parenchymal hemorrhage on the 24-hour follow-up scan combined with a neurological deterioration of \( \geq 4 \) points on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death as specified by the SITS-MOST study).\textsuperscript{22} Additional efficacy analyses included, but were not limited to, mRS shift
Table 2. Primary End Point Results

<table>
<thead>
<tr>
<th>Objective</th>
<th>ITT Population</th>
<th>mITT Population</th>
<th>mAT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled patients</td>
<td>Treatment N=258/control N=257</td>
<td>Treatment N=230/control N=257</td>
<td>Treated N=226/not treated N=261</td>
</tr>
<tr>
<td>Primary efficacy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Evaluable patients*</td>
<td>Treatment N=254/Control N=249</td>
<td>Treatment N=226/Control N=249</td>
<td>Treated N=221/not treated N=254</td>
</tr>
<tr>
<td>Primary efficacy global end point, OR (95% CI); P*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS 0–1</td>
<td>1.23 (0.87–1.76)</td>
<td>1.17 (0.81–1.67)</td>
<td>1.17 (0.81–1.68)</td>
</tr>
<tr>
<td></td>
<td>0.245</td>
<td>0.407</td>
<td>0.402</td>
</tr>
<tr>
<td>mRS score 0–1</td>
<td>32.7%/31.7%</td>
<td>31.9%/31.7%</td>
<td>31.2%/32.3%</td>
</tr>
<tr>
<td></td>
<td>1.17 (0.76–1.80)</td>
<td>1.11 (0.71–1.74)</td>
<td>1.09 (0.70–1.72)</td>
</tr>
<tr>
<td></td>
<td>0.490</td>
<td>0.648</td>
<td>0.693</td>
</tr>
<tr>
<td>Barthel Index 95–100</td>
<td>51.2%/45.8%</td>
<td>50.9%/45.8%</td>
<td>50.7%/46.1%</td>
</tr>
<tr>
<td></td>
<td>1.42 (0.93–2.16)</td>
<td>1.38 (0.89–2.13)</td>
<td>1.40 (0.90–2.16)</td>
</tr>
<tr>
<td></td>
<td>0.106</td>
<td>0.150</td>
<td>0.132</td>
</tr>
<tr>
<td>Glasgow 5 (good recovery)</td>
<td>35.0%/34.1%</td>
<td>34.1%/34.1%</td>
<td>33.5%/34.6%</td>
</tr>
<tr>
<td></td>
<td>1.12 (0.73–1.73)</td>
<td>1.06 (0.68–1.65)</td>
<td>1.05 (0.67–1.63)</td>
</tr>
<tr>
<td></td>
<td>0.597</td>
<td>0.806</td>
<td>0.846</td>
</tr>
<tr>
<td>Primary safety: SAE through 90 d, P (CMH); OR (95% CI)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.0%/42.8 %</td>
<td>43.9%/42.8%</td>
<td>44.2%/42.5%</td>
</tr>
<tr>
<td></td>
<td>0.973</td>
<td>0.923</td>
<td>0.937</td>
</tr>
<tr>
<td></td>
<td>1.01 (0.70–1.46)</td>
<td>0.96 (0.66–1.41)</td>
<td>0.96 (0.66–1.41)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CMH, Cochran-Mantel-Hanszel; ITT, intent-to-treat; mAT, modified as-treated; mITT, modified intent-to-treat; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse event.

*Only evaluable subjects are included in efficacy analysis: those with either 30-day or 90-day follow-up data or who died within study period (see Figure 2).

†OR, 95% confidence intervals, and P were calculated from a logistic regression model for treatment vs control and was adjusted for the following: age, gender, baseline glucose, baseline NIHSS, time from onset (h), and randomization group.

‡All enrolled subjects are included in safety analysis. OR and 95% CI were calculated from a logistic regression model for treatment vs control and were adjusted for the following: age and baseline NIHSS. P are calculated using CMH test of proportions stratified by age and baseline NIHSS.

