

# The IMS Trials

How a combined IV and IA approach utilizing an ultrasound-assisted, drug-delivery microcatheter increases recanalization rates over IV thrombolytic therapy alone.

BY JOSEPH BRODERICK, MD, AND THOMAS TOMSICK, MD

Stroke is the third leading cause of death, the leading cause of serious, long-term disability in the US, and affects more than 700,000 individuals in the US annually. Ischemic stroke accounts for nearly 88% of all strokes.<sup>1</sup> In 1995, a National Institute of Neurological Disorders and Stroke (NINDS) Trial demonstrated intravenous (IV) administration of tissue plasminogen activator (tPA) within 3 hours of the onset of ischemic stroke was an effective method to reopen arteries and improve patient outcomes. Today, IV administration of tPA is the standard of care within the first 3 hours of the onset of a stroke because it can be administered in most hospitals and is effective in a wide range of patients. However, the NINDS trial also showed there is room for improvement in tPA administration for stroke patients because, despite a reduction in mortality from 21% in the placebo group to 17% in the tPA-treated group, the majority of patients are still left disabled even after tPA administration.

The National Institute of Health (NIH)-sponsored Interventional Management of Stroke (IMS) trials were begun in January 2001, with the goal of finding a safer and more effective method of achieving recanalization in ischemic stroke victims. Early results support a promising new treatment.

The first phase of the study was completed in early 2002 and showed that a combined IV and intra-arterial (IA) delivery of tPA was a feasible method for the reopening of blocked arteries warranting further study. Similarly, IMS II, which was completed in late 2005, showed a trend toward better outcomes than treatment with IV alone in ischemic stroke patients. Additionally, in this phase, more than half of the patients were treated with a novel technology that incorporated the use of ultrasound delivered from the tip of the drug delivery catheter, with the goal to better disperse tPA into the clot. Based on the positive findings of both IMS I and IMS II, the NIH has sponsored a 50-center randomized trial called IMS III beginning in late spring of 2006. It will be the largest interventional ischemic stroke trial to date.

“Like cardiology, we are approaching the era of combination therapy for acute stroke . . .”

## IMS I

### Purpose and Overview

The purpose of IMS I was to determine the feasibility of combined IV and IA administration of tPA for treating patients with ischemic stroke. The trial was designed to test the theory from a previous study that indicated IA administration of tPA may accelerate clot thrombolysis and lead to earlier recanalization.<sup>2</sup> The primary measurement of the IMS I trial was to compare the 90-day modified Rankin Scores (mRS) of the subjects to those of the NINDS tPA Stroke Study.

The IMS I study utilized 17 centers to treat 80 subjects between January 31, 2001, and October 23, 2001. Patients ranged in age from 18 to 80 years and each had a National Institutes of Health Stroke Scale (NIHSS) greater than 10, indicating a severe stroke with the intention to compare these subjects of similar age and stroke severity with the NINDS tPA Stroke Study. All subjects in the IMS trials had to have IV tPA initiated within 3 hours of symptom onset, as was the case in the NINDS tPA Stroke Study.

Qualifying patients were first treated with a 0.6-mg/kg dose of IV tPA over half an hour and angiography was performed upon completion. The standard dose of intravenous tPA for ischemic stroke is 0.9 mg/kg infused over 1 hour. If a patient still had a clot and less than 5 hours had passed since symptom onset, the patient was immediately treated with IA administration of tPA using a standard catheter. The treatment was continued for a maximum of 2 hours or until thrombolysis was achieved, with neurologic function evaluated every 15 minutes.

