

EDITORIAL



Endovascular Treatment for Acute Ischemic Stroke — Still Unproven

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Most ischemic strokes are caused by an embolic or thrombotic occlusion of an intracranial artery. The immediate aims of acute stroke treatment are recanalization of the occluded artery and reperfusion of the ischemic brain region. Currently, intravenous thrombolysis that is administered within 4.5 hours after the onset of a stroke is the only proven treatment.^{1,2} However, recanalization rates within 24 hours after the administration of intravenous tissue plasminogen activator (t-PA) are low when the occlusion involves a large intracranial artery, with rates of 14% for internal carotid arteries and 55% for middle cerebral arteries.³ These low rates have prompted the use of endovascular therapies to improve recanalization rates.

In a randomized trial called Prolyse in Acute Cerebral Thromboembolism II (PROACT II)⁴ involving patients who were treated within 6 hours after stroke onset, investigators found that the use of intraarterial prourokinase, as compared with intravenous heparin, significantly increased the recanalization rate of occlusions of the middle cerebral artery (66% vs. 18%) and improved outcomes. However, the Food and Drug Administration (FDA) did not approve the use of prourokinase for this indication, citing the need for a confirmatory trial, which was never performed.

Nevertheless, the PROACT II trial provided proof of concept that endovascular treatment could improve outcomes in patients with acute ischemic stroke. Subsequently, the endovascular strategy for recanalization of occlusions of large intracranial arteries shifted to the use of thrombectomy devices, often in combination with intraarterial t-PA. After uncontrolled trials showed

that the devices were effective in the recanalization of large-artery occlusions,^{5,6} the FDA approved these devices under 510(k) clearance, which does not require proof of clinical efficacy. Later, Medicare provided reimbursement for these procedures, leading to widespread use of the devices despite the absence of evidence establishing their efficacy.

Investigators now report in the *Journal* the results of three long-awaited randomized trials comparing endovascular procedures with medical treatments for acute ischemic stroke.⁷⁻⁹ Key features and results of these trials are described in Table 1. The Interventional Management of Stroke III (IMS III) trial⁷ used an innovative design in which patients in whom intravenous t-PA was administered within 3 hours after stroke onset were randomly assigned to receive intravenous t-PA alone or intravenous t-PA followed by endovascular treatment. Despite a higher recanalization rate in the endovascular group, clinical outcomes were similar in the two groups. In the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial,⁸ the median time from stroke onset to the start of treatment was only 1 hour longer in the endovascular group than in the medical-therapy group, yet endovascular treatment did not improve outcomes, as compared with the use of intravenous t-PA.

If recanalization is critical for better outcomes and endovascular treatment is most effective for the recanalization of arteries,³ why was there no benefit from endovascular treatment in the IMS III and SYNTHESIS Expansion trials? One obvious answer is that there is no benefit from recanalization if it occurs too late (i.e., after the ischemic

region has already undergone infarction). As the findings of the SYNTHESIS Expansion trial suggest, even a 1-hour delay in the time to treatment negates the benefit of a higher recanalization rate with endovascular treatment.⁸ Although results were not statistically significant, subgroup analyses in the IMS III trial raise the possibility that if intravenous t-PA can be started within 2 hours after stroke onset and the endovascular procedure can be initiated within 90 minutes after the start of t-PA, endovascular treatment may add benefit. However, if both these conditions are not met, endovascular treatment may cause harm.⁷

Are there situations in which the time to treatment is not as critical? Nonrandomized studies have suggested that patients who are beyond the 4.5-hour window after stroke onset and who have perfusion imaging showing a large area of ischemia but not infarction (the ischemic penumbra) may benefit from endovascular treatment.^{10,11} The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial⁹ was primarily designed to test this hypothesis by comparing endovascular treatment with medical care in patients within 8 hours after stroke onset. Patients with an ischemic penumbra had better outcomes than patients without a penumbral pattern, but endovascular treatment provided no advantage in either group.⁹ One possible explanation is that the penumbral pattern may identify patients who are likely to have a better outcome regardless of treatment because they have sufficient perfusion through collateral vessels to limit infarct size. However, that hypothesis does not explain why only 14 to 23% of patients with a favorable penumbral pattern had a good outcome in MR RESCUE. It may be because the penumbral pattern lacks specificity as a marker of durable tissue viability — in other words, only a subgroup of patients with a favorable penumbral pattern have ischemic brain tissue that can recover with later reperfusion. Another finding that may have contributed to the similar outcomes in the treatment groups in MR RESCUE was the higher-than-expected revascularization rate in the medical group, a finding that was also shown in the IMS III trial.

What are the implications of these results for clinical practice? The IMS III and SYNTHESIS

Expansion studies show that intravenous thrombolysis should continue to be the first-line treatment for patients with acute ischemic stroke within 4.5 hours after stroke onset, even if imaging shows an occluded major intracranial artery. Beyond 4.5 hours, the MR RESCUE trial does not provide data supporting the use of endovascular treatment in patients with an ischemic penumbra of any size.

The development of more effective intravenous lytic agents and endovascular devices to treat patients with acute ischemic stroke is imperative, since the majority of such patients still have substantial disability after treatment, as these trials show. Progress has already been made on both of these fronts. In recent trials, tenecteplase, a genetically engineered mutant t-PA, was associated with significantly better reperfusion and clinical outcomes at 24 hours than alteplase, the FDA-approved t-PA,¹² and new devices (stent retrievers) were significantly more effective than first-generation devices for improving reperfusion and outcome at 90 days.^{13,14} The IMS III trial provides preliminary data for a randomized trial to determine whether newer endovascular devices add benefit to intravenous thrombolysis if both therapies can be initiated very early after stroke onset, though providing such rapid treatment is challenging. Since the MR RESCUE study is the only randomized trial to test the ischemic-penumbra hypothesis and was limited by the small sample size and use of less effective thrombectomy devices, larger randomized trials will be needed to retest this hypothesis with the use of newer devices once the accuracy of perfusion imaging for identifying viable brain tissue has been more clearly established.