Data Monitoring Body

An independent Data and Safety Monitoring Board (DSMB) included 4 stroke neurologists, an interventionist, and a biostatistician. The DSMB adjudicated every adverse event; all DSMB adjudications were considered final and were used for data analysis. The DSMB also monitored unblinded aggregate group data for safety and alerted the sponsor and sites as needed, evaluated formal interim and final analyses, and provided advice as requested to sites and study sponsor.

Sample Size

The sample size required for this trial was based on demonstration of a statistically significant treatment effect with respect to the primary efficacy end point using a repeated-measures logistic regression model. The trial included a frequentist group sequential design using an O'Brien-Fleming error spending function. Adjusting for α spending in the interim analysis plan, ~500 enrolled patients were expected to provide 80% power to detect an odds ratio of 1.7 for the primary efficacy end point (consistent with the odds ratio achieved in the initial NINDS recombinant tissue plasminogen activator stroke trial).

Statistical Analyses

The prespecified primary analysis cohort for both efficacy and safety included all randomized patients, except for those meeting prespecified exclusion criteria such as anatomic ineligibility, which was established at angiography in the device treatment arm before placement attempt with NeuroFlo. Thus, the primary analysis was a modified intent-to-treat evaluation. In addition, those subjects without either 30-day or 90-day data were considered nonevaluable and were not included in the efficacy analysis. The treatment groups were analyzed according to the principles of intent-to-treat, under which study data were analyzed by the patients’ randomized assignment irrespective of the treatment actually received. For sensitivity purposes, the data were also analyzed using pure intent-to-treat and as-treated groups. The modified intent-to-treat analyses were considered governing for interpreting study outcomes. The as-treated population is presented as most informative for the post hoc exploratory analyses.

Standard summary statistics were calculated for all study variables. For continuous variables, statistics included means, standard deviations, and 95% confidence intervals, whereas categorical variables were summarized in frequency distributions. All probability values, including those comparing the randomized groups for efficacy and safety, are 2-sided; the final 2-sided α for the evaluation of the primary efficacy end point was 0.04988. Because the study was only powered for the primary efficacy end point, there were no α adjustments made for the secondary or post hoc analyses and only nominal probability values are presented for reference. Statistical analyses were conducted in SAS version 9.1 or higher (SAS Institute).
The primary efficacy end point, including the NIHSS score, mRS score, Barthel Index, and Glasgow Outcome scale, was analyzed as a global end point. In this analysis, outcomes on each of the 4 scales are dichotomized as favorable or unfavorable based on predefined criteria. The 4 end points were then analyzed using a repeated-measures logistic regression to account for the four assessments at 90 days and were adjusted for prespecified baseline covariates of age, baseline NIHSS score, gender, baseline glucose, and time from symptom onset. Analyses were also completed for the effect of a number of pretreatment variables on outcomes including, but not limited to, time to treatment, the severity of stroke at onset (as defined by the baseline NIHSS), age of the patient, and other key baseline characteristics.

### Study Organization

The SENTIS trial was conducted in accordance with relevant national and international regulatory and ethical frameworks and was registered with ClinicalTrials.gov (NCT00119717). Each participating site received Institutional Review Board and/or ethics committee approval before trial initiation. The trial was supervised by an international Steering Committee and by an independent DSMB. The trial was funded by CoAxia. All authors vouch for the accuracy and completeness of the data and analysis. All authors had access to all the data in the study and had final responsibility to submit the publication.