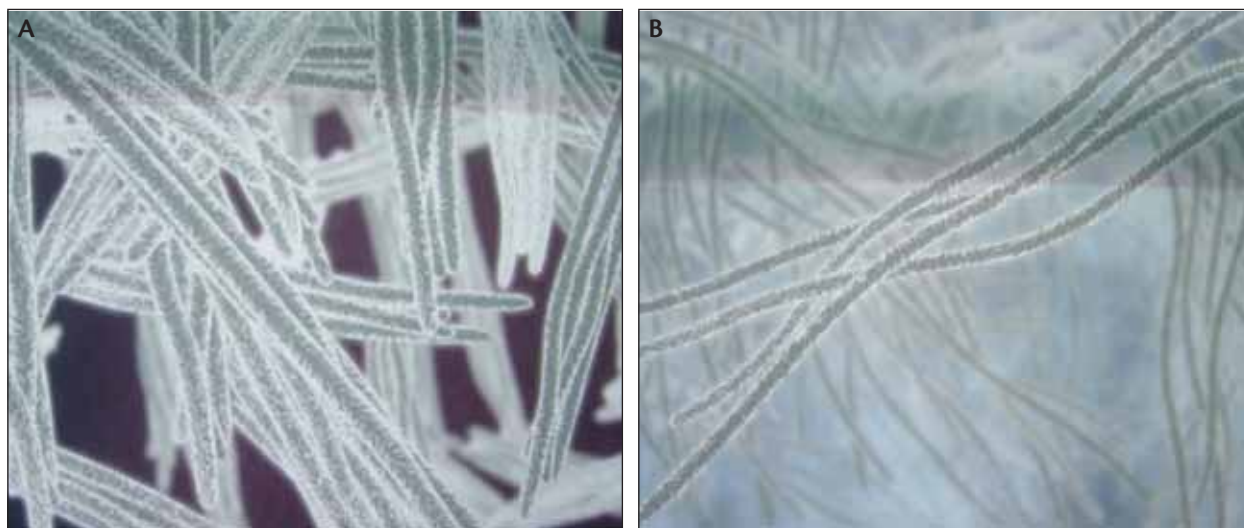


Figure 1. Tightly bound fibrin strands of a clot (A). Fibrin strands of a clot after ultrasound treatment (B).

## Results

Published in the April 2004 edition of *Stroke*, the results of IMS I demonstrated that a higher percentage of IMS I patients with a similar safety profile achieved functional independence within 90 days than in the NINDS tPA Stroke Study.<sup>3</sup> Forty-three percent of patients had an mRS of 0 to 2 at 90 days compared to 39% of NINDS patients (Table 1).

With regard to safety, IMS I patients had a slightly lower, but statistically similar, mortality rate compared to NINDS placebo patients (16% vs 21%). The rate of symptomatic intracerebral hemorrhage of IMS I patients (6.3%) was also similar to NINDS patients (6.6%). Additionally, 51% of the 62 IMS I patients who were treated with a combination of IV and IA tPA achieved partial or complete recanalization of the primary occlusive lesion.

It is important to note that IMS I patients had a higher baseline NIHSS score of 18 compared to NINDS patients who had a median baseline NIHSS score of 17. Additionally, the median time to initiation of IV tPA for IMS patient was much longer (140 minutes) compared to NINDS patients (90 minutes).

## Conclusion

The results of the IMS I warranted a randomized trial comparing the standard IV tPA approach to a combined IV and IA approach. However, there was still some disappointment with the rate of recanalization. Before initiating a fully randomized trial, it was decided to explore the potential benefit of repeating the IMS I study with an advanced catheter that showed promise in accelerating the action of tPA.

## IMS II

### Purpose and Overview

Building on the positive results of IMS I, IMS II sought to continue investigating the feasibility of a combined IV and IA approach for rapidly restoring cerebral blood flow in ischemic stroke patients. The IMS II protocol was identical to that of IMS I, with one important exception: whenever possible, the EKOS Micro-Infusion Catheter (EKOS Corporation, Bothell, WA) would be used to deliver the tPA into the clot to gauge the efficacy of ultrasound technology in delivering the tPA into the blood clot.

To dissolve a blood clot, thrombolytic drugs must bind with plasminogen activation receptor sites, which are located in the tightly bound fibrin of a blood clot (Figure 1A). Locally delivered, low-energy ultrasound helps temporarily loosen and separate the fibrin (Figure 1B), which makes the clot more permeable and increases the availability of more plasminogen activation receptor sites. At the same time, the ultrasound helps drive the thrombolytic agents deep into the blood clot to accelerate the thrombolysis and ultimately dissolve the clot. FDA-approved for use in the periphery for the treatment of peripheral arterial occlusion and deep vein thrombosis, the EKOS Micro-Infusion Catheter, an ultrasound-assisted catheter, was introduced into the IMS II trial to study its effectiveness for the treatment of clots in the neurovasculature.

In the IMS II trial, 73 patients were treated in 13 different centers. The trial began in January 2003 and was completed in February 2005.

