

# Correcting Hypertension Cuts Poststroke Deaths

BY JEFF EVANS  
Senior Writer

NEW ORLEANS — Treatment of dangerously high blood pressure in the period immediately following an acute stroke was associated with significantly reduced 3-month mortality in the randomized, placebo-controlled Control of Hypertension and Hypotension Immediately Post-Stroke trial.

Patients in the CHHIPS pilot trial did not immediately benefit from antihypertensive medications because the trial's primary end point—the rate of death and dependency at 2 weeks after the stroke—was no different between treated and placebo patients, even though the patients who received antihypertensive drugs had significantly greater decline in systolic blood pressure (SBP) within the first 24 hours than did those who received placebo, Dr. John Potter reported at International Stroke Conference 2008.

"We know that elevated blood pressure levels are important in predicting primary and secondary [stroke] prevention, but we don't know much about the relationship in the acute situation," said Dr. Potter of the University of East Anglia, Norwich, England.

Current guidelines on the early management of adult acute ischemic stroke patients advise the use of antihypertensive medications in patients who are eligible for tissue plasminogen activator when their blood pressure is greater than 185 mm Hg/110 mm Hg and in other patients when their blood pressure is above 220 mm Hg/120 mm Hg (*Stroke* 2007;38:1655-711).

To determine if antihypertensive treatment would benefit acute stroke patients with a SBP greater than 160 mm Hg, Dr. Potter and his colleagues randomized 179 patients to receive the  $\beta$ -blocker labetalol, the ACE inhibitor lisinopril, or placebo.

The investigators enrolled patients older than 18 years with a stroke onset within 36 hours and stroke symptoms lasting more than 60 minutes. The patients had not previously been taking antihypertensive medications and had undergone neuroimaging within 72 hours of stroke onset. They excluded any patients who were undergoing thrombolysis as well as those who had impaired consciousness, hypertensive encephalopathy, prestroke dependency (a modified Rankin score of more than 3), any coexisting cardiac or vascular emergencies, contraindications to the study medications, or a primary intracerebral hemorrhage with a SBP greater than 200 mm Hg and/or a diastolic blood pressure greater than 120 mm Hg.

CT scans revealed that about 60% of patients in all groups had an ischemic stroke and about 15% had a primary intracerebral hemorrhage. No relevant abnormality could be seen in the other 25%.

The patients in all groups had a mean National Institutes of Health Stroke Severity score of 11. More than 90% of the patients had no history of stroke or transient ischemic attack. Nearly half of the patients in all groups were dysphagic.

After randomization, patients who could swallow oral medications received 5 mg lisinopril, 50 mg labetalol, or oral placebo. If after 4 hours, their SBP had not dropped to a target range of 145-155 mm Hg or decreased by at

least 15%, then the investigators gave another round of the same doses. This was repeated at 8 hours if necessary. During the next 13 days, patients received 5-15 mg lisinopril, 50-150 mg labetalol, or placebo.

For dysphagic patients, the investigators combined sublingual lisinopril with an intravenous placebo, oral labetalol with sublingual placebo, or sublingual and intravenous placebos. Between days 1 and 5, dysphagic patients were switched to oral medications or received their medications through a nasogastric or percutaneous endoscopic gastrostomy tube. Lisinopril is not approved for use as a sublingual preparation, Dr. Potter noted.

Although the active treatment groups had a significantly greater mean decline in SBP than did placebo-treated patients within the first 24 hours (21 mm Hg vs. 11 mm Hg) and at 2 weeks (31 mm Hg vs. 24 mm Hg), there was no difference between the treatment groups in the rate of death and dependency at 2 weeks (61% vs. 59%). Dependency was defined as a modified Rankin score of more than 3.

Patients who received labetalol or lisinopril reached the target SBP outcomes in significantly higher proportions than did placebo patients at 4 and 8 hours after stroke, but not at 24 hours. There were no differences in neurological status between groups at 72 hours post stroke.

However, patients who received placebo had a 2.2 times higher risk of dying by 3 months than did actively treated patients, based on 12 deaths in the placebo group and 11 deaths in the active treatment groups, Dr. Potter said at the conference, which was sponsored by the American Stroke Association. ■

## BP Protocol Violations in Stroke May Raise Risk of Hemorrhage

BY JEFF EVANS  
Senior Writer

NEW ORLEANS — The administration of tissue plasminogen activator to acute ischemic stroke patients with blood pressure values above the cutoff recommended by current guidelines is associated with significantly higher odds of developing a symptomatic intracerebral hemorrhage, according to a retrospective study.