### Table 3. Additional Analysis Results

<table>
<thead>
<tr>
<th>Objective</th>
<th>ITT Population</th>
<th>mITT Population</th>
<th>mAT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrolled patients</strong></td>
<td>Treatment N=258/control N=257</td>
<td>Treatment N=230/control N=257</td>
<td>Treated N=226/not treated N=261</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Treatment N=254/control N=249</td>
<td>Treatment N=226/control N=249</td>
<td>Treated N=221/not treated N=254</td>
</tr>
<tr>
<td>Acute improvement 24 h: ≥3-point improvement in NIHSS at or NIHSS ≤2, OR (95% CI); P†</td>
<td>42.8%/37.0%</td>
<td>41.9%/37.0%</td>
<td>42.1%/36.9%</td>
</tr>
<tr>
<td>Dichotomized mRS: 0–2 vs 3–6</td>
<td>0.745</td>
<td>0.649</td>
<td>0.619</td>
</tr>
<tr>
<td>Safety P (CMH); OR (95% CI)‡</td>
<td>21.3%/23.7%</td>
<td>20.9%/23.7%</td>
<td>21.2%/23.4%</td>
</tr>
<tr>
<td>Index stroke-related SAE</td>
<td>0.478</td>
<td>0.373</td>
<td>0.391</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>25.6%/26.5%</td>
<td>25.2%/26.5%</td>
<td>25.7%/26.1%</td>
</tr>
<tr>
<td>Reported by core laboratory</td>
<td>0.852</td>
<td>0.796</td>
<td>0.846</td>
</tr>
<tr>
<td>Serious hemorrhage§</td>
<td>4.3%/5.4%</td>
<td>4.3%/5.4%</td>
<td>4.4%/5.4%</td>
</tr>
<tr>
<td>Adjudicated by DSMB</td>
<td>0.501</td>
<td>0.538</td>
<td>0.554</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>1.2%/0.8%</td>
<td>1.3%/0.8%</td>
<td>1.3%/0.8%</td>
</tr>
<tr>
<td>Fatal hemorrhage¶</td>
<td>0.8%/3.1%</td>
<td>0.9%/3.1%</td>
<td>0.9%/3.1%</td>
</tr>
<tr>
<td>Mortality: all-cause</td>
<td>11.2%/16.3%</td>
<td>11.3%/16.3%</td>
<td>11.5%/16.1%</td>
</tr>
<tr>
<td>Total SAE§</td>
<td>0.086</td>
<td>0.087</td>
<td>0.079</td>
</tr>
<tr>
<td>Mortality: stroke-related SAE</td>
<td>1.60 (0.91–2.83)</td>
<td>1.56 (0.87–2.80)</td>
<td>1.59 (0.89–2.85)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CMH, Cochran-Mantel-Hanszel; ITT, intent-to-treat; mAT, modified as-treated; mITT, modified intent-to-treat; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse event; DSMB, data safety monitoring board.

*Only evaluable subjects are included in efficacy analysis: those with either 30-day or 90-day follow-up data or who died within the study period (see Figure 2).

†OR, 95% CI, and P were calculated from a logistic regression model for treatment vs control and were adjusted for the following: age, gender, baseline glucose, baseline NIHSS, time from onset (h), and randomization group.

‡All enrolled subjects are included in the safety analysis. OR and 95% CI were calculated from a logistic regression model for treatment vs control and were adjusted for the following: age and baseline NIHSS. OR, 95% CI, and P were calculated from a logistic regression model for treatment vs control and were adjusted for the following: age and baseline NIHSS. P are calculated using CMH test of proportions stratified by age and baseline NIHSS.

§A serious hemorrhage is any new intracranial hemorrhage that meets the predefined definition of SAE and was adjudicated independently by the DSMB as serious.

¶A fatal hemorrhage is any new intracranial hemorrhage that the DSMB adjudicated as being directly associated with the subject’s death.

In addition to the prespecified secondary analyses, post hoc analyses were also completed for the effect of a number of pretreatment variables on outcomes including, but not limited to, time to treatment, the severity of stroke at onset (as defined by the baseline NIHSS), age of the patient, and other key baseline characteristics.
Results

Between October 2005 and January 2010, 515 patients were enrolled in the trial at 68 centers: United States (47 centers/359 subjects/70%), Canada (3 centers/30 subjects/6%), Europe (14 centers/112 subjects/22%), and Israel (4 centers/14 subjects/3%). Two-hundred fifty-seven patients were randomized to the control group and 258 patients were randomized to the treatment group for pure intent-to-treat (ITT) analysis. After randomization, 28 patients in the treatment group were excluded because of prespecified criteria (rapid improvement, 3 patients; aorta size, 25 patients), leaving 230 patients in the treatment group for modified intent-to-treat. In the treatment group, 5 patients did not receive treatment and 1 patient in the control group was treated (protocol deviation), resulting in 261 patients in the nontreated group and 226 in the treated group for “as treated” (modified as-treated) analysis. Twelve patients were lost to follow-up before their 30-day assessment, deeming them nonevaluable for final efficacy analyses; however, all available safety data (adverse events) for these patients were included in safety analyses. Ninety-day efficacy follow-up was available for 475 patients. The details of randomization and the analysis populations are shown in Figure 2.