## Results

The results of IMS II, which were presented at the International Stroke Conference sponsored by the American

**TABLE 1. EFFICACY OF (PERCENTAGE OF PATIENTS WITH mRS 0-2 AT 90 DAYS) IMS II VS IMS I VS NINDS**

	IMS II (n=73)	IMS I (n=80)	NINDS (n=182)
Median baseline NIHSS	19	18	17
Median age	66	65	68
Median time from onset to IV (minutes)	141	140	90
mRS 0-2 at 3 months	45%*	43%	39%*
<p>*After adjustment for baseline NIHSS, age, and time to treatment, the odds ratio of IMS II subjects attaining an mRS of 0-2 at 3 months was 1.65 (95% CI; 0.88, 3.07) compared to tPA-treated subjects in the NINDS rt-PA Stroke Trial.</p> <p>mRS, modified Rankin Scores; IMS, Interventional Management of Stroke; NINDS, National Institute of Neurological Disorders and Stroke; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.</p>			

Stroke Association in February, provided further support for combined IA and IV stroke therapy. Patients treated with the dual-treatment approach showed a trend toward better outcomes than those treated with IV tPA administration alone. The likelihood of patients to be independent at 3 months was 1.65-fold higher than that of NINDS patients, after adjustment for baseline NIHSS, age, and time to treatment.

In IMS II, 45% of patients had an mRS of 0 to 2 at 90 days compared to 43% of IMS I patients and 39% of NINDS patients (Table 1). Mortality rates were identical in IMS I and IMS II (16%) despite a difference in symptomatic intracranial hemorrhage rate (11% in IMS II vs 6.3% in IMS I).

With regard to the results achieved by the ultrasound catheter specifically, the IMS II study demonstrated a higher rate of reopening of the blocked brain arteries than the IMS I study, which did not use ultrasound catheters (69% in IMS II vs 51% in IMS I for patients treated with the IV/IA approach). In IMS II, the EKOS Micro-Infusion Catheter was used in 41% of the 73 patients.

The median baseline NIHSS score of the 73 IMS II patients was 19, compared to 18 in IMS I and 17 in the NINDS Study. The median time to initiation of IV tPA administration in IMS II was almost identical to IMS I (141 minutes in IMS II vs 140 minutes in IMS I).

## Conclusion

The results of IMS II provided additional evidence that a combined IV/IA approach is a promising treatment for ischemic stroke patients when compared to IV administration of tPA alone. The positive results warrant a random-

ized trial to further investigate the potential of the treatment. The trial also demonstrated for the first time that ultrasound-assisted drug delivery might lead to better results than treatment with a standard microcatheter.

## IMS III

### Purpose and Overview

IMS III will be a randomized, 50-center, 900-patient clinical trial continuing the investigation into the efficacy of a combined IV/IA approach to recanalize ischemic stroke patients. During the trial, patients will be randomized at a ratio of 2:1 for IV/IA therapy versus IV administration of tPA. The primary outcome measure will be an mRS of 0 to 2 at 90 days.

For patients in whom the combined IV/IA approach is appropriate, the physician will select either the EKOS Micro-Infusion Catheter or a standard microcatheter to locally infuse tPA, or alternatively, may select a newly cleared mechanical clot removal device, the Concentric Merci system (Concentric Medical, Inc., Mountain View, CA). The IMS III trial is scheduled to begin in May 2006.

## FINAL COMMENT

As we are about to embark on the largest interventional ischemic stroke trial ever, the institutions and clinicians involved are optimistic about the implications for the medical community and, of course, for victims of ischemic stroke who deserve a therapy that can help restore their quality of life. Like cardiology, we are approaching the era of combination therapy for acute stroke and the IMS III Trial represents an important step toward this goal. With the incidence of stroke on the rise, it is essential that we continue to investigate better treatments of this condition that kills and disables so many people each year. ■

*Joseph Broderick, MD, is Chair of Neurology, University of Cincinnati, Ohio. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Broderick may be reached at (513) 475-8730; broderjp@ucmail.uc.edu.*

*Thomas Tomsick, MD, is Director of Neuroradiology, University of Cincinnati, Ohio. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Tomsick may be reached at (513) 584-7544; tomsick-ta@healthall.com.*

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-151.
2. Lewandowski CA, Frankel M, Tomsick TA. Combined intravenous and intra-arterial r-tPA versus intra-arterial therapy for acute ischemic stroke. *Emergency Management of Stroke (EMS) Bridging Trial*. *Stroke*. 1999;30:2598-2605.
3. The IMS Stroke Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the interventional management of stroke study. *Stroke*. 2004;35:904-912.