

# Guidelines for Thrombolytics Need Updating

BY CHRISTINE KILGORE  
Contributing Writer

Current guidelines on the use of thrombolytic therapy for acute ischemic stroke are “hopelessly outdated,” Louis R. Caplan, M.D., said in an editorial that accompanied several reports of patient outcomes studies published in the *Journal of the American Medical Association*.

The guidelines, which are nearly a decade old, exclude from thrombolytic therapy patients who may indeed benefit from it and do not consider the major advances in diagnostic technology that have occurred during the past two decades, said Dr. Caplan, chief of the division of cerebrovascular diseases at Beth Israel Deaconess Medical Center in Boston.

The results of two recent studies on outcomes after thrombolysis are “an important reminder” that few patients with ischemic stroke receive thrombolytic therapy, he said (*JAMA* 2004;292:1883-5).

On the other hand, this treatment “is not a panacea and may actually cause intracerebral hemorrhage or death” in some patients, said Dr. Caplan, who is also professor of neurology at Harvard Medical School, Boston.

In a study by the German Stroke Registers Study Group on predictors of in-hospital mortality after thrombolysis, only 3% of almost 60,000 patients presenting with acute stroke received intravenous tissue plasminogen activator (tPA). Of the treated patients, 10% died during hospitalization.

In the second study, more than half (51%) of 216 patients treated with alteplase in London, Ont., failed to improve significantly after treatment when the published guidelines were followed.

Neither study reported on causative vascular lesions, or on the extent of infarction before or after treatment—information that can be identified with modern imaging techniques, Dr. Caplan noted.

“If the present guidelines continue to be followed, as in the [two studies], physicians will never know which patients with what degree of infarction and with what vascular lesions and at-risk tissue will benefit from thrombolysis,” he said.

Nor will physicians know “whether intravenous, intraarterial, or combined intravenous and intraarterial [therapies] are best and in what circumstances,” he said. “Clinicians also will not know how alteplase compares with other promising newer thrombolytic agents and, possibly, with other therapies.”

In the German study—a prospective, observational cohort study at 225 community and academic hospitals throughout Germany—researchers reported that the factors predicting in-hospital death after thrombolytic therapy were decreased level of consciousness (an odds ratio of 3.5) and older age (an adjusted odds ratio of 1.6 for each 10-year increment of age).

Each factor independently increased the risk of death, reported Peter U. Heuschmann, M.D., of the University of Münster (Germany), and his associates (*JAMA* 2004;292:1831-38).

The overall rate of symptomatic intracranial hemorrhage was 7%, and the rate increased with age. One or more serious complications occurred in 27% of all patients in the study, and in 84% of those who died after treatment.

Hospital expertise with use of tPA also was independently associated with the probability of early death after tPA treatment. The risk of in-hospital death decreased by 3% for

each additional patient treated with tPA per year, Dr. Heuschmann and his associates reported.

In the Ontario study—a prospective study of acute stroke patients who received alteplase at a university hospital over a 4-year period—investigators reported that a lack of improvement at 24 hours was associated with poor patient outcomes and death at 3 months. At the 3-month follow-up, 20% of the patients had died.

They identified three factors—elevated baseline glucose level (144 mg/dL), cortical involvement, and time to thrombolytic therapy—that predicted a lack of improvement at 24 hours.

For each 5-minute increase in the time

that elapsed from symptom onset to treatment, the chance of no improvement increased by 5%, said Gustavo Saposnik, M.D., of the London Health Sciences Centre, and his associates (*JAMA* 2004;292:1839-44).

Lack of improvement was defined as a difference of 3 points or less between the NIH Stroke Scale score at baseline and at 24 hours.

In his editorial, Dr. Caplan said that although earlier treatment is better, studies have shown that the mandated 3-hour time window for thrombolytic therapy may not be appropriate. “Patients with stroke do not become poor candidates for alteplase when the clock strikes 4 hours,” he said.

In a third study that was reported in the *Journal of the American Medical Association*, for instance, some patients with basilar artery occlusion improved when alteplase was given intravenously more than 12 hours after symptom onset, Dr. Caplan noted.

On the other hand, some patients have large infarcts in less than 2 hours, “so the risk of thrombolytic treatment may outweigh the benefit,” he said.

Dr. Caplan cautioned against “cook-book guidelines” and said that treatment decisions must utilize modern diagnostic technology and be individually focused on “each given patient with a given lesion and a known extent of infarction.”