The mean time from onset of symptoms to randomization was identical in both groups at 8.1±2.9 hours. Median was 7.7 hours in the control group and 7.8 hours in the treatment group. The demographic and baseline characteristics, and medical history findings, are shown in Table 1. Although there were nominal differences between the 2 groups in some characteristics, none of these differences was statistically significant. Similarly, concomitant initial therapies after enrollment, including proportion of patients admitted initially to intensive care units, did not differ between the treatment groups.

Primary End Point Results

The study demonstrated no statistically significant difference between the 2 groups for the primary global efficacy end point (OR, 1.17; CI, 0.81–1.67; P=0.407). The differences in individual global end point components also were not significant. The primary efficacy results are shown in Table 2.

The primary safety analysis showed no statistically significant difference between the 2 groups. The proportion of patients showing SAE was 42.8% (110/257) in the control group and 43.9% (101/230) in the treatment group (P=0.923). The primary safety results are shown in Table 2. SAE rates within all major categories of events were also similar, showing no significant differences.

Secondary End Point and Additional Analysis Results

There were several prespecified secondary efficacy end points in the protocol. These included, but were not limited to, mRS shift analysis, mRS score dichotomized at 0 to 2 versus 3 to 6, and acute improvement at 24 hours. Secondary and additional analysis results are shown in Table 3 with nominal probability values. The mRS shift analysis is shown in Figure 3.

Prespecified secondary safety analyses included: mortality/survival; index stroke-related SAE; all new intracranial hemorrhage; and symptomatic intracerebral hemorrhage. At the 90-day follow-up, in the control group 16.3% (42/257) patients died compared to 11.3% (26/230) in the treatment group.
The causes of death in both groups are shown in Table 4. The Kaplan–Meier survival curve for all-cause mortality is shown in Figure 4. Symptomatic hemorrhages (per the SITS-MOST definition) were reported in 0.8% (2/257) in the control group and 1.3% (3/230) in the treatment group. At 90 days, fatal outcomes among patients with any intracerebral hemorrhage were reported in 3.1% (8/257) of the control group and 0.9% (2/230) of patients in the treatment group ($P=0.091$).

Post hoc analysis showed the measure of avoiding severe disability and death (mRS score 0–4 versus 5–6) was higher in the treatment group (OR, 1.74; CI, 1.00–3.02). Deaths attributed to stroke (stroke-related mortality) were lower in the treatment group at 7.4% (17/230) compared to the control group at 14.4% (37/257). The DSMB defined stroke-related mortality as those deaths that were directly caused by the index stroke, systemic complications related to the index stroke, and/or new stroke. Most deaths occurred early and were related to progression of neurological symptoms (4-point increase in NIHSS), hemorrhagic transformation, or systemic sepsis.

Adverse events of particular interest for a cerebral blood flow-increasing interventional vascular device with occlusive balloons near the renal vessels would include intracranial hemorrhage, renal events, and vascular access complications. Intracranial hemorrhage rates are discussed and show no increase in the treatment group as compared to control. Although there was no statistically significant difference between the groups for all serious renal events, there was a nominal imbalance of renal dysfunction events. Six treatment patients and 0 control patients experienced serious renal dysfunction as defined by the DSMB. Of the 6 events, all were in patients with moderate or severe strokes (5 of the 6 with baseline NIHSS score $\geq 15$). In all of the events, contributing patient factors were present, including dehydration, sepsis, and/or multi-organ dysfunction. Event onset dates ranged from 3 to 89 days after treatment. One event, together with sepsis, occurred in a patient who died. None of the events required dialysis and none was adjudicated as procedure-related or device-related by the DSMB. Regarding aortic/groin complications, there were 6 events (2.6%) constituting SAE in the treatment group compared to 1 event (0.4%) in the control group. Five of the 6 events were adjudicated as procedure-related by the DSMB; 1 event (0.4%) was also adjudicated as likely device-related and resulted in a lower limb amputation. Of the remaining events, 3 of the 6 required intervention; none led to long-term disability. Additional SAE data are provided in Table 5.

