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STATE-OF-THE-ART REVIEW

PERIPHERAL

Endovascular Reperfusion Strategies for Acute Stroke

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ABSTRACT

Stroke is the most common cause of permanent disability, the second most common cause of dementia, and the third most common cause of death in the Western world. About 10% to 20% of strokes are due to large-artery occlusions causing severe disabling strokes. Recently, 5 randomized controlled trials established mechanical thrombectomy in stroke treatment in patients with large-vessel occlusions. The current intra-arterial reperfusion therapies allow high recanalization rates, high rates of favorable clinical outcome, and low complication rates. This review discusses the results of recent randomized trials and describes the current state-of-the-art endovascular treatment in acute ischemic stroke. (J Am Coll Cardiol Intv 2016;9:307–17) © 2016 by the American College of Cardiology Foundation.

Stroke is the most common cause of permanent disability, the second most common cause of dementia, and the third most common cause of death in the Western world (1). The World Health Organization estimates that 5.7 million people die of stroke each year. On average, every 40 seconds, someone in the United States has a stroke. Each year, ~795,000 people experience a new or recurrent stroke in the United States and 1 million people in the European Union (2). Stroke survivors are often burdened with exorbitant rehabilitation costs, lost wages and productivity, limitations in their daily social activity, and significant residual disability. As the world's population continues to age, the incidence of stroke will increase proportionately. Between 2012 and 2030, total direct medical stroke-related costs are projected to triple, with the majority of the increase arising from patients between 65 and 79 years of age (3).

The majority (>80%) of acute strokes are ischemic. The primary principle driving treatment of ischemic stroke is that "time is brain." The following are variables that affect the extent of ischemic brain injury: 1) the time from the onset of symptoms to reperfusion; 2) the presence of collateral circulation including an intact circle of Willis; and 3) the "penumbra of viability" surrounding the infarcted brain tissue. The penumbra is the region of brain surrounding the infarct area where the blood supply is significantly reduced, but energy metabolism is maintained due to collateral flow. The viability of this area is dependent on both the severity and duration of ischemia. If blood flow is rapidly restored, some ischemic brain tissue will be saved. This puts a premium on the rapid assessment of patients presenting with stroke.

Previous trials of endovascular therapy included the intracranial administration of thrombolysis and the use of early generation mechanical thrombectomy devices (Merci [Concentric Medical, Mountain View, California] and Penumbra [Penumbra Inc., Alameda, California] devices) (4–7). The initial trials did not demonstrate conclusive benefit for endovascular therapy, although there were promising signals. There seemed to be a balance between early and effective mechanical reperfusion balanced against the risk of intracranial hemorrhage (ICH) that was perhaps related to reperfusion of nonviable brain. The next step was to deliver rapid, safe, and effective

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ABBREVIATIONS AND ACRONYMS

ASPECTS = Alberta Stroke Program Early CT score

CT = computed tomography

CTA = computed tomography angiography

D2D = door-to-device

IAT = intra-arterial thrombectomy

ICA = internal carotid artery

ICH = intracranial hemorrhage

IV t-PA = intravenous tissue-type plasminogen activator

MCA = middle cerebral artery

NIHSS = National Institutes of Health Stroke Scale

reperfusion therapy in stroke patients with viable brain tissue at risk (penumbra), determined by pretreatment brain imaging.

Between December 2014 and April 2015, 5 randomized, controlled trials provided compelling evidence that intra-arterial thrombectomy (IAT) improves outcomes after acute ischemic stroke. Endovascular treatment significantly improved clinical outcome in patients with proximal intracranial occlusion of the anterior circulation compared with intravenous tissue-type plasminogen activator (IV t-PA), indicating that the preferred treatment of these patients is no longer IV t-PA, but endovascular techniques (8–12).

This review discusses the results of recent randomized trials and describes the current state-of-the-art endovascular treatment for acute ischemic stroke.

RESULTS OF RECENT RANDOMIZED CLINICAL TRIALS

A large number of prospective trials studying mechanical thrombectomy for acute ischemic stroke that predate "stent retriever" devices have been negative or inconclusive. The results of the IMS-III (Interventional Management of Stroke III) trial, published in 2013, showed no benefit of endovascular therapy after the use of intravenous (IV) thrombolysis over IV thrombolysis alone in the treatment of moderate to severe acute ischemic stroke (1,13). However, there were major weaknesses in this study. First, computed tomography angiography (CTA) was not required, which allowed the inclusion of patients who did not have intracranial large-vessel occlusion. Second, the new technology, stent retrievers, were used only in 5 patients.

Between December 2014 and April 2015, 5 multicenter randomized clinical trials were published with positive results with endovascular therapy. The major differences between these positive endovascular trials and past trials were the use of CTA to select patients with proximal intracranial occlusion and the use of stent retrievers for thrombectomy in the majority of cases (**Central Illustration**).

The MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) (2,11), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) (3,10), EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial) (8–12), SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) (8), and REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours After Symptom Onset in Ischemic Stroke) (9) have demonstrated the efficacy of endovascular therapy versus IV-tPA alone in treating patients with acute anterior circulation ischemic stroke. The last 3 studies were terminated early by their Data Safety Monitoring Boards after the MR CLEAN results were published (**Tables 1 and 2**).

INCLUSION CRITERIA AND TIME WINDOW. All 5 trials used CT imaging to select patients. In MR CLEAN, patients were selected based on plain CT imaging using the Alberta Stroke Program Early CT score (ASPECTS). In other trials, patients were selected for having a small ischemic core at baseline and either adequate collaterals (using CTA in ESCAPE) or salvageable brain (using CT perfusion) in EXTEND-IA and SWIFT PRIME.

The documentation of a proximal anterior circulation intracranial occlusion with CTA was required in all trials, which is a major difference from the negative endovascular reperfusion trials in the past.

The baseline age and sex were comparable in all trials. The baseline National Institutes of Health Stroke Scale (NIHSS) score was high, at ~16. In the EXTEND-IA study, the NIHSS was lower in the conservative group compared with the intervention group (13 vs. 16). Patients older than 80 years of age were included in all but SWIFT PRIME trial.

The SWIFT PRIME treated patients up to 4.5 h from the onset of stroke, whereas MR CLEAN and EXTEND-IA included those up to 6 h after onset, REVASCAT up to 8 h, and ESCAPE up to 12 h. In practice, however, only a few patients who could not have groin puncture by 6 h were actually included. Therefore, the positive results of the trials mainly apply to patients treated within 6 h from symptom onset. A combined approach with IV thrombolysis and thrombectomy was required in the SWIFT PRIME and was used in the majority of patients in the other studies. Most patients in the control groups received IV thrombolysis if they presented within the 4.5-h time window (**Table 1**).

FAVORABLE CLINICAL OUTCOME. All 5 randomized, controlled trials showed a benefit for endovascular treatment compared with IV t-PA alone with regard to functional outcomes. The percentage of patients achieving a favorable clinical outcome with IAT varied between 33% and 71%; there was a consistent positive difference across all studies with a favorable clinical outcome (defined as a modified Rankin Scale score of 0 to 2 at 90 days) between the