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EDITORIAL COMMENT

Standards and Barriers in Acute Stroke Therapy

A Leap Forward in the Evolution of Endovascular Interventions for Stroke*

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Whether interventional approaches to stroke neurology have lagged behind those aimed at heart attack—for reasons biological or practical—are topics for another day. However, the balance has changed. Tissue plasminogen activator (tPA) was first approved in the United States for intravenous administration to patients with acute stroke in 1996 (1), and a study for catheter-directed intra-arterial infusion of a thrombolytic agent for this indication was first published in 1998 (2). The first positive randomized controlled study using mechanical thrombectomy devices for stroke came from the Netherlands just last year (3), and results from 4 additional trials published in 2015 support combined treatment with tPA and catheter-based thrombectomy (4–7). In the recent positive stroke trials, removable devices consisting of self-expanding, clot-retrieving stents achieved higher rates of recanalization than earlier methods of thrombus extraction, representing the first effective new treatment for stroke in nearly 20 years. The measures employed in these studies have lengthened the time-to-treatment window and help guide the selection of patients who benefit most from acute endovascular intervention. With absolute benefits substantially greater than systemic intravenous thrombolysis alone, the combination of intravenous tPA and endovascular therapy have improved outcomes for selected patients who receive endovascular treatment within 6 h of symptom onset.

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The meta-analysis of endovascular stroke trials by Elgendy et al. (8) presented in this issue of the *Journal* summarizes the recent series of achievements that collectively represent a landmark in stroke therapy. As with any meta-analysis of heterogeneous trials, it provides cohesiveness by blurring some of the inherent differences among the component studies. The investigators included all randomized trials of endovascular stroke therapy except the Italian SYNTHISIS (A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke) (9), which prohibited intravenous thrombolysis in the group assigned to endovascular therapy per protocol, and the lack of benefit associated with endovascular therapy in that study is noteworthy. Three of the trials included in the analysis (MR RESCUE [Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy], IMS III [Third Interventional Management of Stroke], and THERAPY [Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke]) evaluated mainly first-generation thrombectomy devices and did not find a statistically significant difference between endovascular and medical therapies. The IMS III trial was stopped because of futility after enrollment of 656 patients (10). Similarly, MR RESCUE (11) failed to demonstrate efficacy for endovascular therapy, and the THERAPY trial was halted prematurely

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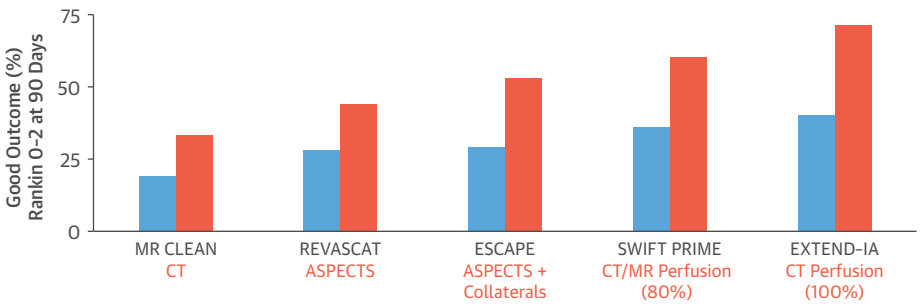
once announcement of positive results from other trials disturbed clinical equipoise. In contrast, trials that predominantly or exclusively involved stent retrievers exhibited substantially higher reperfusion rates and better clinical outcomes than those achieved with the first-generation devices. Each had statistically significant risk ratios (RR) of 1.6 to 1.8 with endovascular treatment (indicating the favorable outcome rate was approximately 1.7-fold higher in the endovascular arms of the studies). Therefore, the benefit of modern endovascular therapy with stent retrievers is likely greater than the overall RR of 1.45 derived by the meta-analysis.

In contrast to the consistent benefit of mechanical thrombectomy in patients with acute stroke, studies of primary revascularization in patients with ST-segment elevation acute myocardial infarction (STEMI) have found that thrombectomy before angioplasty—whether the technology involves thrombus aspiration or rheolytic thrombectomy—has not generally been associated with benefit compared with primary percutaneous coronary intervention (PCI) alone (12–16). Among others, the investigators of the current meta-analysis assessed the role of aspiration thrombectomy before primary PCI in recent randomized trials, and concluded that thrombus removal was not associated with clinical benefit and might increase the risk of stroke (17).