### Baseline Prognostic Variables

The influence of baseline variables on response to treatment was similar in the modified intent-to-treat, intent-to-treat, and modified as-treated populations. Among the baseline characteristics shown in Table 1, 4 baseline variables suggested a difference with treatment effect in attainment of a nondisabled (mRS score 0–2) final outcome: age ($P=0.044$); baseline NIHSS score ($P=0.055$); time from onset to enrollment ($P=0.012$); and history of atrial fibrillation ($P=0.050$). These data are presented in Figure 5 for the as-treated cohort. Baseline variables associated with a beneficial trend toward treatment effect with the NeuroFlo catheter were older age (older than 70 years), moderate baseline neurological deficits (NIHSS score 8–14), earlier enrollment (time from symptom onset 0–5 hours), and a history of atrial fibrillation. In multivariate analysis, 3 of these variables made independent contributions: age; baseline NIHSS score; and time to enrollment.

### Discussion

SENTIS is the first randomized trial of an interventional device in ischemic stroke with a long-term neurological end point. The trial, which included ischemic stroke patients with cortical symptoms up to 14 hours after symptom onset, did not demonstrate a statistically significant increase in the proportion of patients achieving a 90-day return to normal or nearly normal measure using the global disability end point. However, SENTIS did achieve its primary safety end point, demonstrating no increase in the rate of overall serious adverse events. There appeared to be no significant increase in ICH, as might have been anticipated for an aortic cerebral blood flow-
augmenting treatment with the expected and associated femoral access complications.

Although the main efficacy end point was not positive, prespecified secondary efficacy end points in the SENTIS trial suggested potential efficacy signals based on the now more common mRS score 0 to 2 and mRS shift analyses in the entire study population. These signals were strongest in 3 key patient subgroups: those presenting in <5 hours; those with baseline NIHSS scores of 8 to 14; and those older than age 70 years. Investigation of subgroup effects can inform future investigations and may identify populations of stroke patients more likely to benefit from this treatment. First, consistent with many animal models and with human thrombolysis trials, NeuroFlo treatment demonstrated a stronger signal for patients presenting earlier—in this case, within 5 hours of onset. This observation may reflect a reduced possibility of good recovery as salvageable penumbra evolves to completed infarction over time. Second, patients presenting with NIHSS scores 8 to 14 showed a greater potential efficacy signal, whereas those with lower-grade baseline strokes had good outcomes overall and those with higher baseline scores had lower rates of independent outcome. These findings are similar to other research studies showing that patients with moderate deficits at the time of enrollment are most amenable to interventions.24,25 Patients with milder deficits tend to improve regardless of intervention, whereas those with severe deficits in this time window have only a limited capability to improve. Last, an age effect was suggested. For the nearly 50% of the study cohort older than 70 years of age, the odds ratio of independent outcome with treatment was 2.02. Older patients may have more highly developed collaterals, less unaided ability to optimally recruit collaterals, or an inability to maintain collateral filling, and thus be more responsive to a collateral augmentation therapy.

The trend to reduced all-cause mortality, if genuine, appears to have been driven by a reduction in stroke-specific mortality. In the SENTIS trial, the NeuroFlo group had a lower rate of death because of cerebral bleeding, infarct progression, and new stroke. This mortality difference was concentrated in the patients at highest risk—those with NIHSS scores >14 and those older than age 70. Mortality in the control group was similar to that of patients in other studies with comparable NIHSS scores at enrollment.25,26 These findings, which require confirmatory data, suggest that the enhanced blood flow may slow progression of neurological injury in the treated patients. Future analysis of the SENTIS imaging data may help our understanding of these intriguing findings.

