

Current Guidelines for Management of Acute Ischemic Stroke with Large Vessel Occlusion in the Anterior Circulation

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Abstract

The worldwide estimates of stroke incidence, stroke survivors, and stroke deaths are 16.9 million, 33 million, and 5.9 million cases respectively while 102 million disability-adjusted life-years (DALYs) are lost reflecting an overall increasing global burden of stroke [1,2]. About 87% of all strokes is ischemic stroke, leading to high rates of disability and death; half of the survivors have hemiparesis while one third require assistance to walk [3]. Intravenous alteplase has been the only approved reperfusion therapy for acute ischemic stroke with symptom onset of 4.5 hours in European countries while US FDA has approved the use of intravenous alteplase for reperfusion therapy for acute ischemic stroke for only upto 3 hours from symptom onset [4]. But large vessel occlusions (including the intracranial internal carotid artery occlusion, internal carotid artery terminus occlusion, and proximal middle cerebral artery occlusion) account for more than one third of the cases of acute ischemic stroke in which intravenous alteplase is not as much effective and the mortality is 60-80% in 90 days in this patient population [5-7]. This review focuses on the recently updated 2015 stroke management guidelines by American Heart Association/American Stroke Association. The purpose of this review is to get a glance of the trials that led to the revised stroke management guidelines. It is imperative to identify patient population with acute ischemic stroke with large vessel occlusion in the anterior circulation who will benefit from endovascular treatment, which now is current standard of care apart from intravenous alteplase.

Keywords: Stroke; Guidelines; Intervention; Endovascular Thrombectomy; MR CLEAN Trial; ESCAPE Trial; Extend-IA Trial; SWIFT PRIME Trial; REVASCAT Trial

Introduction

Recently 5 randomized clinical trials have shown the efficacy and safety of intra-arterial therapy in acute ischemic stroke secondary to large vessel occlusion (LVO) [8-12]. The first such trial was Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN). Following this trial 4 more randomized trials were published which confirmed the efficacy and safety of intra-arterial treatment in acute ischemic stroke due to LVO.

Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR Clean) [8]

This trial was conducted at 16 centers in Netherlands. In this trial patients were assigned to either intra-arterial treatment plus intravenous alteplase/urokinase or intravenous alteplase/urokinase therapy alone. Patients who had proximal vessel occlusion/LVO in the anterior circulation confirmed with computed Tomographic (CT) angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA), and had a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating more severe neurologic deficits) were included. They used Alberta Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan)

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on the CT scan along with baseline vessel imaging (CTA, MRA, or DSA) for the location of the occlusion to identify patients eligible for intra-arterial therapy.

The patients were randomized to the intra-arterial arm within 6 hours of the symptom onset. Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. Retrievable stents were used in 190 of the 233 patients in the intra-arterial arm. The primary outcome was the modified Rankin scale score at 90 days; which measures functional outcome with scores ranging from 0 (no symptoms) to 6 (death). Between December 2010 and March 2014, 500 patients were enrolled at 16 medical centers in Netherlands (of which 233 were assigned to intra-arterial arm and 267 were to intravenous alteplase/urokinase alone). The authors reported an absolute difference of 13.5 percentage points in the rate of functional dependence (modified Rankin score of 0 to 2), in favor of intervention (32.6% vs 19.1%). There was no significant difference in mortality or symptomatic intracerebral hemorrhage between the two arms.

Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) Trial [9]

This trial was conducted at 22 centers worldwide. It was halted early due to efficacy. In this trial patients were randomized to either endovascular treatment with standard care in form of intravenous alteplase or standard care alone. This trial evaluated acute ischemic stroke with a small infarct core (defined as ASPECTS 6 - 10), a proximal intracranial LVO with moderate to good collateral circulation as assessed by multiphase CTA. No upper age limit was used to enroll patients in the trial, included patients with Barthel Index ≥ 90 (score range between 0 to 100 with higher score indicating greater ability to do activities of daily living independently).

Patients were enrolled in the intra-arterial treatment arm up to 12 hours from the onset of stroke symptoms. Between February 2013 to October 2014, 316 patients were enrolled with 165 in the intervention arm, 150 in the control arm and 1 patient was excluded due to improper consent. The authors reported increased rate of functional independence (90 day modified Rankin score of 0 to 2) with intervention. The primary outcome favored intervention and it was associated with reduced mortality (10.4%, vs. 19.0%). Symptomatic intracerebral hemorrhage occurred more in the intervention group but it was statistically not significant. This trial established mortality benefit of intervention in acute ischemic stroke when compared to MR Clean trial.

Extending the Time for Thrombolysis in Emergency Neurological Deficits --Intra-Arterial (EXTEND-IA) trial [10]

This trial was conducted at 10 study centers (9 in Australia and 1 in New Zealand). A total of 70 patients were enrolled from August 2012 to October 2014. It was halted early due to efficacy. In this trial patients were randomized to either endovascular treatment with the Solitaire FR (Flow Restoration) stent retriever with standard care in form of intravenous alteplase or standard care alone. Patients were enrolled in the intra-arterial treatment arm up to 6 hours from the onset of stroke symptoms. They used the inclusion criteria of ischemic core of less than 70 ml on CT perfusion imaging, which was processed with the use of fully automated software (RAPID, noncommercial research version, Stanford University).