There is also an urgent need for more qualified stroke centers, more experienced stroke clinicians, and new ways to get patients to the centers quickly, he said. ■

**The guidelines, nearly a decade old, exclude from thrombolytic therapy patients who may benefit from it and do not consider diagnostic advances.**

## Ultrasound Improves Thrombolysis in Acute Ischemic Stroke

BY ROBERT FINN  
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Patients suffering from acute ischemic stroke are significantly more likely to achieve recanalization and/or early or dramatic clinical recovery if thrombolytic therapy is combined with continuous transcranial Doppler sonography, according to a study by Andrei V. Alexandrov, M.D., of the University of Texas, Houston, and colleagues.

Of 63 patients receiving ultrasound combined with tissue plasminogen activator (t-PA), 31 (49%) achieved recanalization and/or clinical recovery within 2 hours, compared with 19 of 63 patients (30%) who received t-PA that was combined with sham sonography.

Within 2 hours, 16 (25%) of the patients in the treatment group experienced both recanalization and clinical recovery, compared with 5 (8%) of those in control group. Both of the differences were statistically significant (*N. Engl. J. Med.* 2004; 351:2170-8).

All patients had occlusions of the middle cerebral artery, and all were treated within 3 hours of the onset of symptoms. The patients were randomly assigned to the treatment or the control group, he said.

Known as the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial, the study was funded in part by the National Institute of Neurological Disorders and Stroke, a unit of the National Institutes of Health.

This phase II study was not sufficiently powered to detect a difference in clinical outcome 3 months after the treatment, but there was a statistical trend in that direction.

Of the 53 patients from the treatment group eligible for follow-up, 22 (42%) had achieved a modified Rankin score of 0 or 1, compared with 4 of the 15 eligible patients (27%) in the control group. Given those rates of recovery, the investigators calculated that a phase III study would need to include just 274 patients in each group to repli-

cate the results with statistical significance.

“If you look at the trials being done in cardiology right now, they enroll thousands and tens of thousands of patients to show a difference of a very few percentage points,” Dr. Alexandrov said in an interview. “Cardiologists would love to have an absolute difference of 10% or more between the groups, and that’s what we can shoot for. We can shoot for easily up to a 13% difference between the groups.”

But Dr. Alexandrov is not waiting for the results of that trial, which will likely take 2-3 years, to put the combined treatment into practice.

“At our center, it’s the standard of care right now,” he said. “Both [t-PA and transcranial Doppler sonography] are Food and Drug Administration–approved technologies, and the trial was exempt from investigational new drug status by FDA because these results would not change the labels. Right now in our institution, when we give systemic t-PA within 3 hours [after a stroke], we always put a transcranial Doppler

probe on the scalp to help the patient pass the clot faster.”

Nevertheless, “I will not stand here and recommend that everybody else should do the same,” Dr. Alexandrov said. “The reason is that to do it right, you have to pass through a very lengthy and labor-intensive training that is not a routine part of any neurology residency. To do the protocol, you need 1-6 months of daily practicing of this technique under supervision, and that’s something that very few programs can do in the United States.”

Dr. Alexandrov is involved in an effort to design an operator-independent device that would obviate the need for an experienced operator.

With such a device, “an emergency department physician could do it, a neurologist could do it, and a nurse could mount the ultrasound machine on the head,” he said.

The mechanism by which transcranial Doppler sonography improves thrombolysis is still unclear. In a commentary accompanying Dr. Alexandrov’s paper,

Joseph F. Polak, M.D., of Tufts University, Boston, weighs a number of the possibilities (*N. Engl. J. Med.* 2004;351:2154-5).

It’s clear that the mechanism does not involve cavitation, which ultrasound at high energies can cause. In a cavitation mechanism, the ultrasound energy causes partially dissolved gases to form small bubbles in the blood vessels, which literally explode.

It’s also unlikely that the relatively low energies used in transcranial Doppler ultrasound could accelerate thrombolysis by producing heat.

Dr. Alexandrov believes that the combined treatment works because ultrasound is causing a gentle mechanical pressure wave, which delivers more t-PA molecules to and through the clot.

The study was sparked by a clinical observation, Dr. Alexandrov explained. “Patients who were wearing these transducers for diagnostic purposes started to move their paralyzed arms and legs and to talk to us much faster than we ever [would have] expected otherwise.” ■