<table>
<thead>
<tr>
<th>SAE Type</th>
<th>Treatment N=230</th>
<th>Control N=257</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Any SAE*</td>
<td>174</td>
<td>101</td>
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<tr>
<td>Cardiovascular</td>
<td>24</td>
<td>22</td>
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<tr>
<td>Renal</td>
<td>9</td>
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<tr>
<td>Renal dysfunction</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Renal other</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td>62</td>
<td>55</td>
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<tr>
<td>Hemorrhage</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nonhemorrhage</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>Vascular</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Aortic injury</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Femoral artery occlusion/thrombosis†</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hematoma/pseudoaneurysm</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Venous thrombosis (DVT)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular other</td>
<td>6</td>
<td>6</td>
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<tr>
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<td>Laboratory</td>
<td>8</td>
<td>8</td>
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<tr>
<td>General other</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

*The DSMB adjudicated all adverse events independently and determined if an event was procedure-related, device-related, neither, or both. A procedure-related event is an event possibly related to any endovascular procedure with femoral artery access; a device-related event is an event that possibly occurred because of placement of the NeuroFlo catheter in the descending aorta.

†There was a total of 1 SAE in the study that was adjudicated as device-related: a femoral artery occlusion/thrombosis.
In retrospect, the SENTIS trial may not have selected the appropriate stroke outcome measure cut-points for identifying clinically appropriate patient benefits along the continuum of stroke outcomes in a trial that evaluated an interventional therapy as late as 14 hours after onset. Dichotomizing final outcome scales at excellent versus not excellent (eg, mRS score 0–1 versus 2–6), as in the NINDS study, may be informative for interventions applied in the first 3 hours after onset, when patients often have not yet had substantial irreversible injury develop. However, in later time windows, injury accumulated before intervention places a ceiling on potential recovery, making an excellent final outcome (0–1) highly unlikely. In intermediate timeframes, such as 3 to 8 hours, dichotomizing final outcomes at good versus not good (eg, mRS score 0–2 versus 3–6) may be a more informative statistical approach. Correspondingly, at late timeframes, such as 8 to 14 hours, dichotomizing at final outcomes at fair versus not fair (eg, mRS score 0–4 versus 5–6) or survival versus fatal outcome may be more efficient. Furthermore, with broad time ranges, analyzing over the entire range of final outcomes (shift analysis) may be even more informative than individual scale dichotomizations. The SENTIS results, enrolling patients to 14 hours, potentially illustrate this point, with an increasing efficacy signal being demonstrated as one progresses from the most stringent global disability outcome measure (OR, 1.23; CI, 0.87–1.76), next to the mRS score 0 to 2 measure (OR, 1.40; CI, 0.91–2.16) and, finally, to the mRS score 0 to 4 measure (OR, 1.89; CI, 1.10–3.26).

The present study has limitations. The study design excluded patients from the treatment group after randomization for aortic pathology or if the patient had a rapid improvement before treatment could be initiated. The design did not exclude similar patients in the control arm of the study. This tended to diminish trial power to detect a benefit of treatment. However, adding back the 28 patients excluded from the “active treatment” arm of the study increased efficacy signals only minimally, as is evident from the pure intent-to-treat analysis presented in Table 2. Some patients were also excluded from analysis because they left the study before any outcome data were gathered. The 12 patients lost to follow-up may have had an effect on the results, but the numbers are small and not dissimilar to other trials. Finally, it would have been informative to evaluate the effect of the stroke subtype on the study outcome, but angiographic data on occlusion location and vessel status were not prospectively collected on all patients.

In summary, SENTIS was not positive on its primary efficacy end point but demonstrated the safety of partial aortic occlusion in ischemic stroke as well as favorable trends in overall mortality and secondary efficacy neurological outcomes. Extensive imaging data including those before and after treatment CT, MRI, and angiography are still to be analyzed and may offer important insights into cerebral blood flow dynamics with the technique. Finally, additional studies

### Table 2

<table>
<thead>
<tr>
<th>Population Subgroups</th>
<th>Modified Rankin Scale Score 0 to 2</th>
<th>Odds Ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>106/221</td>
<td>1.37 [0.87–2.16]</td>
<td>0.168</td>
</tr>
<tr>
<td>Not Treated</td>
<td>113/254</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Figure 5

Population subgroups (modified as-treated population): modified Rankin scale score 0 to 2.
may be appropriate to confirm the subgroup trends demonstrated here and to explore the use of this technique in combination with recombinant tissue plasminogen activator as well as other intra-arterial techniques.