The coprimary outcomes were reperfusion at 24 hours and early neurologic improvement (≥ 8 -point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3). Secondary outcomes included the functional score on the modified Rankin scale at 90 days.

They reported that in the endovascular arm there was increased perfusion at 24 hours, early neurological improvement at 3 days, more patients achieved functional independence at 90 days and there was no significant differences in the rates of death or symptomatic intracerebral hemorrhage. The study determined that 2.8 patients have to be treated with endovascular therapy to achieve improvement of at least 1 point on the functional score and 3.2 patients needed to be treated to achieve an independent outcome, as compared to alteplase alone.

Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial [11]

This was a multinational trial performed at 39 centers across the USA and Europe in which 196 patients were randomized from December 2012 through November 2014. In this trial patients were randomized to either endovascular treatment with stent retriever along with standard care in form of intravenous alteplase or standard care alone. Patients were randomized to the intervention arm upto 6 hours from the symptom onset. LVO was detected initially by of RAPID (iSchemaView), an operator-independent image post processing system. The inclusion criteria required patients to have target mismatch penumbral profile with a small core (which was later modified to use small to moderate core) of irreversibly injured tissue and large region of hypoperfused brain at risk of ischemia and was salvageable.

The primary outcome was again the functional outcome measure, modified Rankin scale at 90 days which was higher in the intervention group as compared to the control group (60% vs 35%). There were no significant differences in 90-day mortality or symptomatic intracranial hemorrhage between both the groups. Secondary clinical efficacy outcomes were the rate of death at 90 days, the rate of functional independence (modified Rankin scale score, ≤ 2) at 90 days, and the change in the NIHSS score at 27 hours after randomization was significantly better in the intervention group as compared to the control group.

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 (REVASCAT) trial [12]

This trial was performed in 4 centers in Catalonia, Spain and 206 patients were randomized to receive either medical therapy (including intravenous alteplase when eligible) and endovascular therapy with the Solitaire stent retriever(thrombectomy group) or medical therapy alone (control group). The patients were randomized to the intervention arm within 8 hours of symptom onset. Patients with ASPECTS score of less than 7 on CT scan or less than 6 on diffusion weighted MRI were considered to have large ischemic core and were excluded. The primary outcome was the functional outcome measure at 90 days, modified Rankin scale which was higher in the intervention arm as compared to the control arm (43.7% vs. 28.2%). Again the rates of symptomatic intracranial hemorrhage and mortality were not statically significant.

Secondary outcomes in the study were infarct volumes on CT or MRI at 24 hours, vessel revascularization on CTA or MR angiography (MRA) at 24 hours, early dramatic response to treatment (defined as a decrease in the NIHSS score of ≥ 8 from baseline or an NIHSS score of 0 to 2 at 24 hours), the NIHSS score and Barthel Index (with the latter on a scale from 0 to 100, with higher scores indicating less disability) at 90 days, and health status, as measured on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D, on a scale of -0.33 to 1, with higher values indicating a better quality of life) at 90 days. Secondary outcomes also favored the intervention group.

Based on the above 5 randomized controlled trials performed in different countries of the world by various vascular neurologists and interventional specialist showing an overwhelming favorable 90 day functional outcome measures, modified Rankin scale, in the intervention groups American Heart Association/American Stroke Association in 2015 guidelines made intervention a Class I, Level of evidence A in the management of acute ischemic stroke with LVO in the anterior circulation. Appropriate patient selection will still be very critical to better outcome, as all the patients will LVO might not have small ischemic core or good collaterals as determined by the various neuroimaging modalities. The imaging criteria used was not uniform amongst these trials but all them required the demonstration of LVO using CTA or MRA and all the trials (except MR Clean) used ASPECTS score of 7 - 10 to enroll the patient identifying small infarct core and large area of surrounding salvageable brain tissue. ESCAPE was the only trial which demonstrated mortality benefit in the intervention arm while the rest of the trial did not find any statistical difference in mortality or symptomatic intracranial hemorrhage rates between the two groups. Saver et al. in the recent meta-analysis showed that earlier treatment with endovascular thrombectomy and medical treatment when compared to medical treatment alone decrease the disability rate at 3 months and the benefit became non-significant after 7.3 hours of onset of stroke symptoms [13].

Conclusion

The above trials which included about 1288 patients in total, provide Class 1, Level of evidence A in favor of mechanical thrombectomy along with medical therapy with intravenous alteplase in patients with acute ischemic stroke with LVO in the anterior circulation but careful patient selection will still be prudent driving the long term outcome and further meta-analysis are needed to expand the recommendation.

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