Primary angioplasty in vessels with large thrombus burden is associated with greater risks of distal embolization, no-reflow phenomenon, transmural myocardial necrosis, stent thrombosis, and major adverse cardiac events, including mortality (18–22), yet routinely preceding these interventions with thrombectomy was not associated with improved short- or long-term outcomes in subgroup analyses of the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) (13) and TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) (12) trials. It is unclear whether the difficulty is related to ways in which in the myocardial microcirculation are differentially affected by these interventional technologies or whether similar processes are at work in the brain. Whatever mechanisms are involved, the evolution of interventional technology for acute stroke management has heretofore followed the path paved by frontline management of patients with acute STEMI, and the roads may now diverge. Considerable heterogeneity in clinical presentation of these acute ischemic syndromes contributes to the challenge of case selection for implementation of available revascularization modalities.

In the acute stroke stent retriever trials, clinical outcomes differed considerably although patient age and initial stroke severity were similar. This could be

FIGURE 1 New Randomized Clinical Trials of Endovascular Therapy: Imaging Selection



Results of recent randomized endovascular stroke trials that predominantly or extensively used stent retrievers. The percentage of patients in each trial who achieved a good clinical outcome (modified Rankin score of 0 to 2) at 90 days in the endovascular and control groups is shown for each study. The differences in brain imaging methodology used to select eligible patients is highlighted. CT = computed tomography; MR = magnetic resonance; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTENDA-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial; SWIFT PRIME = Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; REVASCAT = Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset.

related to various imaging criteria employed for subject inclusion, based on the dual need to identify large vessel occlusion and exclude extensive cerebral infarction. In recent trials, computed tomographic (CT) angiography or magnetic resonance (MR) angiography was generally required to document large vessel occlusion. In 2 early, negative trials (IMS III and SYNTHESIS), CT or MR angiography was not required, which compromised the power of the studies because the objective of endovascular therapy is to overcome target vessel occlusion. Exclusion of patients with early ischemic parenchymal injury based on imaging also varied between trials. Among the newer trials, MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) (3) used brain imaging solely to exclude patients with brain hemorrhage. Perhaps as a result, favorable clinical outcomes were relatively uncommon in both the endovascular and the control arms; only 33% of the endovascular patients were left with only slight or no disability at 3 months (**Figure 1**). In the Spanish REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset) study (7), patients with evidence of a substantial volume of early ischemic brain injury as assessed by the ASPECTS (Alberta Stroke Program Early CT Score) CT score were excluded from enrollment, and favorable outcomes were more frequent than in MR CLEAN. The Canadian ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times) trial (6) excluded patients with low ASPECTS scores and those with poor collateral flow evident on CT angiography, and 53% of patients in the endovascular group were left without significant functional disability. The North American/European SWIFT-PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) (5) and Australian EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial) studies (4) used automated analysis of CT or MRI perfusion images to identify patients with salvageable brain regions and relatively small volumes of irreversibly injured ischemic core tissue. Perhaps as a result, patients in these trials enjoyed the highest rates of favorable functional outcomes following endovascular therapy (60% and 71%) and substantial absolute risk reductions compared with those managed with intravenous tPA alone (**Figure 1**). Patients in the control groups who were treated with intravenous tPA also had more favorable outcomes than those in the other trials, which suggested that the perfusion imaging approach was useful in identifying patients with more favorable outlooks with either intravenous or intra-arterial reperfusion.

The majority (>90%) of patients encompassed by the meta-analysis received endovascular therapy within 6 h of symptom onset. In more recent trials, greater emphasis was placed on workflow improvements to abbreviate the interval between arrival at the hospital emergency department and initiation of reperfusion. For example, in SWIFT PRIME, femoral puncture occurred a median of 224 min after symptom onset and a median of 90 min after arrival. Although these metrics represent substantial improvements over those in earlier stroke trials, the elapsed times are considerably longer than typically achieved in centers that provide catheter-based reperfusion for acute STEMI. However, to become the new standard of care for patients with ischemic stroke due to large artery occlusion, effective implementation of this approach requires the evolution of systems of acute stroke care to route appropriate patients to facilities capable of expedient delivery of all validated technologies. Further efforts to shorten the interval between emergency department arrival and treatment hold the promise of even better outcomes.

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