Acknowledgments

Investigative Sites

Universitätsklinikum Erlangen, Erlangen, Germany: P. Schellinger, M. Koehrmann; Hospital Vall d’Hebron, Barcelona, Spain: C. Molina, M. Ribó; Central DuPage Hospital, Winfield, IL: H. Shownkeen, H. Echiverri; University Medical Center Brackenridge - Seton, Austin, TX: J.N. Rutledge, D. Camp; University of California at Los Angeles Medical Center, Los Angeles, CA: S. Starkman, D. Liebeskind; Albany Medical Center, Albany, NY: G. Bernardini, A. Boulos; Penn State Milton S. Hershey Medical Center, Hershey, PA: K. Cockroft, R. Reichwein; Sarasota Memorial Hospital, Sarasota, FL: M. Concha; University of Louisville Hospital, Louisville, KY: A. Abou-Chelb, K. Remmel; University of Alberta Hospital, Edmonton, AB, Canada: A. Shuaib, D. Emery; University of Pittsburgh Medical Center, Pittsburgh, PA: M. Hammer, T. Jovin; Wellmont Holston Valley Medical Center, Kingsport, TN: D.C. Metzger, M. Dew; ZNA Middelheim, Antwerp, Belgium: P. De Deyn, J. Kunnen; St. Thomas Hospital, Nashville, TN: T. Kaminski; University of North Carolina Hospital, Chapel Hill, NC: D. Huang, S. Sen; Moses H. Cone Memorial Hospital, Greensboro, NC: P. Sethi, S. Deshvar; AZ St.-Jan, Brugge, Belgium: G. Vanhooren, J. Ghekiere; Medical University of South Carolina Hospital, Charleston, SC: N. Papamitsakis, M. LaPointe; St. Louis University Hospital, St. Louis, MO: S. Cruz-Flores, S. Nassif; Froedtert and the Medical College of Wisconsin, Milwaukee, WI: J. Lynch, M. Torbey; University of Rochester Strong Memorial Hospital, Rochester, NY: W.S. Burgin, S. Ekholm; Universitätsklinikum Mannheim, Mannheim, Germany: M. Hennerici; JFK Medical Center, Edison, NJ: M. Gizzi, J. Kirmann; Trillium Health Centre, Mississauga, ON, Canada: A. Douen, D. Selchen; Cleveland Clinic, Cleveland, OH: R. Gupta, K. Uchino; Good Samaritan Hospital, San Jose, CA: H. Sachdev, R. Malek; Maimonides Medical Center, Brooklyn, NY: S. Rodnitzky, J. Farkas; Universitätsklinikum Duisburg-Essen, Essen, Germany: H. Diener, C. Weimar; CHUV Lausanne, Lausanne, Switzerland: P. Michel, S. Binaghi; Hadassah Hebrew University Medical Center, Jerusalem, Israel: R. Leker, J. Cohen; London Health Sciences Centre, London, ON, Canada: D. Yavagal; Mount Sinai Hospital, Toronto, ON, Canada: R. Chan; University of Miami Hospital, Miami, FL: D. Yavagal; Lutheran General Hospital, Park Ridge, IL: T. Mikesell, R. Messersmith; The Methodist Hospital, Houston, TX: R. Klucznik, J. Volpi; Morton Plant Hospital, Clearwater, FL: E. Lopez del Valle, A. Arora; Providence Hospital and Medical Center Southfield, MI: R. Fessler; Chaim Sheba Medical Center, Tel Hashomer, Israel: D. Tanne, M. Bakon; Swedish Medical Center, Seattle, WA: W. Likosky, M. Reisman; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel: D. Tanne, M. Bakon; Swedish Medical Center, Houston, TX: J.N. Rutledge, D. Camp; University of California at Los Angeles Medical Center, Los Angeles, CA: H. Hallevi, N. Bornstein; University of California, San Francisco, CA: W. Worchester, Massachusetts. He stepped down from the steering committee of the SENTIS trial after the first results were released in 2016.