However, conducting randomized endovascular trials involving patients with acute ischemic stroke is easier said than done. The two above-mentioned trials that were conducted primarily in the United States (IMS III and MR RESCUE) had substantial difficulty in recruiting patients, because once the FDA approved the devices and Medicare provided reimbursement for these procedures, endovascular treatment became widespread and many physicians who were treating patients with acute stroke felt that the “answer was in.” Therefore, treatment equipoise was lost. It is hoped that equipoise will return on the

Table 1. Key Features and Results of Trials Comparing Endovascular Procedures with Medical Treatment for Acute Ischemic Stroke.*

Trial	No. of Patients and Sites	Enrollment Period	Key Patient Characteristics	Test Treatment†
IMS III ⁷	656 Patients enrolled (target, 900) at 58 sites	2006–2012	NIHSS score, ≥ 10 ¶; anterior or posterior circulation; 92% of 306 patients who underwent baseline CT angiography had large-artery occlusions	IV t-PA followed by endovascular therapy
SYNTHESIS Expansion ⁸	362 Patients enrolled at 24 sites	2008–2012	No limit on NIHSS score; anterior or posterior circulation; no data on percentage of patients with large-artery occlusions	Endovascular therapy
MR RESCUE ⁹	127 Patients enrolled at 22 sites but analysis restricted to 118 patients	2004–2011	NIHSS score, 6–29; large-vessel occlusion involving anterior circulation (ICA, M1, M2) required; 58% had favorable penumbral pattern	Endovascular therapy; 43.8% of patients in this group also initially received IV t-PA

* CT denotes computed tomography, ICA intracranial internal carotid artery, IMS III Interventional Management of Stroke III, IV t-PA intravenous tissue plasminogen activator, M1 stem of the middle cerebral artery, M2 a division of the middle cerebral artery, MR RESCUE Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy, NIHSS National Institutes of Health Stroke Scale, and SYNTHESIS Expansion Local versus Systemic Thrombolysis for Acute Ischemic Stroke.

† Endovascular procedures differed according to study.

‡ Listed are the rates of partial or complete 24-hour recanalization in the two groups in the IMS III trial, as measured in patients for whom data were available on baseline and 24-hour CT angiography. The percentage of patients with Thrombolysis in Cerebral Infarction (TICI) reperfusion grades of 2 or 3 on angiography (indicating partial or complete perfusion) immediately after endovascular treatment were 65% for ICA, 81% for M1, 70% for a single M2, and 77% for multiple M2s. Also listed are TICI reperfusion grades of 2 or 3 in the two treatment groups in the MR RESCUE trial, as measured on day 7 by magnetic resonance angiography or CT angiography. The percentage of patients with TICI reperfusion grades of 2 or 3 on angiography immediately after endovascular treatment was 67%.

§ In all three trials, function was evaluated with the use of the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating greater disability, although the primary-outcome thresholds for disability-free survival varied among the trials. The rates listed here are for patients who had a score of 2 or less (no symptoms or slight disability). A score of 0 to 2 was the primary outcome measure in the IMS III trial and a secondary outcome measure in the MR RESCUE trial. A score of 0 or 1 was the primary outcome measure in the SYNTHESIS Expansion trial (which was reported in 30.4% of patients in the endovascular group and 34.8% of those in the IV t-PA group). The rates in MR RESCUE have been adjusted for age.

¶ The NIHSS score ranges from 0 to 42, with higher scores indicating more severe neurologic deficits. A later protocol amendment led to the enrollment of a few patients with large-artery occlusion on CT angiography and an NIHSS score of 8 or 9.

|| The qualifying stroke was attributed to small-vessel disease on day 7 evaluation in 7% of patients.

basis of the results of these three trials. Nevertheless, recruitment in new trials will still be challenging, particularly among patients with large disabling strokes and their concerned families who “want everything done,” especially with new endovascular devices available and third-party payers willing to reimburse for these procedures. A decision by Medicare to place a moratorium on reimbursement for endovascular treatment of acute ischemic stroke outside of randomized trials would facilitate recruitment in these urgently needed trials. Once the new trials are completed, endovascular treatment will have been given ample opportunity to prove itself.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Control Treatment	Window from Stroke Onset to Randomization	Revascularization Rate in Patients with Large-Artery Occlusion [†]	Rate of Disability-free Survival at 90 Days [‡]
IV t-PA	IV t-PA initiated within 3.0 hr after stroke onset; randomization required within next 40 min	At 24 hr in endovascular-therapy group: ICA, 81%; M1, 86%; M2, 88%; at 24 hr in IV t-PA-therapy group: ICA, 35%; M1, 68%; M2, 77%	Endovascular therapy, 40.8%; IV t-PA therapy, 38.7%
IV t-PA	4.5 hr	Not provided	Endovascular therapy, 42.0%; IV t-PA therapy, 46.4%
Standard care; 29.6% of patients in this group initially received IV t-PA	8 hr	At 7 days in endovascular-therapy group, 71%; at 7 days in standard-care group, 87%	Endovascular therapy, 14% in penumbral group and 9% in nonpenumbral group; standard care, 23% in penumbral group and 10% in nonpenumbral group

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