The study is one of the first to corroborate the recommended cutoff values of a systolic BP of less than 185 mm Hg and a diastolic BP of less than 110 mm Hg for treatment with intravenous tissue plasminogen activator (TPA), Dr. Georgios K. Tsivgoulis reported at the International Stroke Conference 2008.

These thresholds, part of the American Heart Association/American Stroke Association guidelines on the early management of adults with ischemic stroke (*Stroke* 2007;38:1655-711), advise against use of TPA in patients with BP greater than those values, said Dr. Tsivgoulis of the University of Alabama at Birmingham Comprehensive Stroke Research Center at the conference, which was sponsored by the American Stroke Association.

In a review of 510 patients with acute ischemic stroke who received intravenous TPA at a single center during 1996-2005, Dr. Tsivgoulis and his colleagues found 63 (12%) patients received TPA when their blood pressure was above the cutoff. They used blood pressure measurements that were taken closest in time before the TPA bolus was

administered. Overall, the patients had a median onset-to-treatment time of 125 minutes and a median baseline National Institutes of Health Stroke Scale score of 9.

Compared with patients who did not hemorrhage after receiving TPA, the 31 (6%) patients who developed a symptomatic intracerebral hemorrhage had significantly higher mean prebolus systolic BP (169 mm Hg in the bleeders vs. 156 mm Hg in the others) but similar prebolus diastolic BP (85 mm Hg vs. 82 mm Hg). The investigators defined a symptomatic intracerebral hemorrhage by brain-imaging evidence of the hemorrhage and neurological worsening of 4 or more points on the NIHSS within 36 hours of receiving the bolus.

Pretreatment BP protocol violations also were more common in patients who had a symptomatic intracerebral hemorrhage than in those who did not (26% vs. 12%). The absolute risk of developing a symptomatic intracerebral hemorrhage also was significantly greater in patients with a pretreatment BP protocol violation than in those without such a violation (12.7% vs. 5.1%). However, the patients with and without pretreatment BP protocol violations had similar mortality (7.9% vs. 5.8%, respectively).

The occurrence of a pretreatment blood pressure protocol violation was associated with about 2.5 times higher odds of developing a symptomatic intracerebral hemorrhage than in the absence of any blood pressure protocol violation, after adjustment for demographics, stroke risk factors, baseline stroke severity, and onset-to-treatment time. ■

## Stroke Patients on Antiplatelet Drugs May Benefit From TPA

BY MARY ANN MOON  
Contributing Writer

It may not be necessary to withhold tissue plasminogen activator from patients with acute ischemic stroke who are already taking antiplatelet therapy, researchers reported.

The antiplatelet therapy does put these patients at increased risk of developing symptomatic intracerebral hemorrhage when they receive tissue plasminogen activator (TPA). But despite this risk, "prior antiplatelet therapy increased the odds of a favorable outcome" in a single-center observational study involving 301 patients.

The question of whether TPA treatment is safe in patients taking antiplatelet therapy is important because many people who develop acute ischemic stroke have a history of vascular events and are taking the drugs as preventative therapy when a stroke occurs. Many previous studies of the issue have yielded conflicting results, according to Dr. Maarten Uyttenboogaart and his associates at the University of Groningen, the Netherlands.

Dr. Uyttenboogaart and his colleagues studied 301 consecutive patients with acute ischemic stroke given TPA at the university medical center during 2002-2006. Eighty-nine (30%) were already taking aspirin, dipyridamole, combined aspirin plus dipyridamole, or clopidogrel as preventatives.

Symptomatic intracerebral hemor-

rhage occurred in 18 patients (6%), of whom 12 were receiving antiplatelet drugs, and 6 were not. "The absolute risk difference of approximately 10% translates into 1 additional [hemorrhage] in every tenth patient receiving thrombolysis and prior antiplatelet therapy," the investigators said.

Half of the patients on prior antiplatelet therapy had a favorable outcome after TPA administration, compared with 45% of those who were not taking antiplatelet drugs (*Arch. Neurol.* 2008 March 10 [Epub doi:10.1001/archneur.65.5.noc70077]).

Since patients taking antiplatelet therapy were more likely to be older, to have a higher prevalence of vascular risk factors, and to have more previous vascular events than those not taking the agents, the data were adjusted to account for these differences and then re-analyzed. Prior antiplatelet therapy continued to be associated with a favorable outcome after TPA treatment.

"A possible mechanism behind this beneficial effect is that aspirin remains biologically active for 4-6 days and might prevent early reocclusion after TPA treatment," the investigators noted.

Patients in this study were offered TPA for up to 4.5 hours following stroke onset, even though the treatment is approved for use only up to 3 hours after the event. A subgroup analysis of the 188 patients treated within this 3-hour window showed the same results as that for the entire cohort. ■