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Disclosures

A.S. is an employee of the University of Alberta, Canada. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium and consulting fees for consulting and clinical trials design from CoAxia. N.M.B. is employed by Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. The institution’s research center received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. H.C.D. is employed by the University Hospital Essen, Essen, Germany. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. W.D. is employed by the University of California, San Francisco, California. He has received funding from CoAxia for imaging core laboratory and received honorarium for consulting work with CoAxia. M.F. is employed by the University of Massachusetts, Worcester, Massachusetts. He stepped down from the steering committee of the SENTIS trial after the first results were released in 2016.
committee when appointed Editor-in-Chief of the journal Stroke. Before this, he had received honorarium from CoAxia for consulting work with the company. M.D.H. is employed by the University of Pittsburgh, Pittsburgh, Pennsylvania. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. C.A.M. is employed by Hospital Vall d’Hebron, Barcelona, Spain. The institution’s research center received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has no conflicts of interest to disclose. J.N.R. is with the University Medical Center Brackenridge, Seton, Austin, Texas. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. J.L.S. is employed by the University of California at Los Angeles, Los Angeles, California. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. H.S. is with the University Clinic Erlangen, Erlangen, Germany. The University received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has received honorarium from CoAxia for consulting work with the company. H.J.N. is with the Central DuPage Hospital, Chicago, Illinois. The institution’s research center received clinical trial payments based on the number of patients enrolled in the SENTIS trial from CoAxia. He has no conflicts of interest to disclose.

References


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/content/42/11/e632.full.pdf

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Correction

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SUPPLEMENTAL MATERIAL

MS ID#: STROKE/2010/609933
MS TITLE: Partial Aortic Occlusion for Cerebral Perfusion Augmentation: Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke (SENTIS) Trial

Supplemental Tables
Supplementary Table 1

Inclusion and Exclusion Criteria

**Inclusion criteria:**
- Age ≥18 years
- Acute cerebral ischemia with hemispheric cortical dysfunction, defined as new focal neurological deficit of presumed vascular origin
- NIHSS ≤18 and ≥5, except in cases of severe aphasia and/or complete homonymous hemianopsia
- NeuroFlo procedure can begin within 14 hours of symptom onset
- Informed consent
- Negative pregnancy test in females of child-bearing potential

**Exclusion criteria:**
- Etiology other than cerebral ischemia
- Acute infarct restricted to the brainstem and/or cerebellum
- Lacunar syndrome
- Rapidly improving neurologic status
- Pre-existing functional deficit (i.e., mRS ≥2)
- Acute hypodense parenchymal lesion or effacement of the cerebral sulci in more than 1/3 of the middle cerebral artery territory
- History intracerebral hemorrhage or new intracranial bleeding
- Planned thrombolysis or thrombectomy
- Uncontrollable systolic pressure >220 mmHg, or diastolic >140 mmHg
- Known secured or unsecured cerebral aneurysm or AV malformation
- History of abdominal aortic aneurysm or endovascular graft
- Current drug or alcohol addiction
- Heparin sensitivity or unable to be anticoagulated
- Participation in another research study with an active intervention
- Current decompensated heart failure
- Known ejection fraction <30%, or evidence of NYHA Class IV or ACC/AHA Stage D heart failure within the past 3 months
- Known or echo evidence of moderate to severe aortic regurgitation (>3+)
- Acute or recent myocardial infarction
- Current or recent class III or IV angina
- INR >1.7
- Platelet count <100,000
- Creatinine >1.5 times local laboratory standard

*For subjects randomized to treatment, aortogram findings:*
- Aortic diameter at the renal ostia outside of the device limits
- Abdominal aortic aneurysm
- High-grade iliac stenosis or vascular tortuosity
Correction

In the article by Shuaib et al, “Partial Aortic Occlusion for Cerebral Perfusion Augmentation: Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial” which published ahead of print on May 12, 2011, and appeared in the June 2011 issue of the journal (Stroke. 2011;42:1680-1690), included duplication of information in the acknowledgments. The acknowledgment should appear as follows:

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